

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125377Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

PMR/PMC Description: Ipilimumab is associated with autoimmune-related adverse events (irAEs) which may have a genetic component. PMRs pertinent to this PMC include a request from the clinical division to perform a comparative trial of 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy, as well as a PMR from the Genomics Group to obtain comprehensive baseline DNA sample acquisition ($\geq 95\%$ of ITT) in that trial and conduct pharmacogenomic association analyses to assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of irAEs. The proposed PMC (see below) is intended to elucidate additional unspecified genetic risk factors for irAEs in that comparative trial.

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

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	12/29/2016
	Final Protocol Submission:	12/29/2017
	Final Report Submission:	12/31/2018
	Other:	_____

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

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

Associations between autoimmune-related gene variants and irAEs were assessed in four supporting phase 2 studies and were seen with skin, hepatobiliary, and GI events. However, due to limitations related to pharmacogenomic methodology and acquired sample size, no definite conclusions regarding these associations can be made at this point. Given the serious nature of ipilimumab irAEs and limited data available, the genetic determinants of irAEs should be elucidated in the proposed comparative trial (3mg/kg vs. 10mg/kg). This will provide further information on whether an association indeed exists and whether this information significantly affects ipilimumab risk/benefit balance.

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

DNA was collected in four supporting phase 2 studies and associations between autoimmune-related gene variants and irAEs were assessed. Consistent with the sponsor’s analyses, we found a variation in the CD86 gene to be associated with increased risk of GI irAEs in patients receiving ipilimumab. The identified association of CD86 with irAEs will be addressed in a separate PMR. Other associations with skin, hepatobiliary, and GI events were also seen. However, several limitations preclude definitive conclusions regarding the strength of the associations, including 1) lack of uniform DNA sample acquisition from analyzed phase 2 studies; 2) incomplete DNA collection in the pivotal phase 3 study; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 5) questionable irAE definition. To obtain additional information regarding genetic risk factors for irAEs associated with ipilimumab therapy, (e.g. HLA given their recent implication in many AEs) we suggest a genomewide association analysis with samples that will be obtained in the proposed comparative trial (3mg/kg vs. 10mg/kg).

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Under the current PMC, a genomewide association analysis with DNA samples collected in the comparative trial will be performed to identify further genetic determinants of irAEs caused by ipilimumab. Correlation between genetic variants and irAEs will be assessed to evaluate safety and potentially identify a sub-population that is at increased risk of developing irAEs.

Required

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

Continuation of Question 4

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

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

Pharmacogenetic or pharmacogenomic study to further assess safety:

The PMC proposes a genomewide association analysis between genetic variants and irAEs in the proposed comparative trial (3mg/kg vs. 10mg/kg) to evaluate safety and potentially identify a sub-population that is at increased risk of developing irAEs.

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: Ipilimumab is associated with autoimmune-related adverse events (irAEs) which may have a genetic component. There currently is a PMR request from the clinical division to perform a comparative trial of 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy. The proposed PMR (see below) is intended to assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of irAEs given the association seen in the Phase 2 data.

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

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>11/30/2011</u>
	Final Protocol Submission:	<u>05/30/2012</u>
	Final Report Submission:	<u>12/29/2016</u>
	Other:	_____

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

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

Associations between immune-related gene variants (e.g. CD86) and irAEs were assessed in four supporting phase 2 studies and were seen with skin, hepatobiliary, and GI events. However, due to limitations related to pharmacogenomic methodology and acquired sample size, no definite conclusions regarding these associations can be made at this point that would justify a pre-approval requirement. Given the serious nature of ipilimumab irAEs and preliminary data available suggesting an association between CD86 genetic variants and irAEs, the clinical utility of CD86 gene polymorphisms as genetic determinants of autoimmune -related adverse reactions should be elucidated in the proposed comparative trial (3mg/kg vs. 10mg/kg). This will provide further information on whether an association indeed exists and whether this information significantly affects ipilimumab risk/benefit balance.

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

DNA was collected in four supporting phase 2 studies and associations between immune-related gene variants and irAEs were assessed. Consistent with the sponsor’s analyses, we found a variation in the CD86 gene to be associated with increased risk of GI irAEs in patients receiving ipilimumab. Other associations with skin, hepatobiliary, and GI events were seen. However, several limitations preclude definitive conclusions regarding the strength of the associations, including 1) lack of uniform DNA sample acquisition from analyzed phase 2 studies; 2) incomplete DNA collection in the pivotal phase 3 study; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 5) questionable irAE definition. To assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of autoimmune -related adverse reactions, comprehensive baseline DNA collection with a high sample acquisition rate ($\geq 95\%$ of ITT) followed by a pharmacogenomic association analyses of CD86 polymorphisms with irAEs is expected in the proposed comparative trial (3mg/kg vs. 10mg/kg).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

There is a proposed study for a comparative trial (3mg/kg vs. 10mg/kg) that is described in a separate PMR request for this BLA 125377. Under the current PMR, DNA should be collected in \geq 95% of ITT in that trial with advanced melanoma receiving different doses of ipilimumab. Correlation between CD86 gene variants and irAEs will be assessed to evaluate safety and potentially identify a sub-population that is at increased risk of developing irAEs.

Required

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

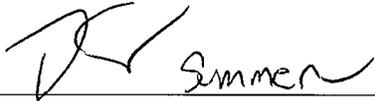
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: Immunogenicity testing (detection of neutralizing antibodies to ipilimumab)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>02/20/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The immunogenicity of ipilimumab at 3 and 10 mg/kg has not been properly assessed in the melanoma patient population. An anti-ipilimumab antibody incidence of 6.9% was observed at the 0.3 mg/kg dose but lower incidences were observed at 3 and 10 mg/kg. This may be due to ipilimumab levels that are present in the patient samples interfering with the assay since the majority of the patients who received 0.3 mg/kg ipilimumab had the lowest levels of ipilimumab present at baseline in their immunogenicity samples. Based on this, it is expected that 3 and 10 mg/kg would have a higher incidence of immunogenicity than 0.3 mg/kg of ipilimumab.

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

The goal of the proposed PMR is to assess the rate immunogenicity by measuring neutralizing antibodies towards ipilimumab in a minimum of 300 patients. The impact of anti-drug antibodies on the pharmacokinetics, efficacy, and safety of ipilimumab will also be determined.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The Agency has requested a study for a comparative trial of 3mg/kg vs. 10mg/kg ipilimumab in melanoma patients which is described in a separate PMR request for this BLA 125377.

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

Required

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Immunogenicity testing in the 3 versus 10 mg/kg ipilimumab study
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

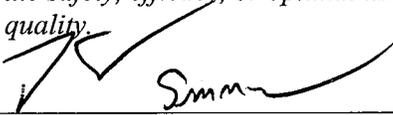
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: Immunogenicity testing (detection of binding antibodies to ipilimumab)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/2/2011</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The immunogenicity of ipilimumab at 3 and 10 mg/kg has not been properly assessed in the melanoma patient population. An anti-ipilimumab antibody incidence of 6.9% was observed at the 0.3 mg/kg dose but lower incidences were observed at 3 and 10 mg/kg. This may be due to ipilimumab levels that are present in the patient samples interfering with the assay since the majority of the patients who received 0.3 mg/kg ipilimumab had the lowest levels of ipilimumab present at baseline in their immunogenicity samples. Based on this, it is expected that 3 and 10 mg/kg would have a higher incidence of immunogenicity than 0.3 mg/kg of ipilimumab.

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

The goal of the proposed PMR is to assess the rate immunogenicity by measuring binding antibodies towards ipilimumab in a minimum of 300 patients. The impact of anti-drug antibodies on the pharmacokinetics, efficacy, and safety of ipilimumab will also be determined.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The Agency has requested a study for a comparative trial of 3mg/kg vs. 10mg/kg ipilimumab in melanoma patients which is described in a separate PMR request for this BLA 125377.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
Immunogenicity testing in the 3 versus 10 mg/kg ipilimumab study
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

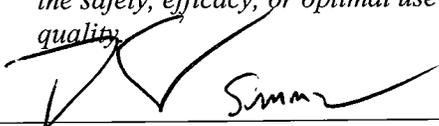
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



 (signature line for BLAs)

PMR

PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/30/2011
	Study/Trial Completion:	08/31/2017
	Final Report Submission:	12/31/2017
	Other: Preliminary CA184024 data submission	06/30/2011
	Draft Protocol Synopsis Submission	06/30/11
	Last Patient Accrued to Trial	12/31/14

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

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

The approval is based on the trial showing survival advantage in patients with metastatic or unresectable melanoma for ipilimumab used at dose of 3 mg/kg. Metastatic or unresectable melanoma is a life-threatening condition that has a uniformly dismal prognosis, and for which there is an unmet medical need. The applicant also has an ongoing study CA184024 which used ipilimumab at 10 mg/kg or placebo with DTIC in patients with metastatic or unresectable melanoma. The preliminary survival results were made available for confidential review by FDA at the request of FDA, prior to taking action on the current application. The proposed PMR is to determine the ipilimumab dose with the optimal risk/benefit ratio for the two doses.

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

The 3 mg/kg dose was used in the trial for which the application is being approved. The applicant has an ongoing study CA184024 which used ipilimumab at 10 mg/kg or placebo with DTIC. The preliminary survival results were made available for confidential review by FDA at the request of FDA prior to taking action on the current application. There appears to be an increased incidence and severity of immune-mediated adverse reactions at 10 mg/kg dose compared to 3 mg/kg dose. The goal of the PMR trial is to determine the dose with the optimal risk/benefit ratio for the two doses of ipilimumab (3mg/kg and 10 mg/kg).

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

A trial to compare the efficacy, with the primary endpoint of overall survival, and the safety of ipilimumab at doses of 3mg/kg versus 10mg/kg given as monotherapy every three weeks for four doses in patients with unresectable stage III or Stage IV melanoma.

