CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125527Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125527 (Type 9) Supplement Number: 0 NDA Supplement Type (e.g. SE5): _____

Division Name:DOP2 PDUFA Goal Date: 6/22/15 Stamp Date: 12/22/2014

Proprietary Name: OPDIVO

Established/Generic Name: Nivolumab

Dosage Form: Injection for Intravenous Infusion

Applicant/Sponsor: Bristol-Myers Squibb Company

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of Melanoma
(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 NSCLC

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]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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 †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

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

☐ Justification attached.

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

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

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

BLA 125527 for Nivolumab (BMS-936558)

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Due to the low incidence of lung cancer in the pediatric population, Bristol-Myers Squibb (BMS) requests a waiver from the pediatric study requirements for nivolumab in the treatment of subjects with advanced squamous non-small cell lung cancer (SQ NSCLC) following platinum-based therapy (b) (4)

The low incidence of NSCLC in the pediatric population is supported by the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program and the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) as reported in Cancer Statistics, 2014 (Siegel R et al., CA Cancer J Clin 2014; 64:9-29). This reference is available upon request.

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

/s/

MEREDITH LIBEG
02/03/2015

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

Memorandum

DATE: February 22, 2015

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

SUBJECT: Review Designation memo

Sponsor:	Bristol-Myers Squibb Company
Product:	Opdivo (nivolumab) Injection for Intravenous Infusion
Proposed Indication:	Treatment of subjects with advanced squamous non-small cell lung cancer (SQ NSCLC) (b) (4)

TO: BLA 125527

The review status of this file submitted as a Type 9 BLA is designated to be:

☐ Standard (10 Months) ☒ Priority (6 Months)

BACKGROUND
In their December 22, 2014, final submission completing the BLA, Bristol-Myers Squibb (BMS) requested priority review designation. This request was based on the following information:

"There is an extremely poor prognosis for patients with advanced SQ NSCLC after prior platinum-based therapy (b) (4). This is an area of high unmet medical need, with no approved or recommended active therapies. This BLA provides compelling evidence of the safety and efficacy of nivolumab in this patient population. Given the substantial and meaningful improvement in ORR over expected historical response rates, DOR,

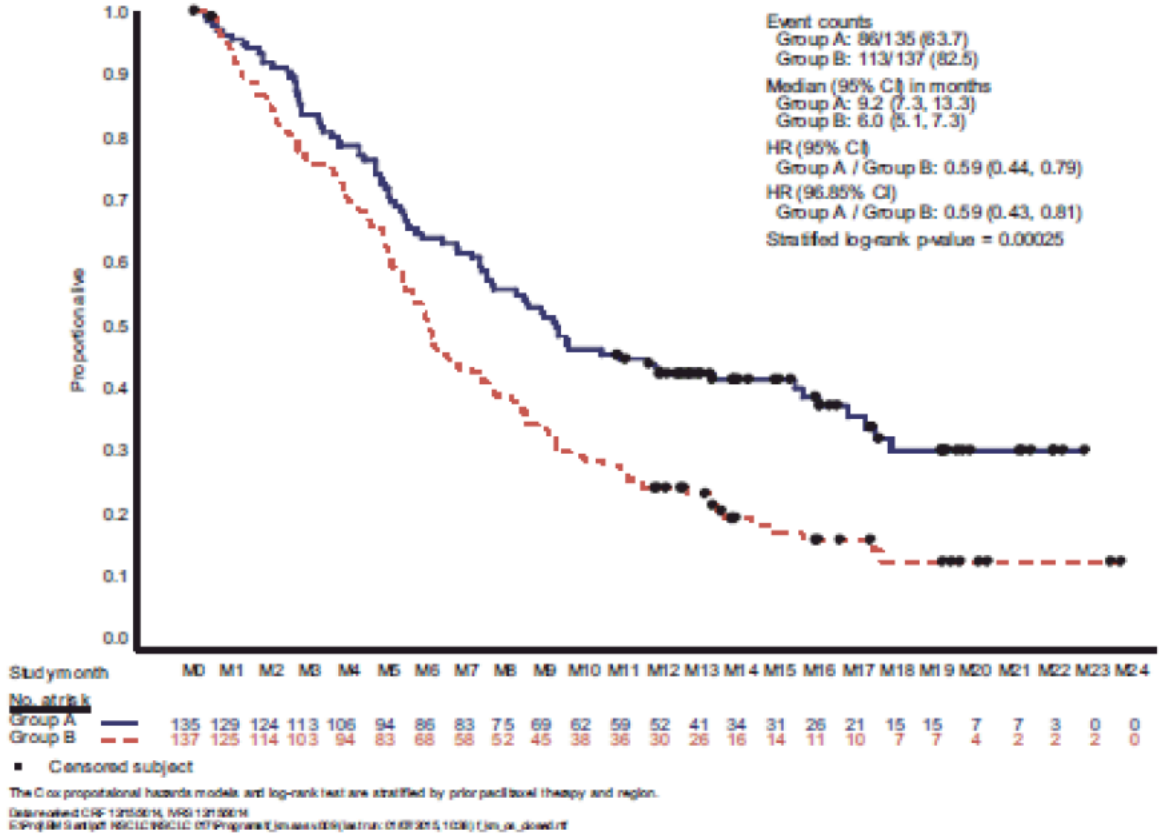
PFS, and OS in the CA209063 and MDX1106-03 studies, it is respectfully requested that the FDA consider assigning a priority review clock to this application."

As stated in the proposed labeling, BMS noted that (b) (4) in a single-arm, multinational, multicenter study. All patients had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen…. Based on IRC review and with a minimum follow-up of approximately (b) (4) months, confirmed ORR was 15% (17/117) (95% CI: 8.7, 22.2); of which all were partial responses. (b) (4)

On January 29, 2015, the efficacy supplement was amended at FDA's request to include a copy of the protocol and statistical analysis plan, the Data Monitoring Committee's summary report of the planned interim analysis of overall survival, and the datasets supporting this analysis for Study CA209017.

As described in the interim study report, there were 272 patients randomized in Study CA209017; 135 were randomized to nivolumab and 137 were randomized to docetaxel. All patients in this study had received a prior platinum-based doublet. At the planned interim analysis conducted after 199 deaths, the O'Brien-Fleming boundary was crossed demonstrating a statistically significant improvement in overall survival for patients randomized to nivolumab [hazard ratio 0.59 (0.43, 0.81); p=0.00025] with a median survival of 9.2 months among those randomized to nivolumab and 6.0 months among those randomized to docetaxel. The separation in the survival curves was observed within one month after initiation of treatment and the curves remained separate and with increasing separation in the curves after 6 months.

Figure 1. Kaplan-Meier curves for overall survival



The Cox proportional hazards models and log-rank test are stratified by prior paclitaxel therapy and region.

Data received CRF 13155014, MR 13155014

ASSESSMENT

In evaluating the review designation for Bristol-Myers Squibb's efficacy supplement for nivolumab for the proposed indication, I considered their rationale, the summary results of Study CA209017, and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment*:*
This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition
The American Cancer Society estimates that there will be 224,210 new cases of lung cancer (NSCLC or SCLC) in the United States in 2014 and an estimated 159,260 deaths due to lung cancer in the US in 2014.[1] The 5-year year relative survival rate between 2010 and 2014 was 4.5% for patients with metastatic, non-small cell lung cancer.[2]

I concur that the indicated population has a serious, life-threatening condition.

[1] American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014.
[2] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

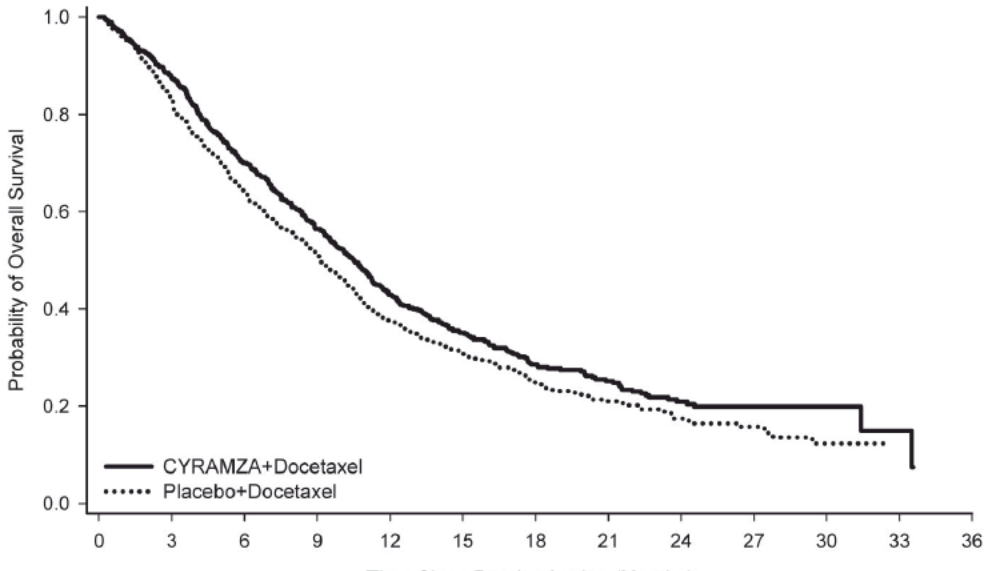
Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

Available therapy for the treatment of patients with squamous cell, non-small cell lung cancer (SQ NSCLC) who have progressed following a platinum-based doublet therapy includes the following FDA-approved drugs:

Docetaxel, as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. This approval was based on the results of two randomized, controlled trials established that docetaxel at a dose of 75 mg/mg^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy. TAX317 compared outcomes in patients randomized to docetaxel or to best supportive care, which TAX320 compared outcomes in patients randomized to docetaxel or to investigator's choice of vinorelbine or ifosfamide. The primary endpoint was survival in both trials. The TAX317 trial showed a significant improvement in overall survival [HR 0.56 (95% CI: 0.35, 0.88); p=0.01] with a median survival of 7.5 months in the doxetaxel arm and 4.6 months in the best supportive care arm. The TAX320 trial showed no significant difference in survival for patients randomized to docetaxel as compared to those randomized to investigator's choice of vinorelbine or ifosfamide.

Ramucirumab, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab. This approval was based on the results in a randomized (1:1), multinational, placebo-controlled, "add-on" trial comparing overall survival in patients randomized to docetaxel 75 mg/mg^2 every 3 weeks plus ramucirumab with patients randomized to docetaxel 75 mg/mg^2 every 3 weeks plus matching placebo. The trial demonstrated a statistically significant improvement in overall survival [HR 0.86 (0.75, 0.90); p=0.024] with median survival times of 10.5 months and 9.1 months for the docetaxel/ramucirumab and docetaxel/placebo arms, respectively. This was supported by an improvement in progression-free survival [HR 0.76 (0.68, 0.86); $p < 0.001$] and a significantly higher overall response rates (23% vs. 14%; $p < 0.001$).

Figure 3: Kaplan-Meier Curves of Overall Survival -CYRAMZA plus Docetaxel versus Placebo plus Docetaxel in NSCLC



Number at Risk													
CYRAMZA+Docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+Docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

Erlotinib is indicated for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. This approval was based on the results of a randomized 92:1), placebo-controlled trial conducted in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. In this trial, 93% of patients had received prior platinum therapy and 30% had squamous histology. The trial demonstrated a statistically significant improvement in overall survival [HR 0.73 (0.61, 0.86); p<0.001 with median survival times of 6.7 months and 4.7 months for the erlotinib and placebo arms, respectively. This was supported by an improvement in progression-free survival [HR 0.59 (0.50, 0.50); p < 0.001] with median PFS times of 9.9 weeks and 7.9 weeks, respectively, and a significantly higher overall response rates (8.9% vs. 0.9%; p <0.001).

Pemetrexed is indicated as a single agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. This approval was based on the results of a multi-center, randomized (1:1), open label study was conducted in 568 patients with Stage III or IV NSCLC after prior chemotherapy to compare the overall survival following treatment with pemetrexed with single agent docetaxel 75 mg/mg^2 every 3 weeks. The study failed to demonstrate an improvement in overall survival, however based on a retrospective subgroup analysis by histology, the adjusted hazard ratio favored the pemetrexed arm for the 399 patients with non-squamous, NSCLC [HR 0.78 (0.61, 100), whereas outcomes were inferior among the 172 patients with SQ NSCLC [HR 1.56 (95% CI: 1.08, 2.26)]. This difference

in treatment effect for pemetrexed based on histology, demonstrating a lack of efficacy in squamous cell histology in NSCLC, was also observed in the first-line combination study and in the maintenance study. This is the basis for the limitation of use in the USPI, stating that pemetrexed is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

Assessment: The results of Study CA209017 demonstrated a clinically large and statistically robust improvement in overall survival over single agent docetaxel based on a planned interim analysis; thus evidence of increased effectiveness in the treatment of SQ NSCLC has been established.

Increased evidence of effectiveness of nivolumab over the combination of docetaxel and ramucirumab has not been demonstrated, since the two regimens were not compared directly in a head-to-head trial. Such a trial was not required, as the trial supporting approval of ramuciurumab was conducted contemporaneously with Study CA209017, with approval of ramucirumab for this indication on December 12, 2014. Furthermore, while cross-study comparisons are generally invalid, there is no suggestion from the available data that the benefits of ramucirumab in combination with docetaxel over docetaxel alone are so large that clinical equipoise does not exist and that the nivolumab would be unequivocally inferior to the combination of ramucirumab and docetaxel . Finally, there is evidence that nivolumab may provide an advantage over the combination with regard to certain safety signals. Specifically, ramucirumab labeling carries a Boxed Warning for serious hemorrhagic events, whereas this is not a safety signal observed with nivolumab.

While erlotinib has an approval that includes this patient population, under current US Oncology Practice Guidelines, its use is limited to patients with sensitive EGFR mutations.

Finally, pemetrexed, which is approved for the second-line treatment of NSCLC has a limitation of use stating that pemetrexed is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

RECOMMENDATION: Priority Review

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
03/04/2015

Libeg, Meredith

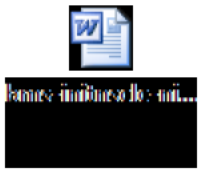
From: Libeg, Meredith
Sent: Monday, March 02, 2015 5:17 PM
To: 'Phillips, Eric'
Subject: BLA 125527 - BMS - Nivolumab - Response to FDA Proposed Labeling Edits (3.2.15)

Importance: High

Hi Eric,

Please find attached FDA's next round of proposed edits to the Nivolumab PI relating to your BLA application (BLA 125527) submitted on December 22, 2014.

Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. When making edits to the label, please update formatting as necessary.



Please submit the updated labeling via email by **noon on Tuesday, March 3, 2015, or sooner if possible**, and follow with a formal submission to the BLA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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

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/s/

MEREDITH LIBEG
03/02/2015

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

Memorandum

Date: January 23, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb Company (BMS)**

Sponsor Face-To-Face/Teleconference – Clinical and Statistical Dataset Meeting

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Date and Time of Face-To-Face/Teleconference: January 23, 2015, 2:30 p.m. to 4:00 p.m.

FDA Participants:

Gideon Blumenthal, M.D.	Clinical Team Leader
Sean Khozin, M.D.	Clinical Reviewer
Dickran Kazandjian, M.D.	Clinical Reviewer
Lijun Zhang, Ph.D.	Statistical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants (Present in Person):

Brian Lestini, M.D., Ph.D.	Director, Global Clinical Research
Ian Waxman, M.D.	Director, Global Clinical Research – Oncology
Jean Viallet, M.D.	Vice President, Global Clinical Research – Oncology
Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Rebecca L Drain	Associate Director, Global Dossier Management
Haolan Lu, Ph.D.	Associate Director, Global Biometric Sciences
Todd Rider	Associate Director, Statistical Programming Manager
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences – Oncology
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology
Eric Phillips, M.P.H., Sc.D.	Director, Global Regulatory Sciences – Oncology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology

Sponsor Participants (Present via Teleconference):

Christine Baudelet, Pharm.D., Ph.D.	Sr. Research Biostatistician, Global Biometric Sciences
Naveed Imshad	Principal Analyst, Global Biometric Sciences

This was an FDA-initiated Face-to-Face to discuss the clinical and statistical aspects of the datasets submitted on December 22, 2014, in support of the pending BLA 125527 for Opdivo (nivolumab) for the treatment of subjects with advanced squamous non-small cell lung cancer (SQ NSCLC) after prior platinum-based therapy (b) (4) Due to the timing of the meeting, several BMS participants joined via teleconference.

