

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125370Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

NDA/BLA#: BLA 125370

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: DPARP

PDUFA Goal Date:
December 9, 2010

Stamp Date: 6/9/2010

Proprietary Name: Benlysta (under review)

Established/Generic Name: belimumab

Dosage Form: IV infusion

Applicant/Sponsor: Human Genome Sciences

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

- (1) _____
- (2) _____
- (3) _____
- (4) _____

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

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____ ^{(b) (4)} in adult patients with active, autoantibody-positive SLE in combination with standard therapy

Q1: Is this application in response to a PREA PMR?

Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

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

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

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

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

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

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

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

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients

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

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

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

☐ Justification attached.

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

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

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

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

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	4 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ y r. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

justification):

‡ Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☒ Justification attached.

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

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

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

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification [†]
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	5 yr. 0 mo.	(b) (4) mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

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

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

(b) (4)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

(See appended electronic signature page)

Gosia M. Ben
Regulatory Project Manager

OCT 04 2010

(Revised: 6/2008)

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



Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850
United States
+1-240-314-4400

03 June 2010

BB-IND 9970

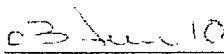
Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

RE: Human Genome Sciences, Inc. (HGS)
Belimumab; BENLYSTA® (Monoclonal Anti-BLyS Antibody)
Biologics License Application (BLA) Number 125370
Debarment Certification Letter

Dear Dr. Chowdhury:

Human Genome Sciences, Inc. (HGS) 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.


Sally Bolmer, PhD, RAC


Date

Senior Vice President
Development and Regulatory Affairs
Human Genome Sciences, Inc
Telephone: 301-610-5806
Fax: 301-309-0311
sally_bolmer@hgsi.com

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125370	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Benlysta® Established/Proper Name: belimumab Dosage Form: intravenous infusion		Applicant: Human Genome Sciences, Inc. Agent for Applicant (if applicable):
RPM: Philantha Montgomery Bowen		Division: DPARP
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 55%;"> <p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>March 10, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

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

❖ Application Characteristics ²		
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):		
<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation		
<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC		
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies		BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request		REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required
Comments:		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)		<input checked="" type="checkbox"/> Yes, dates : 2/1/11
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated		<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

If "No," continue with question (3).

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist³

Officer/Employee List

- ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

☒ Included

Documentation of consent/non-consent by officers/employees

☒ Included

Action Letters

- ❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) AP: 3/9/11

Labeling

- ❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

3/2/11

6/9/10

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/18/11
• Original applicant-proposed labeling	11/23/10
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	2/17/11
❖ Proprietary Name	Letter & review - 8/13/10 Final Review 2/25/11
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	
• Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 1/31/11 <input checked="" type="checkbox"/> DMEPA 11/23/10; 2/24/11 <input checked="" type="checkbox"/> DRISK 2/10/11; 2/11/11 <input checked="" type="checkbox"/> DDMAC 2/14/11 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews - OBP 2/22/11 Labeling Mtgs: 1/5/11; 1/21/11
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	7/21/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	<input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC 10/6/10 If PeRC review not necessary, explain: _____	
• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

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

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	6/11/10; 8/13/10; 9/14/10; 9/21/10; 9/27/10; 10/14/10; 10/15/10; 10/19/10; 11/5/10; 11/12/10; 11/29/10; 12/3/10; 12/7/10; 12/15/10; 12/8/10; 1/13/11; 1/27/11; 1/31/11; 2/1/11; 2/14/11; 2/17/11; 2/18/11; 2/24/11; 3/2/11; 3/4/11
❖ Internal memoranda, telecons, etc.	1/7/11
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	11/16/10
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	11/16/10
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/9/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/9/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/17/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 13
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	7/26/10; 2/18/11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review: 2/18/11 (pg. 17)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	Submissions: 11/23/10; 2/23/11 <input type="checkbox"/> None Review - 2/11/11
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 11/4/10
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/21/10; 2/18/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/2/10; 11/10/10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/3/11
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/14/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/21; 11/24/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/17/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/16/10; 10/14/10; 11/29/10
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	7/16/10; 11/10/10; 11/15/10; 11/30/10; 12/20/10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	11/29/10
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: 3/1/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

(b) (6)

/Philantha Montgomery Bowen/
Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
CDER, DPARP, OND, ODE II

Date: March 9, 2011

Supervisory Comment/Concurrence:

(b) (6)

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

Date: March 9, 2011

Bowen, Philantha

From: Diana Daly [Diana_Daly@hgsi.com]
Sent: Friday, March 04, 2011 1:47 PM
To: Bowen, Philantha
Cc: Michele Shannon
Subject: RE: BLA 125370 - (belimumab) - FDA Request for Medication Guide Revisions

Thanks Philantha.

Diana

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Friday, March 04, 2011 1:45 PM
To: Diana Daly
Cc: Michele Shannon
Subject: RE: BLA 125370 - (belimumab) - FDA Request for Medication Guide Revisions

Hi Diana,

Your application is still under review. So the request/comment is not all-inclusive and we may have additional comments and/or requests as we continue our review of the Medication Guide.

Sincerely,
Philantha

From: Diana Daly [mailto:Diana_Daly@hgsi.com]
Sent: Friday, March 04, 2011 1:34 PM
To: Bowen, Philantha
Cc: Michele Shannon
Subject: RE: BLA 125370 - (belimumab) - FDA Request for Medication Guide Revisions

Hi Philantha,

We have received your request, and have shared with the team and will submit to you by email 10am on Monday at the latest, and will officially file to the BLA by Monday as well.

We were wondering if this was likely to be the only requested change to the Medication Guide?

Thanks!

Diana

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Friday, March 04, 2011 1:17 PM
To: Diana Daly
Cc: Michele Shannon
Subject: BLA 125370 - (belimumab) - FDA Request for Medication Guide Revisions
Importance: High

3/7/2011

Hello Ladies,

Your submission dated February 23, 2011, to BLA 125370 is currently under review and we have the following request for revisions to the Medication Guide:

What is the most important information I should know about BENLYSTA? BENLYSTA can cause serious side effects. Some of these side effects may cause death. (b) (4)

Tell your healthcare provider right away if you have any of the symptoms listed below while receiving BENLYSTA.

The underlined sentence should be revised to read: **It is not known if BENLYSTA causes these serious side effects.**

We are requesting that you submit a response by 10 AM, Monday, March 7, 2011. Submit your response officially to the BLA.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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From: Diana Daly [mailto:Diana_Daly@hgsi.com]
Sent: Friday, March 04, 2011 11:31 AM
To: Bowen, Philantha
Cc: Michele Shannon
Subject: BLA 125370; Medication Guide

Hi Philantha,

I just wanted to check in with you to see if the next version of FDA comments on the Medication Guide might come to us today. I want to make sure we have the right people available on the weekend so we can respond quickly.

3/7/2011

Many thanks, Diana



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: March 2, 2011

To: Diana Daly

Company: HGS, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Montgomery Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 FDA Labeling Recommendations #3: Package Insert

of Pages including cover: 19

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

BLA 125370
Benlysta® (belimumab)
Human Genome Sciences, Inc.

DATE: March 2, 2011

Your submissions dated December 1, 2010, and February 8 and 25, 2011, to BLA 125370 are under review and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label. Submit revised labeling incorporating changes shown in the attached marked up Package Insert. Submit a clean copy and a tracked change version of the label by 10 AM, Friday, March 4, 2011, to the BLA. In addition, please forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert: FDA Recommendations (#3)

Drafted: Bowen/March 2, 2011

Clearance: Barnes/March 2, 2011
Okada/March 2, 2011
Chowdhury/March 2, 2011

Finalized: Bowen/March 2, 2011

Bowen, Philantha

From: Ramanadham, Mahesh
Sent: Tuesday, March 01, 2011 10:23 AM
To: Bowen, Philantha; CDER-TB-EER
Cc: Chi, Bo; Suvarna, Kalavati
Subject: RE: BLA 125370 - FINAL TB-EER (w/in 30 days)
Attachments: BLA STN125370-0 final.doc

Hi Philantha and Bo,

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Human Genome Science's STN 125370/0. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this BLA.

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Division of Manufacturing and Product Quality,
Manufacturing Assessment and Pre-Approval Compliance Branch
(301)796-3272

From: Bowen, Philantha
Sent: Monday, February 28, 2011 8:29 AM
To: CDER-TB-EER
Cc: Chi, Bo; Suvarna, Kalavati
Subject: BLA 125370 - FINAL TB-EER (w/in 30 days)
Importance: High

Hello,

I am following up on the Final TB-EER for BLA 125370 (belimumab). Per the BLA process, a final report is generally provided within 30 days of the goal date. We acknowledge the report provided in December. The PDUFA date was extended for this application which is March 10, 2011. We are planning to take action, however, on March 9, 2011.

Thanks!

Philantha

3/2/2011

From: Chi, Bo
Sent: Thursday, December 02, 2010 9:24 PM
To: Bowen, Philantha
Cc: Hong, Jaewon; Suvarna, Kalavati
Subject: RE: Final TB-EER Response for new BLA STN125370/0

Hi Philantha,
The E-mail I forwarded to you is sufficient.

Bo

From: Bowen, Philantha
Sent: Thursday, December 02, 2010 8:31 AM
To: Chi, Bo
Cc: Hong, Jaewon; Suvarna, Kalavati
Subject: RE: Final TB-EER Response for new BLA STN125370/0

Hi Bo,

Will I be receiving the official TB-EER report sheet?

Sincerely,

Philantha

From: Chi, Bo
Sent: Wednesday, December 01, 2010 8:29 PM
To: Bowen, Philantha
Cc: Hong, Jaewon; Suvarna, Kalavati
Subject: FW: Final TB-EER Response for new BLA STN125370/0

FYI

From: Pohlhaus, Timothy
Sent: Wednesday, December 01, 2010 2:29 PM
To: Chi, Bo
Cc: Suvarna, Kalavati; Pohlhaus, Timothy; CDER-TB-EER
Subject: Final TB-EER Response for new BLA STN125370/0

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Human Genome Science's STN 125370/0. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this BLA.