Required

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

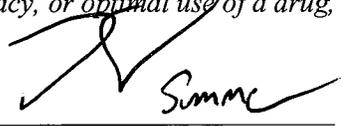
-
- Other
-

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

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

PMR/PMC Development Coordinator:

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



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PMR/PMC Development Template

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

PMR/PMC Description: Immunogenicity testing (detection/assessment of ADA response to ipilimumab)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/30/2011
	Study/Trial Completion:	08/31/2017
	Final Report Submission:	12/29/2017
	Other:	MM/DD/YYYY

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

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

The immunogenicity of ipilimumab at 3 and 10 mg/kg has not been properly assessed in the melanoma patient population. An anti-ipilimumab antibody incidence of 6.9% was observed at the 0.3 mg/kg dose but lower incidences were observed at 3 and 10 mg/kg. This may be due to ipilimumab levels that are present in the patient samples interfering with the assay since the majority of the patients who received 0.3 mg/kg ipilimumab had the lowest levels of ipilimumab present at baseline in their immunogenicity samples. Based on this, it is expected that 3 and 10 mg/kg would have a higher incidence of immunogenicity than 0.3 mg/kg of ipilimumab.

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

The goal of the proposed PMR is to assess any anti-drug antibody (ADA) and neutralizing ADA responses to ipilimumab with a validated assay (required in PMR 1) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The Agency has requested a study for a comparative trial of 3mg/kg vs. 10mg/kg ipilimumab in melanoma patients which is described in a separate PMR request for this BLA 125377.

3. To conduct an assessment of anti-drug antibody (ADA) response and neutralizing ADA responses to ipilimumab with a validated assay (required in PMR 1) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 ipilimumab-treated patients enrolled in the required post-marketing study comparing 3 mg/kg versus 10 mg/kg of ipilimumab monotherapy. The final report will include information on the level of ipilimumab in each patient's test sample at each sampling time point.

Required

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Immunogenicity testing in the 3 versus 10 mg/kg ipilimumab study
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

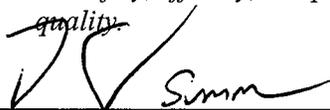
- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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

quality


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PMR

PMR/PMC Development Template

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

PMR Description: “Submit the final report for the nonclinical enhanced pre- and post-natal development (ePPND) study of ipilimumab in monkeys, study # DN10020, on or before December 31, 2011”

Applicant’s proposed language (as of 1/18/2011)



PMR Schedule Milestones: Final Report Submission: December 31, 2011

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

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

Nonclinical data regarding the safety of ipilimumab use during pregnancy were not included in the original BLA submission. For the current patient population (unresectable or metastatic melanoma), the potential benefit to the patients outweighs the potential risk to offspring; however, the applicant will be required to provide data from a completed, enhanced pre-/post-natal developmental toxicity (ePPND) study in cynomolgus monkeys as a post-marketing requirement. The ePPND study is ongoing: all pregnancies have completed but the in-life portion is not complete (i.e. surviving newborns have not yet reached the landmark, 6-month post-natal follow-up time point). FDA considers the interim data, submitted during the BLA review period, to be adequate for the initial labeling for this product and indication, and will follow up with revised labeling when the post-marketing requirement has been fulfilled.

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

The goal is to better inform the use of ipilimumab in pregnant women being treated in accordance with the ipilimumab label. The available interim ePPND data raise serious concerns for treatment-related loss of pregnancy (third trimester abortion and stillbirth), early delivery, and infant death. The final study report is expected to include more detailed evaluations of the early decedent fetuses and newborns than was provided in the interim reporting. The final study report is also expected to include data from 6-month endpoints in newborns (e.g. pathology, additional assays to assess delayed-onset autoimmune toxicity) that were not available at the time of the interim reporting.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The nonclinical ePPND study is ongoing; adult pregnant cynomolgus monkeys received ipilimumab during organogenesis through partuition. The populations being investigated are the mothers, decedent fetuses, decedent newborns, and surviving newborns.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

 *Summers 3/10/11*

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Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: To develop and validate a process-specific host cell protein (HCP) ELISA. This assay will replace the current Cygnus Kit ELISA being used in the drug substance release program. In the event a product specific assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided. The final study and validation reports will be submitted as a CBE-30 by (b) (4).

PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: MM/DD/YYYY
Other: CBE-30 (b) (4)

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

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

This PMC involves the development and validation of a new drug substance release method. It was not feasible to have this method developed and validated prior to approval.

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



3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Development of a drug substance release assay.
-

Agreed upon:

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

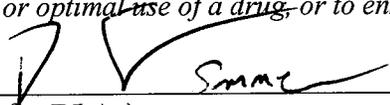
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- Other
-

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

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

PMR/PMC Development Coordinator:

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



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Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>07/29/2011</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

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

This PMC involves method of confirmation of clearance and risk assesment of (b) (4) present in drug product.. It was not feasible to perform additional confirmation study prior to approval.

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

(b) (4)



3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-
- Method of confirming clearance and risk assessment of a process related impurity
-

Agreed upon:

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

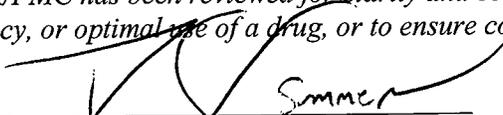
-
- Other
-

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

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

PMR/PMC Development Coordinator:

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



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Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: CBE-30	<u>03/31/2014</u>

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

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

Establishment of a stability specification for the CEX assay requires the acquisition of long term stability data from more drug substance and drug product lots and was not feasible prior to approval.

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

During the review, BMS was requested to set quantitative release and stability specifications that controls (b) (4) major product charge isoforms. Release and stability specifications were established but data provided did not justify the use of CEX assay in the the post-approval stability protocol. As there was not adequate information from the stability studies BMS proposed to collect three years of market life data for the CEX assay on three batches of drug substance and three batches of drug product to establish specification and to discontinue IEF method from stability program.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Will provide long term product stability data.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

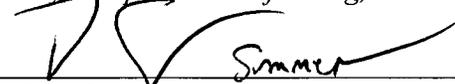
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>06/30/2011</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Establishment of specification for all three major isoforms for CEX assay requires the acquisition of data from more drug product lots and was not feasible prior to approval.

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

During the review, BMS was requested to set quantitative release specifications for CEX assay that controls not only acidic but also basic and main peak isoforms. Release specifications were proposed but there was no drug product release data to support the proposed acceptance criteria for CEX assay. The IEF method is a visual assessment of the product against the reference material with a description of the appearance of the ipilimumab sample profile complying with one or two major bands within the method-defined pI range. This method will be replaced by CEX assay after adequate data has been generated to establish CEX acceptance criteria.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Will provide long term product release data.

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

Agreed upon:

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

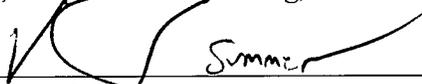
 - Other
-

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAS)

Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: <u>2013 Annual Report</u>	<u>MM/DD/YYYY</u>

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

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

This is a long-term study to monitor the presence of potential drug substance leachates such as volatile organic compounds (VOCs), semi-volatile organic compounds (SVOCs), non-volatile organic compounds (NVOCs) and trace metals. The occurrence of these potential leachates will be monitored during storage of drug substance and formulation buffer samples at the recommended storage temperature and accelerated conditions for the duration of 3 years.

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

During review it was noted that solutions were tested for volatile organic compounds (VOCs), semi-volatile organic compounds (SVOCs), non-volatile organic compounds (NVOCs) and trace metals at time intervals of 24 hours and 6 months at 2° to 8°C and under accelerated aging conditions of 40°C for 95 days which simulated 2° to 8°C storage for 2 years. Additional ipilimumab drug substance and formulation buffer samples are also said to be held at 2 to 8°C for up to 3 years and under accelerated aging conditions of 40°C to simulate 3 years at 2 to 8°C. The results of these studies have not been provided in the BLA and are said to be reported upon study completion. Though leachable testing and interim report submitted in the BLA adequately address the identification and safety assessment of potential leachates, this long term study will provide additional information on drug substance container leachates over the course of the drug substance storage period.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

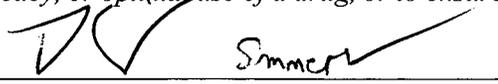
-
- Other
-

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

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

PMR/PMC Development Coordinator:

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

 *Summer*

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: To submit the final study reports for studies performed to confirm product stability over the course of the in-process hold times of (b) (4). Final study results will be submitted in the 2012 Annual Report.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>MM/DD/YYYY</u>
Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
Final Report Submission Date:	<u>MM/DD/YYYY</u>
Other: 2012 Annual Report.	<u>MM/DD/YYYY</u>

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

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

The issue involves investigating and confirming the product stability over in-process hold time. Data provided to support stability of product during the in-process hold times only included data from a single lot. Therefore, additional data needs to be generated to confirm the hold times are appropriate.

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

Data provided to support biochemical stability during the in-process hold times only included data from a single lot. In addition, the SDS-PAGE method used during the in-process stability study was not qualified for assessment of percent purity. Therefore, BMS was asked to confirm the in-process hold times using two additional lots and a more complete set of analytical assays.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Assessment of product stability during in-process hold times and this will add to product quality information.
-

Agreed upon:

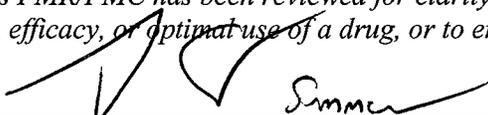
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: MM/DD/YYYY
Other: 2013 Annual Report. MM/DD/YYYY

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

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

An assessment of release and stability specifications requires long-term data. This is a standard post-approval assessment that needs to be done as part of the life cycle approach to manufacturing.

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

An assessment of specification is part of the normal ^{(b) (4)} manufacturing. There are generally a limited number of lots available at the time of licensure and having firms reassess specifications after more lots have been produced ensures they are appropriate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

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

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: 2013 Annual Report.	<u>MM/DD/YYYY</u>

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

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

To confirm available scale-down chromatography column lifetime study results at commercial-scale requires long term subsequent production campaigns and this is not feasible prior to approval.

