

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125370Orig1s000**

**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.

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PMR/PMC Description: To conduct a Phase 2, multicenter study that will evaluate the safety, efficacy and pharmacokinetics of Benlysta in 100 pediatric subjects 5 years to 17 years of age with active systemic lupus erythematosus (SLE) on concomitant standard therapy

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>August 30, 2011</u>
	Study/Trial Completion:	<u>March 31, 2016</u>
	Final Report Submission:	<u>October 31, 2016</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

Due to theoretical safety concerns, pediatric SLE subjects (e.g., individuals less than 18 years of age) were prohibited from participating in the clinical studies conducted with Benlysta until the efficacy of the product had been demonstrated in adults. Although the incidence of SLE is rare in children less than 5 years of age, a clinical trial in subjects between 5 to 17 years of age is necessary in order to support the safety and efficacy of Benlysta in this subpopulation.

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."

In addition to theoretical efficacy concerns, there is a safety concern for the development of malignancies and serious infections associated with the long term administration of Benlysta in pediatric patients in view of the product's immunosuppressive capabilities. The proposed trial will evaluate the safety and efficacy of belimumab in the pediatric population via a (b) (4) trial in children ages 5 to 17 years old with active, seropositive SLE on standard of care therapy. (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.

A (b) (4) trial in children ages 5 to 17 years old with active, seropositive SLE on standard of care therapy. (b) (4)
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**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
- 

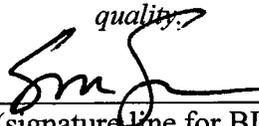
5. Is the PMR/PMC clear, feasible, and appropriate?

- 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?

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**PMR/PMC Development Coordinator:**

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

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### 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.

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PMR/PMC Description: Develop improved immunogenicity assays that are less sensitive to product interference that are capable of detecting human anti-human antibodies (HABA) in the presence of belimumab at ranges that would be expected to occur in patients receiving both high and low doses.

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PMR/PMC Schedule Milestones: Final Protocol Submission: March 31, 2012  
Final Report Submission: January 31, 2013  
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

A multi-tiered approach to assess the immunogenicity of belimumab was applied. While this approach is correct, we find that the assays are sensitive to levels of belimumab in patient sera and cannot be certain that the reported rates of immunogenicity in the clinical studies are accurate.

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."

Since belimumab will likely be used long term in patients demonstrating a response, it is important to accurately assess immunogenicity. Should any patient stop responding to belimumab it will be important to know if this is due to immunogenicity or other reasons.

It may not be feasible for HGS to develop a more sensitive assay. The PMR is that they make the attempt and report back to us if they can or cannot develop a better assay.

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.

If HGS can develop a better assay, they can reanalyze samples if they are still available. Otherwise they can assess immunogenicity in ongoing studies. It should be a decision of the clinical team whether or not a specific study to assess immunogenicity should be performed.

**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
  - X 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)

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Other

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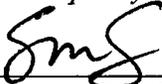
5. Is the PMR/PMC clear, feasible, and appropriate?

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

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**PMR/PMC Development Coordinator:**

X *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: To conduct a randomized clinical trial to evaluate the effects of Benlysta treatment on therapeutic vaccines involving B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>December 31, 2011</u>
	Study/Trial Completion:	<u>March 31, 2014</u>
	Final Report Submission:	<u>September 30, 2014</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

In support of the product's safety profile, the sponsor conducted a small, pilot immunization study as part of pivotal Study 1056 that evaluated the impact of Benlysta on response to vaccines such as pneumococcal, tetanus toxoid and seasonal influenza. Due to the small number of patients who participated in this pilot study, definitive conclusions regarding the immune system's ability to mount antibody responses to vaccines administered while receiving Benlysta therapy could not be performed.

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."

Since Benlysta is an immunomodulatory product, there is a theoretical risk that it may have an impact on host responses to vaccinations that needs to be evaluated further.

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.

Randomized clinical trial in SLE patients receiving Benlysta.

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
- 

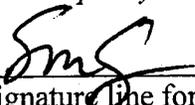
5. Is the PMR/PMC clear, feasible, and appropriate?

- 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?

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**PMR/PMC Development Coordinator:**

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

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### 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 conduct a pregnancy registry in order to evaluate pregnancy outcomes for women exposed to Benlysta during pregnancy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>July 31, 2011</u>
	Study/Trial Completion:	<u>October 31, 2018</u>
	Final Report Submission:	<u>April 30, 2019</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

Patients who participated in the clinical development of Benlysta had to agree not to become pregnant while receiving study therapy. Despite the mandatory requirement for patients of childbearing potential to use an effective form of contraception while participating in clinical trials evaluating the product, a total of 47 pregnancies were reported to have occurred during the Phase 2 and 3 studies. However, no conclusions could be made regarding Benlysta's effect on pregnancy and the fetus due to the limited amount of data collected as a result of the high incidence of auto-antibody-induced spontaneous abortions and elective pregnancy terminations in the population studied.

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."

Since SLE affects young women of childbearing potential and the number of pregnancies that occurred during the Phase 2 and 3 trials despite the mandatory use of effective forms of contraception by subjects of childbearing potential while participating in these trials, a postmarketing pregnancy registry is necessary to determine the potential effects of Benlysta on pregnancy and the fetus.

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 registry of women of childbearing potential who become pregnant while receiving Benlysta as therapy for their underlying SLE.

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?

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**PMR/PMC Development Coordinator:**

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

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## 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 conduct a randomized, placebo-controlled clinical trial with Benlysta in 5,000 patients with active, auto-antibody positive systemic lupus erythematosus.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>September 30, 2011</u>
	Study/Trial Completion: (5 year data)	<u>May 31, 2022</u>
	Final Report Submission: (5 year data)	<u>May 31, 2023</u>
	Other: Trial completion (1 year data)	<u>May 31, 2018</u>
	Trial completion (2 year data)	<u>May 31, 2019</u>
	Final Report Submission: (1 year data)	<u>May 31, 2019</u>
	Final Report Submission: (2 year data)	<u>May 31, 2020</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

Long term safety data is necessary in order to better elucidate safety signals that include a potential increase in risk for mortality, malignancy, serious and opportunistic infections and depression/suicidality in patients exposed to Benlysta which were identified during the Agency's review of the safety database submitted in support of the product's biological licensing application.

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."

Since SLE is a chronic disease, there are theoretical safety concerns regarding a potential increase in risk for serious adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality) to occur in patients with prolonged exposure to Benlysta. Therefore, a 5-year, randomized, controlled study in patients with autoantibody-positive SLE would provide the data necessary to determine the long term safety risk associated with Benlysta therapy.

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 5-year, randomized, placebo-controlled, clinical trial in 5,000 patients with active, autoantibody positive SLE to evaluate Benlysta's long term safety profile including adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality).

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)
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- Other
- 

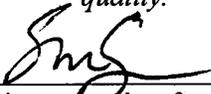
5. Is the PMR/PMC clear, feasible, and appropriate?

- 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?

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**PMR/PMC Development Coordinator:**

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

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(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: To conduct a randomized, controlled, clinical trial evaluating the efficacy and safety of Benlysta in patients with lupus nephritis

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 31, 2012</u>
	Study/Trial Completion:	<u>January 31, 2017</u>
	Final Report Submission:	<u>October 31, 2017</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 protocols for the Phase 2 and 3 studies conducted in support of the safety and efficacy of Benlysta prohibited the participation of patients with severe lupus nephritis. Review of the limited efficacy data generated from patients with renal involvement did not permit assessment of the product's ability to treat SLE involvement of this organ system which is involved in approximately 50-70% of patients with this disease. Additional data is therefore necessary to determine Benlysta's efficacy and safety in treating SLE patients with nephritis which is a life-threatening condition.

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."

There are theoretical concerns regarding Benlysta's safety and efficaciousness as a treatment for lupus nephritis. A pilot study in patients with SLE involvement of this organ system on concomitant immunosuppressive medications could potentially provide additional information regarding the product's efficacy and safety profile.

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 randomized, controlled, pilot study evaluating the safety and efficacy of Benlysta in patients with lupus nephritis.

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

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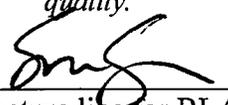
5. Is the PMR/PMC clear, feasible, and appropriate?

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

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**PMR/PMC Development Coordinator:**

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

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### 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 conduct a randomized, controlled, clinical trial evaluating the efficacy and safety of Benlysta in black patients with SLE

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>November 30, 2011</u>
	Study/Trial Completion:	<u>July 31, 2017</u>
	Final Report Submission:	<u>January 31, 2018</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

Post hoc review of the racial subgroup analyses submitted in support of Benlysta suggested that Benlysta may not be an efficacious treatment in black patients as compared to other racial groups. Since black patients are known to have more aggressive disease associated with worse outcomes, additional data is necessary to determine Benlysta's efficacy and safety in treating black SLE patients.

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."

There are theoretical concerns regarding Benlysta's safety and efficaciousness as a treatment for black patients with SLE. A study in these patients could potentially provide additional information regarding the product's efficacy and safety profile in this subpopulation.

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 randomized, controlled study evaluating the safety and efficacy of Benlysta in black patients with SLE.

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

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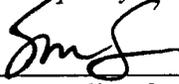
5. Is the PMR/PMC clear, feasible, and appropriate?

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

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**PMR/PMC Development Coordinator:**

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

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## 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.

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PMR/PMC Description: To submit a final study report for the long-term, open-label continuation study LBSL99.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>May 31, 2016</u>
	Final Report Submission:	<u>December 31, 2016</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

Long term safety data is necessary in order to better elucidate safety signals that include a potential increase in risk for mortality, malignancy, serious and opportunistic infections and depression/suicidality in patients exposed to Benlysta which were identified during the Agency's review of the safety database submitted in support of the product's biological licensing application.

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."