Timothy J. Pohlhaus, Ph.D.

3/2/2011

Interdisciplinary Scientist, Chemist
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 1333
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Chi, Bo
Sent: Wednesday, November 17, 2010 11:48 AM
To: CDER-TB-EER
Cc: Suvarna, Kalavati
Subject: Final TB-EER Response for new BLA STN125370/0

Hi,
Please provide a final TB-EER response for HGS' new BLA STN125370/0. The PDUFA date is 12/9/2010. Thanks.

Bo

Drug substance

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850
FEI: 1000303703
Responsibility: [REDACTED]

(b) (4)

Inspected September 6 - October 1, 2010 by CDER-DMPQ and classified VAI. This was a pre-license inspection in support of belimumab (STN 125370/0) drug substance manufacturing. The TRP profile was covered and is acceptable.

Human Genome Sciences, Inc.
9911 Belward Campus Drive
Rockville, MD 20850
FEI: 3003782237
Responsibility: [REDACTED]

(b) (4)

Inspected by CDER-DMPQ April 19-30, 2009 in support of BLA STN 125364/0 and classified VAI. The inspection was comprehensive and systems-based. The TRP profile was covered and is considered acceptable.

This site was also inspected September 6 - October 1, 2010 by CDER-DMPQ in support of belimumab (STN 125370/0) drug substance manufacturing. The inspection was reported

3/2/2011

under FEI 1000303703 since the inspection primarily covered the Shady Grove Road Address (above).

(b) (4)

This (b) (4) facility was inspected by (b) (4) and classified NAI. The CTL profile was covered and is considered acceptable.

(b) (4)

FEI (b) (4) was inspected (b) (4) and classified VAI. The CTL profile was covered and is acceptable. FEI (b) (4) was inspected (b) (4), covering (b) (4) and was classified NAI.

Drug Product

(b) (4)

Inspected (b) (4) and classified NAI. The (b) (4) profiles were covered and are considered acceptable.

(b) (4)

Inspected by (b) (4) and classified NAI. The CTL profile was covered and is considered acceptable. Biologic product manufacturing was also covered during an

(b) (4) inspection by (b) (4) That inspection was classified NAI.

(b) (4)

Inspected (b) (4) and classified NAI. The CTL profile was covered and is considered acceptable.

Thanks.

Bo

3/2/2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: February 24, 2011

To: Diana Daly

Company: HGS, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Montgomery Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 FDA Labeling Recommendations #2: Package Insert

of Pages including cover: 19

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Thank you.


BLA 125370
Benlysta® (belimumab)
Human Genome Sciences, Inc.

DATE: February 24, 2011

Your submissions dated December 1, 2010, and February 8, 2011, to BLA 125370 are under review and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label. Submit revised labeling incorporating changes shown in the attached marked up label for the Package Insert. Submit a clean copy and a tracked change version of the label by 10 AM, Monday, February 28, 2011, to the BLA. In addition, please forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert: FDA Recommendations (#2)

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

Drafted: Bowen/February 24, 2011

Clearance: Barnes/February 24, 2011
Okada/February 24, 2011
Seymour/February 24, 2011
Chowdhury/February 24, 2011

Finalized: Bowen/February 24, 2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: February 18, 2011

To: Diana Daly, Executive Director
Regulatory Affairs

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) Post-Marketing Commitments and
Requirements

of Pages including cover: 4

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Thank you.

Reference is made to discussions regarding the clinical post-marketing requirements (PMRs) and commitments (PMCs) for your BLA 125370 for Benlysta®. We are requesting the following three additional PMCs: Submit the final study reports for ongoing studies LBSL99, C1066, and C1074. In addition, we request timelines for the other PMCs/PMRs previously discussed. We are providing a summary of the agreed upon clinical PMRs and PMCs, as well as the three new PMCs. We request your agreement to conduct the following post-marketing requirements and commitments. Provide the requested milestone timelines for each.

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

Final Protocol Submission: March 2012
Final Report Submission: January 2013

2. Conduct a randomized clinical trial to evaluate the effects of Benlysta treatment on therapeutic vaccines. B cell-dependent antigens (e.g. pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

Final Protocol Submission: December 2011
Study Completion Date: March 2014
Final Report Submission: September 2014

3. Pregnancy registry to evaluate pregnancy outcomes for women exposed to Benlysta during pregnancy.

Final Protocol Submission: July 2011
Study Completion Date: Month, year
Final Report Submission: Month, year

4. Randomized, Placebo-Controlled Clinical Trial with Benlysta in 5000 Patients with Active, Autoantibody-Positive Systemic Lupus Erythematosus

Final Protocol Submission: September 2011
Trial Completion: May 2018 (1 year data)
May 2019 (2 year data)
May 2022 (5 year data)
Final Report Submission: Month, Year (1 year data)
Month, Year (2 year data)
May 2023 (5 year data)

5. Conduct a randomized, controlled clinical trial in patients with lupus nephritis to evaluate the efficacy and safety of Benlysta.

Final Protocol Submission: Month, Year
Trial Completion: Month, Year
Final Report Submission: Month, Year

6. Conduct a randomized, controlled clinical trial to evaluate the efficacy and safety of Benlysta in black patients with SLE.

Final Protocol Submission: November 2011
Trial Completion: July 2017
Final Report Submission: January 2018

7. Submit a final study report for long-term open-label continuation study LBSL99.

Study Completion: Month, Year
Final Report Submission: Month, Year

8. Submit a final study report for long-term open-label continuation study C1066.

Study Completion: Month, Year
Final Report Submission: Month, Year

9. Submit a final study report for long-term open-label continuation study C1074.

Study Completion: Month, Year
Final Report Submission: Month, Year

10. Phase 2, multi-center study to evaluate the safety, efficacy and pharmacokinetics of belimumab plus background standard therapy in 100 pediatric subjects 5 years to 17 years of age with active systemic lupus erythematosus (SLE).

Final Protocol Submission: August 2011
Study/Trial Completion: March 2016
Final Report Submission: October 2016

Submit your agreement to conduct the post-marketing requirements and commitments officially to the BLA and forward a courtesy to me via email. In the submission, include the PMR/PMC milestone schedule for each. We request that you submit a response by February 23, 2011.

If you should have any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'Philantha M. Bowen', with a large, stylized initial 'P'.

/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology

Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/January 17, 2011

Clearance: Barnes/January 17, 2011
Seymour/January 18, 2011
Okada/January 18, 2011
Neuner/January 18, 2011

Finalized by: Bowen/January 18, 2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2011

To: Diana Daly, Executive Director	From: Philantha Bowen Regulatory Project Manager
Company: Human Genome Sciences, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-309-0311	Fax number: 301-796-9718
Phone number: 240-314-4400	Phone number: 301-796-2466

Subject: BLA STN 125370 – FDA Recommendations for a Revised Medication Guide and REMS

Total no. of pages including cover: 18

Comments: Time-Sensitive

Document to be mailed: ☐ Yes ☒ No

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Date: February 18, 2011

Please refer to your BLA submission dated June 9, 2010. We also refer to your November 23, 2010, submission which provided a draft Risk Evaluation and Mitigation Strategy (REMS) and Medication Guide for Benlysta®. We have the following comments and proposed revised REMS and Medication Guide. These comments are not all-inclusive and we may have additional comments as your REMS submission is currently under review. Please ensure that all communication materials accurately reflect the most recent language used in labeling. We ask that you respond to our comments and submit the revised proposed REMS with appended materials and the REMS Supporting Document, and Medication Guide by COB February 23, 2011, in order to facilitate our review. Provide a track changes and clean version of all revised materials and documents.

(b) (4)

- b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document. See our editorial comments on this section of the proposed REMS (see Appendix A)
- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that the Medication Guide should be dispensed to each patient at the infusion site immediately prior to each infusion of Benlysta (belimumab) for injection. You also state that the Medication Guide will be available via sales representatives, the patient and professional web sites for Benlysta (belimumab) for injection, in patient promotional materials, and available when requested from the toll-free product information line. We find this distribution plan acceptable.
 - We remind you that under 21 CFR 208.24, you are responsible for ensuring that the Benlysta (belimumab) for injection carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We suggest the following language if the product is enclosed in the carton. "Dispense accompanying Medication Guide to each patient."

(b) (4)

If there are any questions, contact Philantha Montgomery Bowen, Senior Regulatory Health Project Manager, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/
Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachments: FDA Proposed REMS
FDA Proposed Medication Guide

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

Bowen, Philantha

From: Bowen, Philantha
Sent: Thursday, February 17, 2011 7:59 AM
To: 'Diana Daly'
Cc: Michele Shannon; Christine Pannunzio
Subject: RE: BLA 125370 - CMC PMR: Immunogenicity Final Protocol

Hi Diana,

Your agreement in the email below in response to our request is sufficient.

Sincerely,

Philantha

From: Diana Daly [mailto:Diana_Daly@hgsi.com]
Sent: Wednesday, February 16, 2011 1:05 PM
To: Bowen, Philantha
Cc: Michele Shannon; Christine Pannunzio
Subject: RE: BLA 125370 - CMC PMR: Immunogenicity Final Protocol

Hi Philantha,

This is fine. Would you like us to resubmit the commitment letter with updated wording or is agreement in this email sufficient?

Diana

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Wednesday, February 16, 2011 12:26 PM
To: Diana Daly
Cc: Michele Shannon
Subject: BLA 125370 - CMC PMR: Immunogenicity Final Protocol

Hi,

In your submission dated February 11, 2011, to BLA 125370 (belimumab), submitted in response to our request for a CMC Post-Marketing Requirement for an improved immunogenicity assay, we note that (b) (4)
Please submit your final protocol for this CMC PMR to the IND application, not the BLA.

Sincerely,

Philantha

2/18/2011

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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Bowen, Philantha

From: Greeley, George
nt: Monday, February 14, 2011 12:15 PM
: Bowen, Philantha
Subject: FW: BLA 125370 Benlysta

Importance: High

Hi Philantha,

Here is the summary of the PeRC review for Benlysta.