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

BMS provided small scale study data to support the lifetime limits for the CEX, AEX, and HA chromatography resins. BMS also provided the protocol for commercial-scale resin lifetime studies and committed to perform the studies according to this protocol in upcoming production campaigns to confirm the scale-down resin lifetime study results.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Chromatography column life studies to achieve optimal purification process and product quality
-

Agreed upon:

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

Other

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1. To develop and validate a semi-quantitative assay to evaluate visible particulates in drug product. The assay will be incorporated into the drug product release and stability testing programs. The final validation report with the specifications and method validation will be submitted as a CBE-30 by May 30, 2011.

PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: MM/DD/YYYY
Other: CBE-30 05/30/2011

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

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

This PMC involves the development of a new product release and stability method. It was not feasible to have this method developed and validated prior to approval of the BLA.

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

Drug substance and drug product release and stability data indicates that visible particles may be present in this product. Currently the level of visible particulates is controlled using non-quantitative, descriptive acceptance criteria. Therefore, a validated semi-quantitative assay method which can accurately quantitative the number of visible particulates is needed. Such an assay will provide a more accurate level of control over the presence of visible particles in ipilimumab drug product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Development and validation of a product release assay
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

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

PMC #1 Description: To re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4) sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>03/2013</u>
	Other:	<u>MM/YYYY</u>

PMC #2 Description: Develop and implement a container closure integrity test to replace the sterility test in the stability program. The ability of a container closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf-life should be demonstrated. Submit the summary report and data in a CBE-0 supplement by December 2011.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>12/2011</u>
	Other:	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 506(B) OR WILL BE PUBLICLY REPORTABLE**

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

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

1. The applicant set the bioburden action limits for the process prior to manufacture of the process validation lots. Bioburden data for (b) (4) were submitted in the BLA. The applicant stated that the limits would be re-assessed after data from (b) (4) become available. Therefore, this is not a pre-approval requirement.

2. It is recommended that a container closure integrity test be developed and implemented to replace the sterility test for samples on stability. Container closure integrity maintenance during product shelf-life is more indicative of sterility than results obtained from sterility testing.

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

1. The applicant set the bioburden action limits for the process prior to manufacture of the process validation lots. Bioburden data for (b) (4) were submitted in the BLA. The applicant stated that the limits would be re-assessed after data from (b) (4) become available. However, these tests were performed (b) (4). A (b) (4) sample volume should be tested to improve the sensitivity of the test method. The bioburden data obtained from (b) (4) sample volume should be re-assessed. The bioburden action limits for all (b) (4) based on the commercial scale data using a (b) (4) sample volume should be reported in a CBE-0 supplement by March 31, 2013.

2. Develop and implement a container closure integrity test to replace the sterility test in the stability program. Container closure system should be demonstrated to be capable of maintaining the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf-life. Summary validation data should be submitted in a CBE-0 as a PMC by December 2011.

3. [OMIT—for PMRs only]

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

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

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

Describe the Agreed upon study:

BMS commits to re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4) sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013

BMS commits to develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December 31, 2011. This change will be submitted as a CBE-0.

5. To be completed by ONDQA/OBP/BMT Manager:

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

PMR/PMC Development Coordinator:

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

Summer

(signature line for BLAs only)

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

Date: February 28, 2011

Application Type/Number: BLA 125377

Through: Todd Bridges, RPh, Team Leader *T.B. Bridges 2/28/11*
Carol Holquist, RPh, Director *Carol Holquist 2/28/11*
Division of Medication Error Prevention and Analysis
(DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator *JAS 2/28/11*
Division of Medication Error Prevention and Analysis
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Yervoy (Ipilimumab) Injection,
50 mg/10 mL and 200 mg/40 mL

Applicant: Bristol-Myers Squibb Company

OSE RCM #: 2010-1476

INTRODUCTION

This review evaluates the proposed Yervoy insert labeling submitted by the Applicant on June 25, 2010 and container labels and carton labeling submitted January 20, 2011, for their vulnerability to contribute to medication errors.

1 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) and lessons learned from postmarketing experience to evaluate the insert labeling submitted by the Applicant on June 25, 2010 and container labels and carton labeling submitted by the Applicant on January 20, 2011 (see Appendices A and B, no image of insert labeling).

Our review noted the following deficiencies:

- Instructions for preparation and administration of Yervoy require revision to improve organization, prevent intravenous bolus administration, and prevent rapid intravenous infusion.
- Information on the container label and carton labeling requires relocation and deletion to avoid crowding and provide room for more important information.

2 RECOMMENDATIONS

Our evaluation identified areas of needed improvement in order to minimize the potential for medication errors for this product. DMEPA participated in the labeling meetings with Division of Biologic Oncology Products (DBOP) on October 1, 2010 and February 11, 2011. During these meetings, DMEPA presented our recommendations for the insert labeling with respect to undiluted Yervoy because we anticipated these instructions would lead to administration errors (see Appendix C). DBOP incorporated our recommendations into the insert labeling prior to sending it to the Applicant on February 11, 2011. We provide recommendations to the insert labeling based on the Applicant's revisions, submitted February 18, 2011, in Section 2.1, *Comments to the Division*. Section 2.2, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Sue Kang, OSE project manager, at 301-796-4216.

2.1 COMMENTS TO THE DIVISION

Our evaluation of the preparation and administration instructions identified an increased risk of rapid intravenous infusion of Yervoy. (b) (4)

(b) (4)

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

(b) (4) Thus,

we recommend a concentration range of 1 mg/mL to 2 mg/mL for the final solution to decrease variability in preparation of Yervoy and decrease the likelihood of calculations errors.

2.2 COMMENTS TO THE APPLICANT

Our evaluation identified areas of needed improvement in order to minimize the potential for medication errors for this product. Information on the container labels and carton labeling requires relocation and deletion to avoid crowding and provide room for more important information. We request you revise the following.

A. General Comments from Container Labels and Carton Labeling, 50 mg/10 mL and 200 mg/40 mL vials

- 1. Revise the statement, (b) (4) to read:

Single-Use Vial - Discard Unused Portion

- 2. Relocate the statement, *Single-Use Vial - Discard Unused Portion*, to appear below the route of administration, *For Intravenous Infusion*.
- 3. Delete the box that surrounds the Rx only statement.
- 4. Increase the font size and weight of *injection* to match the font size and weight of the *ipilimumab*.
- 5. Relocate the route of administration, *For Intravenous Infusion*, to appear below the strength. Thus, the proprietary and established name, strength, and route of administration will appear as:

Yervoy
(ipilimumab)
injection

xx mg/xx mL
(x mg/mL)

For Intravenous Infusion

B. Container Labels, 50 mg/10 mL and 200 mg/40 mL vials

Delete the statement, (b) (4)

(b) (4) and replace with the following:

See package insert for full prescribing information and instructions for preparation and administration.

C. Carton Labeling, 50 mg/10 mL and 200 mg/40 mL vials

(b) (4)



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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125377/0

Name of Drug: Yervoy™ (ipilimumab)

Sponsor: Bristol Myers Squibb

Material Reviewed: Yervoy™ (ipilimumab)
Carton and Container Labels
Prescribing Information

Submission Date: June 25, 2010, October 12, 2010, January 20, 2011

EXECUTIVE SUMMARY

The carton and container labels for Yervoy™ (ipilimumab) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 2/1/11-5/1/11, USP 34/NF 29. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background

STN 125377/0 for ipilimumab is an original Biologic License Application (BLA) indicated for the treatment of advance melanoma in patients who have received prior therapy. The product is available as a sterile solution in 50 mg/10 mL and 200 mg/40 mL single-use vials.

Labels Reviewed:

Yervoy™ (ipilimumab) Container Labels
Vial labels-50 mg/10 mL and 200 mg/ 40 mL

Yervoy™ (ipilimumab) Carton Labels
Single vial- 50 mg/10 mL and 200 mg/ 40 mL

Start of Sponsor Material

Vial Labels –January 20, 2011

(b) (4)



End of Sponsor Material

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name (established name) of the product, ipilimumab– is displayed along with the Tradename (proprietary name), Yervoy™. This conforms to the regulation.
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. “Manufactured by: Bristol Myers Squibb Company
Princeton, NJ 08543 USA

License No. 1713” is listed. This conforms to the regulation.

- c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.
 - d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.
 - e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial. This regulation does not apply.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A medication guide is required and appears on the carton label. Due to the size of the label, the statement is located on the carton. This conforms to the regulation.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This regulation does not apply.
 3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – The container bears a full label. This regulation does not apply.
 4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted,

provided the container is placed in a package which bears all the items required for a package label. – The container bears a label. This regulation does not apply.

5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per the assigned Division of Monoclonal Antibodies reviewers.
-
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1 configuration. This conforms to the regulation.
 - C. 21 CFR 201.5 Drugs; adequate directions for use – A reference to the prescribing information is not listed on the container label. This does not conform to the regulation. Recommend adding, “See package insert.”
 - D. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), Yervoy™ and the proper name (established name), ipilimumab. This conforms to the regulation.
 - E. 21 CFR 201.10 Drugs; statement of ingredients – The placement and prominence of the proper name (established name) and Tradename (proprietary name) are appropriate. This conforms to the regulation.
 - F. 21 CFR 201.15 Drugs; prominence of required label statements – This conforms to the regulation.
 - G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot number. This conforms to 21 CFR 610.60 and 21 CFR 201.17.
 - H. 21 CFR 201.25 Bar code label requirements – A bar code placeholder is located on the label. This conforms to the regulation.
 - I. 21 CFR 201.50 Statement of identity – The proper name (established name), ipilimumab is stated on the label with the tradename (proprietary name), Yervoy™. This conforms to the regulation.
 - J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared, “50 mg/10 mL” and “200 mg/40 mL”. This conforms to the regulation.

- K. 21 CFR 201.55 Statement of dosage – There is no statement listed on the label. This does not conform to the regulation. Add “See package insert”
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only” and other pertinent information. However, the label does not conform to 21 CFR 201.55. This does not conform to the regulation.