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on December 22, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification.

Additionally, FDA clarified their January 22, 2015, response to BMS' query on the timing and contents of the 90-day safety update. BMS acknowledged FDA's clarification; and will follow with a formal submission to the BLA.

Attachments:

- FDA email communication of January 22, 2015.

Libeg, Meredith

From: Libeg, Meredith
Sent: Thursday, January 22, 2015 3:33 PM
To: 'Phillips, Eric'
Subject: RE: Nivolumab - BLA 125527 (NSCLC)

Hi Eric,
Did I ever get back to you about the safety update? If not, for safety update, we would like to receive case narratives for all serious adverse events and all cases of positive re-challenge for immune-related events since the data cut-off date. We would like this by the end of January. If this is not achievable, please let me know and we can discuss this further.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

From: Phillips, Eric [mailto:Eric.Phillips@bms.com]
Sent: Tuesday, January 06, 2015 9:49 PM
To: Libeg, Meredith
Subject: Nivolumab - BLA 125527 (NSCLC)

Good morning Meredith,
I hope this email finds you well. When we met in White Oak in November I introduced myself as the point of contact for the aforementioned BLA. While it got a little more complicated with the submission of the additional data from the 017 study last month, I am once again your point of contact on this application. (Please note that I remain blinded to the -017 data for the time being).

As requested, the team is working on combining the -063 NSCLC draft labeling with the recently approved melanoma label. My plan is to submit the updated draft label as an amendment to this BLA next week. We acknowledge certain data in the updated draft labeling still needs to be aligned with some of the requests and methodology that was applied to the approved melanoma label – specifically in the Warnings and Precautions section. We are working on this and will have the information available as soon as possible.

I also noted in the Pre-BLA meeting minutes (28 April 2014) there was lack of agreement on the timing for the database lock for the 90 day Safety Update. Please advise if this would be a reasonable time to get our teams engaged in dialog on this issue.

I look forward to working with you on this project. Please do not hesitate to contact me if there is anything I can do to help you or your team.
Best regards,
Eric

Eric Phillips, MPH, ScD
Director, Global Regulatory Strategy - Oncology
Bristol-Myers Squibb
Office: 609.252.4992

Cell (b) (6)

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/s/

MEREDITH LIBEG
02/27/2015

Libeg, Meredith

From: Libeg, Meredith
Sent: Wednesday, February 25, 2015 6:11 PM
To: 'Phillips, Eric'
Subject: BLA 125527 - BMS - Nivolumab - Response to FDA Proposed Labeling Edits (2.25.15)

Hi Eric,

Please find attached FDA's next round of proposed edits to the Nivolumab PI relating to your BLA application (BLA 125527) submitted on December 22, 2014.

Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. When making edits to the label, please update formatting as necessary.

Please submit the updated labeling via email by **COB on Thursday, February 26, 2015, or sooner if possible**, and follow with a formal submission to the BLA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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MEREDITH LIBEG
02/25/2015

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

Memorandum

Date: February 24, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
Bristol-Myers Squibb Company
Route 206 & Province Line Road, Room D2 204
Princeton NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your responses via email by COB on February 24, 2015, and follow with a formal submission to the BLA.

Clinical Comments:

1. Please submit the patient narratives for the 7 cases excluded from your analysis of adverse reactions leading to discontinuation based on your methodology excluding records with preferred terms that are not study drug related (i.e., where variable AEDECOD does not include values of "malignant neoplasm progression," "superior vena cava syndrome," and "toxicity to various agents).

2. Please perform an analysis of serum calcium level elevations according to laboratory values, stratified by toxicity grade and shift from baseline. Submit methodology for your analysis and any supporting transformed dataset(s).

3. Submit a summary table of all laboratory abnormalities increased from baseline, arranged in descending order, occurring in ≥10% of patients for all NCI CTCAE Grades or ≥2% for Grades 3-4.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
02/24/2015

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

Memorandum

Date: February 24, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
Bristol-Myers Squibb Company
Route 206 & Province Line Road, Room D2 204
Princeton NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your responses via email by noon on February 25, 2015, and follow with a formal submission to the BLA.

Clinical Comments:

1. Provide an assessment of the events leading to administration of packed red blood cell transfusions in patients (n = at least 6 per FDA's ongoing analysis) in STUDY CA209063. Include all relevant laboratory values in your assessment.

2. Provide a narrative summary for CA209063-32-63066, focusing on administration of corticosteroids for the event of ANEMIA.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
02/24/2015

PeRC Meeting Minutes
February 11, 2015

PeRC Members Attending:
Lynne Yao
Rosemary Addy (NON-RESPONSIVE)
George Greeley
Ruthanna Davi
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Peter Starke
Daiva Shetty
Andrew Mulberg
Greg Reaman
Andrew Mosholder (NON-RESPONSIVE)
Hari Cheryl Sachs
Julia Pinto
Olivia Ziolkowski
Gilbert Burckhart
Kevin Krudys
Barbara Buch
Rachel Witten
Dianne Murphy
Maura O'Leary (NON-RESPONSIVE)
Kim Dettlebach (NON-RESPONSIVE)
Sonal Vaid NON-RESPONSIVE
Nisha Jain NON-RESPONSIVE
Adrienne Hornatko-Munoz NON-RESPONSIVE

Agenda

9:00	NON-RESPONSIVE			
9:20				
9:40				
10:00				
10:20				
10:30				
10:50				
	BLA	*125527*	*OPDIVO (nivolumab) Full Waiver*	*NSCLC*
	NON-RESPONSIVE			

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NON-RESPONSIVE

OPDIVO (nivolumab)

- Proposed Indication: NSCLC
- PeRC Recommendations:
  - The PeRC agreed with the plan for full waiver

NON-RESPONSIVE

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/s/

GEORGE E GREELEY
02/23/2015

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

Memorandum

Date: February 20, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb (BMS)**
Proposed PMC/PMR Language

Bristol-Myers Squibb
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
Bristol-Myers Squibb Company
Route 206 & Province Line Road, Room D2 204
Princeton NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

Please see FDA's proposed language for a post-marketing requirement and post-marking commitment. Please provide your agreement by **Tuesday, February 24, 2015**, or sooner if possible. Refer to the resources below and please use due diligence in proposing timelines for completion of these trials. Final language will be included in the action letter.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

Assessment of Known Serious Risk Relating to Use of Nivolumab:

1. Conduct a randomized trial that will characterize the incidence, severity and response to treatment of nivolumab induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

   Final Report Submission: December 31, 2015

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

CLINICAL

Clinical Trials To Further Define the Efficacy of Nivolumab:

2. Submit the Clinical Study Report and efficacy datasets for the open-label randomized trial of nivolumab versus docetaxel in patients with previously treated advanced squamous non-small cell lung cancer.

   Final Report Submission: December 31, 2015

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf.
- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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MEREDITH LIBEG
02/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125527

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Bristol-Myers Squibb Company
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory, Safety and Biometrics, U.S. Oncology
Route 206 & Province Line Road, Room D1 213
Princeton, NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) for which the first portion was submitted and received on April 30, 2014, and the final portion dated December 22, 2014, received December 22, 2014, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) Injection.

We also refer to your amendments dated April 30, 2014, June 20, 2014, July 25, 2014, September 26, 2014, October 6, 2014, October 10, 2014, November 11, 2014, December 22, 2014, December 30, 2014, January 15, 2015, January 16, 2015, January 28, 2015, January 29, 2015, January 30, 2015, February 5, 2015, February 10, 2015, and February 12, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 22, 2015.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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

labeling and, if necessary, any postmarketing requirement/commitment could be communicated as early as February 18, 2015. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
02/22/2015

Libeg, Meredith

From: Libeg, Meredith
Sent: Thursday, February 19, 2015 3:39 PM
To: 'Phillips, Eric'
Subject: BLA 125527 - BMS - Nivolumab - FDA Proposed Labeling Edits (2.19.15)

Importance: High

Hi Eric,

Please find attached FDA's first round of proposed edits to the Nivolumab PI relating to your BLA application (BLA 125527) submitted on December 22, 2014.

Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. When making edits to the label, please update formatting as necessary. Lastly, please make sure that the line on the left margin is present for each section that is required to be listed in the recent major changes section.

Please submit the updated labeling via email by **11 am on Monday, February 23, 2015, or sooner if possible**, and follow with a formal submission to the BLA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,
Meredith

Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-1721

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

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/s/

MEREDITH LIBEG
02/19/2015

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

Memorandum

Date: February 5, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
Bristol-Myers Squibb Company
Route 206 & Province Line Road, Room D2 204
Princeton NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA.

Clinical Comments:

1. At least 7 of the 20 patients identified as having Stage 3b disease had metastatic target lesions. It is unclear for the remaining 13 if the lung target lesions are ipsilateral. Please describe in further detail how patients were staged. Specifically:

    - It appears that patients who had recurrent disease were categorized as Stage 4 regardless of initial staging at diagnosis, please confirm.
    - Out of the 20 patients with 3b disease, clarify how many patients truly had M1 disease.
    - For the entire patient population (117), please provide data on whether patients had M1a or M1b disease.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
02/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125527

BLA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory, Safety and Biometrics, U.S. Oncology
Route 206 & Province Line Road, Room D1 213
Princeton, NJ 08543

Dear Dr. Phillips:

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

Name of Biological Product:	Opdivo (nivolumab) Injection for Intravenous Infusion, 40 mg/4 ml (10 mg/mL) single-use vial, 100 mg/10 ml (10 mg/mL) single-use vial
Date of Application:	December 22, 2014
Date of Receipt:	December 22, 2014
Our Reference Number:	BLA 125527
Proposed Use:	For the treatment of subjects with advanced squamous non-small cell lung cancer (SQ NSCLC) after prior platinum-based therapy (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2015, in accordance with 21 CFR 601.2(a).

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

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Monica L. Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
02/02/2015

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

Memorandum

Date: January 23, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb Company (BMS)**

Sponsor Face-To-Face/Teleconference – Clinical and Statistical Dataset Meeting

---

Date and Time of Face-To-Face/Teleconference: January 23, 2015, 2:30 p.m. to 4:00 p.m.

FDA Participants:

Gideon Blumenthal, M.D.	Clinical Team Leader
Sean Khozin, M.D.	Clinical Reviewer
Dickran Kazandjian, M.D.	Clinical Reviewer
Lijun Zhang, Ph.D.	Statistical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

Sponsor Participants (Present in Person):

Brian Lestini, M.D., Ph.D.	Director, Global Clinical Research
Ian Waxman, M.D.	Director, Global Clinical Research – Oncology
Jean Viallet, M.D.	Vice President, Global Clinical Research – Oncology
Aparna Anderson, Ph.D.	Director, Global Biometric Sciences
Rebecca L Drain	Associate Director, Global Dossier Management
Haolan Lu, Ph.D.	Associate Director, Global Biometric Sciences
Todd Rider	Associate Director, Statistical Programming Manager
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences
MaryBeth Frosco, Ph.D.	Director, Global Regulatory Sciences – Oncology
Kathleen O'Donnell	Director U.S. Regulatory Sciences – Oncology
Eric Phillips, M.P.H., Sc.D.	Director, Global Regulatory Sciences – Oncology
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences - Oncology

Sponsor Participants (Present via Teleconference):

Christine Baudelet, Pharm.D., Ph.D.	Sr. Research Biostatistician, Global Biometric Sciences
Naveed Imshad	Principal Analyst, Global Biometric Sciences

This was an FDA-initiated Face-to-Face to discuss the clinical and statistical aspects of the datasets submitted on December 22, 2014, in support of the pending BLA 125527 for Opdivo (nivolumab) for the treatment of subjects with advanced squamous non-small cell lung cancer (SQ NSCLC) after prior platinum-based therapy (b) (4) Due to the timing of the meeting, several BMS participants joined via teleconference.

BLA 125527
Face-to-Face/Teleconference 1/23/15

Summary of the TCON:

FDA and BMS discussed the clinical and statistical aspects of the datasets submitted on December 22, 2014, specifically where to locate specific information contained in the BLA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification.

Additionally, FDA clarified their January 22, 2015, response to BMS' query on the timing and contents of the 90-day safety update. BMS acknowledged FDA's clarification; and will follow with a formal submission to the BLA.

Attachments:

- FDA email communication of January 22, 2015.

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

Memorandum

Date: January 12, 2015

From: Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2

Subject: **BLA 125527 – Bristol-Myers Squibb (BMS)**
Clinical Review Comments and Information Request

Bristol-Myers Squibb
Attention: Eric Phillips, M.P.H., Sc.D.
Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
Bristol-Myers Squibb Company
Route 206 & Province Line Road, Room D2 204
Princeton NJ 08543

Dear Dr. Phillips:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for "Opdivo (nivolumab) Injection for Intravenous Infusion."

Our Clinical Reviewer has the following request for information. Please provide your response as a formal submission to the BLA by Thursday, January 15, 2015, or sooner if possible.

Clinical Comments:

1. Please provide the Data Monitoring Committee (DMC) charter and minutes of the interim analysis meeting for study CA209017.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
01/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125527/0

BLA PRESUBMISSION ACKNOWLEDGEMENT

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, U.S. Liaison-Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

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: Nivolumab Injection; 100 mg/10 mL and 40 mg/4 mL

Date of Submission: April 30, 2014

Date of Receipt: April 30, 2014

Our Reference Number: BLA 125527/0

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

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

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

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

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

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely yours,

{See appended electronic signature page}

Monica L. Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
07/16/2014

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

Memorandum

Date: July 15, 2014

From: Meredith Libeg, Senior Regulatory Health Project Manager-
CDER/OHOP/DOP2

Subject: **BLA 125527 –** Bristol-Myers Squibb Company –
Nivolumab Injection; 100 mg/10 mL and 40 mg/4 mL
Chemistry, Manufacturing, and Controls (CMC) Review Comments and Information Request

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Director, U.S. Liaison-Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for "Nivolumab Injection."

We also refer to the Part 2 presubmission of your BLA rolling submission dated June 20, 2014, containing CMC information. Based on our preliminary review, the CMC Reviewer has the following comments and requests for information:

1. It appears that the most current manufacturing schedule was not included in the June 20, 2014, presubmission. Please provide this information. Alternatively, please provide the details of the location in the application where this information can be located.

Please provide a response to the above comment and requested information to me electronically (meredith.libeg@fda.hhs.gov) by Tuesday, July 29, 2014, or sooner if possible. Please follow that with a formal amendment submission to **BLA 125527**.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721).

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/s/

MEREDITH LIBEG
07/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543

Dear Ms. O'Donnell:

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

We also refer to the telecon between representatives of your firm and the FDA on April 18, 2014. The purpose of the meeting was to discuss and obtain FDA concurrence for CMC plans for the registrational package to support the potential accelerated approval of nivolumab.