Since SLE is a chronic disease, there are theoretical safety concerns regarding a potential increase in risk for serious adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality) and/or other adverse events to occur in patients with prolonged exposure to Benlysta. Data from this open-label continuation study could help define safety risks associated with long-term administration of Benlysta.

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.

Long term, open-label continuation study in SLE patients administered Benlysta

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  
    Long-term, open-label continuation study in SLE patients
- 

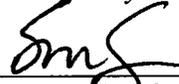
5. Is the PMR/PMC clear, feasible, and appropriate?

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

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**PMR/PMC Development Coordinator:**

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

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### 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.

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PMR/PMC Description: To submit a final study report for the long-term, open-label continuation study C1066

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>May 31, 2015</u>
	Final Report Submission:	<u>December 31, 2015</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

Long term safety data is necessary in order to better elucidate safety signals that include a potential increase in risk for mortality, malignancy, serious and opportunistic infections and depression/suicidality in patients exposed to Benlysta which were identified during the Agency’s review of the safety database submitted in support of the product’s biological licensing application.

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.”

Since SLE is a chronic disease, there are theoretical safety concerns regarding a potential increase in risk for serious adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality) and/or other adverse events to occur in patients with prolonged exposure to Benlysta. Data from this open-label continuation study could help define safety risks associated with long-term administration of Benlysta.

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.

Long term, open-label continuation study in SLE patients administered Benlysta

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  
Long-term, open-label continuation study in SLE patients
- 

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

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

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**PMR/PMC Development Coordinator:**

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

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## 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.

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PMR/PMC Description: To submit a final study report for the long-term, open-label continuation study C1074

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>March 31, 2015</u>
	Final Report Submission:	<u>October 31, 2015</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

Long term safety data is necessary in order to better elucidate safety signals that include a potential increase in risk for mortality, malignancy, serious and opportunistic infections and depression/suicidality in patients exposed to Benlysta which were identified during the Agency's review of the safety database submitted in support of the product's biological licensing application.

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."

Since SLE is a chronic disease, there are theoretical safety concerns regarding a potential increase in risk for serious adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality) and/or other adverse events to occur in patients with prolonged exposure to Benlysta. Data from this open-label continuation study could help define safety risks associated with long-term administration of Benlysta.

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.

Long term, open-label continuation study in SLE patients administered Benlysta

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  
Long-term, open-label continuation study in SLE patients
- 

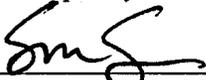
5. Is the PMR/PMC clear, feasible, and appropriate?

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

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**PMR/PMC Development Coordinator:**

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

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## 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.

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PMR/PMC Description: Please submit data supporting microbial control for the (b) (4); lifetime studies in a CBE-0 supplement by June 2012.

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PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>09/24/2010</u>
Study/Clinical trial Completion Date:	<u>12/30/2011</u>
Final Report Submission Date:	<u>06/30/2012</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 sponsor has submitted a protocol of (b) (4) lifetime use and the assessment of microbial control will be performed over the (b) (4) lifetime. The applicant has indicated that the final study report will become available early 2012. This is a concurrent validation study and final data is not available at time of action. Bioburden is monitored at the step so it is not an approvability issue. The final study report upon completion of the study should be reported as a post marketing commitment.

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 sponsor has submitted a protocol of (b) (4) lifetime use and the assessment of microbial control will be performed over the (b) (4) lifetime. The applicant has indicated that the final study report will become available early 2012. This is a concurrent validation study and final data is not available at time of action. Bioburden is monitored at the step so it is not an approvability issue. The final study report upon completion of the study should be reported as a post marketing commitment.

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 sponsor has submitted a protocol of <sup>(b) (4)</sup> lifetime use and the assessment of microbial control will be performed over the <sup>(b) (4)</sup> lifetime. The applicant has indicated that the final study report will become available early 2012. This is a concurrent validation study and final data is not available at time of action. Bioburden is monitored at the step so it is not an approvability issue. The final study report upon completion of the study should be reported as a post marketing commitment.

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:

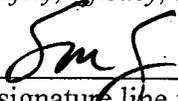
- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, 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:**

*X 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.*

 3/1/11  
\_\_\_\_\_  
(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: Qualify the capper and revalidate the integrity of the belimumab drug product container closure

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>03/31/2011</u>
	Study/Clinical trial Completion Date:	<u>04/29/2011</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

HGS needs to conduct laboratory studies to revalidate the integrity of the belimumab drug product container closure with a container closure integrity test of higher sensitivity. Data from other products with vials crimped by the same capper suggest that the risk of microbial contamination of a breached vial is relatively low.

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."

Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. The preparation of the positive controls and sensitivity (breach size) of the helium leak test will be provided.

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.

Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. The preparation of the positive controls and sensitivity (breach size) of the helium leak test will be provided.

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
- 

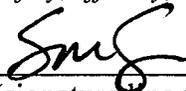
5. Is the PMR/PMC clear, feasible, and appropriate?

- 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.*

 3/1/11  
\_\_\_\_\_  
(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: Provide quantitative data for the (b) (4)

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	03/31/2011
	Study/Clinical trial Completion Date:	04/29/2011
	Final Report Submission Date:	06/30/2011
	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

HGS needs to conduct studies to obtain quantitative data for the (b) (4). This is appropriate for PMC because the (b) (4) does not affect the sterility of the drug product. The qualitative data provided for the (b) (4) met the acceptance criteria.

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."

Provide quantitative data to demonstrate (b) (4). The quantitative qualification data will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

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.

Provide quantitative data to demonstrate

(b) (4)

The quantitative qualification data will be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

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?

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**PMR/PMC Development Coordinator:**

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

 3/1/11  
\_\_\_\_\_  
(signature line for BLAs)

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 24, 2011

Application Type/Number: BLA 125370

To: Badrul Chowdhury, MD, Director  
Division of Pulmonary, Allergy and Rheumatology Products

Through: Carlos Mena-Grillasca, RPh, Team Leader *CMena 2/25/11*  
Carol A. Holquist, RPh, Director *CHolquist 2/28/11*  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Lissa C. Owens, PharmD, Safety Evaluator *LO 2/25/11*  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Benlysta (Belimumab) for Injection  
120 mg/vial and 400 mg/vial

Applicant: Human Genome Sciences

OSE RCM#: 2010-1312

\*\*\*Note: This review contains proprietary and confidential information that should not be released to the public\*\*\*

## **1 INTRODUCTION**

This review evaluates the revised Benlysta (Belimumab) 120 mg/vial and 400 mg/vial labels and labeling submitted on February 17, 2011. DMEPA evaluated these labels and labeling in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products. DMEPA evaluated the initial proposed label and labeling under OSE RCM #2010-1312 dated November 23, 2010

## **2 METHODS AND MATERIALS**

The revised labels and labeling submitted on February 17, 2011 and the OSE review #2010-1312 were evaluated to assess whether the revisions adequately addresses our concerns from a medication error perspective.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised labels and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact OSE Safety Regulatory Project Manager Nichelle Rashid at 301-796-3904.

## **4 REFERENCES**

OSE Review #2010-1312, Label and Labeling Review for Benlysta (Belimumab) 120 mg/vial and 400 mg/vial. Park, Judy. November 23, 2010

**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:** November 23, 2010

**Application Type/Number:** BLA 125370

**To:** Badrul Chowdhury, MD, Director  
Division of Pulmonary, Allergy and Rheumatology Products

**Through:** Carlos Mena-Grillasca, RPh, Team Leader *C Mena 11/25/2010*  
Carol Holquist, RPh, Director *Carol Holquist 11/30/2010*  
Division of Medication Error Prevention and Analysis (DMEPA)

**From:** Judy Park, PharmD, Safety Evaluator *C Mena for Judy Park 11/23/2010*  
Division of Medication Error Prevention and Analysis (DMEPA)

**Subject:** Label and Labeling Review

**Drug Name(s):** Benlysta (Belimumab) for Injection  
120 mg/vial and 400 mg/vial

**Applicant:** Human Genome Sciences

**OSE RCM #:** 2010-1312

## 1 INTRODUCTION

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for DMEPA review of the container labels, carton and insert labeling for the proposed product, Benlysta (Belimumab) for Injection to identify areas that could lead to medication errors.

## 2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted on June 9, 2010 to identify vulnerabilities that could lead to medication errors (see Appendices A and B).

## 3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for the insert labeling in Section 3.1 for discussion during the review team's labeling meetings. We request the recommendations for the container labels and carton labeling in Section 3.2 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 further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Carolyn Volpe, at 301-796-5204.

### 3.1 COMMENTS TO THE DIVISION

#### A. General Comments



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



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 125370/0  
Name of Drug: Benlysta<sup>®</sup> (belimumab)  
Sponsor: Human Genome Sciences  
Material Reviewed: Benlysta<sup>®</sup> (belimumab)  
Carton and Container Labels  
Prescribing Information  
Submission Date: June 6, 2010 and February 17, 2011

### EXECUTIVE SUMMARY

The carton and container labels for Benlysta<sup>®</sup> (belimumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 10/1/10-2/1/11, USP 33/NF28. Labeling deficiencies were identified, mitigated, and resolved. Please see comments in the conclusions section.

### Background

STN 125360/0 for belimumab is an original Biologic License Application (BLA) indicated for (b) (4) in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. The product is available as a sterile lyophilized powder in 120 mg/5 ml vial and 400 mg/20 ml vial.

### Labels Reviewed:

Benlysta<sup>®</sup> (belimumab) Container Labels  
Vial labels-120 mg and 400 mg  
Benlysta<sup>®</sup> (belimumab) Carton Labels  
Single vial- 120 mg and 400 mg  
Benlysta<sup>®</sup> (belimumab) Prescribing Information

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Start of Sponsor Material

**Vial Labels**



(b) (4)

End of Sponsor Material

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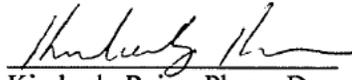
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**I. Container**

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

(b) (4)

The license number was not issued during the review of the carton and container labels and should be included with the submission of the final printed labels.