(b) (4)



II. Carton

A. 21 CFR 610.61 Carton/Package Label –

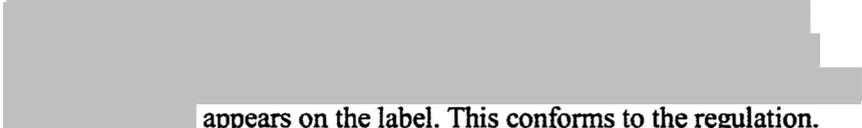
- a. The proper name (established name) of the product (ipilimumab) – is displayed along with the (proprietary name), Yervoy™. This conforms to the regulation.
- b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. “Manufactured by: Bristol-Myers Squibb Company, Princeton Company, NJ 08543 USA, License No 1713” is listed on the side panel of the carton. This conforms to the regulation.

- c. The lot number or other lot identification – There is no placeholder for the lot number on the carton label. This does not conform to the regulation.
- d. The expiration date – There is no placeholder for the expiration date on the carton. This does not conform to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the carton with the content listing. This conforms to the regulation.
- f. The number of containers, if more than one –The product is supplied in a single-use vial. This conforms to the regulation.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as 50 mg/10 mL or 200 mg/40 mL. This conforms to the regulation.
- h. The recommended storage temperature – The statement “Refrigerate at 2°C to 8°C (36°F to 46°F) is displayed on the side panel of the carton. This conforms to the regulation.
- i. The words “Do not Freeze or shake.”, “Protect from light.” or the equivalent, as well as other instructions, when indicated by the character of the product –This conforms to the regulation.
- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –Single-use vial. This regulation does not apply.
- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For intravenous infusion” is located above the strength presentation. This conforms to the regulation.

- l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed. This conforms to the regulation.
- m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.
- n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. The inactive ingredients are listed on the side panel of the carton, in alphabetical order. This conforms to the regulation.
- o. The adjuvant, if present –none listed. This conforms to the regulation.
- p. The source of the product when a factor in safe administration –none listed. This conforms to the regulation.
- q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – none listed. This conforms to the regulation.
- r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” – “No U.S. Standard of Potency” is not displayed on the carton. This does not conform to the regulation.
- s. The statement “Rx only” for prescription biologicals – The statement “Rx only” is located on the carton. This conforms to the regulation.
- t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – The statement, “DISPENSE THE ENCLOSED MEDICATION GUIDE TO EACH PATIENT” is listed on

the primary panel of the carton label. This conforms to the regulation.

- B. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This product is a "specified" biological product and is exempt from this regulation. This regulation does not apply.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – This regulation does not apply.
- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. This conforms to the regulation.
- E. 21 CFR 610.65 Products for export – This product will be distributed in the US. This regulation does not apply.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – A bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC configuration appears as, "NDC 0003-2327-11" on the 50 mg/10 mL and "NDC 0003-2328-22" on the 200 mg/ 40 mL. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "Dosage and Administration: Administer through an intravenous line containing a sterile, non-pyrogenic, low-protein binding in-line filter. See package insert for full prescribing information and instructions for preparation and administration. This conforms to the regulation.
- I. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), Yervoy and the proper name (established name), ipilimumab. This conforms to the regulation.

- J. 21 CFR 201.10 Drugs; statement of ingredients – The placement and prominence of the proper name (established name) ipilimumab and Tradename (proprietary name) Yervoy are appropriate. This conforms to the regulation.
- K. 21 CFR 201.15 Drugs; prominence of required label statements – Required statements appear with appropriate prominence, however the graphic attached to the proprietary name is obscuring. This does not conform to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date does not appear on the label. This does not conform to 21 CFR 610.61 and 21 CFR 201.17.
- M. 21 CFR 201.25 Bar code label requirements – A bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The proper name (established name), ipilimumab is stated on the label with the tradename (proprietary name), Yervoy. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared, “50 mg/10 mL” and “200 mg/40 mL”. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage –The statement (b) (4)

appears on the label. This conforms to the regulation. Recommend removing the descriptive text and retaining the statement, “See package insert for dosage, preparation and administration.”
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements “Rx Only” and other pertinent information. However, the label does not conform to 21 CFR 201.15. This does not conform to the regulation.

Conclusions

The following deficiencies and recommendations were noted in the review of the Yervoy™ container and carton labels.

1. Container
 - a. Per 21 CFR 201.5 and 21 CFR 201.55 please add the statement, “See package insert for dosage and administration.”

- b. Under the "Contents: please remove the statement, [REDACTED] (b) (4)

*The following information is not required for a full container label and may be removed or modified to permit the addition of required statements. "No preservative." [REDACTED] (b) (4)

2. Carton

- a. Per 21 CFR 610.61(r), please add the statement, "No U.S. Standard of Potency."
- b. Per 21 CFR 610.61 and 21 CFR 201.7, please add the lot number and expiration date to the carton labels.
- c. Per 21 CFR 201.15, please remove the obscuring graphic adjacent to the primary presentation of the Trade name. The graphic decreases readability.

3. Container and Carton

- a. Please move the "Single-Use Vial" statement and remove the volume, (XX mL) statement located below the NDC presentation to prevent crowding and provide increased visibility of the NDC number.
*See recommended format
- b. Please consider revising the presentation of the tradename, proper name, dosage form, strength, and route of administration to the following format:
*Recommended format

Yervoy™
(ipilimumab)
Injection

XX mg/ mL
(X mg/ mL)

For Intravenous Infusion Only

*Single-use vial; Discard unused portion

(b) (6)

2/23/11

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

(b) (6)

2/23/11

for

Subramanian Muthukkumar, Ph.D.
Product Reviewer
Division of Monoclonal Antibodies
CDER/OPS/OBP

(b) (6)

Patrick Swann, Ph.D.
Deputy Director
Division of Monoclonal Antibodies
CDER/OPS/OBP

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: February 08, 2011

To: Patricia Keegan, MD, Director
Division of Biologic Oncology Products (DBOP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Patient Labeling Reviewer, Acting Team Leader *LaShawn Griffiths* 2/8/11
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN *Barbara Fuller* 2/8/11
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer *Steve Morin* 2/8/11
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): YERVOY (ipilimumab)

Dosage Form and Route: Injection for intravenous use

Therapeutic Class: Human cytotoxic T-lymphocyte antigen-4 (CTLA-4) blocking monoclonal antibody

Application Type/Number: BLA 125377

Applicant: Bristol-Myers Squibb Company

OSE RCM #: 2010-1503

1 INTRODUCTION

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG). Bristol-Myers Squibb submitted Biologic License Application (BLA) 125377 for YERVOY (ipilimumab) injection for intravenous use on June 25, 2010. YERVOY (ipilimumab) is a human cytotoxic T-lymphocyte antigen-4 (CTLA-4) blocking antibody indicated for the treatment of unresectable or metastatic melanoma.

DRISK's review of the Interim REMS Review was sent to DBOP under separate cover dated December 13, 2010

2 MATERIAL REVIEWED

- Draft YERVOY (ipilimumab) injection for intravenous use Medication Guide (MG) received on June 25, 2010 and revised by the review division throughout the review cycle and submitted to DRISK on January 25, 2011.
- Draft YERVOY (ipilimumab) injection for intravenous use Prescribing Information (PI) received June 25, 2010, revised by the Review Division throughout the current review cycle and submitted to DRISK on January 25, 2011

3 REVIEW METHODS

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

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

In our review of the MG we have:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

Division of Drug Marketing,
Advertising, and Communications

Internal Consult

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

To: Erik Laughner, Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications, CDER

Carole C. Broadnax 2/8/11
Kendra Jones 2/8/11

Date: February 8, 2011

Re: **Yervoy (ipilimumab) Injection, for intravenous infusion**
STN BL 125377/0
DDMAC Comments on proposed labeling

In response to the Division of Biologic Oncology Products' (DBOP) July 13, 2010, consult request, DDMAC has reviewed proposed labeling (PI, Medication Guide, carton and container/vial) for Yervoy (ipilimumab). DDMAC's comments are based on the draft marked-up labeling that DBOP sent via email dated January 25, 2011, to DDMAC. The carton and container/vial labeling used in this review can be found in the original application (amendment 46) at: \\cber-fs3\m\CTD_Submissions\STN125377\125377.enx.

DDMAC's comments for the PI and Medication Guide are provided directly in the attached document. Please note that for the PI we hid most of DBOP's comments to BMS and DBOP's deletions and formatting changes so that our comments are easier to read.

DDMAC does not have comments for the carton and container/vial labeling at this time.

DDMAC did not review the business card that was included with Bristol-Myers Squibb's (BMS) January 20, 2011, submission. Per your February 7, 2011, email attachment, BMS states, "The business card label is an information card that directs a health care provider to sources of additional information should they have any questions about YERVOY. Specifically, it directs a health care provider

to either the BMS toll free telephone number for the BMS medical information department or the product website. BMS strives to ensure anyone with a question on this product has access to a resource that can provide the answer.” Per your February 8, 2011, email attachment, BMS states that “The business card is included with every vial of YERVOY and is intended as a resource for the pharmacist, nurse or other healthcare professional who will be opening the YERVOY packaging.” The business card should be classified as promotional labeling. BMS should be reminded that FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product’s current professional labeling. Therefore, BMS should be reminded that the final version of the business card should be submitted to DDMAC on Form FDA-2253 at the time of initial dissemination. Alternatively, BMS may pre-submit a voluntary request to DDMAC for advisory comments on the business card.

Thank you for your consult. If you have any questions regarding the PI or the carton/container/vial labeling, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Labeling Review

Date: December 13, 2010 **Date Consulted:** September 22, 2010

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, M.D.
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

signing for Dr. Sahin + myself
[Signature] 12/21/10

Lisa Mathis, M.D. *[Signature]* 12/21/2010
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Biologic Oncology Products

Drug: Yervoy (ipilimumab); BLA 125377/0

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Yervoy labeling.