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

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Laurie Graham, M.S.
Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Sciences
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	CMC pre-BLA
Meeting Date and Time:	April 18, 2014, 10:00-11:00 A.M. Eastern Standard Time (EST)
Meeting Location:	Teleconference
Application Number:	100052
Product Name:	nivolumab
Indication:	Patients with recurrent or treatment-refractory malignancies; non-small cell lung cancer
Sponsor/Applicant Name:	Bristol-Myers Squibb
Meeting Chair:	Laurie Graham, M.S.
Meeting Recorder:	Lyndsay Hennessey

FDA ATTENDEES

Laurie Graham, M.S.	Product Quality Team Leader, DMA
Joel Welch, Ph.D.	Product Quality Reviewer, DMA
James Andrews, Ph.D.	Product Quality Reviewer, DMA
Lakshmi Narasimhan, Ph.D.	Microbiology Reviewer, BMAB
Kalavati Suvarna, Ph.D.	Microbiology Reviewer, BMAB
Dickran Kazandjian, M.D.	Clinical Team Leader, DOPII
Meredith Libeg	Regulatory Project Manager, DOPII
Ruth Maduro	Regulatory Project Manager, DOPII
Lyndsay Hennessey	Regulatory Project Manager, OBP

SPONSOR ATTENDEES

Pradip Ghosh-Dastidar, Ph.D.	Associate Director, Global Regulatory and Safety Sciences - CMC
Galina Chernaya, Ph.D.	Integrated Development Team Leader
Steven E. Klohr, Ph.D.	Group Director, Research and Development
Annie Sturgess, Ph.D.	Executive Director, Global Regulatory and Safety Sciences - CMC
Mark Rosolowsky, Ph.D.	Vice-President, Global Regulatory and Safety Sciences - CMC
Peter F. Moesta, Ph.D.	Senior Vice-President, Biologics Manufacturing and Process Development
Edward M. Atkinson, Ph.D.	Vice-President, Biologics Development

Brendan Hughes, Ph.D.	Vice-President, Program Management
Nancy A. Rurkowski	Vice-President, Biologics Quality
David Feltquate, M.D., Ph.D.	Executive Director, Oncology
Tony Mazzeo, Ph.D.	Sr. Principal Scientist, Pharmaceutical Development – Stability

1.0 BACKGROUND

(i) **Purpose of meeting:** To discuss and obtain FDA concurrence for CMC plans for registrational package to support the potential accelerated approval of nivolumab.

(ii) **Names of drug:** Nivolumab, Anti-PD-1 Human Monoclonal Antibody

(iii) **Product Development:** BLA is planned for May/June 2014.

(iv) **Expected outcome for the meeting:** To obtain FDA feedback and agreement on the following topics:

a. Inclusion of BMS SYR as an additional drug substance manufacturing site using [redacted] (b) (4) in the initial BLA.
b. Executed process performance qualification (PPQ) for drug product using [redacted] (b) (4) drug substance is sufficient to support use of BMS-SYR drug substance as there are no changes in drug product manufacturing process or site.
c. Bacterial endotoxin control strategy for drug substance and drug product.
d. Stability update provided during BLA review.
e. Implementation of an enhanced [redacted] (b) (4) scheme.
f. Implementation of host cell protein ELISA assay.

2.0 DISCUSSION

Question 1: The current drug substance (DS) manufacturing site that has been used to supply clinical material is [redacted] (b) (4). BMS intends to register this as a commercial and the initial DS launch site. The DS Process Performance Qualification (PPQ) at [redacted] (b) (4) has been successfully completed. The initial BLA will contain a complete DS section for [redacted] (b) (4) Due to open FDA inspection observations at [redacted] (b) (4) BMS has accelerated development of an additional DS manufacturing site (BMS-Syracuse). BMS is considering inclusion of this site as an additional facility, supported by analytical comparability, in the initial submission. BMS has completed the DS process performance qualification (PPQ) campaign at BMS-Syracuse. However, the PPQ report and batch analyses will not be available until approximately 45 days after the initial BLA submission. In addition, limited DS stability data would be available. BMS would appreciate FDA's feedback regarding inclusion of BMS-Syracuse as an additional DS manufacturing site in the initial BLA and the potential implications to the review timelines.

a) Does the FDA agree to review an update containing DS PPQ data for BMS-Syracuse site provided approximately 45 days after the initial BLA submission?

b) Does the FDA agree that submission of the information within the proposed timeframe is unlikely to delay the designated review times provided that analytical data supports comparability of DS manufactured at (b) (4) and BMS-Syracuse, and there are no significant gaps in the submission?

FDA Response to Question 1:

With regard to process performance qualification data

Under the PDUFA V legislation, applications are expected to be complete at the time of filing with only limited components submitted within 30 days of the BLA submission. The FDA does not consider process validation to be a "limited component" of the submission.

The last inspection of (b) (4) has been closed out and the current GMP status of (b) (4) is acceptable. (b) (4) should be ready for a pre-license inspection in support of the review of the nivolumab BLA.

With regard to the amount of stability data available for BMS derived material

The use of stability data from (b) (4) derived DS and DP to support the shelf-life of BMS Syracuse DS and DP will depend on the assurance that the stability data from (b) (4) derived material are fully representative of BMS-Syracuse derived material. This would include, but is not limited to:

- *the data, including DS and DP stability data, that supports the comparability of the different manufacturing processes;*
- *an evaluation of process, formulation, and container closure changes that might impact stability;*
- *the adequacy of the stability protocols, including the assays used to monitor stability.*

If a shelf life of greater than (b) (4) months is requested for DS and DP, 6 months of stability data from BMS-Syracuse DS and DP would generally be expected to be included in the initial BLA submission.

Discussion: ***The sponsor accepted FDA's response; no discussion occurred.***

Question 2: BMS has completed the drug product PPQ using (b) (4) drug substance from (b) (4) (b) (4) Since the drug product manufacturing process at BMS-Manati remains the same for both and BMS-Syracuse sourced drug substance, BMS plans to include drug product PPQ using only (b) (4) sourced drug substance in the BLA. Does the FDA agree with this plan?

FDA Response to Question 2:

See our response to comment 1. The approval of BMS Syracuse will require the review of data, including comparability data, from drug product manufactured from BMS-Syracuse derived drug substance. The amount and type of drug product data required to support BMS-Syracuse should include consideration for the nature of any DS manufacturing process changes and the

DS comparability assessment. For example, certain attributes are known to be impacted by DP manufacturing and changes in product quality as a result of drug substance manufacturing changes can be magnified during drug product manufacturing.

Discussion: ***The sponsor accepted FDA's response; no discussion occurred.***

Question 3: Does the FDA agree with the approach for monitoring and control of bacterial endotoxin in DS and DP?

FDA Response to Question 3:
In general we do agree with the overall strategy of using the (b) (4) *method to test the DP within the qualified timeframe* (b) (4)*. We agree with the use of the* (b) (4) *assay for DS manufacturing steps. In addition, we recommend testing the endotoxin release specification for the* (b) (4) *. Please clarify the endotoxin limits described on page 14 of the meeting package for* (b) (4) *Why are these not in place at both sites?*

Please include protocols and raw data from the LER studies in the BLA.

Discussion: ***The sponsor provided a response to the Agency's preliminary comment (please see attached). The sponsor requested if LER studies on the*** (b) (4) ***could be provided within 30 days of the initial application submission. The Agency stated this was acceptable.***

The Agency inquired whether a (b) (4) ***method was used on the formulated DS. The sponsor responded not yet and that the method was not in place at the*** (b) (4) ***facility. The Agency requested the LER protocol used by the analysts (the actual testing protocol) be submitted in the initial application. The sponsor confirmed this will be provided.***

Question 4: BMS intends to submit the BLA with available stability data which is outlined in this pre-meeting package. Does the FDA agree to accept for review, an update containing additional drug substance and drug product stability results, provided after the initial submission? This approach was agreed upon at the EOP2 meeting of February 7, 2012 (IND 100052) prior to PDUFA V.

FDA Response to Question 4:
As already indicated, per the PDUFA V legislation, the BLA is expected to be complete at the time of filing. If additional stability data, other than what is provided at the time of filing BLA is required, this information can be requested by the Agency. See our response to question 1.

Discussion: ***The sponsor provided a response to the Agency's preliminary comment (please see attached) and requested to submit an additional stability time-point within 30 days of the***

initial application submission. The Agency stated that the simple stability update proposed by the sponsor could be submitted within the first 30 days of the initial application submission.

Question 5: Does the FDA agree with the implementation plan for an enhanced (b) (4) (b) (4) scheme at (b) (4)

FDA Response to Question 5:
Bioburden data from the (b) (4) should be submitted.

Discussion: ***The sponsor provided a response to the Agency's preliminary comment (please see attached). The sponsor stated that bioburden results from the enhanced (b) (4) will be available at the time of the pre-approval inspection. The Agency stated that, at this time, this appeared acceptable; however, if the information was needed at any point during the review, an Information Request would be sent.***

Question 6: Data generated by BMS indicate that (b) (4) assay is sufficient to demonstrate process clearance of host cell protein (HCP) (b) (4) However, BMS recognizes the limitations of the (b) (4) assay and is assessing development of a process specific HCP assay as a replacement for the (b) (4) assay. Does the agency agree with this strategy?

FDA Response to Question 6:
The proposed strategy of filing the BLA with the current HCP assay may be acceptable depending upon the clinical development data to support the current HCP assay. However, in this situation, it would be the Agency's expectation that an assay with improved coverage would be developed and implemented post-licensure. The BLA should include available information on this updated HCP assay.

Discussion: ***The sponsor provided a response to the Agency's preliminary comment (please see attached). The Agency stated it was acceptable to submit the current HCP assay in the initial BLA submission and that the Agency would work with the sponsor on the implementation of the new assay post-approval.***

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: simple stability update and LER studies on the (b) (4)

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a multidiscipline pre-submission meeting is scheduled for April 28, 2014. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 ATTACHMENTS AND HANDOUTS

Attached is the sponsor's response to the Agency's preliminary comments.

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/s/

LAURIE J GRAHAM
04/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison - Oncology
P.O. Box 4000
Princeton, NJ 08543

Dear Ms. O'Donnell:

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

We also refer to your February 24, 2014 correspondence, received February 24, 2014, requesting a meeting to discuss and obtain FDA concurrence for CMC plans for registrational package to support the potential accelerated approval of nivolumab.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Regulatory Health Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	CMC pre-BLA
Meeting Date and Time:	April 18, 2014, 10:00-11:00 A.M. Eastern Standard Time (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	100052
Product Name:	nivolumab
Indication:	Patients with recurrent or treatment-refractory malignancies; non-small cell lung cancer
Sponsor/Applicant Name:	Bristol-Myers Squibb

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 18, 2014 from 10:00-11:00 A.M. EST at the White Oak Campus between Bristol-Myers Squibb and the Division of Monoclonal Antibodies. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

(i) **Purpose of meeting:** To discuss and obtain FDA concurrence for CMC plans for registrational package to support the potential accelerated approval of nivolumab.

(ii) **Names of drug:** Nivolumab, Anti-PD-1 Human Monoclonal Antibody

(iii) **Product development:** BLA is planned for May/June 2014.

(iv) **Expected outcome for the meeting:** To obtain FDA feedback and agreement on the following topics:

- Inclusion of BMS SYR as an additional drug substance manufacturing site using (b) (4) in the initial BLA.
- Executed process performance qualification (PPQ) for drug product using (b) (4) drug substance is sufficient to support use of BMS-SYR drug substance as there are no changes in drug product manufacturing process or site.
- Bacterial endotoxin control strategy for drug substance and drug product.
- Stability update provided during BLA review.
- Implementation of an enhanced (b) (4) scheme.
- Implementation of host cell protein ELISA assay.

2.0 DISCUSSION

Question 1: The current drug substance (DS) manufacturing site that has been used to supply clinical material is (b) (4). BMS intends to register this as a commercial and the initial DS launch site. The DS Process Performance Qualification (PPQ) at (b) (4) has been successfully completed. The initial BLA will contain a complete DS section for (b) (4) Due to open FDA inspection observations at (b) (4) BMS has accelerated development of an additional DS manufacturing site (BMS-Syracuse). BMS is considering inclusion of this site as an additional facility, supported by analytical comparability, in the initial submission. BMS has completed the DS process performance qualification (PPQ) campaign at BMS-Syracuse. However, the PPQ report and batch analyses will not be available until approximately 45 days after the initial BLA submission. In addition, limited DS stability data would be available. BMS would appreciate FDA's feedback regarding inclusion of BMS-Syracuse as an additional DS manufacturing site in the initial BLA and the potential implications to the review timelines.

a) Does the FDA agree to review an update containing DS PPQ data for BMS-Syracuse site provided approximately 45 days after the initial BLA submission?

b) Does the FDA agree that submission of the information within the proposed timeframe is unlikely to delay the designated review times provided that analytical data supports comparability of DS manufactured at (b) (4) and BMS-Syracuse, and there are no significant gaps in the submission?

FDA Response to Question 1:

With regard to process performance qualification data

Under the PDUFA V legislation, applications are expected to be complete at the time of filing with only limited components submitted within 30 days of the BLA submission. The FDA does not consider process validation to be a "limited component" of the submission.

The last inspection of (b) (4) *has been closed out and the current GMP status of* (b) (4) *is acceptable.* (b) (4) *should be ready for a pre-license inspection in support of the review of the nivolumab BLA.*

With regard to the amount of stability data available for BMS derived material

The use of stability data from (b) (4) *derived DS and DP to support the shelf-life of BMS Syracuse DS and DP will depend on the assurance that the stability data from* (b) (4) *derived material are fully representative of BMS-Syracuse derived material. This would include, but is not limited to:*

- *the data, including DS and DP stability data, that supports the comparability of the different manufacturing processes;*
- *an evaluation of process, formulation, and container closure changes that might impact stability;*
- *the adequacy of the stability protocols, including the assays used to monitor stability.*

If a shelf life of greater than (b) (4) *months is requested for DS and DP, 6 months of stability data from BMS-Syracuse DS and DP would generally be expected to be included in the initial BLA submission.*

Question 2: BMS has completed the drug product PPQ using (b) (4) drug substance from (b) (4) (b) (4) Since the drug product manufacturing process at BMS-Manati remains the same for both and BMS-Syracuse sourced drug substance, BMS plans to include drug product PPQ using only (b) (4) sourced drug substance in the BLA. Does the FDA agree with this plan?

FDA Response to Question 2:

See our response to comment 1. The approval of BMS Syracuse will require the review of data, including comparability data, from drug product manufactured from BMS-Syracuse derived drug substance. The amount and type of drug product data required to support BMS-Syracuse should include consideration for the nature of any DS manufacturing process changes and the DS comparability assessment. For example, certain attributes are known to be impacted by DP manufacturing and changes in product quality as a result of drug substance manufacturing changes can be magnified during drug product manufacturing.

Question 3: Does the FDA agree with the approach for monitoring and control of bacterial endotoxin in DS and DP?

FDA Response to Question 3:
In general we do agree with the overall strategy of using the [redacted] method to test the DP within the qualified timeframe [redacted]. We agree with the use of the [redacted] assay for DS manufacturing steps. In addition, we recommend testing the endotoxin release specification for th [redacted] Please clarify the endotoxin limits described on page 14 of the meeting package for [redacted] Why are these not in place at both sites?

Please include protocols and raw data from the LER studies in the BLA.

Question 4: BMS intends to submit the BLA with available stability data which is outlined in this pre-meeting package. Does the FDA agree to accept for review, an update containing additional drug substance and drug product stability results, provided after the initial submission? This approach was agreed upon at the EOP2 meeting of February 7, 2012 (IND 100052) prior to PDUFA V.

FDA Response to Question 4:
As already indicated, per the PDUFA V legislation, the BLA is expected to be complete at the time of filing. If additional stability data, other than what is provided at the time of filing BLA is required, this information can be requested by the Agency. See our response to question 1.

Question 5: Does the FDA agree with the implementation plan for an enhanced [redacted] scheme at [redacted]

FDA Response to Question 5:
Bioburden data from the [redacted] should be submitted.

Question 6: Data generated by BMS indicate that [redacted] assay is sufficient to demonstrate process clearance of host cell protein (HCP) [redacted] However, BMS recognizes the limitations of the [redacted] assay and is assessing development of a process specific HCP assay as a replacement for the [redacted] assay. Does the agency agree with this strategy?