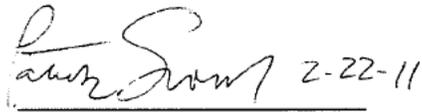


Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBS

Comment/Concurrence:



Sean Fitzsimmons, Ph.D.  
Product Reviewer  
Division of Monoclonal Antibodies  
CDER/OPS/OBP



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

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

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

**Memorandum**

**Date:** 02/14/11

**To:** Philantha Bowen, Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Roberta Szydlo, Regulatory Review Officer *RSzydlo* 2-14-11  
Twyla Thompson, Regulatory Review Officer *Twyla* 2/14/11  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader  
Shefali Doshi, DTC Group Leader  
Olga Salis, Regulatory Health Project Manager  
Michael Wade, Regulatory Health Project Manager  
(DDMAC)

**Subject:** BLA 125370  
DDMAC labeling comments for Benlysta® (belimumab) for injection,  
for intravenous use only

---

DDMAC has reviewed the proposed Package Insert (PI) and proposed Medication Guide (Med Guide) for Benlysta® (belimumab) for injection, for intravenous use which was submitted for consult on June 18, 2010. DDMAC's comments are based on the proposed draft marked-up labeling titled "Belimumab - DPARP complete PI (01Feb2011).doc" that was sent via email from DPARP to DDMAC on February 2, 2011.

DDMAC's comments on the PI and Med Guide are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or [roberta.szydlo@fda.hhs.gov](mailto:roberta.szydlo@fda.hhs.gov). If you have any questions

regarding the Med Guide, please contact Twyla Thompson at (301) 796-4294 or [twyla.thompson@fda.hhs.gov](mailto:twyla.thompson@fda.hhs.gov).

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

**Date:** February 11, 2011

**To:** Badrul Chowdhury, MD, Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

**Through:** Claudia Karwoski PharmD, Director *Claudia Karwoski*  
**Division of Risk Management (DRISK)** 2/11/11

**From:** Shawna Hutchins, MPH, BSN, RN *Shawna Hutchins*  
**Patient Labeling Reviewer**  
**Division of Risk Management (DRISK)** 2/11/10

**Subject:** DRISK Review of Proposed Risk Evaluation and Mitigation  
Strategy (REMS)

**Drug Name(s):** BENLYSTA (belimumab) for injection

**Application  
Type/Number:** BLA 125370

**Applicant/sponsor:** Human Genome Sciences Inc.

**OSE RCM #:** 2010-1340

## 1. INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for Benlysta (belimumab) for injection.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

The DRISK review of the Medication Guide will be provided under a separate cover. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

## 2. BACKGROUND

Human Genome Sciences Inc (HGS), submitted a Biologics Licensing Application (BLA) on June 09, 2010 for Benlysta (belimumab) for injection. Benlysta (belimumab) for injection is a recombinant, fully human, IgG1 monoclonal antibody for the treatment of adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Following the 16 November 2010 Advisory Committee (AC) meeting for belimumab, the FDA held a teleconference with HGS during which the FDA notified HGS that a Medication Guide only REMS was necessary for Benlysta (belimumab) to ensure that the benefits of the drug outweighed the risks.

## 3. MATERIAL REVIEWED

- Proposed Benlysta (belimumab) for injection Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on June 09, 2010, and received by DRISK on February 02, 2011.

## 4. RESULTS OF REVIEW

In our review of the proposed REMS, we have:

- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

## 5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the proposed REMS.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### Comments to Human Genome Sciences Inc.:

See the appended Benlysta (belimumab) for injection REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

(b) (4)

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**Appendix 1      Medication Guide**

APPEARS THIS WAY ON ORIGINAL

**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 10, 2011

To: Badrul Chowdhury, MD, Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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

*LaShawn Griffiths 2/10/11*

Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management (DRISK)**

*Melissa Hulett 2/10/11*

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

*Shawna Hutchins 2/10/11*

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Benlysta (belimumab) for intravenous infusion

Application Type/Number: BLA 125370

Applicant/sponsor: Human Genome Sciences

OSE RCM #: 2010-1340

## **1 INTRODUCTION**

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to provide a review of the Applicant's Medication Guide (MG) of Benlysta (belimumab) for intravenous infusion.

On June 09, 2010 the Applicant submitted a Biologics License Application (BLA) for Benlysta (belimumab) for intravenous infusion indicated for use in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

## **2 MATERIAL REVIEWED**

- Draft Benlysta (belimumab) Prescribing Information (PI) received on June 09, 2010, revised by the reviewing division throughout the reviewing cycle, and received by DRISK on February 02, 2011.
- Draft Benlysta (belimumab) MG received on June 09, 2010 and received by DRISK on February 02, 2011.

## **3 REVIEW METHODS**

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

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

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 within the MG
- 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.

Please let us know if you have any questions.

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Pulmonary, Allergy, and Rheumatology Products

**Application Number:** BLA 125370/0  
**Name of Product:** Benlysta® (belimumab)  
**Applicant:** Human Genome Sciences  
**Review Date:** January 31, 2011

### **Material Reviewed:**

**Submission Date(s):** July 9 and December 1, 2010

**Receipt Date(s):** July 9 and December 1, 2010

**Submission Date of Structure Product Labeling (SPL):** July 9, 2010

**Type of Labeling Reviewed:** Package Insert

### **Background and Summary**

On July 9, 2010, Human Genome Sciences (HGS) submitted a BLA for Benlysta® (belimumab) for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

The proposed labeling text Benlysta® was provided in SPL, including carton and container labels, and a patient information leaflet. Draft labeling text was also submitted in Word format (.doc) for review.

Per the request of the Division, HGS submitted a Medication Guide (MG) only REMS dated November 23, 2010, and revised labeling dated December 1, 2010.

OSE and DDMAC were consulted regarding the PI and MG, as appropriate to their discipline, for recommendations regarding the PI and MG content.

## Review

The WORD and SPL versions of the proposed labeling in PLR format was reviewed using the Label Review Tool provided by SEALD.

The following comments pertain to the Full Prescribing Information-Details section of the product label:

Remove the revision date at the end of the FPL of the package insert. The revision date is located in the Highlights Section of the label.

Address the identified deficiency/issue and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

## Recommendations

Comments/recommendations for the proposed labeling have been identified and will be conveyed to the applicant as apart of the Division's request for revised labeling during labeling negotiations.



/Philantha M. Bowen/  
Philantha M. Bowen  
Sr. Regulatory Project Manager  
CDER, OND, ODE II, DPARP

Supervisory Comment/Concurrence:



/Sandy Barnes/  
Sandy Barnes  
Chief, Project Management Staff  
CDER, OND, ODE II, DPARP

Drafted: Bowen/January 25, 2011  
Initialed: Barnes/January 31, 2011  
Finalized: Bowen/January 31, 2011

**CSO LABELING REVIEW OF PLR FORMAT**

23 November 2010  
Original

**BENLYSTA® (belimumab)**  
**BLA 125370**  
B Lymphocyte Stimulator (BLyS)-specific inhibitor

Human Genome Sciences, Incorporated  
14200 Shady Grove Road  
Rockville, MD 20850  
Telephone: 1-877-423-6597

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**  
**SUPPORTING DOCUMENT**

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

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

**Date:** November 23, 2010

**Application Type/Number:** BLA 125370

**To:** Badrul Chowdhury, MD, Director  
Division of Pulmonary, Allergy and Rheumatology Products

**Through:** Carlos Mena-Grillasca, RPh, Team Leader *C Mena 11/25/2010*  
Carol Holquist, RPh, Director *Carol Holquist 11/30/2010*  
Division of Medication Error Prevention and Analysis (DMEPA)

**From:** Judy Park, PharmD, Safety Evaluator *C Mena for Judy Park 11/23/2010*  
Division of Medication Error Prevention and Analysis (DMEPA)

**Subject:** Label and Labeling Review

**Drug Name(s):** Benlysta (Belimumab) for Injection  
120 mg/vial and 400 mg/vial

**Applicant:** Human Genome Sciences

**OSE RCM #:** 2010-1312

## 1 INTRODUCTION

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for DMEPA review of the container labels, carton and insert labeling for the proposed product, Benlysta (Belimumab) for Injection to identify areas that could lead to medication errors.

## 2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted on June 9, 2010 to identify vulnerabilities that could lead to medication errors (see Appendices A and B).

## 3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations for the insert labeling in Section 3.1 for discussion during the review team's labeling meetings. We request the recommendations for the container labels and carton labeling in Section 3.2 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 further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Carolyn Volpe, at 301-796-5204.

### 3.1 COMMENTS TO THE DIVISION

#### A. General Comments

(b) (4)

(b) (4)

(b) (4)

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

4. Full Prescribing Information. Section 2.1. Revise to read "Benlysta is for intravenous infusion only..."
5. Full Prescribing Information. Section 2.3.
  - a. Revise the statement to read "Benlysta is provided... for intravenous infusion only.."
  - b. Provide separate numbered instructions for Reconstitution (currently steps 1 through 5) and Dilution (currently steps 6 through 9).
  - c. Revise the instruction for step 1 to read "Remove Benlysta from the refrigerator and allow to stand 10 to 15 minutes for the vial to reach room temperature."
  - d. Revise the instruction for step 2 to delete the parenthetical statement (b) (4) and revise the bulleted instructions to use the following format "Reconstitute the 120 mg vial with 1.5 mL Sterile Water for Injection, USP. The concentration of Benlysta in the resulting solution is 80 mg/mL".
  - e. We note that the amount of Sterile Water for Injection required for reconstituting the 400 mg vial is 4.8 mL. However, the carton labeling states that each vial delivers 5 mL of belimumab. For the 120 mg vial these quantities are consistent (i.e. 1.5 mL required for reconstitution and each vial delivers 1.5 mL belimumab). We defer to CMC for resolution on the noted inconsistency. Revise the statement to follow the recommendation from 4. above.
  - f. Revise the instruction for step 6 to begin with the statement "Dextrose solutions are incompatible with Benlysta. Benlysta should only be diluted in 0.9% Sodium Chloride Injection, USP (normal saline)."
6. Full Prescribing Information. Section 2.4. Revise step 1 to read "The diluted solution of Benlysta should be administered by intravenous infusion only, over a period of 1 hour.