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On June 25th, 2010, Bristol-Myers Squibb submitted a biologic license application (BLA) to the Division of Biologic Oncology Products (DBOP) for Yervoy, which is a cytotoxic T-lymphocyte blocking monoclonal antibody. The sponsor's proposed indication for Yervoy is for treatment of advanced melanoma (unresectable stage III and IV) in patients who have had prior therapy.

On September 22, 2010, DBOP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Yervoy package insert, and provide comment. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Yervoy labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of Yervoy labeling.

SUBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)

8.1 Pregnancy

(b) (4)

8.3 Nursing Mothers

(b) (4)

Medication Guide

(b) (4)

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the final rule is being written and cleared, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

MHT discussed with the Division whether Yervoy should be labeled pregnancy category C based on developmental toxicology findings in animal studies or whether it should be labeled as a pregnancy category D, based on its “cytotoxic” mechanism of action. While most traditionally cytotoxic chemotherapeutic drugs are labeled with a pregnancy category D based on mechanism of action, the Division felt that Yervoy should not be labeled pregnancy category D, as its

mechanism of action differs from other cytotoxic agents, in that its cytotoxic activity is specific to blocking the T- lymphocyte.

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling, which were discussed at the labeling meeting with the Division on November 16, 2010. Recommendations from the toxicology reviewers Dr. Andrew McDougal and Dr. Anne Pilaro are included.

Highlights of Prescribing Information:

(b) (4)

(b) (4)

8.3 Nursing Mothers

(b) (4)

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

Medication Guide

(b) (4)

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 1, 2010

TO: Erik Laughner, Regulatory Project Manager
Kaushikkumar Shastri, Medical Officer
Division of Biologic Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125377/0

APPLICANT: Bristol-Myers Squibb Company

DRUG: Ipilimumab (BMS-734016/MDX-010)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: The treatment of advanced melanoma in patients who have received prior therapy.

CONSULTATION REQUEST DATE: 7/9/2010

DIVISION ACTION GOAL DATE: 11/24/2010

PDUFA DATE: 12/24/2010

I. BACKGROUND:

Bristol-Myers Squibb Company (BMS) seeks licensure to market ipilimumab, a fully human monoclonal immunoglobulin (IgG1 κ) for the treatment of advanced melanoma in patients who have received prior therapy. Ipilimumab binds specifically to the cytotoxic T-lymphocyte antigen 4 (CTLA-4; CD152) expressed on a subset of human T cells. The interaction of CTLA-4 with its natural ligands, CD80/CD86, expressed on antigen-presenting cells results in an inhibitory signal for T-cell activation. The proposed mechanism of action of ipilimumab is interference with this CTLA-4/CD80/CD86 interaction, allowing potentiation of the T-cell response.

The application is supported primarily by data from a pivotal study entitled, "A Randomized, Double-Blind, Multicenter Study Comparing MDX-010 Monotherapy, MDS-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201 Positive Patients with Previously Treated Unresectable Stage III or Stage IV Melanoma," sponsored by BMS. This pivotal study was targeted for inspection. Of the 1783 subjects who enrolled and were screened for study participation, a total of 676 subjects were randomized at 125 study centers in Europe, North America, South America, and Africa. This study was conducted under IND 9186.

Four clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Steven O'Day (site number 001), Dr. Robert Weber (site number 004), Dr. Frank Hodi (site number 167), and Dr. Jeffrey Sosman (site number 301). These sites were selected because they were the 4 highest enrolling sites in the pivotal study. Prior to inspections, there were no site-specific concerns. In addition, the Study Sponsor, BMS, was inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI 1: Site #001 Dr. Steven O'Day The Angeles Clinic and Research Institute 11818 Wilshire Boulevard Suite 200 Los Angeles, CA 90025	Protocol: MDX010-20 Site Number: 001 Number of Subjects: 28	9/14/2010 - 9/20/2010	Pending Interim classification: NAI
CI 2: Site #004 Dr. Robert Weber Northern California Melanoma Center St. Mary's Medical Center 450 Stanyan Street, Sixth Floor San Francisco, CA 94117	Protocol: MDX010-20 Site Number: 004 Number of Subjects: 24	9/27/2010 10/5/2010	Pending Interim classification: NAI

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI 3: Site #167 Dr. Frank Stephen Hodi Beth Israel Dec Medical Center 330 Brookline Avenue Boston, MA 02115	Protocol: MDX010-20 Site Number: 167 Number of Subjects: 28	8/30/2010 - 9/9/2010	VAI (Final correspondence to CI pending)
CI 4: Site #301 Dr. Jeffrey Sosman Vanderbilt University Medical Center 777 Preston Research Building Nashville, TN 37232-6307	Protocol: MDX010-20 Site Number: 301 Number of Subjects: 19	9/29/2010 – 10/27/2010	Pending Interim Classification: OAI
Sponsor: Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492-7660	Protocol: MDX010-20 Sites: #001, 004, 167, 301	8/25/2010 – 9/14/2010	Pending Interim Classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 and/or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.**1. CI#1: Dr. Steven O'Day**

(Site Number 001)

The Angeles Clinic and Research Institute

11818 Wilshire Boulevard

Suite 200

Los Angeles, CA 90025

- a. What was inspected:** The site screened 34 subjects, 20 of those were randomized and treated and 16 subjects completed the study. The study records of 8 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable against source records at the site. There was no evidence of under-reporting of AEs. The study was found to be well controlled and well documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125377. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Steven O'Day's site, associated with Study MDX010-20 submitted to the Agency in support of BLA 125377, appear reliable based on available information.

2. CI#2: Dr. Robert Weber

(Site Number 004)

Northern California Melanoma Center

St. Mary's Medical Center

450 Stanyan Street, Sixth Floor

San Francisco, CA 94117

- a. What was inspected:** The site screened 36 subjects, 24 of those were randomized and treated. The study records of 14 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable against source records at the site. There was no evidence of under-reporting of AEs. The study was found to be well controlled and well documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements

with that reported by the sponsor to the agency in BLA 125377. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. Weber's site, associated with Study MDX010-20 submitted to the Agency in support of BLA 125377, appear reliable based on available information.

3. CI #3: Dr. Frank Stephen Hodi

(Site Number 167)

Beth Israel Dec Medical Center

330 Brookline Avenue

Boston, MA 02115

- a. **What was inspected:** The site screened 42 subjects, 28 of those were randomized and 27 subjects completed the study, 1 subject (0277) withdrew consent prior to treatment initiation to pursue another course of treatment. The study records of 28 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. Records were reviewed to verify the following: protocol adherence, informed consent procedures, subject eligibility, AE detection and reporting, subject randomization, handling of laboratory specimens, accuracy of data listings submitted to the BLA 125377 compared to supporting documentation found at the site, and the presence of completed laboratory records among the source documents to verify clinical laboratory testing.
- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable against source records at the site. There was no evidence of under-reporting AEs. Test article accountability records were reviewed without objectionable observation. The study was found to be well controlled and well documented.

There was a minor discrepancy found between the source documents and the data listings taken from the BLA submission, specifically, an AE reported by the clinical investigator on the CRF was not included in the data listings. Briefly, Subject 0056 had a reported AE of "tender mass on left skull", which was not included in the data listings provided in the BLA 125377 submission.

***DSI Reviewer's Note:** Regarding Subject 0056, the AE as recorded in the subject's CRF was for tender mass on left skull, and appears to have a start date of March 28, 2005 and no end date. The CI considered the event as unrelated to study drugs, with no action taken, and outcome listed as "continuing." It is unclear from the available information why this AE was not included on BLA listings, but this appears to be an isolated event and not reflective of a systemic issue with BLA listings.*

The FDA field investigator noted that there were several revisions of the informed consent document approved during the course of the study; however, not all subjects were properly re-consented with the updated version(s) of the informed consent document prior to study treatment administration. Briefly, Subjects 0076, 0426, 0462, and 1304 each received study treatment but had not signed an updated informed consent document. The FDA field investigator further noted that the site had become aware, prior to the current inspection, of the issue of not re-consenting subjects when required and had already taken corrective actions to minimize reoccurrences. The site was observed to have taken steps to implement an informed consent tracking system to document within each subject's chart the current and required informed consent document for that particular study, to be updated each time a new requirement is implemented. For this reason the field investigator chose to not list the inspection observation on a Form FDA 483. Finally, the FDA investigator found that not all SAEs were reported to the sponsor within 24 hours of the site becoming aware of the event, as required in the protocol. The protocol states that each SAE must be reported to the sponsor [Medarex, Inc.] within 24 hours of learning of its occurrence. The site was lacking documentation to show that the following SAEs were reported to the sponsor in accordance with the protocol:

1. Subject 0429 had an SAE, leptomenigeal disease, with onset dated January 22, 2008, but was not reported to the sponsor until June 12 2008.
2. Subject 0402 had an SAE, dehydration and weakness, with onset dated May 16, 2007, but was not reported to the sponsor until June 21, 2007.
3. Subject 0057 had an SAE, shortness of breath and atrial fibrillation with rapid ventricular response, with onset dated May 17, 2005, but was not reported to the sponsor until June 2, 2005.
4. Subject 0076 had an SAE, DVT of right popliteal vein and brain disease progression, with onset dated April 19, 2005, but was not reported to the sponsor until April 26, 2005.
5. Subject 0057 had an SAE, atrial fibrillation with rapid ventricular response, with onset dated April 26, 2005, but was not reported to the sponsor until May 3, 2005.
6. Subject 0425 had an SAE, acute renal insufficiency and hypercalcemia, with onset dated June 5, 2007, but was not reported to the sponsor until June 18, 2007.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125377. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

Specifically, per the protocol, Serious Adverse Events were to be reported to the

Sponsor within 24 hours of the site becoming aware of the event. Six Serious Adverse Events were found to have been reported to the Sponsor after the 24 hour requirement.

- c. **Assessment of data integrity:** Notwithstanding the regulatory violations noted above, overall primary efficacy and safety data for Dr. Hodi's site, associated with Study MDX010-20 submitted to the Agency in support of BLA 125377, appear reliable based on available information.