Thanks,
George

From: Greeley, George
Sent: Friday, October 15, 2010 10:11 AM
To: Benjamin, Jessica
Cc: Salis, Olga
Subject: BLA 125370 Benlysta
Importance: High

Hi Jessica,

The Benlysta (belimumab) partial waiver, deferral and plan was reviewed by the PeRC PREA Subcommittee on October 06, 2010.


The Division presented a partial waiver for patients 0-4 years and deferral for patients 5 to 16 years age.

- The PeRC recommends that the Division consider a long-term observational study or pediatric registry for this product.

The PeRC agreed with the Division to grant a partial waiver because there are too few patients and a deferral because the product is ready for approval in adults.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: February 14, 2011

To: Diana Daly

Company: HGS, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: BLA 125370 Additional Carton and Container Labeling
Recommendations

of Pages: 3

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Thank you.

BLA 125370

Benlysta®

Human Genome Sciences, Inc.

DATE: February 14, 2011

Your submission date June 9, 2010, containing carton and container labels, to BLA 125370 Benlysta® (belimumab) is under review and we have the following recommendations and/or requests for information pertaining to the product carton and container labeling:

1. **Carton Label**

- a. Revise (b) (4) to "Marketed by:" to comply with 21 CFR 610.64.
- b. Add the following medication guide statement, "Dispense the enclosed Medication Guide to each patient" to comply with 21 CFR 208.24(d) and 21 CFR 610.60(g).
- c. The statement (b) (4) is listed with the storage conditions on the carton. Please provide data to support the statement on the carton or revise the statement to reflect temperatures stated in the United States Pharmacopeia, (USP 33/NF 28) General Notices: 10. PRESERVATION, PACKAGING, STORAGE, AND LABELING.

2. **Carton and Container Label**

- a. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1. The NDC configuration appears as (b) (4) on the 120 mg strength and (b) (4) on the 400 mg strength. The Product code must be a unique identifier for each strength. The proposed labels each have the same product code for both strengths. Revise the NDC number such that each product code is a unique identifier for each strength to comply with the regulation.
- b. Revise the route of administration from (b) (4) to "For intravenous infusion after dilution only" and move the route of administration below the strength presentation for clarity.

Recommended format:

Benlysta[®]
(belimumab)

For Injection

XXX mg/vial

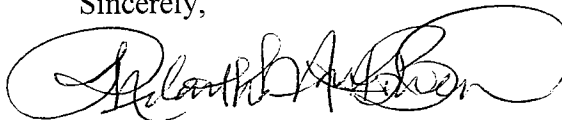
For Intravenous Infusion after dilution only
Single-use vial; Discard unused portion

****Note:** The minimal requirements for a full container label (21 CFR 610.60) do not include storage conditions and may be deleted to provide space for changes.

These comments are not all-inclusive and we may have additional comments as we continue our review. Submit revised draft carton and container labels incorporating changes outlined above, as well as, the carton and container recommendations previously conveyed in the information request facsimile dated January 13, 2011. Provide an official response to the BLA by February 17, 2011.

If there are any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'Phila Bowen', with a large, stylized loop at the end.

/Philantha Montgomery Bowen/

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Rains/February 10, 2011

Clearance: Barnes/February 10, 2011
Rains/February 11, 2011
Fitzsimmons/February 11, 2011
Shapiro/February 11, 2011

Finalized: Bowen/February 14, 2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: February 1, 2011

To: Michelle Shannon, Ph.D.

Company: HGS, Inc.

Fax: 301-309-0311

Phone: 301-354-3930

From: Philantha Montgomery Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 FDA Labeling Recommendations: Package Insert

of Pages including cover: 27

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Thank you.

BLA 125370
Benlysta®
Human Genome Sciences, Inc.


DATE: February 1, 2011

We have begun our review of the label in your December 1, 2010, submission to BLA 125370 Benlysta® (belimumab). The FDA proposed insertions are underlined and deletions are in strike-out.

Submit revised labeling incorporating changes shown in the attached marked up labeling for the Package Insert by February 8, 2011.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/
Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert: FDA Recommendations

25 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/TS) immediately
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Drafted: Bowen/February 1, 2011

Clearance: Barnes/February 1, 2011
Okada/February 1, 2011
Seymour/February 1, 2011
Chowdhury/February 1, 2011

Finalized: Bowen/February 1, 2011

Bowen, Philantha

From: Bowen, Philantha
Sent: Monday, January 31, 2011 11:25 AM
To: 'Christine Pannunzio'
Subject: BLA 125370 - FDA Clarification of CMC PMR

Hello Christine,

Below is our response to your request for clarification regarding the CMC PMR for immunogenicity assays.

FDA Response

The limits of detection of the immunogenicity assays (screening, confirmatory and neutralizing) are all variably sensitive to product interference, such that patients with product levels above certain interference thresholds for each assay will not yield interpretable results. We recommend that you develop assays that are less sensitive to product interference that are capable of detecting HAMA, in the presence of belimumab, at ranges that would be expected to occur in patients receiving both the high and low doses.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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From: Christine Pannunzio [mailto:christine_pannunzio@hgsi.com]
Sent: Friday, January 28, 2011 11:10 AM
To: Bowen, Philantha
Subject: FW: BLA 125370 - FDA Request for CMC PMR

1/31/2011

Hi Philantha,

It would be helpful to us if the Agency could provide more information regarding this request, i.e., are there specific aspects of the assays that need to be improved to align with current regulatory expectations. Would you be able to provide more information pertaining to the scope of this request, or alternatively could we arrange a call with the product reviewer to discuss the immunogenicity assays? We would appreciate further input.

Best regards,

Christine



From: Michele Shannon
Sent: Thursday, January 27, 2011 9:54 AM
To: Christine Pannunzio; Sally Bolmer
Subject: FW: BLA 125370 - FDA Request for CMC PMR

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Thursday, January 27, 2011 9:48 AM
To: Michele Shannon
Cc: Diana Daly
Subject: BLA 125370 - FDA Request for CMC PMR

Hi Michelle,

Attached is an FDA request for a CMC post-marketing requirement for your review. We would appreciate a response at your earliest convenience.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993

1/31/2011

☎ 301-796-2466

☎ 301-796-9718

✉ philantha.bowen@fda.hhs.gov

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: January 27, 2011

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) CMC Post-Marketing Requirement

of Pages including cover: 2

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Thank you.

BLA 125370
Benlysta® (belimumab)
Human Genome Sciences, Inc.

Date: January 27, 2011

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following request for a CMC post-marketing requirement (PMR):

- Develop improved immunogenicity assays.

Submit your response officially to the BLA and forward a courtesy to me via email. In the submission, include a PMR milestone schedule.

- Use the following schedule:

PMR Schedule Milestones:

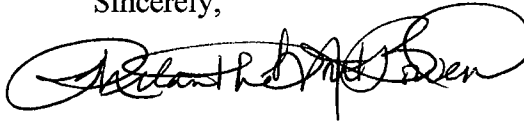
Final protocol Submission Date: MM/DD/YYYY (if applicable)

Study/Clinical trial Completion Date: MM/DD/YYYY (if applicable)

Final Report Submission Date: MM/DD/YYYY

If you should have any questions, contact me at 301-796-2466.

Sincerely,



/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/January 24, 2011

Clearance: Barnes/January 25, 2011
Shapiro/January 26, 2011
Seymour/January 27, 2011

Finalized by: Bowen/January 27, 2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: January 13, 2011

To: Diana Daly

Company: HGS, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: BLA 125370 Product Label & Labeling Recommendations

of Pages: 3

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Thank you.

BLA 125370

Benlysta®

Human Genome Sciences, Inc.

DATE: January 13, 2011

We have begun our review of the label in your December 21, 2010, submission to BLA 125370 Benlysta® (belimumab) and we have the following recommendations and/or requests for information pertaining to the product label and labeling:

General Comments

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

Container Label

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

Carton Labeling

5. Relocate the statements "Single-use vial. Discard unused portion." to the principal display panel.
6. Revise the statement [REDACTED] (b) (4) to "Each single-use vial contains 120 mg of Benlysta" or "Each single-use vial contains 400 mg of Benlysta".
7. 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.

BLA 125370
Benlysta®
Human Genome Sciences, Inc.

Be advised that these comments are not all-inclusive and we will have additional recommendations as we continue our review of the label. Since we will be providing our revisions and comments to specific sections of the label, we do not expect you to provide revised labeling at this time. However, if you have questions regarding any of the recommendations, we request that you forward your comments so that we may address any issues you may have.

If you have any questions, contact me at 301-796-2466.

Sincerely,

Philantha Montgomery Bowen

Digitally signed by Philantha Montgomery Bowen
Reason: I attest to the accuracy and integrity of this document
Date: 2011.01.13 09:15:56 -05'00'

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: December 15, 2010

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) CMC Post-Marketing Commitments

of Pages including cover: 3

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Thank you.

BLA 125370
Benlysta
Human Genome Sciences, Inc.

Date: December 15, 2010

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following requests for CMC post-marketing commitments:

1. Submit data supporting microbial control for the (b) (4) lifetime studies in a CBE-0 supplement by June 2012.
2. Submit data from 3 batches of (b) (4) demonstrating microbial control at the end of established hold time of (b) (4) in a CBE-0 supplement by June 2012.
3. Qualify the cap 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 should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. Include the preparation of the positive controls and sensitivity (breach size) of the helium leak test.
4. Provide quantitative data to demonstrate (b) (4). The quantitative qualification data should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

Submit your commitment officially to the BLA and forward a courtesy to me via email. In the submission, include a PMC milestone schedule.

Use the following schedule for *PMC's 1 and 2*:

PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: 06/30/2012


Use the following schedule for *PMC's 3 and 4*:

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

BLA 125370
Benlysta
Human Genome Sciences, Inc.

If you should have any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'Philantha M. Bowen', with a large, stylized initial 'P'.