**Dosage Forms and Strengths (Highlights and Full Prescribing Information)**

1. Revise the statement to read "Single-use vials of belimumab lyophilized powder for injection."
2. Delete the vial size and revise the strength statement to read "120 mg per vial" and "400 mg per vial".

**How Supplied (Full Prescribing Information)**

1. Revise the statement "Each 5 mL vial delivers 120 mg of belimumab. Each 20 mL vial delivers 400 mg of belimumab" to "Each 5 mL vial contains 120 mg of belimumab. Each 20 mL vial contains 400 mg of belimumab."
2. Delete the table headers that read (b) (4) is the current presentation my be misinterpreted as a carton containing both 120 mg and 400 mg vials.

**3.2 COMMENTS TO THE APPLICANT**

**A. General Comments**

1. The proposed dosage form (b) (4) is not the proper dosage form for this product. Revise the dosage form to read "for Injection."
2. Revise the statement "See package insert..." to "See prescribing information..."
3. Remove the statement (b) (4) as it crowds the labels and the statement "Refrigerate" implies this instruction.

***B. Container Label***

1. Increase the prominence of the strength. Currently, the NDC number has greater prominence than the strength.

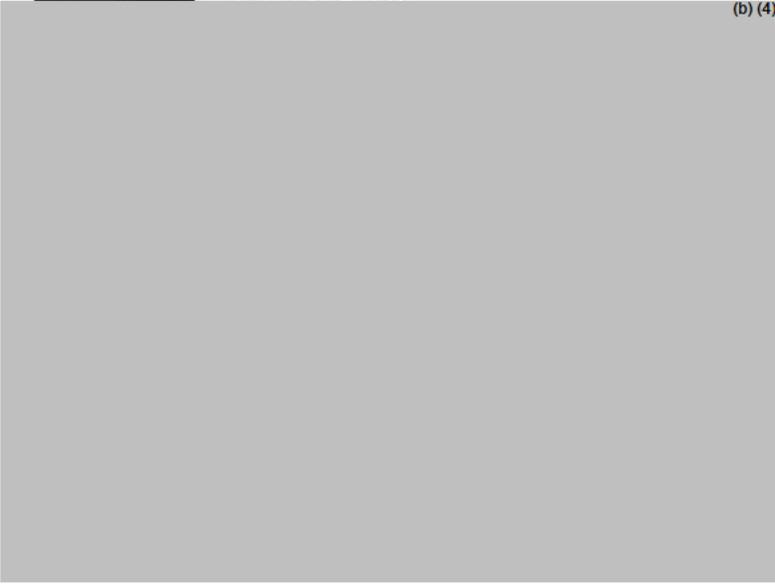
***C. Carton Labeling***

1. Relocate the statements "Single-use vial. Discard unused portion." to the principal display panel.
2. Revise the statement "Carton contains 1 single-use vial of lyophilized Benlysta" to "Each single-use vial contains 120 mg of Benlysta" or "Each single-use vial contains 400 mg of Benlysta".
3. Include the statement "Product must be reconstituted with XX mL Sterile Water for Injection USP. After reconstitution, the concentration of Benlysta is 80 mg/mL. Further dilute in 250 mL of 0.9% sodium chloride injection, USP before use." on the principal display panel. Consider reducing the size of the logo to allow for this important information to be displayed without crowding the carton labeling.

**APPENDICES**

**Appendix A : Container Labels**

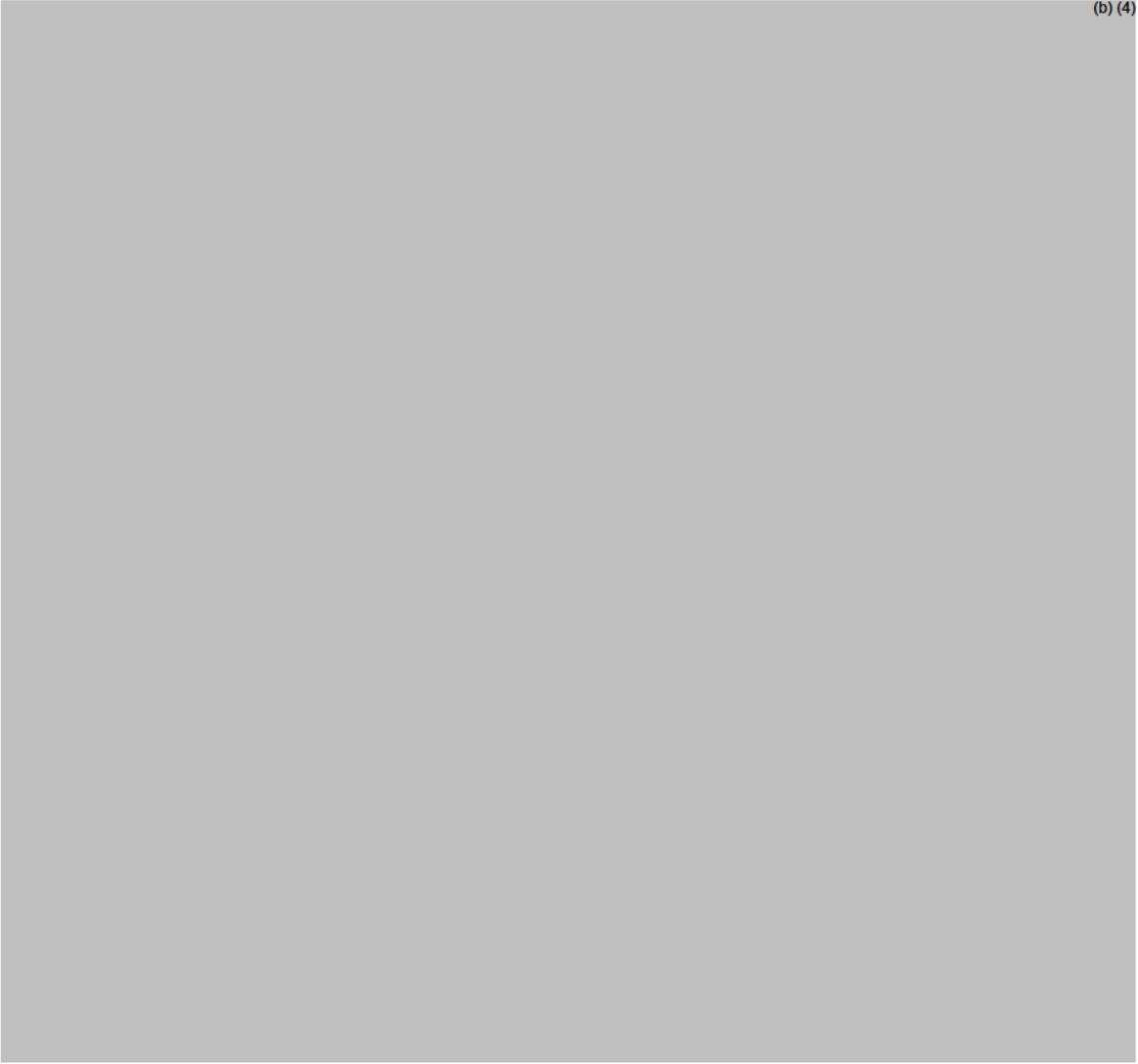
(b) (4)



**Appendix B : Carton Labeling**

(b) (4)





MEMORANDUM

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

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CLINICAL INSPECTION SUMMARY

DATE: November 4, 2010

TO: Philantha Bowen, Regulatory Project Manager  
Rosemarie Neuner, M.D., Medical Officer  
Sarah Okada, M.D., Medical Officer Team Leader  
Division of Pulmonary, Allergy and Rheumatologic Products

THROUGH: Tejashri Purohit-Sheth, MD  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125370

APPLICANT: Human Genome Sciences

DRUG: belimumab (Benlysta)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: treatment of adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) on stable standard therapy

CONSULTATION REQUEST DATE: July 22, 2010 (received September 9, 2010)

DIVISION ACTION GOAL DATE: November 9, 2010

PDUFA DATE: December 9, 2010

## **I. BACKGROUND:**

Human Genome Sciences submitted this application for the use of belimumab (LymphoStat-B™) in the treatment of adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) on stable standard therapy. Systemic lupus erythematosus (SLE) is characterized by autoantibody production and abnormal B lymphocyte function. The etiology of SLE is unknown. Patients with SLE have about a 3-fold greater risk of mortality than the general population. About 70% of SLE patients survive 20 years from time of diagnosis. Although active lupus nephritis and CNS vasculitis can usually be controlled with several courses of high dose steroids and cyclophosphamide over a 1 to 2 year period, there tends to be progressive relapsing of disease over time.

Standard therapies for SLE include corticosteroids, hydroxychloroquine, non-steroidal anti-inflammatory drugs, cytotoxic agents like cyclophosphamide, and immunosuppressive or immunomodulatory agents used in cancer or transplantation (e.g., azathioprine, mycophenolate mofetil, methotrexate, thalidomide, cyclosporine, 6-mercaptopurine and leflunomid. Long-term use of high-dose corticosteroids can cause significant morbidity including osteoporosis and osteonecrosis, exacerbation of diabetes, increased infection risk, edema, weight gain and hyperlipidemia. Cytotoxic agents are immunosuppressive, resulting in increased risk of serious infections and cancers.

Belimumab (also known as LymphoStat-B™) is a recombinant, fully human IgG1 $\lambda$  monoclonal antibody. Belimumab binds soluble B lymphocyte stimulator (BLyS) and inhibits its biological activity, resulting in a decrease of B-cell proliferation and antibody production that are thought to be important in the pathogenesis of SLE. Belimumab was derived by affinity maturation of a parental antibody which itself was derived from screening a phage display library for high affinity binding to BLyS.

Two adequate and well-controlled studies were submitted in support of this NDA for the SLE indication: Studies C-1056 and 1057. Two clinical sites per protocol were selected for field inspection. For C-1056, clinical site inspections were conducted in Vienna Austria (Dr. Zamani) and Prague, Czech Republic (Drs. Tegzova). For C-1057, clinical site inspections were conducted in Taiwan (Drs. Yu and Wei, respectively).

### **STUDY PROTOCOL C-1056**

C-1056 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, 76-week study to evaluate the efficacy, safety, tolerability, and quality of life of belimumab in subjects with clinically and serologically active SLE. Subjects on stable standard therapy were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo administered IV. At randomization, subjects were stratified by their screening SELENA SLEDAI score (6-9 vs  $\geq 10$ ), screening proteinuria level ( $< 2$  g/24 hour vs  $\geq 2$  g/24 hour equivalent) and race (African descent or indigenous-American descent vs other). All subjects were to continue the stable standard therapy they were receiving during the screening period. Subjects were to be dosed with study agent on Days 0, 14, and 28, then every 28 days through 72 weeks, with a final evaluation at Week 76 (4 weeks after the last dose).

This multicenter study comprised 136 centers: 62 (Europe), 65 (North America), and 9 (Latin America). Approximately 810 SLE subjects were to be randomized, with a target of about 270 subjects per treatment group. The first subject was randomized on February 8, 2007 and the last subject completed an 8-week follow-up on September 22, 2009.

The primary efficacy endpoint was response rate at Week 52. A response was defined as:  $\geq 4$  point reduction from baseline in SELENA SLEDAI score, and no worsening (increase of  $< 0.30$  points from baseline) in Physician Global Assessment, and no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52).

### **STUDY PROTOCOL C-1057**

Protocol C-1057 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy, safety, tolerability, and quality of life of belimumab in subjects with clinically and serologically active SLE.

Subjects on stable standard therapy were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo administered intravenously (IV). At randomization, subjects were stratified by their screening SELENA SLEDAI score (6-9 vs  $\geq 10$ ), screening proteinuria level ( $< 2$  g/24 hour vs  $\geq 2$  g/24 hour equivalent) and race (African descent or indigenous-American descent vs other). All subjects were to continue the stable standard therapy they were receiving during the screening period. Subjects were to be dosed with study agent on Days 0, 14, and 28, then every 28 days through 48 weeks, with a final evaluation at Week 52 (4 weeks after the last dose).

This multicenter study comprised 90 centers: 41 (Asia), 38 (Latin America) and 11 (Europe). Approximately 810 SLE subjects were to be randomized, with a target of about 270 subjects per treatment group. The first patient was randomized on May 25, 2007 and the last subject completed an 8-week follow-up on May 19, 2009.

The primary efficacy endpoint was response rate at Week 52. A response was defined as:  $\geq 4$  point reduction from baseline in SELENA SLEDAI score, no worsening (increase of  $< 0.30$  points from baseline) in Physician Global Assessment score, and no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52).

Four foreign clinical investigator sites and a domestic sponsor site were selected for inspection for this new molecular entity as a novel treatment indication in adult patients with active, autoantibody positive SLE on stable standard therapy. Study C1056 had a large proportion (~50%) of foreign sites represented, and Study C1057 was conducted entirely at foreign sites. The Asian sites represented a disproportionately large number (45%) of enrollees in C1057. These international sites could potentially influence overall efficacy findings. For these foreign sites; the clinical investigators also have no prior history of inspections.

**II. RESULTS (by protocol/site):**

<b>Name of CI/Sponsor and site #, if known</b>	<b>City, State</b>	<b>Protocol</b>	<b>Inspection Date</b>	<b>EIR* Received Date</b>	<b>Final Classification</b>
Omid Zamani, M.D./Site AT001	Wien, Austria	Study C-1056	October 18-21, 2010	Pending	Voluntary Action Indicated (VAI)
Dana Tegzova, M.D./CZ002	Prague, Czech	Study C-1056	October 25-27, 2010	Pending	VAI
Chia-Li Yu, M.D., Ph.D./TW011	Taipei, Taiwan	Study C-1057	October 25-27, 2010	Pending	Preliminary field classification: No Action Indicated (NAI)
James Cheng-Chung Wei, MD/Site TW010	Taichung, Taiwan	Study C-1057	October 18-20, 2010	Pending	Preliminary field classification: NAI
Human Genome Sciences	Rockville, MD	Sponsor	September 7-8, 2010	October 4, 2010	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Pending= The EIR has not been received and findings are based on preliminary communication with the field.

\*EIR: Establishment Inspection Report

## **PROTOCOL C1056**

### **1. Omid Zamani, M.D./Site AT001**

**Site #AT001**

**Rheumazentrum Favoriten**

**Wien, 1100 AUSTRIA**

#### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from October 18 to 21, 2010. There were 62 subjects screened, 32 randomized, and 25 subjects who completed the study. A total of 15 study subject records were reviewed in-depth. These included the following subjects: #2, 4, 6, 8, 10, 15, 16, 21, 23, 25, 27, 29, 30, 31 and 32. The clinic was a stand-alone rheumatology ambulatory care center at the Favoriten District in Vienna, Austria. Dr. Zamani used to be Chief of Ambulatory Rheumatology Clinic at a hospital in Vienna prior to his current clinical practice location.

#### **b. Limitations of inspection:**

None.

#### **c. General observations/commentary:**

There was no evidence of under-reporting of adverse events. No discrepancies between the source records and the case report forms (CRFs) were found. No prohibited medications and therapies during study C-1056 were administered, such as plasmapheresis, anti-TNF therapy (e.g., infliximab and etanercept), intravenous immunoglobulin, or IV cyclophosphamide. Study drug accountability documentation was maintained. With the exception of Subject 02, patients were properly consented.

The following three primary study endpoints were evaluated: SELINA SLEDAI Score Disease Assessment Scales, Physician's Global Disease Assessment (PGA) score from none (score=0) to severe (score=3). For the PGA, vertical tic marks were marked by the examining physician to assess his patient's current disease activity. The relative position in the visual analog picture line score was compared with the data listing scores at Site AT001. No discrepancies were found. Finally, the BILAG index score, an 86-item raw score, covering 8 organ systems (i.e., general, mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculities, renal and hematology) was assessed. To derive the alphabet category score from the raw score, the BILAG may be conceptualized as five steps or phases. At the clinical site, however, only "Phase 1 and Phase 2" were available, namely, the raw item scores and its corresponding data entry into their electronic Case Report Form (eCRF). "Phase 3" which required an algorithm and automated programming software (e.g., to sum, weight, possibly ignore other raw score items, final score), and translate to "Phase 4" numeric category scores (A=9. B=3. C=1. D=0 and E=0) were not verifiable at the clinical site. Thus, the data listing submitted by the sponsor to the BLA, "Phase 5," which consisted of character category scores (A-E) could not be verified against/compared with the source documents ("Phase 1"), and this is anticipated.

At the end of the inspection at site AT001, a Form FDA 483 was issued. Principally, the research investigation was not conducted in accordance with the investigational plan.

(1) The following patients did not meet study eligibility criteria:

- Subjects 23 and 32, respectively, did not have two independent, unequivocal, positive, anti-nuclear antibody or anti-dsDNA screening laboratory sample test results.
- Subject 17 had an Ig A value of <0.08 g/L at screening, indicating Ig A deficiency.
- Subject 08 a glucose value of 274 mg/dL (15.2 mmol/L) at screening, classified as a Grade 3 toxicity screening laboratory test result.
- Subject 16's 5 mg daily prednisone dose was below the protocol section 4.1 dose requirement of 7.5 to 40 mg/day, for patients whose SLE stable treatment only is steroids.

(2) Subject 06 signed a version of the Informed Consent Form that was not approved by the Ethics Committee, although the subject was initially consented, and

(3) Subject 02 received intra-articular triamcinolone injection for SLE exacerbation in violation of protocol section 5.5.1.2.2, instead of being withdrawn from the study per research protocol, during the course of the research study.

The clinical site visit not only permitted ORA to complete the BIMO inspection according to the compliance program directives, but also allowed pursuit of additional clarifications posed by DPARP's medical team. These issues were developed in the course of several interactions with DSI, close to the planned visit at the Vienna site (AT001). DSI's participation provided a value-added clinical, regulatory, and scientific perspective to a non-routine clinical site audit for a complicated clinical trial involving, for example, long diagnostic and outcomes criteria, immunosuppressant concomitant medications, medications allowed, or stringent study monitoring procedures during the course of study C-1056.

Specifically, DPARP were also interested in the following:

- (1) Were there pregnancies at this study site during C-1056? NO
- (2) Were there allergic study infusion reactions at this study site? Referable signs and symptoms of anaphylactic/anaphylactoid reactions during and post-study infusion were enumerated (e.g., presyncopal symptoms, pruritus, rash, shortness of breath, laryngeal edema, hypotension, dizziness, and other clinical features). Dr. Zamani, PI, denied any allergic manifestations that ever developed in his study subjects during the course of study C-1056.

Dr. Zamani, however, intubated a patient who developed laryngeal edema in another therapeutic biologics study over two years ago. He also showed his life support set-up and equipments in an adjacent room. He also discussed briefly a scenario and his procedural approach in case a study infusion reaction situation ever occurred. Per Dr. Zamani, his study staff (i.e., pharmacists, physicians, nurses and allied health personnel), are certified every two years by the anesthesia department of a nearby hospital where he refers his patients for in-patient care.