4. CI#4: Dr. Jeffrey Sosman

(Site Number 301)

Vanderbilt University Medical Center

777 Preston Research Building

Nashville, TN 37232-6307

- a. **What was inspected:** The site screened 24 subjects, 19 of those were randomized and treated, and 4 subjects completed the study. The study records of 19 subjects were audited for compliance with inclusion criteria and informed consent, and 14 of those were selected for complete audit in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol, and all 19 subjects' pharmacy records. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR

- b. **General observations/commentary:** Overall the investigator's execution of the protocol was found to be inadequate. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and assessed their treatment regimens. While the primary efficacy endpoint data of overall survival were verifiable against source documents found at the site the totality of protocol deviations and deficient record keeping practices calls into question the overall efficacy and safety data generated by this site. The inspection revealed multiple protocol deviations and inadequate recordkeeping. There were two instances where a sub-investigator apparently retrospectively changed a subject's (Subject #0435) ECOG score from a score of 2 on two study visits, which occurred shortly after screening, to a score of 0 and 1, respectively. The same subject had an ECOG score of 2 at screening, therefore, this subject was ineligible at screening and should not have been randomized into the study. It is unclear what the intent was on the part of the sub-investigator in changing ECOG scores in the source records months after the relevant study visits. Subject #1270 also did not meet entry criteria in that this subject had received chemotherapeutic treatment within 28 days of randomization and treatment on study.

Consistent with the routine clinical investigator compliance program assessments, the inspection assessed data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125377. A Form FDA 483 was issued to the clinical investigator citing 4 inspectional observations. The following is a summary of findings listed in the Form FDA 483 inspectional observations for Dr. Sosman's site.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

Specifically, the principal investigator failed to personally conduct or supervise the investigation in accordance with the protocol in that:

A. Investigator failed to ensure that all subjects met all inclusion criteria. Two of nineteen subjects reviewed were ineligible for the study.

1. Subject 1270 was treated with a chemotherapeutic drug until 06/10/08. Subject started treatment on this study on 06/30/08 which is prior to the 28 day inclusion criteria. This subject was ineligible at the time of randomization.
2. Subject 0435 did not meet inclusion criteria #10, which states in the protocol that the subject must have an "ECOG performance status of 0 or 1." Subject 0435 was Randomized on 07/23/08. A sub-investigator originally gave the subject an ECOG score of 2 and then went back and amended 2 of the 3 scores to a 1 or a 0. The subject should not have been allowed in the study based on the ECOG score of 2.

B. Of the fourteen subjects reviewed for adverse events and study drug administration, one subject received treatment before an adverse event improved to less than or equal to a grade 1 severity.

Subject 0336 was seen on 10/26/06, which was documented as Day 64, Visit 5. Subject's adverse events listing had the subject documented as experiencing diarrhea, Grade 2, and "Probable" in relation to study drug since 10/19/06. The Protocol states that in patients with a non-skin-related immune mediated toxicity of Grade 2 severity...., additional treatment will be delayed until the event improves to less than or equal to Grade 1 severity. The subject received treatment without documented resolution of the grade 2 diarrhea.

C. Failure to report a serious adverse event to the Sponsor within 24 hours per protocol.

Subject 0195 was admitted to the hospital on 03/31/06 due to a serious adverse event, diarrhea (grade 2), which was listed as "probably" caused by the investigational drug. The Investigator was aware of the event on 03/31/06 but did not notify the Sponsor until 04/05/06.

D. Failure to ensure that vaccine injections were administered prior to their three hour expiration time.

Subject 0336 - On 09/12/06, "Day 22, Visit 3" - a pharmacy vaccine sticker had an expiration time documented as "1530". The nurse noted that at 16:00 the injections were given per protocol. The infusion record ends at 15:50. This subject was given expired vaccine injections.

E. The Investigator failed to ensure that vital signs were taken from nine of the fourteen subjects reviewed at the required times per protocol.

Subjects 0336, 0432, 0435, 0195, 0212, 0240, 0255, 0508, and 0311 were missing one or more protocol-specified vital signs.

F. The Investigator failed to ensure that six of fourteen subjects reviewed had the Erythrocyte Sedimentation Rate taken per protocol.

Subjects 0336, 0195, 0255, 0331, 0338, and 0263 failed to have one or more protocol-specified Erythrocyte Sedimentation Rate done per protocol.

G. The Investigator failed to ensure that five of the fourteen subjects reviewed had the TSH laboratory test done per protocol.

Subjects 0336, 0509, 0195, 0338 and 0263 failed to have one or more protocol-specified TSH tests done per protocol.

H. The Investigator failed to ensure that five of the fourteen subjects reviewed had the Urinalysis lab test per protocol.

Subjects 0336, 0509, 0195, 0311 and 0263 failed to have one or more protocol-specified Urinalysis tests done per protocol.

I. The Investigator failed to ensure that four of the fourteen subjects reviewed had the HAHA lab test done per protocol.

Subjects 0336, 0195, 0212 and 0263 failed to have one or more protocol-specified HAHA tests done per protocol.

J. The Investigator failed to ensure that a physical exam was done on three of the fourteen subjects reviewed.

Subjects 0195, 0509 and 0328 missed at least one protocol-specified PE per protocol.

K. The Investigator failed to ensure that four of the fourteen subjects reviewed had the Quality of Life Surveys completed per protocol.

Subjects 0336, 0195, 0212 and 0263 failed to have one or more protocol-specified QoL surveys completed per protocol.

L. There is no documentation that all abnormal laboratory results were reviewed prior to subjects receiving study medication per protocol. The protocol also states "If significant changes or abnormalities are noted, administration of study medication must be postponed so that appropriate workup and possible treatment can be implemented." For example,

1. Subject 0311

- Lab tests were performed on 07/10/06. Results were reported on 07/11/06. The documented review date of the abnormal labs by Dr. Sosman was 09/15/06 and indicates that a chemistry lab result was clinically significant. Subject 0311 received study medication on 07/18/06. The Treatment Room Assessment form which lists local lab results prior to medication administration, did not capture the abnormal results from the central lab.
- Lab tests were performed on 07/18/06. Results were reported on 07/29/06. The documented review date of the abnormal labs by Dr. Sosman was 09/15/06 and indicates that a chemistry lab result was clinically significant. Subject 0311 received study medication on 08/10/06. The Treatment Room Assessment form which lists local lab results prior to medication administration, did not capture the abnormal results from the central lab.

2. Subject 0255 had lab tests performed on 10/13/06. Results were reported on 10/18/06. The documented review date of the abnormal labs was 12/04/06. Subject received study medication on 11/02/06. The Treatment Room assessment form which lists local lab results prior to medication administration, did not capture the abnormal results from the central lab.

3. Subject 0195

- Lab tests were performed on 12/16/05. Results were reported on 12/19/05. The documented review date of the abnormal labs was 10/23/06. Subject 0195 received study medication on 01/17/06. The Treatment Room Assessment form which lists local lab results prior to medication administration, did not capture the abnormal results from the central lab.
- Lab tests were performed on 02/07/06. Results were reported on 02/09/06. The documented review date of the abnormal labs was 10/23/06. Subject 0195 received study medication on 03/14/06. The Treatment Room Assessment form which lists local lab results prior to medication administration, did not capture the abnormal results from the central lab.

M. There was no documentation that the breaking of the blind study was reported to the sponsor as soon as possible. Per protocol "the date, time, and reason for unblinding will be documented in the appropriate section of the CRF and in the source document; the fax copy received from the study site will be retained with the CRF."

Subject 0212 was unblinded on 03/23/06 due to physician request. No date, time, or reason for unblinding was documented in the CRF, and there was no faxed copy from the study site found to accompany the CRF.

Observation 2: Failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigation drug.

Specifically, Subject 0338 - On 11/30/06, subject had Grade 2 Diarrhea listed as "definitely related" to the study drug in the source documents. There is no documentation that this adverse event was reported to the sponsor.

Observation 3: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

A. Two subjects out of fifteen reviewed, do not have any documentation in their charts that the vaccine injections were actually administered immediately after infusion.

1. Subject 0195 does not have any documentation in their chart that the vaccine injections were actually administered on 03/14/06 after infusion of study drug.
2. Subject 1305 does not have any documentation in their chart that the vaccine injections were actually administered on 09/03/08 after infusion of study drug.

B. Pharmacy records contain incomplete or contradictory information regarding storage conditions of test articles.

1. The Investigational Drug Accountability Record for subject 0195 has contradictory information. It has a sticker indicating that the Vaccine or Vaccine Placebo should be stored at -30° to -10° C. The same form has another sticker on it that says "Keep in Refrigerator." The protocol states that the Vaccine or Vaccine Placebo should be stored at -30° to -10° C.
2. The Investigational Drug Accountability Record for subject 0195 has contradictory information. It has a sticker indicating that the Study Drug or Study Drug Placebo should be stored at 2° to 8° C. The same form has another sticker on it that says "Store at Room Temperature." The protocol states that the Study Drug or Study Drug Placebo should be stored at 2° to 8° C.
3. The Investigational Drug Accountability Record for subject 0212 has contradictory information. It has a sticker indicating that the Vaccine or Vaccine

- Placebo should be stored at -30° to -10° C. The same form has another sticker on it that says "Keep in Refrigerator." The protocol states that the Vaccine or Vaccine Placebo should be stored at -30° to -10° C.
4. The Investigational Drug Accountability Record for subject 0212 has contradictory information. It has a sticker indicating that the Study Drug or Study Drug Placebo should be stored at 2° to 8° C. The same form has another sticker on it that says "Store at Room Temperature." The protocol states that the Study Drug or Study Drug Placebo should be stored at 2° to 8° C.
 5. The only source documents to indicate vaccine preparation time and vaccine expiration time are the pharmacy injection labels. Per the protocol, the vaccine must be administered within 3 hours of preparation.
 - Out of the 19 subjects enrolled, pharmacy injection labels were available for only 8 subjects. Pharmacy injection labels for these 8 subjects covered a total of 24 days. Vaccine expiration times were recorded for 22 of these 24 days.
 - Vaccine preparation time was only recorded for one subject on one of these 24 days, 7/30/08 for subject 0435. No other vaccine preparation times are documented.
 - On 2/21/08 and 6/24/08, Subjects 1103 and 0432, respectively, did not have either vaccine preparation or expiration times recorded on their pharmacy injection labels.
 6. Test article receiving records are inadequate to establish if proper storage temperatures were maintained during shipment and upon receipt. Out of the 19 pharmacy records reviewed, subjects 0195, 0331, 0311, 0338, 0336, 0263, 0212, 0313, and 0328 all had missing "receipt verification" records.