FDA Response to Question 6:
The proposed strategy of filing the BLA with the current HCP assay may be acceptable depending upon the clinical development data to support the current HCP assay. However, in this situation, it would be the Agency's expectation that an assay with improved coverage would be developed and implemented post-licensure. The BLA should include available information on this updated HCP assay.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 6, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

LYNDSAY J HENNESSEY
04/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O' Donnell
Director, Global Regulatory Sciences, US-Oncology
Route 206 & Province Line Road, Rm D3.218
Princeton, NJ 08543-4000

Dear Ms. O' Donnell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "MDX-1106, anti-PD-1 Monoclonal Antibody (BMS-936558)."

We also refer to the Type A meeting that was held on May 25, 2012, between the Agency and Bristol-Myers Squibb to discuss the updated preliminary data from the ongoing Phase 1 study CA209003 and the proposed clinical development plan for non-small cell lung cancer (NSCLC). Additional, we refer to your amendment dated October 17, 2012, containing a new protocol CA209063, entitled, "A Single-Arm Phase 2 Study of BMS-936558 in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens."

Lastly, we refer to your amendment dated October 24, 2012, requesting advice regarding your proposal to change the analysis of the primary endpoint (overall response rate (ORR)) from Independent Review Committee (IRC)-assessed to investigator-assessed for both BMS-936558 proposed phase 3 pivotal studies: CA209017 (squamous non-small cell lung cancer [(NSCLC)) and CA209037 (melanoma) conducted under IND 100052 and IND 115195, respectively.

We have the following comments regarding protocol CA209063:

1. The proposed primary efficacy endpoint in Protocol CA209003, investigator-assessed overall response rate, is not acceptable to provide evidence of substantial evidence of effectiveness in this open-label trial. If you intend to seek labeling claims based on this trial, review the protocol to require determination of the primary efficacy endpoint of ORR as determined by an independent review committee.

2. As discussed during the May 25, 2012 meeting, the effect size for objective response rate which may support accelerated approval should be similar to that observed in study CA209003 (i.e., approximately 50%) with a clinically important duration of responses, similar to that seen in the responding patients in CA209003. Please note that in the

proposed study, although the sample size calculation appears to be acceptable, the assumed rate response rate, which may be as low as 15% based on the lower limit of the 95% confidence boundary would not be considered to be reasonably likely to predict clinical benefit.

We have the following response to the question contained in your October 24, 2012, submission:

3. **Sponsor Question:** In light of the potential bias introduced by Independent Review Committee (IRC) assessment of scans for subjects treated beyond investigator-determined progression, Bristol-Myers Squibb proposes to conduct the primary analysis of the ORR co-primary endpoint based on investigator assessment, for both Study CA209017 and Study CA209037. All scans will be submitted for IRC review. Their assessments will be used to conduct sensitivity analyses. Does the agency agree with this proposal?

   FDA Response: No, we do not agree with your proposal. For US regulatory purposes, IRC-determined objective responses rates (ORR) will be considered the primary efficacy endpoint to support a regulatory action. We note that both CA209017 and CA209037 are open-labeled studies with potential for investigator bias in determining the disease progression/response. As discussed during the July 24, 2012, Oncologic Drugs Advisory Committee, our assessment of data from multiple applications demonstrated that use of investigator-determined ORR led to an overestimation of ORR size compared to IRC-determined ORR. We recommend that you include investigator-determined ORR as a secondary endpoint in both trials with sufficient allocation of Type I error and adjustment for multiplicity because both IRC-determined ORR and investigator-determined ORR may be included in product labeling.

   Please be advised that consistent with objective response rates provided in the labels of FDA approved products in disease settings similar to those in the proposed indications, the objective response rates for the purpose of labeling claims of BMS-936558 would be limited to analyses of those patients with objective responses that have been confirmed.

If you have any questions, contact Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
01/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology,
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell,

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

We also refer to your amendment dated July 3, 2013, containing Independent Review Committee (IRC) charters for Study CA209063: "A Single-Arm Phase 2 Study of BMS-936558 in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received At Least Two Prior Systemic Regimens" and Study CA209017: "An Open-label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)." Lastly, we refer to your amendment dated August 16, 2013, containing a Statistical Analysis Plans (SAPs) for Study CA209017 and Study CA209057: "An Open-Label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Metastatic Non-squamous Non-small cell Lung Cancer (NSCLC)."

Regarding the IRC for Study CA209063, we have the following comments and recommendations:

1. Please capture the information for which Time Point Response assessment (TPR) may be updated to reflect the updated clinical data (see section 3.5 Global Radiology Analysis).

2. For section 3.6 Derivation of Subject Response Variable, please provide more detailed information with regard to how each radiological reviewer and the adjudicator derives the subject level response variables based on the TPR, including, but limit to, the software that will be used to assist for such derivation.

Regarding the IRC for Study CA209017, we have the following comments and recommendations:

3. Please capture the information for which TPR may be updated to reflect the updated clinical data (indicated in the third paragraphs in section 4.7 Global Radiology Analysis) after the Global Radiology Analysis has been conducted at the interim analysis for overall survival (OS).

4. For section 4.8 Derivation of Subject Response Variable, please provide more detailed information with regard to how each radiological reviewer and the adjudicator derives the subject level response variables based on the TPR, including, but limit to, the software that will be used to assist for such derivation.

Regarding both SAPs for Study CA209017 and Study CA209057, we have the following comments and recommendations:

5. For the primary analysis of PFS, please also consider censoring the patients at the last tumor assessment when deaths or progression occurred after two or more missing assessments as discussed in Table A PFS1 in the guidance ('Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics").

6. Please perform the subgroup analysis based on age using < 65 years and ≥ 65 years groups.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

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

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PATRICIA KEEGAN
09/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kathleen O'Donnell
Director, US Liaison – Oncology
Global Regulatory Sciences
Route 206 & Province Line Road, Rm D2.267
Princeton, NJ 08543

Dear Ms. O' Donnell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "MDX-1106 anti-PD-1 Monoclonal Antibody (BMS-936558)."

We also refer to the Type A meeting that was held on May 25, 2012, between the Agency and Bristol-Myers Squibb to discuss the updated preliminary data from the ongoing Phase 1 study CA209003 and the proposed clinical development plan for non-small cell lung cancer (NSCLC). Additionally, we refer to your amendment dated June 25, 2012, containing your request for clarification from the FDA regarding a discrepancy between FDA preliminary comments dated May 25, 2012, and the meeting minutes dated June 19, 2012, for the Type A meeting that was held on May 25, 2012.

We will not be issuing amended meeting minutes as this correspondence provides sufficient clarification of FDA's position. Please see below our responses to your questions for clarification contained in the amendment dated June 25, 2012, referenced above:

CLINICAL

1. **Sponsor Question #1:** Does FDA agree that the magnitude of effect to support an accelerated approval would need to be similar to that observed in the expansion cohort [of study CA209-003] (i.e., approximately 50%) with a clinical important durability similar to that seen in the responding patients in the expansion cohort, per FDA's original recommendation? Could the 19-June-2012 FDA minutes of the Type A meeting be amended to reflect this?

   FDA response: The magnitude of an effect on durable overall response rate intended to support a request for accelerated approval should be sufficiently high that it is likely to predict clinical benefit. We agree that response rates of approximately 50% as

determined with a high degree of certainty (i.e. narrow confidence intervals around that estimate) in a setting of unmet medical need are likely to predict clinical benefit.

2. **Sponsor Question #2:** Does FDA acknowledge that the proposed Phase 3 study, CA209-017 is sufficiently and appropriately powered for a clinically meaningful effect in OS? Could the 19-June-2012 FDA minutes of the Type A meeting be amended to reflect this?

FDA response: Yes, we agree. However whether the trial are sufficiently robust to demonstrate a clinically meaningful effect for a single trial intended to support a marketing application, or whether additional trials may be required, is contingent upon the effect observed and thus cannot be addressed at this time. Please refer to our response to question 2 in the June 19, 2012, meeting minutes of the May 25, 2012, meeting, a portion of which is reproduced below:

> "As stated during the November 2011 meeting, please be aware that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Acceptance of the results of a single trial will be based upon the magnitude of effect and robustness of results. Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" at http://www.fda.gov/downloads/Durgs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf."

If you have any questions, contact Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
09/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

ADVICE/INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Kinnari Patel PharmD., R.Ph.
Associate Director
Global Regulatory Sciences, US-Oncology
Route 206 & Province Line Road, Rm D2.267
Princeton, NJ 08543

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "MDX-1106 anti-PD-1 Monoclonal Antibody (BMS-936558)."

We also refer to your amendment dated July 3, 2012 containing your responses to address the recommendations outlined in the May 25, 2012, FDA preliminary meeting comments and reiterated in the June 19, 2012 meeting minutes from the May 25, 2012, Type A meeting for NSCLC, including submission of a revised clinical protocol entitled, CA209017, "An Open-label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non Small Cell Lung Cancer."

We have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, response to them is requested:

CLINICAL

Safety Comments

1. Section 4.3.5.1 of the protocol should be revised to indicate that BMS-936558 will be permanently discontinued in the event of a grade 3 or 4 uveitis or grade 3 or 4 pneumonitis, regardless of the AE duration.

Comments concerning the trial design

2. We acknowledge BMS' response to our recommendations in the May 25, 2012 pre-phase 3 meeting to discuss the adequacy of CA209017 to support a potential accelerated approval based on ORR difference and positive trend in OS at interim analysis and to support full approval if OS is significant at interim or final analysis. Please note that based on the statistical assumption provided in the protocol, the minimally detectable,

statistically significant increase in ORR in the study may not be reasonably likely to predict clinical benefit.

3. Please note that we consider the ORR and OS subgroup analysis based on PDL1 expression status to be exploratory in nature.

4. In addition to using NCI CTCAE v4 for adverse event severity grading, please specify in the protocol that the Medical Dictionary for Regulatory Affairs (MedDRA) will be used to categorize adverse events in the study.

BIOSTATISTICS

5. Provide detailed descriptions of the timing and censoring for PFS including sensitivity analyses that consider the events in which patients take anti-cancer therapy, have missing assessments and are lost-to-follow-up in the statistical analysis plan. Refer to the guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf for more details.

ADDITIONAL COMMENTS

6. Please submit a copy of the patient informed consent document for study CA209017.

7. We have reviewed the case report form (CRF) included in this submission for CA209017 based on CDISC data collection specification requirements for adverse event data. The CRF is acceptable.

If you have any questions, contact Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Joseph Gootenberg, M.D.
Deputy Director
Division of Oncology Drug Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JOSEPH E GOOTENBERG
08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

MEETING MINUTES

Bristol-Myer Squibb
Attention: Pradip Ghosh-Dastidar, Ph.D.
Associate Director, Chemistry Manufacturing and Controls
311 Pennington Rocky Hill Road
Pennington, NJ 08804

Dear Dr. Ghosh-Dastidar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Anti-PD-1 (BMS-936558).

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2012. The purpose of the meeting was a Type B End-of-Phase II CMC meeting.

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

If you have any questions, call me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Health Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase II
Meeting Date and Time:	February 7, 2012; 2:00 PM to 3:00 PM (EST)
Meeting Location:	Teleconference
PIND Number:	100052
Product Name:	Anti-PD-1 (BMS-936558)
Sponsor Name:	Bristol-Myers Squibb
Meeting Requestor:	Pradip Ghosh-Dastidar
Meeting Chair:	Barbara Rellahan
Meeting Recorder:	Joel Welch

Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Laurie Graham, M.S.	Quality Reviewer
Barbara Rellahan, Ph.D.	CMC Team Leader
Joel Welch, Ph.D.	Regulatory Health Project Manager
Anita Brown	Regulatory Health Project Manager

Office of Compliance
Biotechnology Manufacturing Assessment Branch

Bo Chi, Ph.D.	Microbiology Reviewer
Reyes Candau-Chacon, Ph.D.	Microbiology Reviewer
Patricia Hughes, Ph.D.	Acting Branch Chief

SPONSOR ATTENDEES

Rajesh Gandhi, Ph.D.	Director, Drug Product Science and Technology
Michael Grace, Ph.D.	Executive Director, BPPD - Analytical
Pradip Ghosh-Dastidar, Ph.D.	Associate Director, Global Regulatory Sciences - CMC
Paul Guptill, M.S.	Director, Manufacturing Launch Planning
Chris Lee, PE	Principal Technical Investigator, Manufacturing Technology - Sterile Products
Anthony Mazzeo, Ph.D.	Principal Scientist, Analytical and Bioanalytical Development
Shih-hsie Pan, Ph.D.	Executive Director, Manufacturing Sciences

1.0 BACKGROUND

Bristol-Myers Squibb is developing Anti-PD-1 (BMS-936558) as a monotherapy for previously treated locally advanced or metastatic non-small cell lung cancer (b) (4) On November 22, 2011, Bristol-Myers Squibb requested an End-of-Phase II CMC only meeting with the FDA. The FDA granted that meeting on December 7, 2011. Draft written responses (denoted below in italics) were provided to the Sponsor on February 3, 2012. Upon review of those responses, the Sponsor asked to switch the format of the meeting from face-to-face to a teleconference.

2.0 DISCUSSION

Sponsor Submitted Questions and FDA Response:

Question 1
Does FDA agree with the process validation plans as described below?

FDA Response:
In general, based on the summary information supplied in the briefing package, the proposed process validation plans appear reasonable. A final determination as to the sufficiency of the validation process will be a review issue. We have the following additional comments:

a) *It is noted that multiple studies will be performed based on a risk assessment methodology and that you intend to define a process design space. It is recommended that a high level summary of your plans and methodology for definition of a design space (e.g., identification of critical product attributes, CPPs, design space, proposed control strategy) be submitted to the IND when feasible. While we would not be able to provide detailed comments on your proposed plans and methodologies, major issues that are identified could be brought to your attention.*

b) *The validation of the* (b) (4) *should include validation of the* (b) (4) *at scale from microbiology perspective.* (b) (4)

[redacted] should also be validated at scale from microbiology perspective. The effectiveness of the [redacted] should be validated using microbiology data.

c) *In addition, refer to our response to Question 4.*

Additional Discussion During Meeting:
There was no additional discussion.

Question 2
Does FDA agree with proposed analytical methodology for the release and stability testing and subsequent use of these methods for developing BLA specifications?

FDA Response:
In general, based on the summary information supplied in the briefing package, the proposed assays for inclusion in the release and stability programs appear reasonable. A final determination as to the sufficiency of the release and stability programs will be a review issue.

It was not clear from the meeting package how [redacted] was being monitored. Specifications should include an assay that can sensitively detect [redacted] While acceptance criteria do not need to be established at this time, batch analyses and stability reports should report the [redacted].

It is noted that you intend to replace the [redacted] methods. While acceptance criteria do not need to be established for the new methods at this time, batch analyses and stability reports should include the results from these methods.

Since the drug product formulation contains polysorbate 80, drug product specifications should include an assay to control for polysorbate 80 content.

Additional Discussion During Meeting:
The Sponsor noted they accept the Agency's feedback. The Sponsor indicated that values for both [redacted] will be reported.

Question 3 -
Does FDA agree to the use of [redacted] for registration?

FDA Response:
No, [redacted], there was insufficient information in the briefing package for a decision on the suitability of the [redacted] to be made. We have the following comments:

[redacted]

(b) (4)

Additional Discussion During Meeting:
The Sponsor thanked the Agency for the feedback and agreed the approach of using a (b) (4) was a good suggestion. The sponsor stated that they would continue to collect data using the (b) (4) assays (or another bioassay). If a suitable bioassay (b) (4)) was developed, the assay would be used during phase III to collect data to use for establishment of acceptance criteria for the assay. (b) (4)

Question 4
Does the FDA agree on the approach for the drug substance and drug product registrational stability studies as described below?

FDA Response:
No. Stability studies should conform to principles outlined in ICH and FDA guidance. In general, based on the summary information supplied in the briefing package, the proposed approach for performing the registrational stability studies appears reasonable. A final determination as to the sufficiency of the stability data will be a review issue. However, it was not clear from the meeting package how much drug substance and drug product stability data from the validation lots would be provided and whether there would be sufficient data to allow establishment of drug substance and drug product expiries based on this data. (b) (4) *extrapolation of stability from the clinical process may be limited, and it is possible that the primary data used to establish product expiries will need to be derived from lots produced by the validated process.*

Clarify the extent of stability data that will be provided in the BLA for drug substance and drug product lots produced by the commercial process.

Additional Discussion During Meeting:
The Sponsor stated they intend to include stability data for three batches of both drug substance and drug product in the BLA and that one year of data for the new process will be available at the time of submission. The Sponsor stated that data for the (b) (4) process should be available in the summer for drug substance, and in the fall for drug product. The Agency noted that generally one stability update is allowed after the submission of the BLA.

FDA clarification: Stability updates submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf life determinations.
During the meeting it was stated that the stability updates should be supportive of the proposed shelf-life. In actuality, a simple stability update (see definition below) can be used to extend the proposed shelf-life. A "simple stability update" is defined as stability data and analyses performed under the same conditions, and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA/NDA.

If there is any deviation from the stability protocol as described in the original submission, or if additional CMC information not related to a simple stability update is included, the amendment will not be considered as a "simple stability update". In such cases, it will be treated as a general CMC amendment to the BLA/NDA. Amendments submitted to the BLA/NDA may or may not be reviewed as Agency resources and timing allow. For submissions designated as major amendments, the review clock may be extended by three months to allow time to review the submission.

Question 5
Does FDA agree to the plan for introduction of the new vial/stopper as described below?

FDA Response:
In general, based on the summary information supplied in the briefing package, the proposed approach for introduction of a new vial/stopper system appears reasonable. A final determination as to the acceptability of the new vial/stopper system will be a review issue. Data to support comparability of the new vial/stopper system to the current vial/stopper system will need to be submitted to the IND prior to their introduction to the clinic. The comparability data will need to include stability data that demonstrates the rate and pathway of drug product degradation is unchanged. It is recommended that the new vial/stopper system change be implemented as early as possible to maximize clinical experience with the new container/closure.

In addition, a risk assessment on the potential for the new glass vials to form (b) (4) *during product storage should be provided.*

Additional Discussion During Meeting:

The Sponsor noted they intend to perform an additional side-by-side study evaluating the effect of the change in the stopper. The Sponsor stated they have completed a study at (b) (4)C for (b) (4) months. The Sponsor then inquired how much data and how long of a study Agency typically requested. The Agency noted that it would need to review the data, but that traditionally, enough time should be allotted to the study to see product degradation and that the degradation should be slow enough that it allows for a meaningful comparison to be made. The Sponsor agreed to perform a study at (b) (4)°C and stated that at least one month of stability data for one clinical drug product lot would be provided to support the change.

Question 6
Does FDA agree to the proposed strategy of drug product manufacturing site change from clinical manufacturing site to commercial manufacturing site during pivotal trials?

FDA Response*:*
In general, based on the summary information supplied in the briefing package, the proposed approach for introduction of a new drug product manufacturing site appears reasonable. A final determination as to the acceptability of the data to support the new site will be a review issue. It is recommended that the site change be made as early as possible to maximize clinical experience with product made from the new site.

Additional Discussion During Meeting:
There was no additional discussion.

Question 7
Does FDA agree to the strategy as described below for introduction of product from the (b) (4) process?

FDA Response:
No. While in general the summary plans provided in the meeting package for assessment of drug substance (DS) physiochemical comparability appear reasonable, we have the following comments.

a) For all DS release results with quantitative acceptance criteria, the comparability study should include the results from the statistical analysis conducted to determine historical ranges (based on the (b) (4)% tolerance intervals) from all clinical processes. Data from this analysis should be compared with the average ± SD of at least three (b) (4) drug substance (DS) lots. Extended characterization studies to support comparability should include data from three DS lots produced by each process.

b) The comparability study should include a comparison of the potency of DS made by the new and current process using one or more qualified cell based bioassays.

c) The comparability study should include data comparing the performance of the current and new (b) (4) processes.

d) The comparability study should include data to support drug product comparability, including stability data indicating the rate and pathways of degradation of the new process is comparable to the current process.

e) *Depending on the physicochemical and process comparability results, there is the possibility that additional pre-clinical or clinical studies will be required to support commercial use of the new process.*

Additional Discussion During Meeting:
There was no additional discussion.

Additional CMC issues that should be addressed as development proceeds:

1. [redacted] *It is recommended that the drug product stability program include a storage temperature that induces product degradation so that the typical degradation pathway can be characterized and assurance gained that the testing program includes assays capable of sensitively detecting product degradation.* [redacted] *it is recommended that all accelerated and stressed testing protocols include a measure of visible and sub-visible particulate formation at regular intervals.*

2. *If visible particulate formation is found to be a drug product pathway of degradation, the composition of the visible particulates and the basis for their formation should be investigated and procedures implemented to control/limit their formation. If visible particulates are present at the time of licensure, a semi-quantitative method will need to be developed and incorporated into the release and stability testing programs.*

3. *It is recommended that in addition to <USP 788> particulate testing,* [redacted] *sub-visible particles (e.g. between* [redacted] *µm in size) be monitored at release and at regular intervals in the drug product stability program including under accelerated and/or stressed condition. Data from these characterization studies can be used to develop and provide support for an overall control strategy for particulate matter for the manufacturing process.*

4. *The anti-HCP antiserum used for assessment of host cell protein (HCP) impurities needs to be qualified for its ability to detect potential HCP impurities.* [redacted]

5. *21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. The BLA should contain information confirming that identity testing meets this CFR requirement.*

6. *The bioburden release specification for the* [redacted] *drug substance should be* [redacted] *mL, as the* [redacted] *is stored at r* [redacted] *temperature.*

7. [redacted] *should be established at critical steps for the commercial process. There are no* [redacted] *in Tables 8.4.T01 and 8.4.T02 for the drug substance manufacturing process.*

8. [redacted]

9. *With regard to the DP manufacturing process,* [redacted]

Additional Discussion During Meeting:
There was no additional discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified which required further discussion.

4.0 ACTION ITEMS

There were no action items identified.

5.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts.

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

/s/

JOEL T WELCH
02/24/2012

BARBARA L RELLAHAN
02/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kinnari Patel PharmD., R.Ph.
Associate Director
Global Regulatory Sciences, US-Oncology
Route 206 & Province Line Road, Rm D2.267
Princeton, NJ 08543

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) file for "MDX-1106 anti-PD-1 Monoclonal Antibody (BMS-936558)."

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2011. The purpose of the meeting was to discuss the clinical development plan and registrational strategy of BMS-936558 for the indication of non-small cell lung cancer (NSCLC).

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

If you have any questions, call me at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Vaishali Jarral, M.S., M.B.A
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes, DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications and Additional DOP2 CDISC Guidance

MEMORANDUM OF MEETING MINUTES

IND Number:	IND 100052
Meeting Type:	Type B
Meeting Category:	End-of-Phase 1/Pre-Phase 3
Meeting Date and Time:	December 6, 2011; 2:00 PM to 3:00 PM (ET)
Product Name:	BMS-936558
Received Briefing Package:	November 5, 2011
Sponsor Name:	Bristol- Myers Squibb [BMS]
Meeting Chair:	Ke Liu
Meeting Recorder:	Vaishali Jarral

List of FDA Attendees:

Office of New Drugs
Office of Hematology and Oncology Products
Division of Oncology Products 2

Patricia Keegan	Division Director
Ke Liu	Clinical Team Leader
Marc Theoret	Clinical Reviewer
Vaishali Jarral	Regulatory Project Manager

Division of Clinical Pharmacology:

Jun Yang	Clinical Pharmacology Reviewer
Hong Zhao	Clinical Pharmacology Team Leader

Office of Translational Sciences
Office of Biostatistics
Division of Biometrics V

Yuan Li Shen	Statistics Reviewer
Kun He	Statistics Team Leader

List of Bristol-Myers Squibb's Attendees:

- Shruti Agrawal, MS, PhD, Senior Research Investigator
- Aparna Anderson, PhD, Director, Global Biometric Sciences
- David Feltquate, MD, PhD, Group Director, Global Clinical Research
- Michael Giordano, MD, Sr. Vice President, Head of Development, Oncology & Immunology
- Lilit Khatchikian, MD, Associate Director, Global Pharmacoviligance & Epidemiology
- Lamendola, PhD, Vice President, U.S. Regulatory Sciences and Regulatory Relations & Policy
- Mark Moyer, MS, Vice President, Global Regulatory Sciences – Oncology
  Fouad Namouni, MD, Vice President, Development Lead
- Eric Sbar, MD; Director GCR Oncology
- Kinnari Patel, PharmD, Associate Director, U.S. Regulatory Science

BACKGROUND

On September 16, 2011, Bristol-Myers Squibb (BMS) requested a Type B, End of Phase 1 meeting to discuss their preliminary BMS-936558 (MDX-1106) data from the Phase 1 study CA209003 and to receive FDA feedback and agreement on the following:

- Clinical pharmacology plan for the development of BMS-936558.
- Registrational plan for BMS-936558 in non-small cell lung cancer (NSCLC) and specifically, Phase 3 study CA209017 titled "An open-label, randomized Phase 3 trial of BMS-936558 versus docetaxel in previously treated metastatic non-small cell lung cancer (NSCLC)

The BMS-936558 clinical development program in non-small cell lung cancer includes a completed phase 1 trial (CA209001), (b) (4) ongoing phase 1 trials (CA209003, (b) (4) and the proposed phase 3 trial (CA209017) submitted in this meeting package. BMS reports that five of 19 previously treated metastatic NSCLC patients experienced an objective tumor response following BMS-936558 monotherapy in trial CA209003. BMS has chosen to expand the NSCLC cohort in CA209003 (phase 1) to better characterize efficacy and safety of BMS-936558 in lieu of conducting a separate phase 2 study. BMS reports that data from an additional 96 NSCLC patients will be available prior to starting phase 3 trial, CA209017.

The proposed phase 3 trial, CA209017, is an open-label, randomized (1:1) study of BMS-936558 or docetaxel in 720 adult (≥18 years old) male and female patients with metastatic or recurrent NSCLC that has progressed during or after one prior platinum-containing chemotherapy regimen. Patients with known EGFR mutations or an ALK translocations must also have received an EGFR tyrosine kinase inhibitor or an ALK inhibitor, respectively. The proposed protocol specifies four randomization stratification factors: histology (squamous versus nonsquamous), prior therapy (maintenance versus no maintenance), presence of driver mutation versus absence/ unknown driver mutation, and region (US/ Canada versus Europe versus Rest of World)

Key inclusion criteria include histologically or cytologically-documented Stage IV or recurrent, locally advanced NSCLC; disease progression during or after one prior platinum containing chemotherapy regimen; measurable disease by CT or MRI per RECIST 1.1; Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1; and submission of a formalin fixed, paraffin-embedded tumor tissue block or a minimum of 10 unstained slides of tumor sample (archival or recent).

Key exclusion criteria include an active or recent history of known or suspected autoimmune disease; requirement for systemic steroids; prior antibody therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4, or other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways; and prior docetaxel treatment.

The primary endpoint proposed for the study is overall survival (OS). Proposed secondary objectives include objective response rate (ORR), progression-free survival (PFS), duration of objective response, time to objective response, survival rates at 6 and 12 months, safety, and disease-related symptom progression rate measured by Lung Cancer Symptom Scale.

Patients randomized to Arm A will receive BMS-936558 dosed intravenously over 60 minutes on Day 1 of each treatment cycle until disease progression or unacceptable toxicity. The selection of the BMS-936558 dose and dosing interval (i.e., every 2 or 3 weeks) for the proposed study is pending BMS' analysis of data from Study CA209003. Patients randomized to Arm B will receive docetaxel 75 mg/M² intravenously over 60 minutes on Day 1 of each 21 day treatment cycle until disease progression or unacceptable toxicity. The proposed study includes a provision to allow patients with progressive disease to continue to receive docetaxel or BMS-936558 provided that the patient is experiencing clinical benefit as determined by the investigator.

OS will be followed continuously while patients are receiving the study drug and then every 3 months thereafter via in-person or phone contact after subjects discontinue the study drug. Investigators will assess patients for tumor responses (RECIST 1.1) by CT or MRI beginning 9 weeks after randomization and continuing every 6 weeks for the first 6 months and then every 12 weeks until progression or treatment discontinuation, whichever occurs later.

BMS calculated a required sample size of 720 patients to observe 516 death events based on a two-sided, 0.05 significance level with 90% power to detect an improvement in the median overall survival from 9 months on the control arm to 12 months on the experimental arm (hazard ratio of 0.75). BMS estimates that 22 months will be required to complete accrual and 11 additional months will be required to observe the required number of death events to trigger the final analysis. At the time of the final OS analysis, the minimum hazard ratio and median OS projected to result in a statistically significant improvement in OS on the BMS-936558 arm compared to the docetaxel arm would be 0.84 and 1.7 months (9 vs. 10.7 months), respectively. BMS plans to conduct one interim overall survival analysis for superiority after 336 events are observed, which is projected to occur approximately 24 months after study initiation. If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints [ORR (1st secondary endpoint) and PFS (2nd secondary endpoint)] will be used to preserve a study-wise type I error rate at 0.05.

The meeting briefing package was received on November 4, 2011. Draft FDA responses were communicated to BMS on December 5, 2011.

Meeting Purpose: The purpose of this meeting is to review preliminary BMS-936558 (MDX-1106) data from the Phase 1 study CA209003 and to receive FDA feedback and agreement on the following:

1. Clinical pharmacology plan for the development of BMS-936558.
2. Registrational plan for BMS-936558 in non-small cell lung cancer (NSCLC) and specifically, the efficacy trial, CA209017, titled "An open-label, randomized

Phase 3 trial of BMS-936558 versus docetaxel in previously treated metastatic non-small cell lung cancer (NSCLC)."

General Comment: FDA responses should be considered preliminary because of the early stage of drug development. This advice may change upon receipt of additional data.

Sponsor Submitted Questions and FDA Response

1. **Sponsor Question #1**: BMS proposes to utilize the methodology described in Section 4.1.1 to support selection of the dose for Phase 3 development of BMS-936558. Does FDA agree with the proposed methodology?

   FDA Response: The proposed methodology and rationale to support selection of the dose and regimen for phase 3 development of BMS-936558 appears reasonable. However, please see additional FDA comment 9.

   Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

2. **Sponsor Question #2**: Does FDA agree with the proposed clinical pharmacology plan that includes characterization of PK, immunogenicity, effect on QT prolongation and exposure-response relationship of BMS-936558?

   FDA Response: In general, the proposed clinical pharmacology plans including PK characterization, immunogenicity, and QT evaluation appear acceptable. Please include race as a covariate in the proposed population PK analysis. Whether drug-drug interaction studies are needed will be determined after review of data characterizing the extent of cytokine modulation. Please submit this data as soon as it is available.

   Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

3. **Sponsor Question #3**: Does FDA agree with the overall design of the proposed Phase 3 study CA209017 (Section 4.2.1) including:
   a. Key eligibility criteria for target population
   b. Randomization stratification factors
   c. Comparator
   d. Open-label design of the proposed Phase 3 study in NSCLC
   e. Disease assessment schedule
   f. Allowance for treatment beyond initial RECIST-defined progression in cases where the subject continues to exhibit investigator-assessed clinical benefit and is also tolerating study drug?

   FDA Response:
   a. Key eligibility criteria for target population: Yes.

   Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

b. Randomization stratification factors: No. There is insufficient information regarding the criteria for selection of the proposed stratification variables and the protocol is inadequate in design to ensure the important variables are equally allocated between study arms for the following reasons:
(1) the protocol does not specify the driver mutations to be assessed
(2) the protocol does not require testing for the specific mutations to be used for stratification

In addition, FDA recommends that BMS ultimately include stratification factors having the largest effect on the primary endpoint. Provide justification for the chosen stratification factors in the final protocol submitted to the IND.