/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/December 7, 2010

Clearance: Barnes/December 10, 2010
Chi/December 14, 2010
Suvarna/December 14, 2010
Seymour/December 14, 2010
Jafari/December 15, 2010

Finalized by: Bowen/December 15, 2010

MEMORANDUM

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

DATE: January 7, 2011

TO: BLA 125370/0 File

THROUGH : Sally Seymour, M.D., Deputy Director for Safety, DPARP

FROM: Philantha Montgomery Bowen, MPH, RN, Sr. Regulatory Project Management Officer, DPARP

SUBJECT: **GRMP - FDA Teleconference to Communicate:
Label/Timelines, PMCs/PMRs, and REMS Requests**

APPLICATION/DRUG: BLA 125370 Benlysta® (belimumab)

On January 6, 2011, the FDA initiated a teleconference for GRMPs with Human Genome Sciences, Inc. and discussed the following:

Label/Timeline

The FDA informed HGS that substantial revisions are to be expected for the product label, including the addition of a Boxed Warning for mortality based on the imbalance of deaths observed in the clinical program. The mortality safety issue will also be incorporated into the REMS. The FDA proposes to send HGS a comprehensive revised label by the end of this month. (b) (4)

The FDA explained that the warning will be informational with the intent to raise awareness of the deaths associated with belimumab therapy noted in the clinical trials. With regards to further label discussions, the FDA stated that once HGS has received the Agency's labeling revisions, a teleconference can be held to discuss the labeling.

PMCs/PMRs

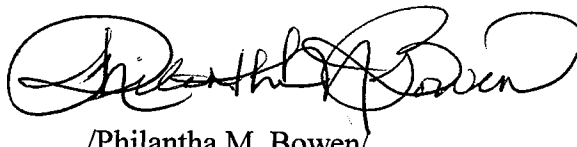
The FDA acknowledged that CMC PMCs have been conveyed to HGS; however, it appears there maybe another CMC PMC requested regarding an immunogenicity assay.

For the clinical program, the FDA communicated a PMR for a randomized, controlled trial to address the safety issue of mortality. Although HGS has proposed to conduct an observational

study, the FDA will require a more rigorous trial. It is recommended that HGS consider the study design (i.e. sample size, duration, etc.) to address the issue of mortality. The FDA pointed out the study size and scope proposed in the HGS observational study was reasonable, thus it is acceptable to replace the observational study with the randomized, controlled clinical trial. HGS will need to incorporate additional endpoints (e.g. neuropsychiatric events, malignancies) and obtain follow-up information in the randomized, controlled trial that had been proposed in the observational study. No additional details for the PMR were provided during this teleconference, but the FDA stated that an agreement on concepts and the timeline needed to be established. HGS agreed to submit a clinical trial proposal by the end of January 2011. The FDA agreed that HGS may update/revise any timelines for the pediatric plan, as well as, any other PMC/PMRs within the same submission.

REMS

The FDA informed HGS that multiple communications should be expected regarding recommendations for the REMS following labeling discussions. At this time, no comments could be provided until the revised label was substantially complete.

A handwritten signature in black ink, appearing to read 'Philantha M. Bowen', with a large, stylized loop at the end.

/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: December 15, 2010

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) CMC Post-Marketing Commitments

of Pages including cover: 3

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Thank you.

BLA 125370
Benlysta
Human Genome Sciences, Inc.

Date: December 15, 2010

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following requests for CMC post-marketing commitments:

1. Submit data supporting microbial control for the (b) (4); lifetime studies in a CBE-0 supplement by June 2012.

(b) (4)

3. Qualify the cap 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 should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. Include the preparation of the positive controls and sensitivity (breach size) of the helium leak test.
4. Provide quantitative data to demonstrate (b) (4). The quantitative qualification data should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.

Submit your commitment officially to the BLA and forward a courtesy to me via email. In the submission, include a PMC milestone schedule.

Use the following schedule for *PMC's 1 and 2*:

PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY
Study/Clinical trial Completion Date: MM/DD/YYYY
Final Report Submission Date: 06/30/2012

Use the following schedule for *PMC's 3 and 4*:

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

BLA 125370
Benlysta
Human Genome Sciences, Inc.

If you should have any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'Philantha M. Bowen', with a large, stylized initial 'P'.

/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/December 7, 2010

Clearance: Barnes/December 10, 2010
Chi/December 14, 2010
Suvarna/December 14, 2010
Seymour/December 14, 2010
Jafari/December 15, 2010

Finalized by: Bowen/December 15, 2010



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: December 7, 2010

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) Re: Clinical & CMC Information Request

of Pages including cover: 3

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Thank you.

DATE: December 7, 2010

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following comments and requests for information:

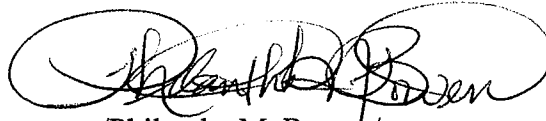
1. Over the course of our review of psychiatric adverse events reported to have occurred during LBSL02, C1056 and C1057, we noted that verbatim terms related to anxiety were coded to the following four preferred terms: anxiety, anxiety disorder, nervousness, and generalized anxiety disorder. We have concerns that coding the verbatim terms for anxiety to these four preferred terms may have resulted in an underestimation of this adverse event. Re-analyze anxiety reported events from these 3 double-blind studies into a single composite term and submit the recalculated reporting rate to the BLA.
2. Over the course of our review of psychiatric adverse events reported to have occurred during LBSL02, C1056 and C1057, we noted that verbatim terms related to depressed mood were coded to the following four preferred terms: depressed mood, depressive symptom, depression and major depression. We have concerns that coding the verbatim terms for depressed mood to these four preferred terms may have resulted in an underestimation of this adverse event. Re-analyze depressed mood reported events for these 3 double-blind studies into a single composite term and submit the recalculated reporting rate to the BLA.

The following request for information pertains to the manufacturer information listed on the carton labels and in the prescribing information:

3. Clarify the statement (b) (4) as listed on the carton labels and at the end of prescribing information. Explain GlaxoSmithKline's role.

Submit your response officially to the BLA and forward a courtesy copy via email. If you should have any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'Philantha M. Bowen', enclosed within a large, loopy oval shape.

/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/December 7, 2010

Clearance: Barnes/December 7, 2010
Neuner/December 6, 2010
Okada/December 6, 2010
Kimberly Rains /December 2, 2010
Seans Fitzsimmons/December 2, 2010

Finalized by: Bowen/December 7, 2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125370/0

EXTENSION USER FEE GOAL DATE

DATE: December 3, 2010

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

Attention: Diana Daly
Executive Director, Regulatory Affairs

Dear Ms. Daly:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Benlysta® (belimumab).

We received your November 23, 2010, amendment to this application on November 23, 2010, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to March 10, 2011, to provide time for a full review of the amendment.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Philantha Montgomery Bowen, at (301) 796-2466.

Sincerely,

/Badrul A. Chowdhury/

Badrul A. Chowdhury, M.D., Ph.D.

Director

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Biotechnology Products

FACSIMILE TRANSMITTAL SHEET

DATE: November 29, 2010

To: Christine Pannunzio	From: Joel Welch, Ph.D.
Company: Human Genome Sciences	CDER/OPS/OBP
Fax number: (301) 309-0311	Fax number: (301) 796-4798
Phone number: (301) 610-5818	Phone number: (301) 796-2017

Subject: Teleconference minutes from October 22, 2010 teleconference

Total no. of pages including cover: 6

Comments: Please find attached the minutes from this teleconference.

Document to be mailed: ☐ YES ☒ NO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125370

November 29, 2010

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

Dear Ms. Pannunzio:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for Belimumab.

We also refer to the meeting held on October 22, 2010, between representatives of your firm and this Agency. A copy of the official minutes of the meeting is attached for your information.

Please refer to <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm> for information regarding therapeutic biologic products, including the addresses for submissions.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Joel Welch", is positioned above the printed name.

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

Enclosure: Meeting Summary

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

Memorandum

Date: November 29, 2010
From: Joel Welch, Ph.D.; IO/OBP/OPS/CDER
Subject: October 22, 2010 BLA meeting minutes

Meeting Type: Teleconference
Meeting Date and Time: October 22, 2010, 9:00 a.m. – 10:00 a.m.
Product: Belimumab
Sponsor: Human Genome Sciences

FDA Participants:

Marjorie Shapiro, Ph.D.	Branch Chief, DHHS/FDA/CDER/OPS/OBP/DMA
Sean Fitzsimmons, Ph.D.	Microbiologist, DHHS/FDA/CDER/OPS/OBP/DMA <i>S. Fitz</i> 11-29-2010
Joel Welch, Ph.D.	Regulatory Project Manager, DHHS/FDA/CDER/OPS/OBP

Human Genome Sciences Participants:

Alicia Gilbert	Associate Director, Regulatory Affairs
Christine Pannunzio	Executive Director, Regulatory Affairs
David Kahn	Senior Director, Purification Sciences
Helmut Schneider	Senior Scientist II, Analytical Sciences
Michael Byrne	Director, Analytical Sciences
Scott Richmond	Senior Project Manager II, Supply Chain
Tara Ward	Specialist, Regulatory Affairs
Tom Spitznagel	Vice President, Biopharma Development

Meeting Purpose: The Agency requested a teleconference to obtain clarification during the CMC review of the BLA for Belimumab.

Introductory Comment: The Agency provided the list of draft questions to the sponsor prior to the teleconference for the purposes of discussion.

Question 1:

Section 3.2.S.2.2.2 Cell Culture and Harvest and Table 3.2.S.2.4-2. Is bioburden and mycoplasma testing of (b) (4) bulk material done prior to (b) (4)?

Sponsor Response: Yes, the bioburden and mycoplasma samples (b) (4) from the (b) (4) bulk, prior to (b) (4)

(b) (4)

Question 3:

Section 3.2.S.2.2.4 Filling, Storage and Transportation. How long are BDS lots stored long term at both HGS (b) (4)?

Sponsor Response: BDS lots can be stored for up to the claimed expiry of 36 months at a combination of either storage temperature/location. The storage conditions are supported by primary stability studies that include real-time stability data at both -40°C and -80°C (Table 3.2.S.7.1-1), and by temperature cycling studies (Section 3.2.S.7.3.4.2).

Post Meeting Note: Clarification has been provided in Section 3.2.S.7.1.1.