- (3) As it would be highly complicated to directly address any under-reported renal complications at clinical site AT-001 in study C-1056, the DSI Medical Officer asked the PI to identify which patients, according to his recollection, had lupus nephritis. Per PI, 3 study subjects had lupus nephritis: subject 06 also on azathioprine (Imurek), subject 14 also on mycophenolate (Cellcept) and subject 16, also on cyclophosphamide (Endoxan). A brief review of their records indicated that the maximum allowable daily doses (azathioprine- 300 mg/day, mycophenolate (PO)-2.88 g/day, and cyclophosphamide (PO)-2.5 mg/kg/day) were not exceeded.

Despite the above regulatory deficiencies noted, this clinical site appeared to adhere to good clinical practice. Current inspection showed no discrepancies with source data, and no evidence of scientific misconduct. Despite the sponsor providing limited translation capabilities, via their CRO study monitor (b) (4), and Dr. Zamani's facility with English, the challenges for this site visit language translations were overcome. The principal investigator was forthright and available to answer both the ORA field inspector and DSI Medical Officer's questions during the clinical site visit. Dr. Zamani also indicated his forthcoming written response to the Form FDA 483 list of inspectional observations about the corrective action preventive action (CAPA) plans as part of his quality management system initiative at his clinical study site.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Although regulatory violations were noted, these are considered isolated in nature and unlikely to importantly impact data reliability. The data in support of clinical efficacy and safety at this clinical site appear acceptable.

*NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.*

**2. Dana Tegzova, M.D./CZ002**

**Institute of Rheumatology –Na Slupi 4**

**Prague 2, 12850 CZECH REPUBLIC**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, with inspection completed on October 25-27, 2010. There were 24 subjects screened, 22 enrolled and randomized, and 17 completed the study. A 100% audit was conducted for informed consents. An audit was conducted on the 10 subjects who were randomized in the study, e.g., study eligibility criteria, concomitant medication use, prohibited medications, and for primary efficacy endpoints. These included the following patients: 1, 2, 3, 4, 5, 7, 13, 15, 18, and 20. The study was conducted at the Institute of Rheumatology that is integrated with the historic Charles University Medical School in Prague, Czech Republic. This clinic functions as a tertiary level or where complicated connective tissue/rheumatologic diseases are referred for further management from the entire Czech Republic, and also for primary rheumatologic continuity care. Dr. Tegzova

was the principal investigator and Dr. Forejtova, the Vice-Chair of the outpatient clinic as the co-PI for study C-1056 at Site CZ002. Both were present and available to respond to BIMO as well as clinical and scientific questions related to management of their SLE and rheumatology patients.

**b. Limitations of inspection:**

None.

**c. General observations/commentary:**

There was no evidence of under-reporting of adverse events. No discrepancies between the source records and the case report form (CRFs) were found. No prohibited medications and therapies during study C-1056 were administered, such as plasmapheresis, anti-TNF therapy (e.g., infliximab and etanercept), intravenous immunoglobulin, or IV cyclophosphamide. Study drug accountability documentation was maintained.

Similar to all other study sites in C-1056 as well as C-1057, the composite primary efficacy endpoint, BILAG Index assessment could not be verified, as this was a derived assessment.

At the end of the inspection at site CZ002, a Form FDA 483 was issued. Principally, the research investigation was not conducted in accordance with the investigational plan. Specifically, the following were protocol violations:

(1) Protocol violation: Did not meet eligibility criteria. During the screening phase of Study C-1056, Subject 05 had evidence of thrombocytopenia, which was a protocol exclusion criterion.

(2) Protocol violation: Developed and met withdrawal criteria, but patient was not withdrawn. During the course of research Study C-1056, Subject 15 met criteria for treatment failure and was to be withdrawn from the study per section 5.5 (Concurrent Medications) of the research protocol; however, subject was not withdrawn. [Note: Patient's methylprednisolone dose was increased from 4 to 12 mg during the study].

These FDA-verified observations were noted a priori by the study monitor CRO

(b) (4). During preliminary discussions regarding the inspectional observations with the principal investigator, in the presence of the study monitor as well as the Sponsor who provided input and assistance to the P.I., on October 27, 2010, there were two additional items not included on the Form FDA 483 that were verified by the Medical Officer and noted a priori by the study monitor during the conduct of study C-1056:

(1) Protocol violation: Did not meet eligibility criteria. During the screening phase of Study C-1056, Subject 04 did not meet eligibility criteria of stable standard therapy received while on warfarin treatment, as part of this patient's anticoagulant therapy. [Note: Dr. Tegzova considered an INR of 2.5 to 3.5 as therapeutic AC treatment for this specific patient, but there was a value of 2.31 during the screening period. Further, she conceded that it was and is challenging to maintain the patient at therapeutic levels due to numerous factors that affect INR such as diet, medication compliance, drug-drug

interactions, drug-dietary supplement interactions, or related patient co-morbid conditions].

(2) Protocol violation: Developed and met withdrawal criteria, but patient was not withdrawn. During both screening and the course of Study C-1056, Subject 07 met criteria for treatment failure and was to be withdrawn from the study per section 5.5 (Concurrent Medications) of the research protocol; however, subject was not withdrawn. [Note: Per Dr. Tegzova, the patient had bronchitis/URI (i.e., steroids for reasons other than SLE disease activity) at the screening period for which steroid was increased from methylprednisolone 6 mg to 10 mg. Further, patient also had another dose increase during the study to methylprednisolone to 10 mg for a SLE-related disease activity].

Finally, the PI, Dr. Tegzova, indicated the protocol itself was restrictive and the steroid medication titration was difficult to follow. In her future participation in clinical rheumatologic trials, she emphasized that her research team would advocate for ease of research protocol use, especially with the stringent and unclear rules for corticosteroid use. And, further, she would pointed this out during clinical trial investigator site initiation meetings or earlier, during protocol development if possible. The DSI Medical Officer concurred.

Specifically, DPARP were also interested in the following:

- (1) Were there pregnancies at this study site during C-1056? NO
- (2) Were there allergic study infusion reactions at this study site? Referable signs and symptoms of anaphylactic/anaphylactoid reactions during and post-study infusion were enumerated (e.g., presyncopal symptoms, pruritus, rash, shortness of breath, laryngeal edema, hypotension, dizziness, and other clinical features).

Per the procedures of the Czech Resuscitation Council, the study staff had to be certified every two years to be current in managing not only, cardiac life support events, but also in the face of any allergic reactions. From what I learned from Dr. Tegzova, antihistamines and hydrocortisone are examples of the usual cocktail of drugs administered during mild-moderate drug reactions during and post-study infusion as observed here, in addition to other clinical procedures in managing the patient.

Patients 05, 08, and 18 all developed drug infusion “allergic” reactions towards the end of the drug infusion. These patients described the reactions as “chills.” No other signs or symptoms of anaphylactic/anaphylactoid reactions were observed.

- (3) As with clinical site AT-001 in study C-1056, CZ002 also identified 8 patients who had lupus nephritis. Per PI, Patients 2, 4, 6, 13, 14, 17, 20 and 21 had prior evidence (i.e., prevalent case) of lupus nephritis (e.g., protein creatinine ratio of over 200 mg/mg protein, or confirmed by renal biopsy at the Institute of Rheumatology). In contrast, patient 21 developed lupus nephritis (i.e., incident case) during the course of the research study. Dr. Tegzova, PI, further described that, whenever possible, a renal biopsy is usually done for SLE patients seeking care at the Institute of Rheumatology to guide or to closely monitor therapy. The

biopsy is done with the patient on an overnight stay to monitor for potential complications related to the procedure. Specifically, this biopsy is ultrasound-guided by an experienced nephrologist who is specialized in this technique.

Despite the isolated regulatory deficiencies noted above, this clinical site appeared to adhere to good clinical practice. The ORA field investigator pointed out that the list of inspectional observations and the Establishment Inspection Report will be forwarded to the "Center" (*aka* CDER DSI) where this will undergo final review. Current inspection showed no discrepancies with source data, and no evidence of scientific fraud. The Medical Officer was privileged to have the (b) (4) who translated the primary source medical records of the PI, Dr. Tegzova and co-PI, Dr. Forejtova. The CRO (b) (4) study monitor translated documents for the ORA field staff. This provided optimal efficiencies in use of time, especially in the presence of translation challenges from Czech to English and vice versa.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Although regulatory violations were noted, these are considered isolated in nature and unlikely to importantly impact data reliability. The data in support of clinical efficacy and safety at this clinical site appear acceptable.

*NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.*

**PROTOCOL C-1057**

**1. Chia-Li Yu, M.D., Ph.D./Site TW011**

**Division of Rheumatology Immunology and Allergy**

**National Taiwan University hospital**

**Taipei, 100 TAIWAN**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from October 25 to 27, 2010. There were 37 subjects screened, 24 subjects were enrolled and randomized, and 24 subjects completed the study. A total of 24 study subject records were reviewed.

**b. Limitations of inspection:**

None.

**c. General observations/commentary:**

There was no evidence of under-reporting of adverse events. No deaths were reported. No discrepancies between the source records and the case report form (CRFs) were

found. Patients were properly consented. Study drug accountability documentation was maintained. The primary efficacy endpoints were verifiable for SELENA-SLEDAI and PGA. The BILAG primary endpoint could not be verified. No problems were noted in cross-checking procedures performed and laboratory tests. Current inspection showed no discrepancies with source data. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

The data in support of clinical efficacy and safety from this clinical site appear acceptable.

*NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.*

**2. James Cheng-Chung Wei, MD/Site TW010**  
**Department of Immunology-Rheumatology**  
**Chung Shan Medical University Hospital**  
**Taichung, 402 TAIWAN**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from October 18 to 20, 2010.

A total of 25 subjects were screened at this clinical site; 14 subjects were enrolled and randomized, and 13 subjects completed the study. There were four SAEs and no deaths in the study. All subject records were inspected for informed consent. There were 9 subject records that were reviewed for primary efficacy endpoint and adverse event data, and for other potential discrepancies between source documents and CRFs.

**b. Limitations of inspection:**

None.

**c. General observations/commentary:**

No evidence of under-reporting of adverse events was noted. Subject #11 (Placebo) dropped out due to pneumonia. No pregnancies occurred during the trial in C-1057. Test article accountability was documented adequately. This clinical site appeared to adhere to good clinical practice. Current inspection showed no discrepancies with source data. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

The data in support of clinical efficacy and safety from this clinical site appear acceptable.

*NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.*

## **SPONSOR**

**Human Genome Sciences (HGS)  
Shady Grove  
Rockville, MD**

### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.810 from September 7-8, 2010. The regulatory files for six randomly selected clinical sites for each study were reviewed during the inspection, which included monitoring reports, Investigator Agreements, Financial Disclosure forms, test article accountability records, Institutional Review Board approvals, and approved informed consent forms. Correspondence (a) between the sponsor and clinical sites regarding safety issues, (b) Data Monitoring Committee meeting minutes, (c) minutes of meetings between the study sponsor and the Contract Research Organization, (d) site monitoring plans, and (e) data management plans, respectively, were reviewed. No data line listing audits were performed as these were conducted at the clinical investigator sites where source documents are located.

### **b. Limitations of inspection:**

None.

### **c. General observations/commentary:**

Human Genome Sciences appears to have executed their sponsor responsibilities adequately and no significant issues were identified during the inspection. No Form FDA 483 was issued at the end of the inspection.

### **d. Data acceptability/reliability for consideration in the NDA review decision:**

The data in support of clinical efficacy and safety at the sponsor site appear acceptable.

## **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four foreign clinical investigator sites and the sponsor were inspected in support of this application for study Protocols C-1056 and C-1057, respectively, in support of this fast-track BLA application for belimumab, an NME, in the treatment of SLE.

In general, inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Although minor regulatory violations were noted for the Vienna (AT001) and Prague (CZ002) sites, these are not

pervasive in nature, and are unlikely to impact data integrity and patient safety. The data generated by these inspected sites appear reliable in support of the application. The sponsor appeared to execute its responsibilities properly in the conduct of studies C-1056 and C-1057, respectively.

While the SELINA-SLEDAI and PGA endpoints could be verified, BILAG as part of the trial's composite primary efficacy endpoint per protocol could not be verified at both the Taiwan sites (TW010 and TW011, respectively), and also for the Czech (CZ002) and Austrian (AT001) sites. DSI recommends that the algorithm to convert the raw 86-item scores into numeric and alphabetical (A to E) scores, respectively, (via a programming software) be clarified descriptively and quantitatively. DSI, however, defers this matter to both Biostatistics and Medical Teams for further consideration.

The data, at the limited number of inspected clinical sites and sponsor's data repository site, are acceptable and appear reliable in support of the NDA application.

**Note:** Observations noted above, for these four foreign clinical sites (Austria, Czech Republic and Taiwan (2)), are based on the Form FDA 483 or preliminary communications from field investigator, an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.



/Anthony Orenca, M.D./

Anthony Orenca, M.D.

Medical Officer

Good Clinical Practice Branch II

Division of Scientific Investigations

CONCURRENCE:



/Tejashri Purohit-Sheth, M.D./

Tejashri Purohit-Sheth, M.D.

Branch Chief

Good Clinical Practice Branch II

Division of Scientific Investigations

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA  
CONSULT #11,243**

**Consultant Reviewer:** Gregory M. Dubitsky, M.D.  
Medical Officer  
Division of Psychiatry Products

**Consultation Requestor:** Jessica Benjamin  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and  
Rheumatology Products

**Subject of Request:** BLA 125370: Belimumab/Neuropsychiatric  
Adverse Events

**Date of Request:** October 14, 2010

**Date Received:** October 14, 2010

**Desired Completion Date:** November 2, 2010

**I. Background**

Human Genome Sciences, Inc., has submitted BLA 125370, which is intended to support a licensing application for Benlysta® (belimumab) in the treatment of patients with active, seropositive systemic lupus erythematosus (SLE). Belimumab is a recombinant human monoclonal antibody that binds to soluble B lymphocyte stimulator (BLyS) and inhibits its activity. This action results in a decrease in B-cell proliferation and antibody production, events felt to be important in the pathogenesis of SLE.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is reviewing this application and has noted a possible imbalance in suicides and other neuropsychiatric adverse events in the safety database. They have consulted with the Division of Psychiatry Products (DPP) to address the following two questions:

- 1) Do you believe this imbalance represents a neuropsychiatric safety signal in this population?
- 2) Do you recommend any specific analyses that would be helpful in providing clarification of this issue (i.e., Columbia Classification Algorithm of Suicide Assessment (C-CASA))?

## II. Review Of Clinical Data

### A. Description of Relevant Clinical Trials

Relatively high rates of psychiatric symptoms among patients with SLE have been reported. For example, Wolfe and colleagues reported a rate of current comorbid depression, adjusted for age and gender, of 21% in a sample of 1,316 SLE patients.<sup>1</sup> Thus, an evaluation of adverse events associated with belimumab treatment in SLE patients seems most fruitfully conducted by focusing on data from placebo-controlled trials. Therefore, this review concentrates on the three placebo-controlled studies in SLE described in this application: LBSL02, C1056, and C1057. These studies are summarized in Table 1 below.

<b>Study</b>	<b>Description</b>
LBSL02	Phase 2, randomized, double-blind, 52 week study of 3 doses (1.0, 4.0, and 10.0 mg/kg IV). N=336 on drug, 113 on placebo.
C1056	Phase 3, randomized, double-blind, 72 week study of 2 doses (1 and 10 mg/kg IV). N=544 on drug, 275 on placebo.
C1057	Phase 3, randomized, double-blind, 52 week study of 2 doses (1 and 10 mg/kg IV). N=578 on drug, 287 on placebo.

In all three studies, patients were randomized in equal proportions to one of two or three fixed doses of belimumab or placebo. Study drug was given in addition to “standard of care” treatment. Doses were administered by intravenous infusion over at least 2 hours (LBSL02) or over 1 hour (C1056 and C1057) on study days 0, 14, 28, and every 28 days thereafter.

No instruments specific to psychiatric symptoms (such as the Columbia-Suicide Severity Rating Scale or C-SSRS) were utilized in these studies.

Given differences in study design across these three trials, it was decided not to pool these studies for the purposes of this review.

### B. Assessment of Adverse Event Coding

Prior to assessing a potential safety signal based on adverse event coded terms, it is important to establish that the coding of investigator, or verbatim, terms to preferred terms was acceptable. Accordingly, I examined the adverse event dataset (ae.xpt) using JMP 7 for each of the above three studies in the following fashion:

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<sup>1</sup> Wolfe F, et al. Chronic Conditions and Health Problems in Rheumatic Diseases: Comparisons with Rheumatoid Arthritis, Noninflammatory Rheumatic Disorders, Systemic Lupus Erythematosus, and Fibromyalgia. *J Rheumatol* 2010;37:305-315.

1) I examined all verbatim terms that were coded to a preferred term not under the “Psychiatric Disorders” System Organ Class to insure that no psychiatric adverse event was miscoded to a term in another body system. No such miscoding was identified.

2) I then examined all verbatim terms coded to a preferred term under the “Psychiatric Disorders” System Organ Class to insure that coding was accurate and that no appreciable splitting or lumping of terms had occurred during the coding process. In general, the coding was acceptable. However, it did appear that splitting of verbatim terms related to anxiety and depression had occurred. More specifically, verbatim terms related to anxiety were coded to the following preferred terms:

- anxiety.
- anxiety disorder.
- nervousness.
- generalised anxiety disorder.

Also, verbatim terms related to depressed mood were coded to one of the following preferred terms:

- depressed mood.
- depressive symptom.
- depression.
- major depression.

Thus, the reporting rates presented by the sponsor for these preferred terms are likely to underestimate the actual reporting rates for anxiety- and depression-related events. It is recommended that the sponsor reanalyze these data to combine the four anxiety-related preferred terms into a single composite term and do likewise for the four depression-related preferred terms.

### **C. Evaluation of Reporting Rates of Psychiatric Adverse Events**

I reviewed tables of reporting rates for all preferred terms under the Psychiatric Disorders System Organ Class for each of the three placebo-controlled studies.<sup>2</sup> Within each study, mean patient exposure was not substantially different across treatment groups, including placebo. Hence, there was no compelling need to adjust reporting rates for exposure.

For most events, the number of patients reporting the event was very low (1 or 2), making a definitive assessment of drug-relatedness difficult. For many other events, drug rates approximated or were less than placebo rates or the dose-response pattern was not compatible with drug-relatedness (e.g., rates in the

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<sup>2</sup> The following tables within each Clinical Study Report were examined: Table T11a for LBSL02, Table T30 for C1056, and Table T30 for C1057.

high dose group were substantially lower than in the low dose rate). The reporting rates for “depression” in study C1056 suggested a safety signal, where drug rates were about twice the placebo rate:

Placebo	2.9% (8/275)
1 mg/kg	5.5% (15/271)
10 mg/kg	5.9% (16/273)

But this finding was not confirmed in the other two studies, where rates in the high dose group were only slightly higher than placebo rates.

An examination of adverse events coded as serious, as defined in 21CFR 312.32(a), similarly revealed a potential signal for “depression” in study C1056:

Placebo	0.0% (0/275)
1 mg/kg	0.7% (2/271)
10mg/kg	0.7% (2/273)

Again, this finding was not replicated in the other two placebo-controlled studies.