C. Subjects had contradictory data in the source documents and/or the Case Report Forms (CRF's).

1. Subject 0255
 - The source documents list that the best overall response was "Stable Disease", but the CRF stated that the subject had "Progressive Disease." A query by the monitor corrected the discrepant data on the CRF.
 - On 11/02/06, "Day 64, Visit 5" - the CRF states that vital signs were not taken at the 90 minute infusion time. The source document for vital signs taken during the infusion state that vital signs were taken at the 90 minute time.
2. Subject 0195 - the source documents list that the best overall response was "Partial Response", but the CRF stated that the subject had "Progressive Disease." A query by the monitor corrected the discrepant data on the CRF.
3. Subject 0336 - On 09/12/06, Day 22, Visit 3, the source document shows that the start time vital signs were taken at 14:00. The infusion record states that the infusion actually started at 14:20. The CRF shows that the start time vital signs were at 14:20. The infusion time was documented as ending at 15:50. The source vital signs for the 150 minute time shows they were taken at 16:00. The CRF states that the 150 minute time vital signs were taken at 16:00.
4. Subject 0432 - the source document shows that the start time of the infusion was

- 14:05 on 06/02/08, Day 1, Visit 2. The CRF states that the infusion start time vital signs were taken at 13:50 on 06/02/08, Day 1, Visit 2.
5. Subject 0435 - the CRF for 07/16/08 was filled out incorrectly using vital signs taken from a visit dated on 07/30/08.
 6. Subject 0509 - the source documents indicate that the last dose of a chemotherapeutic drug treatment for the subject was completed on 10/30/07. The CRF states that the last dose of the chemotherapeutic drug was on 11/27/07. A query was asked by the monitor and it was answered incorrectly with a last treatment date of the chemotherapeutic drug on 11/15/07.
 7. Subject 1305 - the source documents indicate that the last dose of a chemotherapeutic drug treatment for the subject was completed on 06/17/08. The CRF states that the last dose of the chemotherapeutic drug treatment was on 07/09/08.

***DSI Reviewer's Note:** With respect to inspectional observations 3.C.1 and 3.C.2, it cannot be confirmed whether or not these are violations until the EIR is made available and reviewed. However, based on available information it appears that the respective data listings provided in the application are accurate.*

Observation 4: Unused supplies of an investigational drug were not returned to the sponsor and disposed of in accordance with sponsor instructions.

Specifically,

The protocol states that "All unused investigational products will be returned to the Sponsor at the closure of the study site or at an earlier time point if notified by the Sponsor." The Investigational Drug Accountability Records indicate that subjects 0195, 0331, 0311, 0212, 0240, 0508, and 1270 all had unused investigational products destroyed on site, not returned to the sponsor. There is no record of any unused investigational product being returned to the sponsor at any time during the study. There is also no documentation of when the product was destroyed, just a note stating that it had been destroyed.

***DSI Reviewer's Note:** DSI had numerous personal communications with the FDA field investigators while the inspection of Dr. Sosman was ongoing and at the conclusion of the inspection. The FDA field investigators indicated that after almost 4 weeks at the firm they still felt that they had by no means uncovered all deficiencies associated with this site's conduct of the study. Therefore, the deficiencies listed above and in the Form FDA 483 are not all inclusive of the deficient conduct of clinical research practiced by this site, but merely exemplar.*

DSI discussed the preliminary inspectional observations developing during the inspection of Dr. Sosman with DBOP representatives on several occasions prior to receipt of the Form FDA 483 for Dr. Sosman's site. At that time, it was suggested that the data from Dr. Sosman's site may be compromised given the extent of noncompliance with the investigational plan (eligibility criteria violations, issues with drug

accountability and storage conditions, missed safety data, etc.). As preliminary findings have raised a concern about overall data reliability from the site, DSI suggested that the review division conduct sensitivity analyses in which data from Dr. Sosman's site is removed to assess the impact on overall efficacy and safety conclusions and DBOP representatives agreed with this approach.

- c. Assessment of data integrity:** The data for Dr. Sosman's site, associated with Study MDX010-20 submitted to the Agency in support of BLA 125377, appear unreliable based on available information. This conclusion is based largely on the totality of protocol compliance violations, numerous missed protocol-specified periodic assessments, calling into question important safety assessments based on this data. In addition, there were inadequate drug storage and accountability records, calling into question how and when drug was prepared and administered and whether it was expired or not prior to use. As per previous discussions with the review division, based on DSI's review of preliminary findings provided by FDA field investigators, DSI recommends that data from Dr. Sosman's site not be used to support a regulatory decision.

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

5. Sponsor: Bristol-Myers Squibb Company

POC: Jessica A. Parchman

Executive Director of Global Quality and Regulatory Compliance

5 Research Parkway

Wallingford, CT 06492-7660

- a. What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study was conducted at 170 clinical sites and 133 sites enrolled subjects, in 15 Countries. The total number of subjects enrolled was 1783 and 676 subjects were randomized. During the inspection, the FDA investigator assessed records/files from 5 clinical sites, the 4 sites listed above plus one additional, randomly selected clinical site, that of Dr. Harriet Kluger, Site 171. Specifically, the inspection covered organization and personnel, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, QA, Adverse events/effects and reporting, data collection, data tabulations, test article integrity and accountability. In addition, primary efficacy endpoint data were assessed.

Note: The EIR was not available at the time this CIS was written. The EIR for the sponsor is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. Overall, site monitoring appeared adequate. The primary efficacy endpoint data were verifiable at the sponsor site for the 5 audited clinical sites. No objectionable conditions were noted. No Form FDA 483 was issued.

With respect to overall responsibilities of the study, MDX10-20, Medarex (MDX) was initially the study sponsor. The inspection found documentation that in November 2004 MDX and BMS engaged in a collaboration agreement that identified BMS as responsible for daily development activities of MDX-010, but that MDX remained the development lead for the study MDX10-20. MDX was initially responsible for study site qualification and initiation visits. Notably, monitoring responsibilities, as well as data management, were contracted by MDX to (b) (4)

DSI Reviewer's Note: Given the preliminary inspectional observations from Dr. Sosman's site, the FDA field investigators conducting the BMS inspection were directed by DSI to assess monitoring activities and actions by the sponsor related to the Sosman site. The FDA field investigators reported that they found no significant issues related to overall study monitoring. It remains unclear based on available information whether site monitoring was sufficient for Dr. Sosman's site to bring the site into compliance with the investigational plan. It is also unclear whether the study sponsor was aware of the site's poor conduct while the study was ongoing. While DSI and DBOP representatives considered the possibility of conducting additional inspections to further evaluate the application, DBOP indicated that they believe the current set of inspections are sufficient to inform decision making regarding approvability of the application. In anticipation of Dr. Sosman's data being deemed unreliable DBOP indicated that they planned to conduct sensitivity analyses in which data from Dr. Sosman's site are removed to evaluate the impact of his data on study conclusions.

During the conduct of this inspection the review division Medical Officer, Dr. Kaushikkumar Shastri, requested via email, dated September 2, 2010, that the FDA field investigators focus on the sequence of events, with respect to study (MDX10-20) database unblinding, that occurred sometime between enrollment stoppage on July 25, 2008 to October 30, 2009, when the sponsor states that the study was unblinded. Specifically, when did the data unblinding occur and who at BMS may have had access to the unblinded data?

Briefly, Dr. Shastri informed that BMS stopped subject enrollment in the study and changed the primary efficacy endpoint to overall survival, and notified the FDA of this decision on July 25, 2008. The protocol was revised on January 15, 2009, to include a new primary efficacy endpoint of overall survival. Based on sample size recalculation for the revised protocol it was determined that enrolled subjects in the study thus far were considered sufficient. With respect to the revised protocol, the statistical analysis plan was finalized and signed off on October 28, 2009, the clinical database was locked on October 29, 2009 and the data were unblinded on October 30, 2009.

Dr. Shastri noted that the survival probabilities assumption for the different treatment arms used in the sample size recalculation of the revised protocol, dated January 15, 2009, appear to closely match the actual survival observed in the unblinded data at that time, raising concerns as to when the unblinding of the data occurred and who at BMS had access to the unblinded data, if at all.

The FDA field investigator's findings follow. MDX and (b) (4) were responsible for sending/resolving data queries and verification. Per (b) (4) SOPs, the (b) (4) data manager locked the final study database and delivered it to MDX. The clinical database was reconciled with the safety database by MDX. Finally, the data quality assurance checklist was signed off by MDX on October 29, 2009. The MDX statistician unblinded the locked database on October 30, 2009.

The FDA investigators interviewed Dan McDonald, Study MDX10-20 Team Leader; Axel Hoos, M.D. Ph.D., the BMS Group Director/Medical Lead, Immunology/Oncology; and Tai Chen, Ph.D., BMS Global Biometric Science Lead for Ipilimumab. The FDA field investigators asked specifically whether BMS personnel had access to unblinded MDX10-20 data and if yes, then when. Mr. McDonald stated (corroborated by BMS managers) that site pharmacists could not be blinded because the active test articles were by nature distinguishable from the placebo/dummy articles due to viscosity of the peptide. Mr. McDonald further stated that the clinical research associates monitored both the site procedures and test article accountability/test article storage and thus needed access to the unblinded pharmacy log. That fact, that these site personnel were to be unblinded, is described in the protocol.