(b) (4)

(b) (4)

Question 11:

Section 3.2.S.2.5.2.16 Quantitation of (b) (4) Please comment on the qualification/validation of the (b) (4) assay.

Sponsor Response:

The original BLA contained (b) (4) clearance data from development studies. The (b) (4) assay was qualified subsequent to submission of the original BLA.

Additional Discussion: The sponsor commits to providing a report on the qualification of the assay.

Post Meeting Note: A summary of the assay qualification has been added to Section 3.2.S.2.5.2.16. The qualified assay has been used to validate the clearance of (b) (4), and the corresponding process validation report, PVP-06-034R, has been linked in Section 3.2.S.2.5, Table 3.2.S.2.5-12.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Biotechnology Products

FACSIMILE TRANSMITTAL SHEET

DATE: November 29, 2010

To: Christine Pannunzio

From: Joel Welch, Ph.D.

Company: Human Genome Sciences

CDER/OPS/OBP

Fax number: (301) 309-0311

Fax number: (301) 796-4798

Phone number: (301) 610-5818

Phone number: (301) 796-2017

Subject: Teleconference minutes from October 29, 2010 teleconference

Total no. of pages including cover: 11

Comments: Please find attached the minutes from this teleconference.

Document to be mailed:

☐ YES

☒ NO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125370

November 29, 2010

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

Dear Ms. Pannunzio:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for belimumab.

We also refer to the meeting held on October 29, 2010, between representatives of your firm and this Agency. A copy of the official minutes of the meeting is attached for your information.

Please refer to <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm> for information regarding therapeutic biologic products, including the addresses for submissions.

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

Sincerely,

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

Enclosure: Meeting Summary

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

Memorandum

Date: November 29, 2010
From: Joel Welch, Ph.D.; IO/OBP/OPS/CDER
Subject: October 29, 2010 BLA meeting minutes

Meeting Type: Teleconference
Meeting Date and Time: October 29, 2010, 8:30 a.m. – 10:00 a.m.
Product: Belimumab
Sponsor: Human Genome Sciences

FDA Participants:

Marjorie Shapiro, Ph.D.	Branch Chief, DHHS/FDA/CDER/OPS/OBP/DMA
Sean Fitzsimmons, Ph.D.	Microbiologist, DHHS/FDA/CDER/OPS/OBP/DMA
Joel Welch, Ph.D.	Regulatory Project Manager, DHHS/FDA/CDER/OPS/OBP

J. fit 11-29-2010

Human Genome Sciences Participants:

Angela Blake-Haskins	Senior Scientist II, Drug Product Sciences
Arpan Nayak	Scientist, Drug Product Sciences
Christine Pannunzio	Executive Director, Regulatory Affairs
Marla French	Manager, QC
Melissa Perkins	Director, Drug Product Sciences
Michele Fiscella	Associate Director, Clinical Immunology
Michael Byrne	Director, Analytical Sciences
Mike Lemar	Senior Scientist I, Analytical Sciences
Olga Galperina	Associate Director, Purification Sciences
Rob Lynch	Senior Manager, Validation
Tara Ward	Specialist, Regulatory Affairs
Tom Spitznagel	Vice President, Biopharma Development
Zhenhong Li	Senior Director, QC
Zhuchun Wu	Senior Scientist II, Analytical Sciences

Meeting Purpose: The Agency requested a teleconference to obtain clarification during the CMC review of the BLA for Belimumab.

Introductory Comment: The Agency provided the list of draft questions to the sponsor prior to the teleconference for the purposes of discussion.

(b) (4)

Question 2:

Section 3.2.S.3.1.2.8, Hydrodynamic Properties by AUC, states that (b) (4) accounts for over (b) (4) of the total protein. The remaining form is consistent with dimer. The analytical results are claimed to be in agreement with the SEC results presented in 3.2.S.3.1.2.4. Why doesn't AUC detect the (b) (4) as seen in SEC? See figure 3.2.S.3.1-25 for the SEC profile.

Sponsor Response: The difference in detection of (b) (4) is due to the different detection limits of the assays (0.04% for SEC-HPLC vs 0.3% for AUC). The amount of (b) (4) in the product is very low, (b) (4) thus it is detected by SEC-HPLC but not by AUC.

(b) (4)

Question 4:

Section 3.2.S.3.2.2.2 Product-Related Impurities and section 3.2.P.5.5 (table 3.2.5.5-1). Please comment on the biological activity of the (b) (4)

Sponsor Response: The (b) (4) was enriched from BDS. The sample contained (b) (4). The biological activity of the sample is almost solely generated by the (b) (4) present in the sample. The (b) (4) is not biologically active in the receptor binding with BLYS assay.

Question 5:

Section 3.2.S.4.5.2, Drug Substance Specifications. Statistical analysis for BDS was performed with 10 lots produced by the commercial process (b) (4) at the commercial scale (b) (4) to form proposed release specifications. Why weren't data from all of the available commercial scale BDS lots utilized in the analysis?

Sponsor Response: The amount of data taken into account to set specifications is a BLA timing issue, as there were 10 lots of BDS available at the time when a data cutoff needed to be made during preparation of the BLA. Subsequent lots of BDS have been generated and their release data have been consistent with the proposed commercial specifications. We plan to assess the acceptance criteria when additional data are available from at least 30-40 released BDS batches.

Question 6:

Section 3.2.S.4.5.3.5, Potency by Inhibition of Binding, states that all potency data to date has been generated from one lab, but future data will have to be generated from multiple labs, potentially increasing the assay variability. Please comment on the status of the planning for the technology transfer.

Sponsor Response: Currently, HGS performs the potency assay for release. Due to European (EU) requirements, we will also have a testing lab in the EU (ie GSK) to release product for use in those countries. The technology transfer to that lab is ongoing and data are still being gathered, but we do expect to see increased to lab-to-lab variability for the potency assay in particular (b) (4)

Question 7:

Section 3.2.S.4.5.3.5, Potency by Inhibition of Binding, states, "Therefore, an extra (b) (4) is included to widen from the tolerance interval ranges and the acceptance criterion for the belimumab potency assay for BDS release will be (b) (4) from (b) (4). It is unclear what this statement means. Please clarify.

Sponsor Response: The proposed commercial acceptance criterion for the potency assay is (b) (4). This includes the extra (b) (4) which was factored in to accommodate the possible addition of the alternate testing site, as described in the answer to Question 6 above.

(b) (4)

Question 13:

Section 3.2.P.3.5.5, Critical Process Steps and Parameters. The steps for lyophilization are listed in table 3.2.P.3.5-3 as “key” process parameters. Why are these parameters not classified as CPPs?

Sponsor Response: The lyophilization steps are listed as key process parameters because they meet HGS' internal definition of a key process parameter. That definition was truncated in the BLA. A key process parameter is defined as a process parameter that should be controlled to within a defined range for optimal process performance. It is not deemed a critical process parameter because it does not affect critical product quality attributes, or because of the minor extent to which it may affect overall process performance, or because it is readily controlled within a defined range.

Post Meeting Note: This definition has been updated in Section 3.2.P.3.5.5.

Question 14:

Section 3.2.P.3.5.9.4, FDP Shipping Validation Study Results. Has shipment of FDP from GSK to wholesalers been qualified? The BLA stated that the packaging solutions and the shipping process would be qualified.

Sponsor Response: GSK has successfully completed the qualification of shippers to be used in shipping from GSK to wholesalers for both vial sizes using winter and summer profiles. All shippers will include temperature monitoring devices.

Question 15:

Section 3.2.P.5.1.1, Commercial FDP Specification. The description of the vial sampling for FDP release testing does not make sense. For example, (b) (4) Similar wording is used elsewhere in this section. Please clarify how sampling is performed.

Sponsor Response: For all sampling points, we pull samples (b) (4) needed to perform the test.

(b) (4)

Question 17:

Section 3.2.P.8.1.6, Discussion of Primary Stability Results and Section 3.2.P.2.3.4.6, Analysis of Real Time Stability Data (figures 3.2.P.2.3-33 and 34). The rates of degradation (IE-HPLC) of the 400 mg/vial pilot scale lyophilizer lots differ from the commercial scale lots. The acidic peak slope line for the full scale lots is near the acceptance limit (figure 3.2.P.2.3-34) and the longest time point is 24 months for a full scale lot (lot 71080). It is not clear if the acceptance criteria will be met at 60 months for acidic peaks for the full scale lots.

Sponsor Response: The limited amount of data at the time of BLA filing caused the appearance of exaggerated differences in stability trends between pilot scale and commercial scale lots. When data for individual lots were evaluated, no significant trends were observed that caused any concern that the commercial scale lots would not meet acceptance criteria at 60 months.

Stability Sections 3.2.P.8.1 and 3.2.P.8.3 were updated with additional FDP stability data and trend analyses from the primary stability studies (both pilot-scale and full-scale lots) in BLA amendment SN 0006, submitted on 29 September 2010. The stability data to support the lyophilizer scale-up comparability study in Section 3.2.P.2.3.4.6 was not updated at that time.

Post Meeting Note: An update to Section 3.2.P.2.3.4.6 has been provided.

Question 18:

Section 3.2.P.8.1.6, Discussion of Primary Stability Results and Section 3.2.P.2.3.4.6, Analysis of Real Time Stability Data (figures 3.2.P.2.3-29 and 30). The rates of degradation (IE-HPLC acidic and main peaks) of the 120 mg/vial pilot scale lyophilizer lots significantly differ from the commercial scale lots and it is not clear if this difference in rates will result in a faster failure of the acidic and main peak specifications for the commercial scale lyophilizer lots. The acidic peak slope line for the full scale lots is near the acceptance limit (figure 3.2.P.2.3-34) and the longest time point is 24 months for a full scale lot (lot 71080). It is not clear if the acceptance criteria will be met at 36 months for the full scale 120 mg/vial lots.

Sponsor Response: See response for Question 17.

Question 19:

Section 3.2.P.8.3.5.1, Photostability. How are vials stored immediately after filling but before being put into cartons? How is light exposure controlled and documented?