Of note, there were two completed suicides in these studies:

- subject US034-002, a 43 year old female in the 1.0 mg/kg dose group in study LBSL02, committed suicide by gunshot wound (b) (4) after receiving her second dose on study (b) (4). She had an ongoing diagnosis of depression, which was being treated with citalopram.
- subject KR008-001, a 23 year old Asian female in the 10 mg/kg dose group in study C1057, committed suicide (b) (4) after the last dose on (b) (4) of the study. There was a past history of, but no current, depression and psychosis due to a general medical condition. Her suicide was attributed by her family to a conflict with her father.

Otherwise, in terms of suicidal ideation and behavior, only one other patient in these trials was reported to have experienced suicidal ideation (in the 4.0 mg/kg dose group in study LBSL02).

Suicide and suicide attempts are not uncommon among patients with SLE. For instance, Harris and Barraclough reported a four-fold increase in suicide risk in SLE patients over that expected for a population cohort adjusted for observation period, age, and gender.<sup>3</sup> The small number of reports of suicidal behavior and ideation in these trials suggest that ascertainment of these events was incomplete. The use of the C-SSRS in future trials with belimumab is strongly recommended to improve the detection of these events.

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<sup>3</sup> Harris E and Barraclough B. Suicide as an Outcome for Medical Disorders. *Medicine* 1994;73:281-296.

### **III. Conclusions**

Based on the presented reporting rates for psychiatric adverse events in the three placebo-controlled SLE studies, I find no convincing evidence of a signal for belimumab-related psychiatric experiences. Of course, this is not to say that a psychiatric safety signal has been definitively ruled out. An important limitation in the assessment of these data is probable incomplete ascertainment of psychiatric events, including suicidal thoughts and behavior.

The occurrence of two suicides, both on drug, merits careful consideration. If suicide were a rare event in the SLE population, I would be more inclined to view these events as a signal for suicidality. Other factors that might hint that these are drug-related events are a dose-response relationship (e.g., if both occurred in the high dose group) or a temporal clustering of the events (e.g., if both occurred very early in treatment). However, none of these factors were operative and I cannot conclude that belimumab treatment plays a significant etiologic role in suicide at this time. Although both cases involve possible non-drug explanatory factors (depression in one and conflict with a parental figure in the other), these do not necessarily vindicate belimumab since any pro-suicidal properties of the drug may have compounded the effects of depression and psychosocial stress in leading these patients to commit suicide.

### **IV. Recommendations**

As discussed in section II.B above, I recommend that the sponsor be asked to recalculate the reporting rates for anxiety-related and depression-related adverse events in the three placebo-controlled trials after combining similar preferred terms. A more distinct signal may emerge from the recalculated reporting rates.

In addition, to improve the timely ascertainment of suicidality-related events in studies with belimumab, it is strongly recommended that future protocols rate patients using the C-SSRS at baseline and at each visit. You may wish to refer to our draft Guidance for Industry regarding the prospective assessment of suicidality in clinical trials located at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf>

Also, systematic assessment of depression and anxiety is suggested in future trials to clarify any signals for these psychiatric symptoms.

Based on my review of the adverse event verbatim terms and the reporting rates of suicidal behavior and ideation in these trials, I do not think that a formal analysis of these data using the C-CASA classification will be productive and it is not recommended.

Please let us know if you have any questions or require further advice regarding this issue.

A handwritten signature in black ink, appearing to read "Gregory M. Dubitsky, M.D.", with a stylized flourish at the end.

Gregory M. Dubitsky, M.D.  
October 29, 2010

cc: BLA #125370  
HFD-130/Dubitsky  
/Zhang  
/Mathis  
/Laughren  
/Berman  
HFD-170/Benjamin  
/Neuner

SUPERVISORY CONCURRENCE/NON-CONCURRENCE

1 concur.

[Redacted] (b) (6)

Medical Team Leader

Nov. 1, 2010

[Redacted] (b) (6)

Director, DPT

11-3-10

**Inspection Waiver Memorandum**

**Date:** October 15, 2010  
**From:** Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT  
**To:** BLA File – STN 125370/0  
**Subject:** Recommendation to waive a pre-approval inspection at the drug product manufacturing facility  
**Sponsor:** Human Genome Sciences, Inc., U.S. License # 1820  
**Facility:** (b) (4)  
**Product:** Benlysta® (belimumab)  
**Dosage:** Lyophilized powder for intravenous infusion, 80 mg/mL after reconstitution  
**Indication:** (b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus  
**Through:** Patricia Hughes, Ph.D., Team leader, *APR 10/21/10*  
CDER/OC/DMPQ/MAPCB/BMT

**Waiver Recommendation:**

There are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at (b) (4). Based on the compliance history of (b) (4), concurrence is requested to waive the pre-approval inspection at (b) (4).

**Clearance Routing**

*[Signature]* CONCUR / DO NOT CONCUR      DATE 11/8/10

*fr* Rick Friedman, Director, Division of Manufacturing and Product Quality, Office of Compliance, CDER

*[Signature]* CONCUR / DO NOT CONCUR      DATE 10/25/2010  
Kathleen Clouse, Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, Office of Pharmaceutical Science, CDER, HFD-123

**Summary:**

Human Genome Sciences, Inc. (HGS) has submitted this BLA for belimumab drug product to treat adult patients with active, autoantibody positive system lupus erythematosus (SLE) who are receiving standard therapy. The drug product is manufactured at (b) (4). Based on a review of the submission and the compliance history of (b) (4), the pre-approval inspection should be waived.

**Facility Information**

(b) (4) is a multi-product facility. Other products include drugs (human and veterinary) and biologics. There is no manufacture of products containing penicillin, cephalosporin, live viruses, spore-forming organisms, or cytotoxic drugs on the (b) (4) filling line. All product-contact equipment associated with the belimumab process is product dedicated and/or single use. Only one product is allowed in a given area at a given time.

The process includes:

(b) (4)

**Supporting information**

Relevant inspectional history --

(b) (4)

Inspection  
Dates

(b) (4)

Inspection conclusions

The GMP inspection was conducted by (b) (4). The (b) (4) profiles were covered. The inspection covered Quality, Production, and Laboratory systems. The inspection was classified NAI.

The inspection was conducted by (b) (4). The inspection is a pre-approval inspection for a NDA product and also covered biological products (b) (4). The systems covered included Quality, material, production, laboratory, and facilities. The inspection was classified NAI. The (b) (4) profiles were covered.

**Evaluation of criteria that may warrant inspection**

The following information is provided in support of waiving the pre-approval inspection in accordance with SOPP 8410 v.2, effective Dec. 4, 2001:

*1. The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4) is approved for manufacturing licensed biological products, including (b) (4)

*2. FDA has not inspected the establishment in the last 2 years.*

(b) (4) was last inspected on (b) (4) The inspection was classified as NAI.

*3. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

No serious or systemic GMP deficiencies were identified during the recent inspections that indicate a need for extra inspectional scrutiny.

*4. The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

The facility is a multi-product facility and no new areas are involved. The previous two inspections covered biological products. The 2009 inspection covered (b) (4) profiles.

*5. The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:*

The manufacturing process for this BLA is substantially equivalent to other parenteral products manufactured in the same facility.

Signed:

Bo Chi, WO, Building 51 (b) (6) DATE 10/21/10

(b) (4) inspection waiver, STN 125370/0

Sean Fitzsimmons, HFD-123



DATE 10-22-2010

Marjorie Shapiro, HFD-123

DATE 10-22-10

Jessica M. Benza  
21 July 2010

### RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # BLA# 125370	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Benlysta Established/Proper Name: belimumab Dosage Form: 10mg/kg every 2 weeks for 1 <sup>st</sup> 3 doses, then every 4 weeks thereafter Strengths:		
Applicant: Human Genome Sciences Agent for Applicant (if applicable):		
Date of Application: June 9, 2010 Date of Receipt: June 9, 2010 Date clock started after UN:		
PDUFA Goal Date: December 9, 2010	Action Goal Date (if different):	
Filing Date: August 6, 2010	Date of Filing Meeting: July 21, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s) <sup>(b) (4)</sup> in adult patients with active, antibody-positive SLE in combo with standard 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:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>            and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<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>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): IND 9970				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system?  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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 Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				X	
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)]?				X	
<p><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></p>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>				X	
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>			X		
<b>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</b>				X	
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>					

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements only)  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?			X	
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)?  If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input 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?			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 ( <i>BLA</i> s/ <i>BLA</i> efficacy supplements) including:  <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)  If no, explain.	X			

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

<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act</i>				

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...”				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</b>  <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>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	X			
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	X			

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

<b>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)</b>	X			
<i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>				
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?		X		Risk Management Plan was submitted
<i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>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?</b>				

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

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<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? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
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?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent: DSI 9/10/2010</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? Date(s): 4/26/2006	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/8/2010	X			
<i>If yes, distribute minutes before filing meeting</i>				

<b>Any Special Protocol Assessments (SPAs)?</b> <b>Date(s):</b> 10/19/2006  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			
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ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 21, 2010

**BLA/NDA/Supp #:** BLA 125370

**PROPRIETARY NAME:** Benlysta

**ESTABLISHED/PROPER NAME:** belimumab

**DOSAGE FORM/STRENGTH:** 10 mg/kg every 2 weeks for 1<sup>st</sup> 3 doses, than every 4 weeks thereafter

**APPLICANT:** Human Genome Sciences

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** (b) (4) in adult patients with active antibody-positive SLE in combination with standard therapy

**BACKGROUND:** IND 9970

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Rosemarie Neuner	Y
	TL:	Sarah Okada	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:	Ping Ji	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Ruthie Davies	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mamata De	Y
	TL:	Molly Topper	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sean Fitzsimmons	Y
	TL:	Marjorie Shapiro	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kalavati Suvarna Bo Chi	Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Michael Orenca	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: 11/16/2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <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
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

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

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Curtis Rosebraugh  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are 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 type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>

<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other