BMS response via electronic mail dated December 6, 2011: *We agree with the FDA comments and agree that a stratification factor for driver mutations will have minimal impact. As such, we propose to remove it. Does the FDA agree? Therefore, BMS presumes that the additional three stratification factors are appropriate.*

Discussion during the meeting: FDA agreed with removal of this stratification factor. FDA requested, and BMS agreed to provide justification for the remaining factors with the final protocol.

c. Comparator: Yes, however, the informed consent document will need to describe the known benefits of docetaxel on survival in detail and accurately characterize known effects of BMS-936558. In addition, a data monitoring committee (DMC) should be established to regularly assess for impaired survival on the investigational arm and be provided with recommendation for early termination of trials for safety reasons. Please see additional FDA comment 8.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

d. Open-label design of the proposed Phase 3 study in NSCLC: Yes, given the primary endpoint of overall survival.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

e. Disease assessment schedule: Yes.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

f. Allowance for treatment beyond initial RECIST-defined progression in cases where the subject continues to exhibit investigator-assessed clinical benefit and is also tolerating study drug: No. The meeting package and the proposed protocol did not provide information that supports continued

use of docetaxel in patients experiencing disease progression. FDA acknowledges that there is a potential for introducing bias into the study if only one arm of the study may receive additional therapy beyond progression as you point out on page 36 of the pre-meeting package.

If BMS chooses to allow patients to continue treatment with BMS-936558 beyond initial RECIST-defined progression, FDA recommends that protocol CA209017 include the following requirements in order to allow continued treatment of these patients:

(1) Patients continue to meet all other study protocol eligibility criteria

(2) Patients do not have rapid disease progression

(3) Patients have a stable performance status

(4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

(5) Patients will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomforts and other alternative treatment options

BMS response via electronic mail dated December 6, 2011: *The Sponsor requests a dialogue to gain a better understanding of FDA's perspective regarding rapid disease progression in the context of lung cancer, which may help us further refine the criteria.*

Discussion during the meeting: FDA stated that the spirit of the request was to avoid unacceptable toxicity and imminent morbidity. FDA recommended consideration of the criteria used in the ipilmumab program with appropriate modification for the underlying disease. FDA also stated that the re-consent process would be important.

4. **Sponsor Question #4**: Does FDA agree with the primary and secondary objectives and hierarchy proposed for CA209017? Does FDA agree with the method of analysis for the primary and key secondary objectives?

FDA Response: The proposed methods of analysis for the primary and secondary objectives and the hierarchical testing procedure appear to be acceptable, except that the, time to objective response, survival rates at 6 and 12 months and disease-related symptom progression rate measured by Lung Cancer Symptom Scale (LCSS) will not be included in product labeling. Duration of objective response can not be accepted for statistical testing purpose because the result is not based on all randomized patients.

BMS response via electronic mail dated December 6, 2011: *BMS acknowledges FDA comments on the primary and secondary objectives. The additional endpoints are included to support global health authority needs*

including payer requirement needs. BMS would like to take the opportunity to have a dialogue with the Agency regarding the landmark analysis (i.e. survival rates at 6 and 12 months), as these analyses may help to characterize primary analysis of overall survival given the possibility of delayed benefit often seen with immune therapies. BMS's objective is to appropriately describe the potential benefit and provide information to treating physicians and their patients to make treatment decisions.

Discussion during the meeting: FDA's previous statement stands, however, BMS is free to propose whatever labeling they believe is most appropriate based on the data.

5. **Sponsor Question #5**: Does FDA agree that the safety database and the proposed safety monitoring plan for the planned Phase 3 study, CA209017, which specifically addresses AEs of interest, described in Section 4.2.3, is adequate to characterize the safety profile of BMS-936558 in second-line NSCLC?

   FDA Response: No. FDA recommends making the following modifications to the planned safety assessments in protocol CA209017:

   a. Record all adverse events including serious adverse events (not only those deemed to be treatment-related) continuously during treatment and for a minimum of 100 days following the last dose of study treatment.

   b. Add glucose to the panel of serum chemistry tests to be performed at baseline and while on-study.

   c. Perform endocrine function testing at baseline and throughout the protocol.

   d. Require that LFT tests results are available prior to dosing on infusion days.

   FDA recommends that BMS submit draft case report forms related to the collection of safety information for Agency review prior to conducting trial CA209017. The case report forms documenting adverse events should be adequately designed to record all treatment interventions performed in addition to onset and resolution dates.

   Please see additional FDA Comment 7.

   Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

6. **Sponsor Question #6**: Does FDA agree that the development program, including the scope of proposed safety database at the time of the BLA, provides for an acceptable basis for evaluation of the benefit/risk balance of BMS-936558 for previously treated locally advanced, metastatic NSCLC that is unresectable?

   FDA Response: No. Please refer to FDA Responses and Comments 3(c), 3(f) and 5.

Please be aware that for a single randomized trial to support a BLA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Acceptance of the results of a single trial will be based upon the magnitude of effect and robustness of results. Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

In addition, please note that the proposed primary analysis may not support a broad labeling claim for treatment of non-small cell lung cancer (squamous and non-squamous histologies). Substantial evidence should be provided on the efficacy in previously treated, metastatic NSCLC of each histology. Treatment comparisons within each histology may be supportive of each other. Comparing arms by combining both histologies may be supportive. If a positive finding from a combined analysis is driven by the results of one histology, the indication may be limited to that histology only.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

ADDITIONAL COMMENTS:

Clinical

7. FDA recommends that protocol CA209017 be revised to discontinue docetaxel dosing in patients with a total bilirubin above the institution upper limit of normal (IULN) or in patients with an AST and/or ALT > 1.5 × IULN concomitant with alkaline phosphatase > 2.5.

   Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

8. The choice of docetaxel as a comparator is appropriate based on your planned clinical development of BMS-936558 in NSCLC irrespective of histologic subtype and based on the described benefit of docetaxel on overall survival in the second-line treatment of metastatic NSCLC patients. However, the investigational arm proposed for trial CA209017 contains BMS-936558 alone. Given that only limited number of NSCLC patients have received BMS-936558 in early phase trials, your estimate for the treatment effect of this product on overall survival in the proposed patient population remains largely unknown and questionable. FDA suggests conducting a clinical trial to obtain an estimate of the treatment effect of BMS-936558 on overall survival prior to proceeding to large,

randomized trials intended for registration. Alternatively, BMS may consider an add-on design evaluating the combination of BMS-936558 with docetaxel.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

9. FDA recommends considering alternative clinical trial designs in the NSCLC development program that will provide dose-response information for BMS-936558. Please refer to the International Conference on Harmonization (ICH) Tripartite Guideline E4 titled "Dose-Response Information to Support Drug Registration" which can be accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

10. FDA recommends contacting the Center for Devices and Radiological Health (CDRH) if BMS intends to integrate the use of PD-L1 biomarker into the development program for BMS-936558.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

11. Please be advised that due to the re-organization of the Office of Hematology and Oncology Products, please submit a new IND for Protocol CA209017 to Division of Oncology Product 2.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

Office of Prescription Drug Promotion/Division of Professional Promotion

12. Regarding BMS's request for OPDP review and comment on proposed promotional claims, OPDP's comments are contingent upon the review division's assessment of BMS's development plan. BMS will need to address the review division's comments (1 to 10 above) before proposing promotional claims. For future consideration, OPDP recommends that BMS submit a mock-up of a proposed promotional piece to OPDP so that the proposed promotional claims may be reviewed in the context of a promotional piece.

Discussion during the meeting: BMS acknowledged FDA's response and there was no discussion at the meeting.

APPEARS THIS WAY ON ORIGINAL

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635 htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601

CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)
CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--

DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601
DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601

DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601

MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601
RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601

SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TR	TRLINKID	Link ID	--	Yes	Exp	Char	--

TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null

TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--
TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C
AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C

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CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. three domains are related but each domain has a distinct purpose:

(Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the and timing information.

(Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement because this would be a duplication of information already represented in TU. This duplication of data was a

deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:
(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)
MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x x* ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL=”INDEPENDENT ASSESSOR” and RSEVALID=”RADIOLOGIST 1”. The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

DOP2's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The **Study Data Standards Common Issues Document** can be found at:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635 htm The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. The DOP2 is using these domains

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval:
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing

document:

- Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').
- A description of your drug development plan, including each indication that is being or has been studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission:

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
   - If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
     - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
     - Applicability of comparator treatment or of disease characteristics to U.S. population
   - Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot ethically be performed.

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)), which under § 314.510 and 601.41 would usually be underway at the time of accelerated approval in your SPA request and NDA/BLA submission.
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the

proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following:
   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
   k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
8) Pediatric Studies:

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

9) Quantitative Safety Analysis Plan (QSAP):

The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

b) Safety endpoints for Adverse Events of Special Interest (AERI)

c) Definition of Treatment Emergent Adverse Event (TEAE)

d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))

e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)

f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:

a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)

b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:

There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:

a) Site number
b) Principle investigator
c) Location: City State, Country
d) Number of subjects screened
e) Number of subjects randomized
f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
g) Number of protocol violations (Major, minor, including definition)

17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:

a) subject age and gender
b) signs and symptoms related to the adverse event being discussed
c) an assessment of the relationship of exposure duration to the development of the adverse event
d) pertinent medical history
e) concomitant medications with start dates relative to the adverse event

f) pertinent physical exam findings

g) pertinent test results (for example: lab data, ECG data, biopsy data)

h) discussion of the diagnosis as supported by available clinical data

i) a list of the differential diagnoses, for events without a definitive diagnosis

j) treatment provided

k) re-challenge and de-challenge results (if performed)

l) outcomes and follow-up information

m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.

b) Exposure-Response Relationships – important exposure-response assessments.

c) Less common adverse events (between 0.1% and 1%).

d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.

e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.

f) Marked outliers and dropouts for laboratory abnormalities.

g) Analysis of vital signs focused on measures of central tendencies.

h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.

i) Marked outliers for vital signs and dropouts for vital sign abnormalities.

j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.

l) Standard analyses and explorations of ECG data.

m) Overdose experience.

n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

o) Explorations for:

   i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

   ii) Dosedependency for adverse findings, which should be supported by

   summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

   iii) Time dependency for adverse finding, which should be supported by analyses

   summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

   iv) Drug-demographic interactions

   v) Drug-disease interactions

p) Drug-drug interactions

   i) Dosing considerations for important drug-drug interactions.

ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832 htm).

Physician's Labeling Rule

Highlights

1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).

6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).

7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].

11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights

12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]

13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Table of Contents

15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be

included in the Contents.

19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy

8.3 Nursing Mothers *(not 8.2)*

8.4 Pediatric Use *(not 8.3)*

8.5 Geriatric Use *(not 8.4)*

20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:

"*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.

24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).

25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]

26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that

important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31) If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

32) Refer to www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.

33) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

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

/s/

VAISHALI JARRAL
12/09/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100052

MEETING MINUTES

Bristol-Myers Squibb
Attention: Kinnari Patel PharmD., R.Ph.
Associate Director
Global Regulatory Sciences, US-Oncology
Route 206 & Province Line Road, Rm D2.267
Princeton, NJ 08543

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) file for "MDX-1106 anti-PD-1 Monoclonal Antibody (BMS-936558)."

We also refer to the meeting between representatives of your firm and the FDA on May 25, 2012. The purpose of the meeting was to provide the updated preliminary data from the ongoing Phase 1 study CA209003 and to seek FDA feedback on the proposed clinical development plan based on histologies for non-small cell lung cancer (NSCLC).

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

If you have any questions, call me, at (301) 796-4248.

Sincerely,
{See appended electronic signature page}
Vaishali Jarral, M.S., M.B.A
Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
BMS Presentation slides
OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications
Additional DOP2 CDISC Guidance
Establishment Information

Meeting Template (Draft)

IND Number:	IND 100052
Meeting Type:	Type A
Meeting Category:	Pre-Phase 3
Meeting Date and Time:	May 25, 2011; 2:30 PM to 3:30 PM (ET)
Product Name:	MDX-1106 anti-PD-1Monoclonal Antibody (BMS-936558)
Received Briefing Package:	May 25, 2012
Sponsor Name:	Bristol- Myers Squibb [BMS]
Meeting Chair:	Patricia Keegan, M.D.
Meeting Recorder:	Vaishali Jarral

FDA ATTENDEES:
Office of New Drugs
Office of Hematology and Oncology Products
Division of Oncology Products 2

Patricia Keegan	Director
Vaishali Jarral	Regulatory Project Manager
Lee Pai-Scherf	Clinical Reviewer
Shakun Malik	Clinical Reviewer

Office of Clinical Pharmacology

Jun Yang	Clinical Pharmacology Reviewer, DCP5/OCP
Hong Zhao	Clinical Pharmacology Team Leader, DCP5/OCP

Office of Translational Sciences
Office of Biostatistics
Division of Biometrics V

Yuan Li Shen	Statistics Reviewer
Kun He	Statistics Team Leader

TENTATIVE LIST OF BMS ATTENDEES:
Aparna Anderson, PhD, Director, Global Biometric Sciences
Renzo Canetta, MD, Vice President, Oncology Global Clinical Research
David Feltquate, MD, PhD, Group Director, Global Clinical Research
MaryBeth Frosco, PhD, Director, Global Regulatory Sciences
Michael Giordano, MD, Sr. Vice President, Head of Development, Oncology & Immunology

Mark Moyer, MS, Vice President, Global Regulatory Sciences – Oncology
Fouad Namouni, MD, Vice President, Development Lead
Kinnari Patel, PharmD, Associate Director, U.S. Regulatory Sciences

1.0 BACKGROUND AND MEETING PURPOSE:

BACKGROUND

On May 11, 2012, Bristol-Myers Squibb (BMS) requested a Type A, Pre-Phase 3 meeting to propose separate registrational clinical development programs for BMS-936558 in non-small cell lung cancer (NSCLC) for squamous and non-squamous histology and to discuss potential for accelerated approval regulatory pathway for squamous NSCLC.

BMS-936558 (MDX-1106) is a fully human monoclonal IgG4 antibody that targets the programmed death-1 (PD-1, cell differentiation 279 [CD379]) cell surface membrane receptor. The BMS-936558 clinical development program in NSCLC includes a completed phase 1 trial (CA209001), (b) (4) ongoing phase 1 trials (CA209003, (b) (4) and two proposed phase 3 trials (CA209017 and CA209057).

On Dec 6, 2011, BMS had an End-of-Phase 1/Pre-Phase 3 meeting with the FDA/Division of Oncology Products 2 to review the preliminary data from the phase 1 study CA209003, and to obtain feedback and agreement on the clinical pharmacology and the registrational plan for BMS-936558 in NSCLC. Protocol CA2099003 is a multi-dose, dose escalation trial designed to characterize the safety, tolerability, and determine the maximum tolerated dose (MTD) of BMS 936558 administered every 2 weeks in patients with advanced colorectal cancer (CRC), melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and metastatic castrate-resistant prostate cancer (mCRPC) with progressive disease after 1-5 systematic therapies. As of August 29, 2011, 235 patients with NSCLC, CRC, melanoma, RCC, or mCRPC had been treated. Objective responses were reported at doses 1, 3 and 10 mg/kg in NSCLC, RCC and melanoma. At the dose of 10 mg/kg, responses were reported in 4/18 patients (22%) with NSCLC, 5/16 patients (31%) with RCC and 4/19 patients (21%) with melanoma. Safety information from the 235 patients enrolled in CA209003 who received at least 1 dose of BMS 936558 (0.1, 0.3, 1. 3 and 10 mg/kg) was also provided. The most frequent adverse reactions occurring in > 20% of the patients were fatigue, diarrhea, decreased appetite, nausea and vomiting. Serious adverse reactions were reported in 34.5% of the patients. Adverse events considered to be related to BMS-936558 that may have been the result of tissue-specific immune-based toxicity include pneumonitis (2.1%) , rash (19.1%), diarrhea (26.8%), colitis, endocrinopathy, including hypothyroidism, hypophysitis (4.7%), and hepatitis (13.3%). Fatal adverse reactions, possibly related to BMS 936558, consisted of pneumonitis, which occurred in 2 patients: one patient who received BMS 936558 at 1.0 mg/kg and one patient who receive BMS 936558 at 10 mg/kg.

Based on the preliminary results from CA2090003, BMS proposed to conduct a phase 3 study, CA209017, comparing BMS-936558 to docetaxel as monotherapy in patients with advanced recurrent, unresectable or metastatic NSCLC. Eligible patients will be stratified by histology (squamous vs. nonsquamous), prior first-line therapy (maintenance vs. no maintenance), presence of driver mutation vs. absence/unknown driver mutation, and region. The primary endpoint of the study is overall survival. Secondary endpoints include objective response rate (ORR), progression-free survival (PFS), safety, and disease-related symptom progression rate as measured by the Lung Cancer Symptoms Scale. During the December 6, 2011 meeting, FDA provided comments concerning the design of the study and stated that, in general, the proposed methods of analysis for the primary and secondary endpoints were acceptable.

Clinical

In the current meeting package, BMS provided a 26-slide deck with an update of the efficacy data from the phase I expanded cohort study CA209003 with additional patients enrolled in the melanoma, NSCL and RCC cohorts (cut-off date of February 24, 2012) and a new proposal for BMS-936558 development in NSCLC.

Objective response rates in NSCLC, RCC and melanoma are summarized in the slides with this table below (snapshot from the BMS's meeting package).

The table below shows the clinical activity of BMS-936558 in efficacy-evaluable NSCLC patients by histology (retrieved from the BMS meeting package):

Based on the updated response rate data in NSCLC, BMS is proposing to initiate separate registrational clinical development programs for BMS-936558 in NSCLC for squamous and non-squamous histology by conducting two separate Phase 3 studies (CA209017 and CA209057).

Revised Protocol CA209017:
As currently written, the trial remains an open-label, randomized (1:1) study of BMS-936558 or docetaxel in patients with metastatic or recurrent NSCLC that has progressed during or after one prior platinum-containing chemotherapy regimen. Major modifications include (1) a change from a single primary endpoint (OS) to co-primary endpoints of ORR and OS, (2) limitation of enrollment to patients receiving second-line treatment for stage III/IV or recurrent, locally advanced NSCLC of squamous cell histologic subtype, and the addition of a final analysis of ORR with an interim analysis of OS at the time of the final analysis of ORR. If there is a statistically significant and clinically important improvement in ORR for BMS-936558 versus docetaxel and a positive trend in OS at the interim analysis, BMS will consider submission of an NDA seeking accelerated approval, which would be verified by the final analysis of OS in this trial. If OS is both statistically significant and clinically meaningful at the interim analysis, BMS is planning to submit the data for review with a request for full approval. The table below is a snapshot from the BMS's meeting package.

Regulatory

BMS is planning to request for a fast track designation for NSCLC in May 2012. For squamous NSCLC, BMS will propose to pursue an accelerated approval pathway for this unmet medical need population with a success in study CA209017 based on demonstration of a clinically important and statistically significant improvement in ORR with BMS-936558 as compared to docetaxel, supported by a positive trend in OS at interim analysis after approximately 65% of the planned deaths for the final analysis.

2.0 DISCUSSION

SPONSOR QUESTIONS AND FDA RESPONSES:

Clinical/ Statistical:

1. **Sponsor Question #1:** Does FDA agree with proposal to split NSCLC development by histologies?

   FDA Response: Yes. The proposal to split NSCLC development by histology is acceptable.

   Discussion: BMS acknowledged FDA's comment and there was no further discussion during the meeting.

2. **Sponsor Question #2:** Does FDA agree that proposed squamous NSCLC study as designed versus taxotere with co-primary endpoints could lead to a potential accelerated approval based on ORR difference and positive trend in OS at interim and full approval if OS is significant at interim or final analysis?

   FDA Response: Whether demonstration of a statistically significant effect on objective response rate, in the absence of a detrimental effect on survival in an interim analysis would be sufficient to support a request for accelerated approval will depend on the magnitude of the treatment effect and the risk: benefit evaluation.

   With regard to the proposed development program, FDA has the following recommendations

   - The effect size for objective response rate which may support accelerated approval should be similar to that observed in the expansion cohort (i.e., approximately 50%) with a clinical important durability similar to that seen in the responding patients in the expansion cohort;
   - The proposed Phase 3 trial should incorporate a plan for an interim analysis of the objective response rate for the purpose of re-sizing the trial, given the uncertainty of the true effect size based on limited data;
   - The proposed Phase 3 trial should employ a (2:1) randomization of BMS-936558 to docetaxel;
   - An additional, single-arm trial of BMS-936558 for the third-line treatment of patients with squamous cell NSCLC in which a clinically important rate of durable objective responses are observed may also serve to support a request for accelerated approval.

   As stated during the November 2011 meeting, please be aware that for a single randomized trial to support a BLA, the trial should be well-designed, well-

conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Acceptance of the results of a single trial will be based upon the magnitude of effect and robustness of results. Please refer to FA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" at http://www.fda.gov/downloads/Durgs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

BMS additional questions submitted by e-mail on May 25, 2012, prior to the meeting:

a. Regarding an interim analysis of ORR:

1) Does the FDA envision demonstration of an ORR threshold in the anti-PD-1 arm per se or in comparison to docetaxel? If it's the former, what ORR does the FDA want to rule out?

Discussion: FDA stated that the Agency envisions demonstration of an ORR threshold in the anti-PD-1 arm and would like to rule out any response rate less than 50%. FDA expressed concern that if BMS demonstrate a very large treatment effect on ORR, it would be unethical for them to conduct the study further to demonstrate the effect on OS. FDA stated that BMS's approach should minimize exposure to a potentially less effective marginal drug and recommended that BMS further revise Protocol CA209-017 to incorporate a 2:1 randomization plan (BMS-936658 to docetaxel) and incorporate a plan for an interim analysis to assess the effects on overall survival (e.g., 6 month survival rates) for the purpose of re-sizing the trial. FDA is proposing this approach because the study should not "way overpower" for detection of an effect on ORR because this could lead to the early termination of the study based on detection of significant but clinically modest effects on ORR and then there will be no data to assess the effects on survival.

FDA also recommended that BMS can conduct parallel single arm studies in the third-line treatment of squamous and non- squamous NSCLC as an additional trial(s) evaluating ORR as the primary endpoint. FDA emphasized that goal is to optimize and expedite the drug development so that BMS-936658, if highly effective, is available for patients who are in need.

2) *How would the Agency propose controlling Type 1 error?*

Discussion: There was no discussion of this question.

3) *Does the re-sizing include both increasing and/or decreasing the sample size?*

Discussion: Yes. Please see additional discussion under Sponsor's question 2.a.1), above.

4) *What would be the suggested role of the three parties (DMC, Sponsor and FDA) in recommendation of change in sample size?*

Discussion: FDA stated that the Agency plays no role in making any recommendation relating to change in sample size based on the interim data, although FDA will review the proposed analysis plan for comment. FDA further recommended BMS that the company should set-up rules for DMC and should incorporate those rules in their Statistical Analysis Plan.

5) *The sponsor is interested in maintaining the potential to demonstrate an overall survival benefit in this study to support full approval. Does the Agency have any suggestion to help support this objective?*

Discussion: No.

b. *If the 3rd line study is conducted as proposed by the FDA, could such a single-arm trial support accelerated approval as a stand alone study?*

Discussion: Yes, a single-arm trial in third-line treatment could support accelerated approval, however as previously stated, this will depend on the magnitude of the treatment effect and durability of responses as well as the risk:benefit assessment.

c. *Could this single-arm trial in the 3rd line setting be for any histology (both Squamous and Non-squamous)?*

Discussion: Yes.

d. *If both the 2nd and 3rd line studies are supportive of ORR, could the sponsor request accelerated approval for both lines of therapy?*

Discussion: Yes, but FDA recommends that BMS should consider overall survival to be a primary endpoint.

e. *Would the Agency consider a Phase 2 study in the 1st line setting, as noted in the development plan timeline, with demonstration of ORR potentially supportive of the 2nd line accelerated approval?*

Discussion: No discussion.

3. **Sponsor Question #3:** (b) (4)

FDA Response: (b) (4)

Discussion: BMS acknowledged FDA's comment and there was no further discussion during the meeting.

ADDITIONAL SPONSOR QUESTIONS/COMMENTS

4. (b) (4)

Discussion: (b) (4)

5. (b) (4)

Discussion: (b) (4)

(b) (4)

ACTION ITEMS:

- BMS will submit a request for a pre-IDE meeting to CDRH by June of 2012.
- BMS will submit a revised protocol for Trial CA209017 to this IND by August of 2012.
- The revised protocol will be supported by data supporting the safety and potential benefits for their proposed plan for continuation of BMS-936558 past disease progression past on clinical experience (treatment history, tumor measurements, and safety information) from patients treated in completed and ongoing studies.
- BMS will submit the case report forms (CRFs) for capturing adverse event information for Trial CA209017 with the revised protocol. BMS stated that these CRFs which will be adequate to ensure collection of data sufficient to characterize the unique toxicities of BMS-936558.

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

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL=”INDEPENDENT ASSESSOR” and TREVALID=”RADIOLOGIST 1”. The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x x* ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL=”INDEPENDENT ASSESSOR” and RSEVALID=”RADIOLOGIST 1”. The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

OHOP's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

In addition, the **CDER Data and Programs Standards checklist** is a separate document (appended to the end of OHOP's End-of-Phase 2 General Advice) that includes points to be considered for electronic submission, but it is not guidance. These recommendations represent our current advice to Sponsors. They do not create or confer any rights for or upon any person and are not binding on FDA or the public. An applicant can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Division. The purpose of the checklist and supporting documentation is to **highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant** regarding submission of CDISC data in support of an application for registration.

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval *Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.*
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: • Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. *See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'*). • A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an

application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
   - If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
     - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
     - Applicability of comparator treatment or of disease characteristics to U.S. population
   - Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB)

and adjudication committee charters, and all amendments.

2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.

3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure

4) All randomization lists and, if used, IVRS datasets (in SAS transport format)

5) All datasets used to track adjudications (in SAS transport format)

6) A Reviewers Guide to the data submission that includes, but is not limited to the following:
   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
   k) documentation of programs

7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).

8) Pediatric Studies:

   All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

9) Quantitative Safety Analysis Plan (QSAP):

   The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

   a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

b) Safety endpoints for Adverse Events of Special Interest (AERI)
c) Definition of Treatment Emergent Adverse Event (TEAE)
d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:

There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:
a) Site number
b) Principle investigator
c) Location: City State, Country
d) Number of subjects screened
e) Number of subjects randomized
f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
g) Number of protocol violations (Major, minor, including definition)

17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07200

2.pdf).

18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
    a) subject age and gender
    b) signs and symptoms related to the adverse event being discussed
    c) an assessment of the relationship of exposure duration to the development of the adverse event
    d) pertinent medical history
    e) concomitant medications with start dates relative to the adverse event
    f) pertinent physical exam findings
    g) pertinent test results (for example: lab data, ECG data, biopsy data)
    h) discussion of the diagnosis as supported by available clinical data
    i) a list of the differential diagnoses, for events without a definitive diagnosis
    j) treatment provided
    k) re-challenge and de-challenge results (if performed)
    l) outcomes and follow-up information
    m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
    a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
    b) Exposure-Response Relationships – important exposure-response assessments.
    c) Less common adverse events (between 0.1% and 1%).
    d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges

for the laboratory values.

e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.

f) Marked outliers and dropouts for laboratory abnormalities.

g) Analysis of vital signs focused on measures of central tendencies.

h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.

i) Marked outliers for vital signs and dropouts for vital sign abnormalities.

j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.

l) Standard analyses and explorations of ECG data.

m) Overdose experience.

n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

o) Explorations for:

   i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

   ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

   iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

   iv) Drug-demographic interactions

   v) Drug-disease interactions

p) Drug-drug interactions

   i) Dosing considerations for important drug-drug interactions.

   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule
Highlights
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the

time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers *(not 8.2)* 8.4 Pediatric Use *(not 8.3)* 8.5 Geriatric Use *(not 8.4)*
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

CDER Data Standards Check-list

(Version 1.0/April, 2010)

The purpose of this check-list and supporting documentation is to **facilitate discussion** between reviewers/review divisions and sponsors with regard to the submission of CDISC data in support of product approval.

This document will be **updated regularly** (every 6-12 months) based on division/reviewer feedback and experience. Therefore, it is important that reviewers refer to the CSC website to ensure that they are using the most up-to-date version. (http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm)

When a sponsor or review division is uncertain about a particular issue related to CDISC (Clinical Data Interchange Standards Consortium) standards implementation or submission, the review division should **request assistance from the CSC** at (CSCDataStandards@fda hhs.gov)

(Each Bullet with link to Appendix for further details)

GENERAL CONSIDERATIONS

- ☐ Implementation of SDTM
- ☐ Follow SDTM (Study Data Tabulation Model) Implementations Guide (SDTM v. 3.1.2, www.cdisc.org)
- ☐ Follow ADaM (Analysis Data Model) Implementation Guide (ADaM v. 2.1, www.cdisc.org)
- ☐ Sponsor to discuss with review division and submit supporting documentation for non-Implementation Guide Decisions/Issues
- ☐ Define file
- ☐ SEND (Standard for Exchange of Non-Clinical Data) Data
- ☐ CDISC legacy conversion and analysis data

TERMINOLOGY

- ☐ Use of CDISC Controlled Terminology via NCI Enterprise Vocabulary Services (EVS) at (http://www.cancer.gov/cancertopics/terminologyresources/page6)
- ☐ Use of WHO DRUG terminology
- ☐ Use of Adverse Event Terminology (i.e., MedDRA, etc)
- ☐ Use of non-standard terminology
- ☐ Coded Variables
- ☐ Implementation of variable dictionaries

SDTM DOMAINS

- ☐ SUPPQUAL (Supplemental Qualifiers)
- ☐ DM domain (Demographics)
- ☐ EX domain (Exposure)
- ☐ DS domain (Disposition)
- ☐ AE domain (Adverse Events)
- ☐ Custom Domains
- ☐ LB domain (Laboratory)

ADaM DOMAINS

- ☐ Referral to CDER Analysis Data Submission Document and Data Specifications Document
- ☐ ADaM Implementation Guide
- ☐ Assessment of which domains to submit
- ☐ ADSL (Analysis Data Subject Level)
- ☐ ADAE (Analysis Data Adverse Events)

VARIABLES

- ☐ Required vs. Expected vs. Permissible
- ☐ Naming conventions and formats
- ☐ Dates
- ☐ USUBJID (unique subject identifier variable)
- ☐ Derived variables
- ☐ Imputed data variables

COMMON ERRORS

- ☐ Define.xml does not validate
- ☐ Invalid ISO8601 date format for SDTM datasets
- ☐ Begin date must be ≤ to end date
- ☐ Required variable not found
- ☐ Inconsistent value for standard units
- ☐ Invalid value for preferred term
- ☐ If ARMCD equals “SCRNFAIL’ then ARM must equal “Screen Failure’

Narratives

- ☐ pdf and non-pdf format

APPENDIX

GENERAL CONSIDERATIONS

The ideal time to **implement** SDTM standards is prior to the conduct of the study. Use of CDASH-designed case report forms allows for a simplified process for creation of SDTM domains. It is strongly encouraged that discussions with CDER divisions regarding use of SDTM data standards take place as early as possible in the review cycle, such as at end of phase 2, rather than pre-submission. If a sponsor decides to convert clinical trial data to SDTM that was originally collected in non-SDTM format, it is important to note that the resulting SDTM data should support the accompanying analysis data sets and sponsors' reports (study reports, etc.).

CDER has received numerous "CDISC-like" applications over the past several years in which sponsors have not followed the CDISC implementation guides.

The **SDTM Implementation Guide (SDTMIG)** should be followed carefully (CDISC.org). Section 3.2.2 of the SDTMIG provides general criteria conformance with the SDTM data model. These criteria should not be interpreted as the sole indication of the adequacy of submitted CDISC data, however, they should be followed unless otherwise indicated. If there is uncertainty with regards to implementation, the sponsor should discuss with the division.

For **analysis datasets**, sponsors should refer to the recently published ADaM Implementation Guide as well as the CDER Study Data Specifications Document and the CDER Analysis Data Request Document. It is expected that significant discussion between the sponsor and CDER clinical and statistical reviewers will be necessary to appropriately determine which analysis datasets as well as dataset content are needed to support application review.

It is understood that CDISC data standards are evolving and that there may be instances in which the current implementation guides do not provide specific instruction as to how certain clinical trial data should be represented. In this instance, sponsors should discuss their proposed solution with the review division and submit supporting documentation at the time of submission that describes these decisions/solutions.

CDER would prefer that sponsors submit the **define file** in both .pdf and .xml formats.

CDER is currently involved in pilot testing of the **SEND** standard for the submission of pre-clinical data. Sponsors who are interested in submitting SEND-compliant data should discuss with the toxicology reviewers from the appropriate review division.

CDISC legacy data conversion: It is strongly preferred that sponsors design their phase 3 trials using CDISC-defined data elements which allow for much easier SDTM domain creation (such as is possible with use of CDASH-specified CRFs). Conversion of non-CDISC data to CDISC format at the end of the drug development process is more challenging and if pursued, sponsors must ensure that converted SDTM datasets support key analyses contained in the sponsor's study/integrated reports. In addition, the accompanying analyses datasets should be derived from the SDTM data sets and also must support the analyses contained in the sponsors' reports.

TERMINOLOGY

Field entries for CDISC specified variables should use the **CDISC Controlled Terminology** which can be found at the NCI Enterprise Vocabulary Services (http://www.cancer.gov/cancertopics/terminologyresources/page6).

It is strongly preferred that the **WHO DRUG Dictionary** terminology be used for the concomitant medications domain. The generic WHO Drug term should be used for the CDISC standardized medication name variable. The SDTM medication class variable (CMCLAS) should be used to represent the WHO Drug level 3 ATC term (pharmacological subgroup) associated with the standardized medication name.

When using **MedDRA** for adverse events and past medical history terms, sponsors should exactly follow the spelling and case of the MedDRA terms. Sometimes clinical trials are conducted at different times during the development cycle which results in the use of different versions of MedDRA from one study to the next. It is expected that the Adverse Event data set for the Integrated Summary of Safety include MedDRA preferred terms from a single harmonized version of MedDRA.

For variables/field entries for which **no standard terminology exists**, the sponsor may propose their own terminology. Please provide supporting documentation that describes the non-standard terminology that is used.

No numerically **coded variables** should be submitted as part of the SDTM datasets.

It is expected that **common dictionaries** are used across all trials and throughout the submission for each the following: adverse events, concomitant medications, procedures, indications, study drug names, and medical history. Implementation of such dictionaries should be careful to exactly follow the spelling and case specified by the dictionary (for existing dictionaries such as MedDRA) or according to a single consistent sponsor specification if no pre-existing terminology exists.

SDTM DOMAINS

SUPPQUAL is a dataset domain in SDTM. It is intended to include data variables that are not specified in SDTM. SUPPQUAL datasets are often used as a "waste-basket" for data elements that the sponsor is not sure what to do with. Discussion needs to occur if the sponsor intends to include important variables (that support key analyses) in the SUPPQUAL domains. One way to deal with this issue for important data elements that are likely to be needed to support review work, is to ensure that analysis datasets are prepared in a way that includes these and other relevant data elements.

In the **DM** domain (Demographics), if ARMCD ('Planned Arm Code') equals "SCRNFAIL' then ARM ('Description of Planned Arm') must equal "Screen Failure' There is also terminology (NOTASSGN) for subjects who are not screen failures but, for other reasons, are never assigned to an arm. Uncertainty occurs in the situation that a subject was randomized, however, did not receive

treatment for other reasons. The recommended solution for this situation is to use the terminology of 'NOTTXD' for the ARMCD variable and 'Not Treated' for the ARM variable, and make a comment in the define.xml regarding the use of this terminology. For ARMCD, the arm entry is equal to the therapy the patient was randomized to, even if they mistakenly were treated under a different arm. However, there is no current variable included in the **DM** domain that denotes actual therapy received which can be used to determine the safety population. For example, if a subject is randomized to one arm, but then actually receives therapy in accordance with a different arm, there is no variable in the DM dataset that captures this. The recommended solution for this is to include in the DM dataset a variable called "ACTARM" with a label of "Actual Arm". Terminology for this variable should include the name of the arm that the patient was treated under (consistent with the terminology used for the ARM and ARMCD variables) and patients must have received at least one dose of drug in order to have a treatment arm entry for this variable.
The DM variable "RFENDTC" should correspond to the date/time of last exposure to study treatment. Also, the variable "RFSTDTC" should represent the start date/time of active study drug exposure (or placebo exposure for subjects who are receiving only placebo). There is also a need for a variable that represents the date/time for when the subject ended participation/follow-up in the trial. This variable should be called "RFTREDTC" with a label of "Reference Trial End Date." In the DM domain, each subject should have only one single record.

The **EX** domain. **Exposure:** Provide the exposure data in a consistent format across all the studies ("one record per dose per day").

DS domain: Deaths: The current SDTM version 3.1.2 does not address the need for a unique place for recording deaths. To simplify our safety analysis, for each patient who died there should be one record in the Disposition (DS) domain where DSCAT='DISPOSITION EVENT' and DSDECOD='DEATH'. When there is more than one disposition event the EPOCH variable should be used to distinguish between them so that if the death occurred during the treatment period EPOCH='TREATMENT' and if the death occurred during the follow-up period EPOCH='FOLLOW-UP'. Other values may be used for epoch depending upon the terminology used in the trial design model datasets.

AE domain (Adverse events): There is currently no variable in the AE domain that indicates if a variable was "treatment emergent." CDER would like the AE domain to include all adverse events recorded in any way in the patients' case report forms. An additional variable (called TREMR, label "Treatment emergent") should be added to the AE domain that indicates if the event was or was not treatment emergent. This variable should be a simple yes or no (Y/N) response. In addition, the AE domain does not include variables for levels of the MedDRA hierarchy other than the preferred term or system organ class levels. To address this issue, sponsors should include the following variables: LLT (Lower Level Term), HLT (High Level Term), and HLGT (High Level Group Term). The field entries for these terms should exactly follow the MedDRA terminology. Also, please include an EPOCH variable in the AE domain. This will allow the reviewer to easily determine what phase of the trial the AE occurred during (i.e., screening, on-therapy, follow-up…). The SOC variable entry should represent the MedDRA-defined, primary mapped SOC. The SDTM Implementation Guide states that sponsors have the choice to use secondary mapped SOC in place of primary mapped SOC as they wish, however, CDER generally does not agree with this.

Custom Domains: The SDTM Implementation Guide does allow for the creation of custom domains if the data do not fit into an existing domain. Custom domains are highly discouraged. Prior to creating a custom domain, sponsors should confirm that the data do not fit an existing domain and also check the CDISC website for domains added after the most recent published implementation guide. If necessary, sponsors should follow the recommendations in the SDTM Implementation guide for how to create a custom domain (section 2.6).

LB Domain (Laboratory): The size of the LB domain is often quite large and can exceed the clinical reviewers' ability to open the file using standard-issue computers. This issue can be addressed by splitting the large LB dataset into smaller data sets according to lab type: chemistry (named "LBC"), hematology (named "LBH"), UA (LBU), serology (LBS), etc. Splitting it other ways (by subject or file size, etc) makes the data less useable. Sponsors should submit these smaller files **in addition to** the larger non-split standard LB domain file. File size of 400 megabytes is usually fine, however, it is recommended to confirm this with the review division.

ADaM DOMAINS (ANALYSIS DATASETS)

In determining how to create CDISC analysis datasets for submission to CDER, sponsors should refer to **three documents**: the ADaM Implementation Guide, the FDA Data Specifications Document, and the CDER Analysis Data Submission Document. Close adherence to the ADaMIG is expected and any specific questions that result from attempts to adhere to these documents should be discussed with the review division.

A careful assessment of **which analysis datasets** will be needed should occur. Sponsors must submit analysis datasets with their application to support key analyses. Additionally, it is important to remember that SDTM datasets do not have core variables (such as demographic and population variables) repeated across the different domains. The need for such duplication of core variables across various domains can be fulfilled through their inclusion in the corresponding analysis datasets. This need is sufficient for the purposes of justifying a request for analysis datasets. For example, the SDTM adverse event dataset does not allow for the inclusion of variables such as treatment arm, sex, age, or race. These and other variables may be included in an adverse event analysis dataset.

ADSL is the subject level analysis dataset for ADaM. CDER expects all CDISC submissions to include this ADaM-defined dataset along with the other supporting analysis datasets. In addition to the variables specified for ADSL in the ADaM Implementation Guide, it is expected that the sponsor will include multiple additional variables representing various important baseline patient characteristics. A few examples could include: disease severity scores such as APACHE scores or FINE scores; baseline organ function measurements such as calculated creatinine clearance or FEV1; range categories for continuous variables; numeric date variables in non-ISO format such as SAS or Oracle.

ADAE is the ADaM adverse events domain. As with the AE domain, it is preferred that the ADAE domain include variables for grouping-term levels of the MedDRA hierarchy. Also, sponsors should explain how they intend to represent events which were not treatment emergent or those terms which could represent efficacy endpoints.

VARIABLES

CDISC data standards categorize variables as being **Required, Expected, and Permissible**. Some sponsors have interpreted Permissible variables as being optional. However, for the purposes of submission of CDISC data to CDER, all permissible variables for which data were collected or for which derivations are possible should be submitted. **Examples** of some of the permissible variables that CDER expects to see include:

- Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic, Microbiology results
- EPOCH designators
- STDY variables in SE or other findings domains
- Exposure – total dose

Naming conventions (variable name and label) and variable **formats** should be followed as specified in the implementation guides.

Dates: Dates in SDTM domains should conform to the ISO8601 format. Examples of how to implement this are included in the SDTMIG. Because of the usefulness of numeric date formats in common software/systems used in CDER, it is expected that for the ADaM datasets, dates be also provided using numeric formats such as SAS and/or Oracle dates. Follow the same CDISC format for dates across all the trials and datasets. If no time measurements are available, the sponsor should truncate the format at the T instead of submitting dates with a T:00:00:00 attached to the end.

USUBJID: Each individual patient must be assigned a single unique identifier (USUBJID) across the entire submission. An individual subject should have the same unique identifier across all datasets including SDTM and ADaM. Do not add leading or trailing spaces in any dataset.

Derived variables: The sponsor should be encouraged to include in the SDTM domains derived variables which essentially represent derived extensions of existing variables (although not to the exclusion of those existing variables). An example would be the following: a creatinine clearance is derived from a patient's measured serum creatinine (and other variables). This could be represented in the LB data set with LABTEST equal to calculated creatinine clearance. Of course, supporting documentation must be provided to describe the methods of calculation and the original data elements, if collected, that were used to derive the variable should still be submitted.

Imputed data: SDTM should not include any imputed data. If there is a need for data imputation, this should occur in an analysis dataset and the relevant supporting documentation must be provided.

COMMON ERRORS

The **define.xml** does not validate. Please refer to www.cdisc.org/define-xml for instructions. Here sponsors can find the white paper for XML Schema Validation for Define.xml which provides

guidance on validating define.xml version 1.0 documents against the define.xml XML schemas. Prior to submission, a sponsor may submit their define.xml for testing to determine whether it validates. The submission of a define.xlm is expected with all CDISC applications. If sponsors would like to also include a define.pdf document additionally, this would be ok.

Invalid ISO8601 date format. All dates in the SDTM domains must conform to the ISO8601 format. ADaM datasets can have numeric date formats such as SAS or ORACLE.

Begin date must be ≤ to end date. This is a common error. Examples include a concomitant medication or adverse event begin date that is after the end date.

Required variable not found. A Required variable is any variable that is basic to the identification of a data record (such as the unique subject identifier) or is necessary to make the record meaningful. Required variables must always be included in the dataset and cannot be null for any record.

Inconsistent value for standard units.

Invalid value for preferred term. This occurs when the sponsor has not accurately represented the MedDRA preferred term as it appears in the MedDRA terminology.

If **ARMCD** ('Planned Arm Code') equals "SCRNFAIL' then ARM ('Description of Planned Arm') must equal "Screen Failure'. Uncertainty occurs in the situation that a subject was not a screen failure, however, did not receive treatment for other reasons. A recommended work-around for this situation is to use the 'SCRNFAIL' and 'Screen Failure' terminology for ARMCD and ARM variables respectively and make a comment in the define.xml that this is what was done.

Narratives:
In addition to narratives provided in .pdf format, CDER would strongly desire that narratives are also provided in a format that is a computer readable textual description of the patient's events and patient's care. The narrative text should integrate the information on all serious events, outcomes of serious adverse events, withdrawals, deaths, and Causes of Death, autopsy reports, concomitant conditions and procedures, etc. into a single narrative text. The narrative text should describe the patient's disease and event progression and patient's care.

File format: Narrative data should be submitted as plain ASCII text (txt) files. Each row of the file has two fields delimited by tab characters.
The first field is the unique subject ID (USUBJID) that is used in the submission. Because the USUBJID will be used to link the narratives to other data in the submission, the USUBJID should be *identical* to the USUBJID used in all other submission data sets, such as the SDTM datasets. The second field is the text of the narrative. The narrative must not contain TABS, HARD RETURNS, non-printing characters, or hidden "funny" or formatted characters.

Narrative Files
Naming narrative files: The file should be named narrative.txt.
It helps the process of preparation of the narrative text files, if these files are checked for the presence of only two fields: the first one with only the USUBJID (with the right character length), and the second one with only the "long" or "clob" field.

Narrative template format:

USUBJID	**Narrative**
01019929944	Patient made full recovery, and has no residual pain
01888777666	Patient is still hospitalized in ICU
Etc.	

To facilitate the review of your IND treatment protocol, the Agency requests that you provide an updated list of all proposed manufacturing, labeling, testing and packaging sites to be used for clinical supplies of the investigational drug substance and drug product. For the purposes of facilitating the review, the Agency recommends the submission of the same manufacturing, labeling, testing and packaging sites for both the proposed treatment protocol and the forthcoming NDA. Note that any proposed changes to manufacturing, packaging, labeling, or testing sites in the NDA, relative to those proposed for the treatment protocol, may require additional justification.

Clearly identify *in a single location*, preferably located after the cover letter and 1571 Form, the manufacturing facilities associated with your treatment protocol. Include the full corporate name of the facility and address where the manufacturing function is performed, the FEI number, and specific manufacturing responsibilities for each facility. Also include the DUNS number, if available.

Provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the following example:

List of All Establishments Involved in the Manufacture of the Finished Product and the Active Pharmaceutical Ingredient for XX.

Drug Substance

Establishment Name	Site Address	Federal Establishment Indicator (FEI) or FDA Registration Number (CFN)	Contact Person Information	Responsibilities*	Comments	Ready for Inspection
ABC Lab			Name: Phone: Fax: Email:	Drug Substance manufacture	DMF 1234 DUNS 4567	Yes
XYZ Lab				Performs stability and release testing for drug substance	Never Inspected by FDA DUNS 8910	Yes

Drug Product

Establishment Name	Site Address	Federal Establishment Indicator (FEI) or FDA Registration Number (CFN)	Contact Person Information	Responsibilities*	Comments	Ready for Inspection
DEF Lab			Name: Phone: Fax: Email:	Drug Product manufacture, stability and release testing (except microbiological testing)		Yes
MNO Lab				Performs microbiological testing for drug product		Yes

*Manufacturing Step(s) or Type of Testing (Establishment function)

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

/s/

VAISHALI JARRAL
06/19/2012