Sponsor Response: After lyophilization, vials are removed from the lyophilizer, capped, inspected, (b) (4) and placed in 2-8°C storage (b) (4).

(b) (4)

Post Meeting Note: This data has been updated in BLA Section 3.2.A.2, Tables 3.2.A.2-16 and 3.2.A.2-19.

Question 21:

Section 3.2.A.2.2.7, Virus Clearance Studies. In table 3.2.A.2-24, the lower LRV was not always used in the overall calculation of virus removal. A worst-case scenario should be used.

Sponsor Response: *BLA Section 3.2.A.2 and Table 3.2.A.2-26 have been updated based on a worst-case scenario.*

Question 22:

Phase 3 immunogenicity screening assay. Amendment 1 of TR-06-07-018 stated that the review of data previously obtained for the assay validation (TR-06-07-028, 24JUN08), specifically the LOD data generated during the performance of the Assay A using ADA spikes in pooled serum, cast some uncertainty as to whether the LOD spike listed as 0.05 µg/ml of ADA indeed contained the nominal concentration of ADA. Because they could not conclusively rule out the possibility that a mistake was made in making this spike, and because the ECL reading generated by the PC during validation (0.1 µg/ml ADA) fulfills the LOD criteria, they conservatively re-established the LOD for this assay at 0.1 µg/ml of ADA. Why was the study not repeated with the correct spike?

Sponsor Response: *The uncertainty about the concentration of the LOD spikes was raised upon the review of the validation report TR-06-07-028. Such review was performed when the Phase 3 clinical studies had already been initiated and the analysis of the available immunogenicity samples performed (first c1056 samples analyzed on 07 December 2007). The validation experiments used positive control (PC) at 0.1 µg/mL, and the criterion for positive samples was set based on the Log Sample/Log Negative Control (NC) \geq Log PC/Log*

NC. The analysis of Phase 3 samples started after the conclusion of the validation experiments, and the criterion for positive samples was identical to the one set prospectively in the validation.

The analysis of the PC performance over the course of the assay validation indicates that the PC concentration reproducibly generates signal above the NC signal. In addition, the lower 95%PI (LPI) of the PC signal is near the upper 95% PI (UPI) signal of the NC (PC LPI=412 vs NC UPI=242) further suggesting that the concentration of 0.1 µg/mL is appropriate as the assay LOD for this assay platform.

The Validation spike at 0.05 µg/mL and the PC (0.01 µg/mL) generated very similar mean ECL signals (TR-06-07-028; 436 and 476, respectively).

The LogPC/LogNC signal remained fairly stable over the course of the Phase 3 studies, indicating that this PC concentration was appropriate.

The analysis of the PC performance over the course of the Phase 3 studies indicates that the PC concentration reproducibly generates signal above the NC signal. In addition, the lower 95% prediction interval (PI) of the PC signal is near the upper 95% PI signal of the NC (PC LPI=394 vs NC UPI=281 for passed plates and PC LPI=374 vs NC UPI=294 for all plates), further suggesting that the concentration of 0.1 µg/mL is appropriate as the assay LOD.

Three additional items were discussed which were not included in the original list of questions:

Additional Question #1:

The comparability protocol only calls for one DP configuration (120 mg/vial or 400 mg/vial).

Sponsor Response: Multiple lots of DS will be analyzed and this is where differences would likely be observed.

Additional Question #2

In the stability section of the comparability protocol, you state that BDS lots will be stored at 25C/60% relative humidity for 0, 3 and 6 weeks in (b) (4) USP Type 1 vial. BDS is normally stored in bags. Is this an error?

Sponsor Response: This is correct as the vessel is more conducive for examining and detecting small differences that might exist in the BDS.

Additional Question #3

In the comparability assessment section it was stated that comparable results from the analytical methods will be based on meeting the acceptance criteria defined in the proposed commercial specification for BDS (Table 6-2) and FDP (Table 6-4) release methods or the specification approved in the BLA.

Sponsor Response: There are no differences in the tables versus the specification. The phrase "or the specification approved in the BLA" was put there in case the Agency did not agree with the proposed specifications in table 6-2 and 6-4.

Bowen, Philantha

From: Bowen, Philantha
Sent: Friday, November 05, 2010 11:20 AM
To: 'Christine Pannunzio'
Cc: Tara Ward
Subject: RE: BLA 125370- Belimumab - Information Request
Importance: High

Hi,

Your approach is acceptable as long as your response addresses the Agency's requests in order to update the relevant sections of the BLA.

Sincerely,
Philantha

From: Christine Pannunzio [mailto:christine_pannunzio@hgsi.com]
Sent: Friday, November 05, 2010 8:44 AM
To: Bowen, Philantha
Cc: Tara Ward
Subject: FW: BLA 125370- Belimumab - Information Request
Importance: High

Dear Philantha,

We have completed the bioburden assay qualification studies requested in item #3 (see attached Information Request). We had provided an interim response to the BLA in SN 0013, submitted 27 October 2010. I understand that it is late in the review process, therefore I wanted your guidance whether the Agency can accept this final response (2 page cover letter with 15 data tables attached) without an impact to the review timelines. If so, we are prepared to submit this to the BLA today. Please advise.

Best regards,
Christine

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Christine Pannunzio
Sent: Tuesday, October 19, 2010 4:46 PM
To: 'Philantha.Bowen@fda.hhs.gov'

12/3/2010

Cc: Michele Shannon; Tara Ward
Subject: FW: BLA 125370- Belimumab - Information Request
Importance: High

Dear Philantha,

We have received this CMC microbiology information request for BLA 125370. We will provide a response by October 27, 2010.

Best regards,
Christine Pannunzio

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Michele Shannon
Sent: Tuesday, October 19, 2010 4:03 PM
To: Christine Pannunzio; Tara Ward; Alicia Gilbert
Subject: FW: BLA 125370- Belimumab - Information Request
Importance: High

Tara, will you confirm receipt and file?

Thanks,

Michele

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Tuesday, October 19, 2010 4:01 PM
To: Diana Daly; Michele Shannon
Subject: BLA 125370- Belimumab - Information Request
Importance: High

Hello,

Attached is a CMC micro information request regarding BLA 125370. We are asking for a response by October 27, 2010. I would appreciate you confirming receipt of this email.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service

12/3/2010

Sr. Regulatory Management Officer

Food and Drug Administration

Center for Drug Evaluation and Research/ODEII

Division of Pulmonary, Allergy, and Rheumatology Products

10903 New Hampshire Ave., Bldg 22, Room 3317

Silver Spring, MD 20993

☎ 301-796-2466

☎ 301-796-9718

✉ philantha.bowen@fda.hhs.gov

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: November 5, 2010

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 - Benlysta® re: CMC Microbiology Information Request

of Pages including cover: 2

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Thank you.

BLA 125370
Benlysta® (belimumab)
Human Genome Sciences, Inc.

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following requests for information:

1. With regard to the container closure integrity test used to qualify the integrity of the drug product container closure, the provided sensitivity (breach size of (b) (4)) in 10/26/10 amendment appears inadequate. Develop a container closure integrity test with adequate sensitivity (breach size and the corresponding leak volume) to qualify the capper and validate the integrity of the drug product container closure. If a dye ingress test is used, the sensitivity of the test should be correlated to a microbial ingress test using the same challenge conditions (pressure/vacuum and duration).
2. With regard to the dye ingress test on stability, confirm that the 18 gauge needle is removed after inserting the 2-3 micron ID capillary tubing and the breach size for a positive control vial is 2 to 3 micron.
3. With regard to (b) (4) validation, justify the rationale for categorizing the change to (b) (4) requiring only one validation run. In addition, provide more information on the first validation runs after the change to (b) (4) that were invalidated due to incorrect (b) (4) preparation.
4. Submit F₀ data to justify that the (b) (4) plungers are the most-difficult-to-sterilize items to be used in the (b) (4).
5. The original qualification study of the (b) (4) does not include quantitative data demonstrating (b) (4). Submit quantitative validation data for the (b) (4).
6. The bioburden specification (b) (4) for sucrose is high and does not ensure that the in-process bioburden limit of ≤ 10 CFU/100 mL (b) (4) is met. Lower the bioburden specification for sucrose.
7. In your response to question 11 in the information request dated October 15, 2010, you stated that in routine endotoxin and bioburden testing, belimumab drug product samples are diluted at (b) (4). Clarify if the (b) (4) dilution is for endotoxin test only or for both the endotoxin and bioburden testing.
8. With regard to the (b) (4) used for sterility test, provide a short description of how the false negative test provided in Report QP342PQR-95-01 was conducted.

Clarify if the containers tested for (b) (4) are relevant to the materials used in the sterility test for belimumab drug product.

9. There were viable EM data missing and viable EM action level excursions for media fills PQR0625.M6-06-04, PQR0625.M6-07-02, PQR0625.M6-08-02, PQR0625.M4-09-03, PQR0625.M6-10-01, and PQR0625.M6-10-03. Submit a summary of the root cause, corrective and preventive actions, and impact on products. In addition, clarify if the environment in the (b) (4) was monitored during the PQR0625.M6-10-01 Media fills.

Submit a response by COB on November 10, 2010. If you should have any questions, contact me at 301-796-2466.

Philantha Montgomery Bowen

Digitally signed by Philantha Montgomery Bowen
DN: cn=Philantha Montgomery Bowen, o=FDA, ou, email=philantha.
bowen@hhs.gov, c=US
Date: 2010.11.05 12:52:41 -0400

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Chi/November 5, 2010

Finalized by: Bowen/November 5, 2010

Bowen, Philantha

From: Christine Pannunzio [christine_pannunzio@hgsi.com]
Sent: Friday, November 12, 2010 4:27 PM
To: Bowen, Philantha
Cc: Alicia Gilbert
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Philantha,

Thank you for the reply, we will comply with the requested design to use minimum and maximum sealing pressure forces. That commitment was included in the response submitted on 10 November 2010 (Sequence 0016).

Best regards,
Christine

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Friday, November 12, 2010 4:12 PM
To: Christine Pannunzio
Cc: Alicia Gilbert; Bowen, Philantha
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hello Christine,

The following is our response to your request for clarification:

FDA response:

In the initial validation studies, vials sealed with minimum and maximum sealing pressure forces were evaluated with container closure integrity tests with inadequate sensitivity. Please commit to qualify the capper with the helium leak test using vials sealed with minimum and maximum sealing pressure forces.

Sincerely,

Philantha

12/3/2010

From: Christine Pannunzio [mailto:christine_pannunzio@hgsi.com]
Sent: Tuesday, November 09, 2010 4:54 PM
To: Bowen, Philantha
Cc: Alicia Gilbert
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hi Philantha,

Thank you for the feedback. It is helpful to understand the Agency's expectations for these items.

Upon further discussion with (b) (4) and in order to execute the container closure integrity testing in the most timely manner, we plan to pull vials from an upcoming GMP fill of belimumab to use for container closure integrity testing. Therefore, the most prudent approach in preparing these vials is to use the nominal sealing force as used in our commercial process. Since we have provided the initial studies tested by microbial challenge and dye ingress using vials sealed with minimum and maximum sealing pressure forces, do you agree that the nominal sealing force is sufficient for the vials to be used in the confirmatory study with the helium leak test. I appreciate your further consideration of this slight revision to our proposal.

Best regards,
Christine

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Tuesday, November 09, 2010 4:28 PM
To: Christine Pannunzio
Cc: Alicia Gilbert
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hello Christine,

We have provided our response to your proposed responses to our information request dated November 5, 2010, under each of your questions.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN

12/3/2010

CDR, U.S. Public Health Service
 Sr. Regulatory Management Officer
 Food and Drug Administration
 Center for Drug Evaluation and Research/ODEII
 Division of Pulmonary, Allergy, and Rheumatology Products
 10903 New Hampshire Ave., Bldg 22, Room 3317
 Silver Spring, MD 20993
 ☎ 301-796-2466
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 ✉ philantha.bowen@fda.hhs.gov

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From: Christine Pannunzio [mailto:christine_pannunzio@hgsi.com]
Sent: Tuesday, November 09, 2010 11:33 AM
To: Bowen, Philantha
Cc: Alicia Gilbert
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hi Philantha,

Here are our proposals for responses that we would like to discuss with the reviewer to assure we are addressing the concerns raised in the questions.

For item 1, HGS proposes to perform a validated helium leak test at an outside vendor using 5 mL (120 mg configuration) vials prepared at the minimum and maximum sealing forces. Both vial configurations of belimumab have an identical 20 mm opening, stopper and crimp. We plan to provide the data from this test by Dec 3, 2010. Does the Agency agree that this approach is sufficient to validate the integrity of the container closure?

FDA response: The approach is acceptable. The validation of the helium leak test and validation of the integrity of the belimumab DP container closure using the helium leak test will be reviewed as a post-market commitment. Please commit to submit the information and summary validation data in a CBE-0.

For item 6, HGS proposes to tighten the bioburden specification to (b) (4) for sucrose. The bioburden specification needed to mathematically assure an in-process bioburden limit of ≤ 10 CFU/100 mL would be (b) (4). The vendor will not agree to lower their limit to this level. As stated in our initial response, in conjunction with the proposed, tightened bioburden limit for sucrose, (b) (4)

Does the Agency agree that tightening the sucrose bioburden specification to (b) (4) adequate measures of control for the sucrose used in the formulation buffer?

12/3/2010

FDA response: This is acceptable.

Please let me know if it is feasible to discuss these responses today with the reviewer.

Best regards,
Christine

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Tuesday, November 09, 2010 9:25 AM
To: Christine Pannunzio
Subject: RE: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hi Christine,

We would appreciate you providing us with the questions/comments you have regarding your response to our information request.

Thanks!

Philantha

From: Christine Pannunzio [mailto:christine_pannunzio@hgsi.com]
Sent: Monday, November 08, 2010 8:52 PM
To: Bowen, Philantha
Subject: FW: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hi Philantha,

Would it be possible to schedule a brief teleconference with the appropriate reviewer to discuss our response to items 1 and 6. We would like to ensure we are fully addressing your concerns in the planned responses. Any time on Tuesday could be accommodated.

Thanks for considering this request,
Christine

12/3/2010

Christine Pannunzio
Executive Director, Regulatory Affairs CMC
Human Genome Sciences, Inc.
Office 310-610-5818
Cell 301-828-7093
Email christine_pannunzio@hgsi.com

From: Michele Shannon
Sent: Friday, November 05, 2010 4:49 PM
To: Tara Ward; Christine Pannunzio; Alicia Gilbert
Subject: FW: BLA 125370 - Benlysta - CMC Microbiology IR Attached

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Friday, November 05, 2010 1:37 PM
To: Michele Shannon; Diana Daly
Subject: BLA 125370 - Benlysta - CMC Microbiology IR Attached

Hello Ladies,

Attached is a CMC Micro information request for BLA 125370 (Benlysta). It is time-sensitive and we would appreciate a response by November 10, 2010. In addition to submitting a response to the application, please send a courtesy of your response to me by email.

Thanks!


Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3317
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☎301-796-2466
☎301-796-9718
✉philantha.bowen@fda.hhs.gov

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12/3/2010

APPEARS THIS WAY ON ORIGINAL





**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: October 19, 2010

To: Diana Daly

Company: Human Genome Sciences, Inc.

Fax: 301-309-0311

Phone: 240-314-4400

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: BLA 125370 (Benlysta) re: CMC Microbiology Information Request

of Pages including cover: 2

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Thank you.

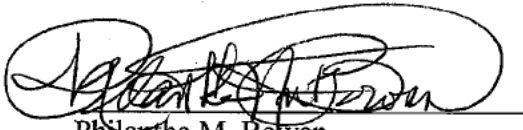
BLA 125370
Benlysta
Human Genome Sciences, Inc.

OCT 19 2010

Your submission dated June 9, 2010, to BLA 125370 is under review and we have the following request for information:

1. You mention that bioburden samples are collected at the expansion. State the bioburden acceptance criteria for the expansion. (b) (4)
2. As discussed at the recent pre-license inspection for belimumab, the conclusion drawn from a small scale laboratory rejection limit study are limited to the conditions under which the study was performed and does not broadly apply to all downstream intermediates for all contaminating microorganisms. The Agency expectation is that lot disposition decisions will be made after appropriate investigations when action limits are exceeded. Delete references to the rejection limit from the BLA. (b) (4)
3. Submit summary data to support bioburden qualification for process validation lots and explain the differences in the bioburden test methods used for process validation versus commercial manufacture, along with the reason for the change.

Submit a response by COB on October 27, 2010. If you should have any questions, contact me at 301-796-2466.



Phlantha M. Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: KSuvarna/October 18, 2010

Initialed by: PHughes/October 18, 2010

Finalized by: PBowen/October 19, 2010

Bowen, Philantha

From: Benjamin, Jessica
Sent: Friday, October 15, 2010 11:24 AM
To: Diana Daly; 'Michele Shannon'
Cc: Bowen, Philantha; Benjamin, Jessica
Subject: CMC Microbiology information request - BLA 125370

Hi Diana and Michele,

Please refer to BLA 125370 for belimumab. As a result of our ongoing review of your application, we have the following CMC microbiology questions:

1. Provide the sensitivities (i.e., breach size and the corresponding leak volume) of the microbial challenge test and vacuum/dye leak test used to qualify the integrity of the container closure for belimumab drug product. The sensitivity of the microbial challenge test should be correlated to that of the dye ingress test using the same challenge conditions (pressure/vacuum) and evaluated. Provide the validation of the tests and how the positive controls are prepared. In addition, provide the sensitivity of the dye leak test used on stability program.
2. The sucrose used for the (b) (4) has a bioburden specification of (b) (4). At the maximum bioburden level, this would cause the (b) (4) to have a bioburden of (b) (4) (sucrose concentration). This bioburden level would exceed the bioburden limit (b) (4). In fact, the (b) (4) bioburden results of (b) (4) exceeded the limit for two FDP conformance lots (Lots 71079 and 71082). It is recommended that you filter the sucrose solution prior to use.
3. With regard to (b) (4) validation (b) (4). Both (b) (4) failed the first validation run. Provide information and summary data for two additional maximum validation runs to qualify the (b) (4).
4. Provide one minimum validation run with the most-difficult-to-sterilize item(s) for the belimumab load for each of the (b) (4).
5. Provide information and summary validation data for the (b) (4). The validation data for (b) (4). The removal of bioburden should also be provided. Alternatively, provide bioburden specification for incoming stoppers.
6. Provide information and summary validation data of the (b) (4) from three runs to demonstrate removal (b) (4).
7. Provide summary data for two additional recent (b) (4) requalification runs for lyophilizer K5789.
8. Clarify if lyophilizer 4 (K5789) will be the only lyophilizer used for belimumab drug product manufacturing. The provided media fill data is for lyophilizer 2 (K2999). Provide information and summary data of three media fill simulations using the lyophilizer(s) involved in belimumab drug product manufacturing. (b) (4).
9. Provide the root cause for raised or missing stoppers following the lyophilizer simulation for media fill run 0625.M6-10-0005.
10. The sterility test and endotoxin test for belimumab drug product was qualified using one drug product lot. Provide summary qualification data of the tests using two additional drug product lots.
11. With regard to the endotoxin test for belimumab drug product, you indicated that dilution factors of (b) (4) considered suitable for use. Provide the specific dilution you will use for belimumab drug

product endotoxin test.

12. Provide information and summary data for decontamination validation of the (b) (4) used for sterility test at (b) (4). In addition, provide summary data that demonstrates that (b) (4) does not penetrate packaged media and materials used in sterility test.
13. You indicated that a study was performed to evaluate the microbiological attributes of reconstituted FDP in vials for 8 hours at 2–8°C, and also after dilution of FDP in IV infusion bags containing normal saline for 8 hours at room temperature. Provide information and summary data for the study.

Due to our upcoming deadlines, please respond to this request by October 27th via official EDR submission and email. Let me know if you have any questions.

Regards,
Jessica

Bowen, Philantha

From: Benjamin, Jessica
Sent: Thursday, October 14, 2010 3:55 PM
To: 'Michele Shannon'; Diana Daly
Cc: Benjamin, Jessica; Bowen, Philantha
Subject: BLA 125370 - belimumab

Hi Michelle,

Please refer to BLA 125370 for belimumab. As a result of our ongoing review of your application, we have the following questions:

1. We note that a number of patients erroneously received the wrong treatment, e.g. patients who were assigned to placebo received a dose of belimumab. Address how these protocol violations may have impacted the safety assessment. Provide the adverse event line listings for the individual patients who received the incorrect treatment, noting the dates of dose administration and the actual treatment administered.

2. Patients appear to have been treated with various prophylaxis regimens for infusion reactions at the discretion of the individual investigators. Address how prophylaxis may have impacted the incidence and assessment of infusion reactions and hypersensitivity events and discuss whether the data support the use of specific medications for routine prophylaxis.

Due to our upcoming deadlines, please respond to this request by October 25th. Let me know if you have any questions.

Regards,
Jessica

From: Diana Daly
To: Benjamin, Jessica; Michele Shannon;
Subject: RE: BLA 125370 - pediatric assessment deferral
Date: Monday, September 27, 2010 11:10:17 AM

Hi Jessica,

Here is our current plan for pediatric protocol development. We would like to receive FDA comments on the protocol before finalizing it, so have suggested a draft protocol submission prior to the final protocol. Please let us know if you have any concerns with this approach.

Draft protocol to FDA for comment: Jan 2011
Comments back from FDA: Mar 2011 (2 months from submission of draft)
Submission of final protocol after comments received from FDA:
May 2011 (or 2 months after FDA comments received)
Study start (first patient in): Mar 2012

Best wishes,

Diana

Diana J. Daly
Executive Director, Regulatory Affairs
Telephone (240) 314-4416
Cell (240) 676-5238
Fax (301) 309-0311
Email: diana_daly@hgsi.com

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Friday, September 24, 2010 2:42 PM
To: Michele Shannon; Diana Daly
Cc: Benjamin, Jessica
Subject: BLA 125370 - pediatric assessment deferral
Importance: High

Hi Michele,

Please refer to BLA 125370 for belimumab and your request for deferral of the pediatric assessment. We note that the projected completion of the pediatric clinical study is December 2015 and study

submission is expected to occur in the third quarter of 2016. However, we also need to know the protocol submission date. Please supply this information by noon on Monday, September 27th. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: Michele Shannon;
cc: Benjamin, Jessica; Diana Daly;
Subject: BLA 125370 information request
Date: Tuesday, September 21, 2010 5:57:43 PM

Hi Michele,

Please refer to BLA 125370 for belimumab. As a result of our ongoing review of your application, we have the following information request:

1. Provide a tabulation and list of patients (including unique identifier codes, study number, and treatment group) divided in the following categories:

a. Experienced discontinuation or interruption of treatment due to hypersensitivity reactions or infusion reactions, regardless of day of occurrence

b. Experienced a serious and/or severe infusion or hypersensitivity reaction, regardless of day of occurrence

c. Reported an adverse event starting on the day of infusion mapping to one of the following preferred terms:

• **allergic oedema**

- 1 anaphylactic reaction**
- 2 anaphylactic shock**
- 3 anaphylactoid reaction**
- 4 anaphylactoid shock**
- 5 angioedema**
- 6 blood pressure decreased**
- 7 bronchospasm**
- 8 chest discomfort**
- 9 chest pain**
- 10 circumoral oedema**
- 11 cough**
- 12 cyanosis**
- 13 dermatitis**

14	dermatitis allergic
15	dizziness
16	dizziness postural
17	drug hypersensitivity
18	dyspnoea
19	ear pruritus
20	erythema
21	eye oedema
22	eye pruritus
23	eye swelling
24	eyelid oedema
25	eyelid pruritus
26	face oedema
27	flushing
28	generalised erythema
29	generalised oedema
30	heart rate increased
31	heart rate irregular
32	hot flush
33	hypersensitivity
34	hypotension
35	hypoxia
36	infusion related reaction
37	infusion site hypersensitivity
38	infusion site pruritus
39	infusion site rash
40	infusion site urticaria
41	injection site pruritus
42	injection site rash
43	laryngeal oedema
44	laryngospasm
45	laryngotracheal oedema
46	lip oedema
47	lip swelling
48	oedema mouth
49	oral pruritus
50	orthostatis hypotension
51	pallor

52	palpitations
53	periorbital edema
54	presyncope
55	pruritus
56	pruritus allergic
57	pruritus generalised
58	rash
59	rash erythematous
60	rash generalized
61	rash macular
62	rash pruritic
63	rhinorrhea
64	swelling
65	swelling face
66	swollen tongue
67	tachypnoea
68	throat irritation
69	throat tightness
70	tongue oedema
71	type I hypersensitivity reaction
72	type IV hypersensitivity reaction
73	urticaria
74	wheezing

Due to our upcoming deadlines, please respond to this request by Sept. 30th. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Benjamin, Jessica
To: "Michele Shannon"; Diana Daly;
cc: Benjamin, Jessica;
Subject: BLA 125370 information request
Date: Tuesday, September 14, 2010 11:30:12 AM

Hi Michelle,

Please refer to BLA 125370 for belimumab. As a result of our initial review of your application, we have the following questions:

1. Explain the microbial controls you have in place during the individual (b) (4) (b) (4)
(b) (4)
2. You have indicated that when a bioburden action limit is exceeded, an investigation to determine the root cause and disposition of lot will be performed. Explain why you have in addition a reject limit of (b) (4).
3. The qualification for bioburden testing of in process intermediates and bulk drug substance uses only 1 commercial lot. Provide summary data from 2 additional lots of each in process intermediate and bulk drug substance.
4. The established hold time for (b) (4)
(b) (4) The submitted data support a hold time of (b) (4).
Provide data to support the (b) (4) hold time or revise the established hold time for the (b) (4).
5. Provide bioburden and endotoxin limits and data obtained after cleaning of each column and (b) (4) used in purification.
6. The evaluation of microbiological stability of buffers used two worst case buffers. Provide justification for selection of the two buffers as representative of all buffers used in purification.
7. Provide the protocol and protocol report for (b) (4) lifetime study.

8. Provide bioburden and endotoxin limits and data to support hold time of the following in process intermediates (b) (4)

9. Provide the viral clearance validation report PVP-06-021R and all of the reports listed in table 3.2.1.2-21 "List of final reports for belimumab viral clearance studies".

Thank you for your prompt attention to these requests. Feel free to contact me with any questions or concerns.

Regards,
Jessica

Jessica M. Benjamin
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BLA 125370

FILING ISSUES

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

AUG 13 2010

Attention: Diana Daly
Executive Director, Regulatory Affairs

Dear Ms. Daly:

Please refer to your biologics license application (BLA) dated June 9, 2010, received June 9, 2010, submitted under section 351 of the Public Health Service Act for belimumab.

We have completed an initial review of your application for belimumab to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application August 6, 2010. The user fee goal date is **December 9, 2010**. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 15, 2010.

We request that you submit the following information:

1. The potential for belimumab to alter male and female fertility parameters was not evaluated as per ICH S6 (R1) draft dated December 2009. Therefore, provide clear and adequate justification for not conducting male and female fertility studies with your product. Provide all of the existing data and published literature regarding these endpoints (this information was also requested at pre BLA meeting dated March 08, 2010).

2. The carcinogenic potential for belimumab has not been evaluated as per ICH S6 (R1) draft dated December 2009. Provide a clear rationale on how you intend to address the carcinogenicity section of your product labeling (this information was also requested at pre BLA meeting dated March 08, 2010).
3. The embryo-fetal development/postnatal development study does not appear to have functional characterization of the impact of belimumab on the developing immune system. Exposure of belimumab during development can alter the offspring's immune system. Provide information with regards to what is known and expected and how you intend to address this concern in the product labeling (this information was also requested at pre BLA meeting dated March 08, 2010).
4. Provide details regarding the source and history of the (b) (4) that was used to develop the belimumab expression construct. This should include the source of the phage (b) (4) a description of the how it was manufactured and how it was screened for antigen.

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

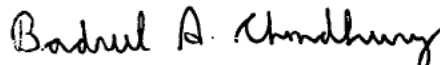
REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies in children <5 years of age and a partial deferral for pediatric studies in children aged 5 to 17 years of age for this application. Once we have reviewed your requests, we will notify you if the partial waiver and partial deferral requests are denied.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,



Badrul A. Chowdhury, MD, PhD
Division Director
Division of Pulmonary, Allergy,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125370

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850

Attention: Diana Daly
Executive Director, Regulatory Affairs

Dear Ms. Daly:

Please refer to your Biologic License Application (BLA) dated June 9, 2010, received June 9, 2010, submitted under section 351 of the Public Health Service Act, for Belimumab for Injection, 120 mg and 400 mg.

We also refer to your June 9, 2010, correspondence, received June 9, 2010, requesting review of your proposed proprietary name, Benlysta. We have completed our review of the proposed proprietary name, Benlysta and have concluded that it is acceptable.

The proposed proprietary name, Benlysta, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your June 9, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Carolyn Volpe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5204. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Jessica Benjamin at (301) 796-3924.

Sincerely,

Carol Holquist
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125370

BLA ACKNOWLEDGEMENT

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, MD 20850

Attention: Diana Daly
Executive Director, Regulatory Affairs

JUN 11 2010

Dear Ms. Daly:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: belimumab

Date of Application: June 9, 2010

Date of Receipt: June 9, 2010

Our Submission Tracking Number (STN): BLA 125370

Proposed Use: (b) (4) adult patients with active, autoantibody-positive systemic lupus erythematosus

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

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

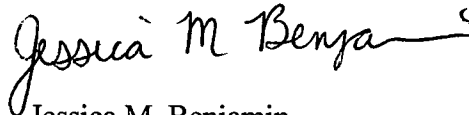
The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-3924.

Sincerely,

A handwritten signature in black ink that reads "Jessica M Benjamin". The signature is written in a cursive style with a long horizontal flourish at the end.

Jessica M. Benjamin
Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research