The FDA investigators interviewed Dr. Axel Hoos regarding the responsibilities of the MDX10-20 Study Data Management Committee (DMC) and what data were to them. Dr. Hoos stated that MDX contracted the members of the DMC to monitor study safety, conduct, and drop-out, in accordance with the protocol. He explained that the DMC was originally formed to monitor the MDX10-20 study, but as BMS initiated new studies of Ipilimumab, the DMC membership grew to accommodate all the studies. Each Ipilimumab study was monitored by the DMC according to its own DMC charter. According to Dr. Hoos, the DMC was given safety/survival data "semi-blinded" by Arms A, B, and C, in sealed envelopes by the independent consultants (b) (4) (b) (4), contracted by MDX) to review the AE and OS listings, primarily for safety. Dr. Hoos stated that it might be possible for the DMC to ascertain the active treatment arm given the 3:1:1 randomization. A review of the DMC charter (Medarex Protocol MDX010-20, dated July 1, 2004) clearly stated that the DMC will be provided data in an unblinded format. Dr. Hoos and Dr. Chen affirmed to the FDA field investigators that they never saw nor discussed the unblinded study data with the DMC members or anyone else before the data base lock. They stated they were not privy to the closed sessions of the DMC and that BMS personnel were never in possession of the closed session minutes. In general, the inspectional findings revealed no evidence that BMS or MDX personnel had inappropriate access to unblinded data from Study MDX010-20 prior to database unblinding that occurred on October 30, 2009.

- c. **Assessment of data integrity:** Based on a preliminary review of the inspectional findings the study appears to have been conducted adequately. The data generated at this site, as it pertains to Study MDX010-20 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor submitted to the agency as part and in support of BLA 125377 appear reliable.

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

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. O'Day, Dr. Weber, and Dr. Hodi and study sponsor Bristol-Myers Squibb Company the study data collected appear reliable. However, the preliminary inspectional findings for Dr. Sosman's site indicate that the data generated by this site are unreliable and DSI recommends that data from this site not be used to support a regulatory decision.

The FDA field investigators reported that inspection of the sponsor, Bristol-Myers Squibb Company, covered organization and personnel, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, QA, Adverse events/effects and reporting, data collection, data tabulations, test article integrity and accountability. In addition, primary efficacy endpoint data were assessed. No deficiencies were noted. Inspectional findings revealed no evidence that BMS or MDX personnel had inappropriate access to unblinded data from Study MDX010-20 prior to database unblinding that occurred on October 30, 2009.

The FDA field investigators did not note any regulatory violations during inspection of Dr. O'Day or Dr. Weber, and neither was issued a Form FDA 483.

A single observation Form FDA 483 was issued to Dr. Hodi for essentially, failure to report all SAEs to the sponsor within 24 ours of becoming aware of the event, as required by the protocol. Briefly, according the FDA field investigator, 6 SAEs were found to have been reported to the sponsor after the 24 hour requirement. No other deficiencies were noted.

A Form FDA 483 was issued to Dr. Sosman for significant deficiencies in the overall conduct of Study MDX010-20. The investigator's execution of the protocol was found to be inadequate. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and assessed their treatment regimens. While the primary efficacy endpoint data of overall survival were verifiable against source found at the site the totality of protocol deviations and deficient record keeping practices calls into question the overall efficacy and safety data generated by this site. The inspection revealed multiple protocol deviations (enrollment of ineligible subjects, inadequate control

of investigational product, missing safety assessments, etc.), inadequate recordkeeping, adverse event reporting deficiencies, and drug storage and accountability records deficiencies. Notably, there were two instances where a sub-investigator apparently retrospectively changed a subject's (Subject #0435) ECOG score from a score of 2 on two study visits, that occurred shortly after screening, to a score of 0 and 1, respectively, without justification. Further, Subject 0435 had an ECOG score of 2 at screening, thus was ineligible for the study, yet the subject was randomized and treated. Subject 1270 was also ineligible for the study due to prior recent treatment with chemotherapeutics yet the subject was randomized and treated.

While it is unclear, based on available information, whether site monitoring was sufficient for Dr. Sosman's site to identify and correct noncompliance at the site, or whether the study sponsor was made aware of the site's poor conduct while the study was ongoing, the paucity of findings during the other inspections conducted for this application suggest that the inspectional observations for Dr. Sosman's site appear specific to this site and that they are not representative of overall systemic issues with the conduct of the study. While DSI and DBOP representatives discussed the possibility of conducting additional CI inspections for this application, DBOP indicated that they believe the current set of inspections was sufficient to inform decision making regarding approvability of the application and that additional site inspections were not needed during this review cycle.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations, and one EIR [Hodi]. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the outstanding EIRs and supporting inspection evidence and exhibits.

/Lauren Iacono-Connors/
Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Jean Mulinde for Tejashri Purohit-Sheth/
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # BLA# 125377/0	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: Ipilimumab Dosage Form: Injection for IV use Strengths: 50 or 200mg single use vials		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):		
Date of Application: 06/25/10 Date of Receipt: 06/25/10 Date clock started after UN:		
PDUFA Goal Date: 12/25/10	Action Goal Date (if different): 12/23/10	
Filing Date: August 24, 2010	Date of Filing Meeting: July 30,2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of advanced melanoma (unresectable Stage III and Stage IV melanoma) in patients who have received prior therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR	

<input type="checkbox"/> Direct-to-OTC	314.510/21 CFR 601.41			
Other:	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>																				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance¹? If not, explain (e.g., waiver granted).</p>	X			
Index: Does the submission contain an accurate comprehensive index?	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X			
<p>Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p>			X	
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g. /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?				
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?				
<i>Forms must be signed by the APPLICANT, not an Agent.</i>	X			
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)				
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>	X			
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		ORPHAN STATUS
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/>			Package Insert (PI) Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) Carton labels Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/>			Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				NDC numbers
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT, OSE, DDMAC, DSI

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 23, 2004 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 25, 2008, March 4, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): October 7, 2005 (revised October 29, 2009) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 20, 2010

BLA/NDA/Supp #: STN 125377

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Ipilimumab

DOSAGE FORM/STRENGTH: Injection for IV use; 50 or 200mg single use vials

APPLICANT: Bristol-Myers Squibb Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of advanced melanoma (unresectable Stage III and Stage IV melanoma) in patients who have received prior therapy.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Erik Laughner	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Kaushik Shastri		Y
Clinical	Reviewer:	Kaushik Shastri	Y
	TL:	Patricia Keegan	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Aakanksha Khandelwal	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Yuan Li Shen	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew McDougal	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	SEE PRODUCT QUALITY TEAM	
	TL:		
Product Quality (CMC)	Reviewer:	Subramanian Muthukkumar	Y
	TL:	Barbara Rellahan	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kalavati Suvarna Don Obenhuber	Y N
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N
	TL:	Todd Bridges	
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	Y
	TL:	Suzanne Robottom	Y
Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connors	N
	TL:		

Other reviewers DRISK/OSE Patient labeling	Steven Morin Sharon Mills TL	N Y
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: Early December <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: NME

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Handled by DMA review team</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDA/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: NME, inspection of facility required</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments: Container/carton labeling reviews will be consulted to OSE, DDMAC, and OBP</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, OODP Director	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other



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

Memorandum

Date: July 30 2010 *ESC 07/30/10*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Filing Meeting

Regulatory Management

Erik Laughner
Karen Jones (CPMS)

Clinical

Pat Keegan (TL/Director)

Biostats

Yuan Li Shen
Kun He (TL)

Nonclinical

Andrew McDougal
Anne Pilaro (TL)

Clinical Pharmacology

Aakanksha Khandelwal
Hong Zhao (TL)
Anshu Marathe
Christine Garnett (TL)

Product

Subramanian Muthukkumar
Barbara Rellahan (TL)

Facilities

Kalavati Suvarna- Drug Substance
Patricia Hughes, (TL)

DBOP Safety Team

Jeff Summers- DDS
Grace Carmouze

OSE

Sue Kang
Joyce Weaver
Sharon Mills
Suzanne Robottom

Discussion:

Filing meeting was held. Participants were present from all disciplines. The filing review checklists were reviewed by each discipline to determine whether application should be filed. Review milestones and upcoming internal meetings were also discussed.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Review Date: July 8, 2010

Division of Biologic Oncology Products

Application Number: Original BLA STN 125377

Name of Drug: Ipilimumab, Injection for intravenous infusion

Applicant: BRISTOL-MYERS SQUIBB CO

Material Reviewed:

Submission Date(s): June 25, 2010

Receipt Date(s): June 25, 2010

Submission Date of Structure Product Labeling (SPL): June 25, 2010

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

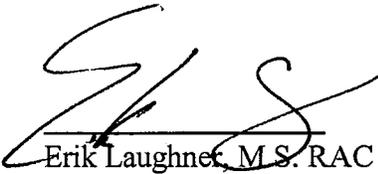
Review

This is a preliminary review of the proposed labeling submitted in this application.

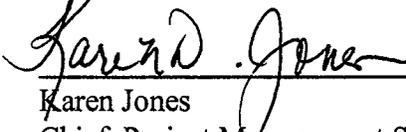
Recommendations

I completed a preliminary review of the proposed PLR labeling submitted in this application largely based on 21 CFR Parts 201.56 and 201.57, the preamble to the Final Rule, and FDA Guidance documents. The applicant complied with the major requirements for a PLR label in terms of required sections, headings/sub-headings, font size, etc. A search for the most common formatting deficiencies routinely encountered in a proposed PLR label did not yield any serious

omissions by the applicant. Therefore, a list of deficiencies that required applicant notification in a 74-day letter was not needed. I note that the proposed label did not include a proprietary name as the applicant was waiting for approval by FDA. Substantial team review and revision of this label would begin after the mid-cycle meeting

 07/28/10
Erik Laughner, M.S. RAC (US)
Senior Regulatory Health Project Manager

Supervisory Comment/Concurrence:


Karen Jones
Chief, Project Management Staff

Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT