CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

NDA/BLA#: 125349 | Supplement Number: 0 | NDA Supplement Type (e.g. SE5): n/a

Division Name: Division of Special Pathogen and Transplant Products | PDUFA Goal Date: November 14, 2009 | Stamp Date: 5/14/2009

Proprietary Name: n/a

Established/Generic Name: raxibacumab

Dosage Form: IV

Applicant/Sponsor: Human Genome Sciences, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

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

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of inhalation anthrax

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

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

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

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

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

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

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

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

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page} RMcKinnon 6/18/09

Regulatory Project Manager Rebecca D. McKinnon

(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

16 April 2009

Renata Albrecht, MD
Director, Division of Special Pathogens and Transplant Products
Office of Antimicrobial Products
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)
Raxibacumab Biologics License Application
Debarment Certification Letter

Dear Dr. Albrecht:

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.

S. Bolmer

Sally Bolmer, PhD, RAC

16 Apr 09
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 INFORMATION[1]

NDA # BLA # 125349	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: raxibacumab Dosage Form: injection, 1700 mg/34 mL (50 mg/mL)		Applicant: Human Genome Sciences, Inc. Agent for Applicant (if applicable):
RPM: Jane Dean, RN, MSN		Division: Division of Anti-Infective Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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.)

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)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is December 15, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR, 11/14/09

[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.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ 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 _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☒ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, date: 12/3/12
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

• [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? (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))).	☐ Yes ☐ No
*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? (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))).	☐ Yes ☐ No
*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).*	

Reference ID: 3233727

(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? (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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	X
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) CR, 11/14/09 AP, 12/14/12
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.	12/12/12
• Original applicant-proposed labeling	9/5/12
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3233727

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/12/12
• Original applicant-proposed labeling	9/5/12
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	12/7/12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 9/7/12 (2) ☒ DMEPA 11/19/12 ☒ DMPP/PLT (DRISK) 12/3/12 ☐ ODPD (DDMAC) 11/27/12, 11/30/12 ☐ SEALD ☐ CSS ☒ Other reviews DMA 11/9/12; 12/13/12; DMPP, 12/4/12
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	N/A ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 10/10/12 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Reference ID: 3233727

❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 3/19/12
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	11/2/12
• 48-hour alert or minutes, if available *(do not include transcript)*	Not available
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	First Cycle: 11/14/09 Second Cycle: 12/14/12
Division Director Summary Review *(indicate date for each review)*	First Cycle: 11/14/09 Second Cycle: 12/14/12
Cross-Discipline Team Leader Review *(indicate date for each review)*	First Cycle: 11/13/09 Second Cycle: 12/12/12
PMR/PMC Development Templates *(indicate total number)*	4
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	First Cycle: 7/20/09 Second Cycle: 12/1212
• Clinical review(s) *(indicate date for each review)*	First Cycle: 10/19/09, 11/13/09, 11/19/09 Second Cycle: 11/21/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	First Cycle: 4/20/09 Second Cycle: Clinical Review, 11/21/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	First Cycle: OTS - 10/1/09 Second cycle: PMHS - 11/5/12, Ethics - 11/8/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

Reference ID: 3233727

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 12/3/12
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	First Cycle: 10/7/09 Second Cycle: ☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	First Cycle: 10/19/09 Second Cycle: 8/13/12
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	First Cycle: 10/19/09 (2) Second Cycle: 11/21/12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	First Cycle: 10/19/09, 11/12/09 Second Cycle: 11/21/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	First Cycle: 10/19/09 Second Cycle: 11/21/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	First Cycle: 10/19/09 (Neurology) Second Cycle: ☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	11/7/12

Reference ID: 3233727

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	First Cycle: 10/19/09, 11/12/09 Second Cycle: 11/15/12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	First Cycle: 10/19/09 Second Cycle: 11/15/12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed First Cycle: 10/20/09, 11/3/09 Second Cycle: 11/26/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/15/12
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	11/15/12
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(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 sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 11/28/12 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] 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.

Reference ID: 3233727

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.

Reference ID: 3233727

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/s/

JANE A DEAN
12/18/2012

MEMORANDUM

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

DATE: December 11, 2012

TO: Administrative File

THROUGH: Ed Cox, MD, MPH

SUBJECT: Telecon with Biomedical Advanced Research and Development Authority (**BARDA**) to Discuss the Post Exposure Prophylaxis Indication for Raxibacumab

APPLICATION/DRUG: BLA 125349 (raxibacumab)

PARTICIPANTS:

Edward Cox, MD, MPH	Director, Office of Antimicrobial Products (OAP)
John Farley, MD, MPH	Acting Director, Division of Antimicrobial Products (DAIP)
Katherine Laessig, MD	Deputy Director (DAIP)
John Alexander, MD, MPH	Clinical Team Leader (DAIP)
Yuliya Yasinskaya, MD	Clinical Reviewer (DAIP)
Rosemary Roberts, MD	Director, Office of Counterterrorism and Emergency Coordination (OCTEC)
Brad Leissa, MD	Deputy Director (OCTEC)
Jane Dean, RN, MSN	Project Manage, (DAIP)
Robin Robinson, MD	Deputy Assistant Secretary, Office of Assistant Secretary for Preparedness and Response (ASPR)
Gerald Kovacs, MD	Director (BARDA)
Debra Yeskey, PharmD	Director, Regulatory and Quality Affairs Division (BARDA)

This telecon was scheduled at the request of BARDA. BARDA requested a discussion on a post exposure prophylaxis (PEP) indication being added to the treatment indication for raxibacumab as well as a postmarketing commitment to study the drug's potential for interference with anthrax vaccine. BARDA conveyed their concerns about the PEP indication being part of the label. The PHEMCE requirement for the use of the anthrax antitoxins, such as raxibacumab, is for treatment of anthrax from an intentional inhalational release. There is no requirement for anthrax PEP. The contract between BARDA and Human Genome Sciences, (HGS) established with input from the Centers for Disease Prevention (CDC) was to study raxibacumab as a

treatment option for intentional exposure to anthrax.

BARDA also expressed concern about learning from HGS the Agency's intention to include PEP as an indication. The major issue for BARDA was that the original contractual agreement established under the medical countermeasures initiative did not include PEP, only treatment. HHS could possibly be required to continue funding for PEP when that was not part of the original contract. At the beginning, there was no requirement for HGS to study PEP.

The Agency explained that the indication for PEP was spontaneously brought up by Advisory Committee (AC) members during the November 2, 2012, AC meeting. The purpose of the AC meeting was to discuss the scientific information available in the BLA submission that evaluates the safety and efficacy of raxibacumab.

The Agency noted that BARDA's contractual, logistical, and policy issues should not be brought up to influence an Agency regulatory decision. The Agency noted that the regulatory decision is based on the reviews of the scientific information on the product.

BARDA expressed concern that they had first learned that prophylaxis was being considered from HGS. BARDA would have preferred that they be called before this information was shared with HGS. The Agency apologized for that happening but restated that they must base the regulatory decision on the science and the information included in the application submitted by HGS.

The Agency stated that HGS was committed to supporting the interference with anthrax vaccine study. BARDA noted that they have received mixed messages regarding this study from HGS (GSK). The Agency asked if BARDA had expressed their concerns to HGS.

BARDA asked if the Agency had talked to reviewers from the Center for Biologic Evaluation Products (CBER) to discuss the study. The Agency noted that we in CDER do talk with CBER for questions that involve vaccines.

BARDA said they would deal with any issues related to a prophylaxis indication once a regulatory decision has been made on the BLA.

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/s/

JANE A DEAN
12/12/2012

From: Dean, Jane
Sent: Wednesday, December 05, 2012 4:55 PM
To: 'Sally Bolmer'
Cc: Maggie Lewis
Subject: BLA 125349 (raxibacumab) - FDA revised label

Importance: High

Attachments: draft-labeling_v12-05-12.doc; Draft PPI 1 page v 12-5-12.doc

Hi, Sally/Maggie, attached below is the agency's revisions to the label. This version includes only the changes we made to Section 12.3 and 14 of the label. It does not include anything you have sent since the telecon on Monday, 12/3/12.

draft-labeling
l2-05-12.doc

Please note that the Patient Information section at the end of the label is in a separate document. The Agency has changed the requirements for such labeling. We are putting it in a separate document so it will retain its SPL format. You will need to make certain that the formatting is retained when you attach it to your label.

Draft PPI 1
e v 12-5-12.d

During the telecon, in Section 11, first paragraph, the use of "murine" versus "mammalian" came up – the team would like to keep the term "murine" here in the label.

Also, I'm including comments from the statisticians explaining their changes to the table in Section 14:

> The P-value of 0.0002 reported by FDA in Study 4 is based on a two-sided Fisher's exact test, which is appropriate for data with small cell entries. This is also consistent with Studies 2 and 3 where P-values are all based on a two-sided Fisher's exact test.
>
> As for 95% CI in Studies 2 and 3, FDA computed the exact CI using standardized statistics by inverting a two-sided test while the sponsor used standardized statistics by inverting two 1-sided tests.

Jane

Jane A. Dean, RN, MSN

Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
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/s/

JANE A DEAN
12/05/2012

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: 20 November, 2012

From: Colleen Thomas, Ph.D., CDER/OC/OMPQ/DGMP/BMAB
David Frucht, M.D., CDER/OPS/OBP/DMA

To: BLA File, STN 125349/0

Endorsed: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB

Subject: Biological License Application (BLA)

Applicant: Human Genome Sciences, Inc.

Facility: [redacted] (b) (4)

Product: Raxibacumab drug product (no proprietary name)

Dosage: Supplied as a sterile, preservative-free, 50 mg/ml solution in glass vials. Administered by intravenous infusion.

Indication: For treatment of inhalation anthrax.

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that [redacted] (b) (4) has been approved to manufacture multiple licensed products [redacted] (b) (4) we recommend that the pre-approval inspection of the [redacted] (b) (4) drug product manufacturing facility at [redacted] (b) (4) be waived for the BLA 125349 resubmission dated 15 June 2012.

Summary

BLA 125349 was first submitted by Human Genome Sciences, Inc. on 13-Nov-2009 to license raxibacumab for treatment of inhalation anthrax. The sponsor received a complete response (CR) letter on 14-Nov-2009. The Agency granted the sponsor a two year filing extension for resubmission of BLA 125349 on 4-Nov-2010. The BLA was resubmitted on 15-Jun-2012 and granted a priority review.

Raxibacumab is a recombinant fully human IgG_1 monoclonal antibody composed of two identical heavy chains and two identical light chains. It specifically binds to the protective antigen (PA) of anthrax toxin and prevents binding of PA to anthrax toxin receptors on target cells. Raxibacumab is expressed and secreted by NS0 mouse myeloma cells [redacted] (b) (4). The drug substance is manufactured at Human Genome Sciences in Rockville, MD. The manufacturing process includes [redacted] (b) (4) steps. The bulk drug

substance is (b) (4)

Raxibacumab drug product is supplied as a single-dose, preservative-free, sterile liquid in a 50 ml glass vial. The required volume of product for a 40 mg/kg dose is diluted to 250 ml with 0.9% NaCl Injection (USP), 0.45% NaCl Injection (USP), (b) (4) and administered by intravenous infusion. The diluent is not supplied with the drug product.

Facility Information

(b) (4)

The process includes:
(b) (4)

Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

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

   Raxibacumab drug product will be manufactured at (b) (4) a contract manufacturer that produces multiple CDER-approved products (b) (4)

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

   A CGMP inspection of the (b) (4) site was conducted by (b) (4) from (b) (4) to (b) (4). The inspection was classified VAI. The SVS profile was updated and is acceptable.

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

   The site has acceptable compliance status.

4. *The establishment is performing* (b) (4) (b) (4)

   The site is approved to manufacture multiple drug and biologic products (b) (4)

5. *The manufacturing process is* (b) (4)

   The manufacturing process for raxibacumab drug product is (b) (4)

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/s/

COLLEEN THOMAS
11/26/2012

PATRICIA F HUGHES TROOST
11/27/2012

DAVID M FRUCHT
11/27/2012

KATHLEEN A CLOUSE STREBEL
11/27/2012

JOSEPH D DOLESKI
11/28/2012

From: Dean, Jane
Sent: Monday, November 19, 2012 11:57 AM
To: 'Sally Bolmer'
Cc: Maggie Lewis
Subject: BLA 125349 (raxibacumab) - PMC/PMR language

Importance: High

Hi, Sally, here is the language being proposed by the agency for PMCs/PMRs:

Postmarketing Requirements:

1. In the resubmission of the BLA 125349 dated June 15, 2012 you agreed to conduct a field study to evaluate the efficacy, pharmacokinetics, and safety of raxibacumab use for *Bacillus anthracis* in the United States and submitted a field study protocol for which we have the following comments:

    - Consider a revision to limit the protocol to PK and clinical (safety and efficacy) data collection in the subjects who have received raxibacumab as part of clinical care, rather than protocol defined administration of raxibacumab treatment.
    - Population PK analysis of the scavenged blood samples or sparse sampling rather than prespecified timed collection of samples in all patients for raxibacumab concentration may be more feasible in the emergency use of the product.
    - Timely access to anthrax patients and the ability to collect all pre-specified blood/CSF samples are anticipated to be limited during a bioterrorism event if not at all feasible. Consider a coordinated effort in implementing the protocol with emergency response agencies, such as CDC. It is possible that BARDA could serve as a liaison for the development and logistics of implementation of the field study protocol for raxibacumab in an emergency anthrax bioterrorism event.

    We recommend you conduct this study according to the following proposed schedule:

Final Protocol Submission:	June 15, 2013
Study/Trial Completion:	To be determined should an event occur
Final Report Submission:	To be determined should an event occur

Postmarketing Commitments:

1. Perform spiking studies of undiluted formulated bulk drug substance during which the samples are assayed initially and at periodic time points after spiking, simulating worst-case manufacturing conditions (hold time and temperature) to evaluate whether endotoxin masking occurs over time in undiluted samples..

We recommend you conduct this study according to the following proposed schedule:

Final Protocol Submission:	November 30, 2012
Study/Trial Completion:	December 5, 2012
Final Report Submission:	December 15, 2012

2. Develop and validate a new [redacted] (b) (4) assay that has improved sensitivity and capability to detect a greater range of potential [redacted] (b) (4) contaminants compared to the current assay and to provide this information as a prior approval supplement to the BLA by June 30, 2015.

We recommend you conduct this study according to the following proposed schedule:

Final Protocol Submission:	December 31, 2014
Study/Trial Completion:	April 30, 2015
Final Report Submission:	June 30, 2015

We are also considering a postmarketing commitment to conduct a study to evaluate the effect of raxibacumab on immunogenicity of AVA vaccine in human subjects. The study design could include [redacted] (b) (4)

We would like to discuss this proposal with you. We also need to determine feasible timelines for this study.

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	

This will be the main topic of our telecon Wednesday. Should you have any changes, please be prepared to share them with the agency at that time so that we can reach agreement on the exact wording.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
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/s/

JANE A DEAN
11/19/2012

From: Dean, Jane
Sent: Friday, November 16, 2012 5:55 PM
To: 'Sally Bolmer'
Cc: Maggie Lewis
Subject: BLA 125349 (raxibacumab) - an additional IR

Importance: High

Hi, Sally – here is the IR I was talking about. It will most likely require an amendment to the BLA .

> An information amendment submitted to IND 10069 (SN 0116, 28-Jun-2010) indicated that the MVDs for endotoxin testing of drug substance and drug product by the kinetic turbidimetric assay were recalculated as [redacted] (b) (4) (respectively) based on the revised endotoxin specification for the drug product. However, the BLA file was not updated with the recalculated MVDs. Please update the information in sections 3.2.S.4 and 3.2.P.5 with the recalculated MVDs and ensure that the dilutions indicated for routine testing are not more dilute than the MVD.

The reviewer requests that this be addressed as soon as possible. Thanks!!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

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/s/

JANE A DEAN
11/16/2012

From: Dean, Jane
Sent: Wednesday, October 31, 2012 4:43 PM
To: 'Maggie Lewis'; Sally Bolmer
Subject: RE: BLA 125349 (raxibacumab) - information request

Hi, Maggie – here is the response I got to your question . . .

> We understand the rationale behind your proposed correlation analysis. However, because we do not have agreed-upon criteria for interpretation of a correlation analysis, we would prefer to wait for the PK reanalysis we originally requested.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

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From: Maggie Lewis [mailto:Maggie_Lewis@hgsi.com]
Sent: Wednesday, October 31, 2012 2:05 PM
To: Dean, Jane; Sally Bolmer
Subject: RE: BLA 125349 (raxibacumab) - information request

Hi Jane,

We can run a correlation analysis between the reassay (b) (4) and original assay (b) (4) removing the samples/subjects as requested below, which we could provide by the end of the week. Can you confirm if the correlation analysis is sufficient?

If you would like us to rerun the entire PK analysis that will take a bit longer.

Thanks,
Maggie

From: Dean, Jane [mailto:Jane.Dean@fda.hhs.gov]
Sent: Wednesday, October 31, 2012 1:02 PM
To: Sally Bolmer
Cc: Maggie Lewis
Subject: BLA 125349 (raxibacumab) - information request
Importance: High

Hi, Sally, we have an additional information request for you. Can you let me know how quickly you'll be able to turn this around?

Based on preliminary inspection findings, the reliability of some plasma ciprofloxacin samples from Study HGS1021-C1064 is questionable. Specifically, the exact number of freeze/thaw cycles for certain samples cannot be determined. Please re-run the ciprofloxacin equivalence analyses between the [redacted] (b) (4) methods and the [redacted] (b) (4) methods after removing the following subjects and individual concentrations:

Full Subjects
US003-000013
US003-000017
US003-000018
US003-000021
US003-000025
US003-000030

Individual Samples
Subject US001-000012, sample IDs 01371305 and 01371309
Subject US001-000015, sample ID 01371721
Subject US002-000002, sample ID 02052515
Subject US002-000005, sample IDs 02052947 and 02052951
Subject US003-000060, sample ID 02087080
Subject US003-000061, sample ID 02087258

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
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/s/

JANE A DEAN
10/31/2012

From: Dean, Jane
Sent: Wednesday, October 31, 2012 1:02 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - information request

Importance: High

Hi, Sally, we have an additional information request for you. Can you let me know how quickly you'll be able to turn this around?

> Based on preliminary inspection findings, the reliability of some plasma ciprofloxacin samples from Study HGS1021-C1064 is questionable. Specifically, the exact number of freeze/thaw cycles for certain samples cannot be determined. Please re-run the ciprofloxacin equivalence analyses between the (b) (4) methods and the (b) (4) methods after removing the following subjects and individual concentrations:
>
> Full Subjects
> US003-000013
> US003-000017
> US003-000018
> US003-000021
> US003-000025
> US003-000030
>
> Individual Samples
> Subject US001-000012, sample IDs 01371305 and 01371309
> Subject US001-000015, sample ID 01371721
> Subject US002-000002, sample ID 02052515
> Subject US002-000005, sample IDs 02052947 and 02052951
> Subject US003-000060, sample ID 02087080
> Subject US003-000061, sample ID 02087258

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

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/s/

JANE A DEAN
10/31/2012

From: Dean, Jane
Sent: Wednesday, October 24, 2012 10:21 AM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - information request

Hi, Sally/Maggie – we have an additional information request – please let me know your TAT – thanks!!

> Endotoxin recovery as measured by LAL test methods can be inhibited in formulations containing citrate and polysorbate when the material is held for days prior to sampling and/or testing. Please describe studies performed to evaluate the effect of hold time on endotoxin recovery in BDS samples. These studies should be performed in addition to method qualification studies described in USP <85> for the kinetic chromogenic and the kinetic tubidimetric LAL methods.
>
> Please explain why the [redacted] (b) (4) endotoxin result was considered acceptable for validation of the [redacted] (b) (4) hold time, and indicate the actual EU/ml measured in that sample.

Jane

Jane A. Dean, RN, MSN
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/s/

JANE A DEAN
10/24/2012

MEMORANDUM

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

DATE: October 9, 2012

TO: BLA 125349 Administrative File

FROM: Jane A. Dean, RN, MSN, Regulatory Health Project Manager

SUBJECT: BARDA and November 2, 2012 Advisory Committee

APPLICATION/DRUG: BLA 125349

The purpose of this memorandum is to document the invitation extended to Biomedical Advanced Research and Development Authority (BARDA) to speak at the November 2, 2012 Advisory Committee meeting. The invitation came from both the Division of Anti-Infective Products (DAIP) and Advisors and Consultants Staff (ACS). The purpose of the advisory committee meeting is to discuss the Biologic License Application (BLA) for raxibacumab submitted by Human Genome Sciences, Inc. which is currently under review in DAIP.

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/s/

JANE A DEAN
10/16/2012

From: Dean, Jane
Sent: Wednesday, September 19, 2012 3:49 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - add'l IR

Importance: High

Hi, Sally, please see below the additional information request we have:

1. In your 30 August 2012 response to our information request, you provide 2D electrophoresis gel data [redacted] (b) (4), this could be due to differing orientations of the two images. Please address this concern. In addition, please provide calculations derived from 2D gel data [redacted] (b) (4) (i.e., the overlap).

2. You state that bulk drug substance lots 410408 and 410411 were out-of-specification [redacted] (b) (4) measured by IE-HPLC. In addition, you state that corrective actions were implemented, including screening and dedicating [redacted] (b) (4) lots. Please provide more detailed information regarding the investigation of these deviations and determination of their root cause(s).

Please let me know what your turn around will be – thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
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/s/

JANE A DEAN
09/19/2012

From: Dean, Jane
Sent: Wednesday, August 29, 2012 10:38 AM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - information request dated 8-29-12

Importance: High

Hi Sally – we have the following information request. Please let me know what your turn around will be – thanks!

> The validation study for the dye ingress test method used for container closure integrity testing of stability samples was performed [redacted] (b) (4)
>
> Therefore, the system variability for the assay is not clear. Please provide method validation data for additional samples with a variety of breach sizes that clearly demonstrates the ability of the method to detect various breach sizes that could allow microbial ingress. Alternatively, justify performing the method validation study [redacted] (b) (4)

Jane

Jane A. Dean, RN, MSN
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/s/

JANE A DEAN
08/29/2012

From: Dean, Jane
Sent: Wednesday, August 22, 2012 4:40 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - additional information request

Hi, Sally, our pharm/tox reviewer has the following information request. Please let me know what your approximate TAT will be – thanks!

1) Provide the necessary SOP(s) and/or descriptions of the methodology, chemicals (i.e. antibody(s), dyes, blocking reagents, buffers, etc), and positive and negative control data for the immunohistochemical and histochemical staining for raxibacumab, GFAP, IgG and Fluoro-Jade C in the paraffin embedded brain sections in the CNS study (Study #: 1103-G923704). In addition, provide any data you may have on the sensitivity/specificity of the detection method(s), particularly for the primary and secondary antibodies, that were used to detect raxibacumab and IgG in the brain slides from anthrax challenged rabbits.

2) Provide the histopathology severity scores for the tissues collected in the CNS study (Study #: 1103-G923704), particularly those from the brains of the control and treated anthrax challenged rabbits. If these were already submitted, please provide the location in the NDA resubmission.

Jane

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/s/

JANE A DEAN
08/22/2012

From: Dean, Jane
Sent: Monday, August 20, 2012 11:05 AM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - summary of telecon with FDA on 8/17/12

Dear Sally,

The summary of the t-con that took place between HGS and the Agency on August 17, 2012, is as follows:

1.The November 2009 letter to HGS were comments intended only for Drug Product manufactured following approval of the BLA and do not apply to product already in the SNS.

2. Product in the SNS remains under the labeling exception until the BLA has been approved.

3. Relabeling of SNS product once the BLA is approved will involve: (b) (4) [redacted] inclusion of a new vial label (overlabel) that will include the additional approved product elements (U.S. license #, lot # , and expiration date).

4. The information request sent on 8/14/12 for relabeling details applies to the amended process for handling SNS product. A response to this request will be sent in an amendment to the BLA.

Attendees included the following:

FDA

Jane Dean, Regulatory Health Project Manager (DAIP)
David Frucht, Team Leader Product Quality (OBP)
Joanne Holmes, Associate Director of Regulatory Affairs (OCTEC)
Katherine Laessig, Deputy Director (DAIP)
Rosemary Roberts, Director (OCTEC)
Kimberly Rains, Labeling Reviewer (OPS)
Chen Sun, Product Quality Reviewer (OBP)
Yuliya Yasinskaya, Medical Reviewer (DAIP)

HGS

Angela Blake-Haskins, Drug Product Sciences
Sally Bolmer, Development & Regulatory Affairs
Alicia Gilbert, Regulatory Affairs - CMC
Maggie Lewis, Regulatory Affairs
Nancy Nidel, Manufacturing Outsourcing
Christine Pannunzio, Regulatory Affairs - CMC
Melissa Perkins, Drug Product Sciences

BARDA
Stephen Morris
Quentin Scott
Chia-Wei Tsai
Debra Yeskey

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
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/s/

JANE A DEAN
08/20/2012

From: Dean, Jane
Sent: Tuesday, August 14, 2012 11:15 AM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - information request as a basis for this Friday's telecon with the Division

Hi, Sally, the Division has the following information request that will be the basis for this Friday's telecon:

You have provided an outline of a revised proposal for relabeling [redacted] (b) (4) raxibacumab Drug Product currently stored in the Strategic National Stockpile. However, you have not provided key data required to determine the acceptability of this revised procedure. The following information should be provided as soon as possible:

(1) The [redacted] (b) (4) deviation that will occur during the proposed relabeling [redacted] (b) (4) process
(2) The equipment to be used during the proposed relabeling/[redacted] (b) (4) process
(3) The [redacted] (b) (4) during the proposed relabeling/[redacted] (b) (4) process
(4) Quality control measures and acceptance criteria to monitor the overlabeling process.
(5) Information regarding where the relabeling [redacted] (b) (4) will occur; [redacted] (b) (4)
(6) Product stability data supporting the conclusion that this proposed relabeling/[redacted] (b) (4) process will not adversely affect product quality
(7) Commitments to assess the long-term stability of Drug Product lots subjected to the new relabeling/[redacted] (b) (4) process

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
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/s/

JANE A DEAN
08/14/2012

From: Dean, Jane
Sent: Friday, August 10, 2012 4:57 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - general advice re minor edits of PLR formatting

Hi, Sally, the following comments are minor formatting issues of your PLR label submitted in the 6/15/12 resubmission of raxibacumab. These won't be coming to you in a filing issues letter since such a letter is not necessary for resubmissions.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL) > General Format

1) The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement). We note that the **HIGHLIGHTS OF PRESRIBING INFORMATION** section is more than one half page.

2) Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet). We note the 1st bullet under **DOSAGE AND ADMINISTRATION** does not have the numerical identifier.

Highlights (HL) > Highlights Details > Highlights Limitation Statement

3) The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**." We note that the drug product name is in lower case in both instances.

Highlights (HL) > Highlights Details > Indications and Usage

4) If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]." We note that the statement in your label is broken into two sentences.

Full Prescribing Information (FPI) > General Format

5) FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval. We note the Medication Guide is included as 17.4.

Full Prescribing Information (FPI) >Full Prescribing Information Details > Patient Counseling Information

6) You must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

   - "See FDA-approved patient labeling (Medication Guide)"
   - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
   - "See FDA-approved patient labeling (Patient Information)"
   - "See FDA-approved patient labeling (Instructions for Use)"
   - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

   We note the information in the parentheses is missing.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by September 4, 2012. The resubmitted labeling will be used for further labeling discussions.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

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/s/

JANE A DEAN
09/07/2012

From: Dean, Jane
Sent: Friday, August 10, 2012 1:47 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'
Subject: BLA 125349 (raxibacumab) - information request

Hi, Sally, we have the following information request:

> Provide more information regarding the source (in-house or commercial) of the antiserum used for detection of [redacted] (b) (4) impurities [redacted] (b) (4). The submitted data should include 2D SDS-PAGE gels of the range of [redacted] (b) (4) detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antiserum employed in the assay. These data should be used to determine the approximate percent of potential [redacted] (b) (4) impurities that are recognized by the [redacted] (b) (4) antiserum. It is the Agency's experience that analysis of [redacted] (b) (4) coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose. It might be possible to provide data generated using a similarly sensitive and discriminating assay in lieu of the 2D SDS-PAGE assay. If an alternative to 2D SDS-PAGE analysis is pursued, consultation with the Agency is recommended.

Please let me know your turn around time, thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

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/s/

JANE A DEAN
08/10/2012

From: Dean, Jane
Sent: Monday, July 23, 2012 5:53 PM
To: Sally Bolmer
Cc: 'Maggie Lewis'; Julie Hagan
Subject: BLA 125349 (raxibacumab) - another quick IR for you

Hi, Sally – we have the following information request:

> Please provide an analysis dataset TXTIMES for study 1141 (added benefit) that contains data on the baseline temperature average, date and time for onset of fever (1.5 above baseline for >2 hours), time to fever onset post challenge and date and time of temperature normalization for animals that survived.

Thanks!

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
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/s/

JANE A DEAN
07/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125349/25

ACKNOWLEDGE - CLASS 2 RESPONSE

Human Genome Sciences, Inc.
Attention: Sally Bolmer, PhD, RAC
Senior Vice President, Development & Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

We have received your June 15, 2012 resubmission to your biologics license application for Raxibacumab on June 15, 2012.

The resubmission contains your response to address deficiencies identified by the Division in our November 14, 2009, complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is December 15, 2012.

If you have any questions, call Jane A. Dean RN, MSN, Regulatory Health Project Manager, at (301) 796-796-1202.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

FRANCES V LESANE
06/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125349/0

MEETING MINUTES

Human Genome Sciences, Inc.
Attention: Sally Bolmer, PhD, RAC
Senior Vice President, Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Raxibacumab.

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2012. The purpose of the meeting was to receive FDA input regarding the adequacy of the data to support resubmission of the raxibacumab BLA.

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

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-resubmission of BLA
Meeting Date and Time:	March 19, 2012, 3:00 pm – 4:00 pm
Meeting Location:	Building 2, Conference Room 2045 10903 New Hampshire Avenue Silver Spring, MD 20903
Application Number:	BLA 125349/0
Product Name:	Raxibacumab
Indication:	Treatment of inhalation anthrax
Sponsor/Applicant Name:	Human Genome Sciences, Inc.
Meeting Chair:	John Farley, MD, MPH
Meeting Recorder:	Jane A. Dean, RN, MSN

FDA ATTENDEES
CDER participants:
Division of Anti-Infective Products (DAIP):

John Alexander, MD, MPH	Clinical Team Leader
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
Lynette Berkeley, PhD, MT (ASCP)	Clinical Microbiology Reviewer
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Maureen Dillon-Parker	Chief, Project Management Staff
John Farley, MD, MPH	Acting Director
Caroline Fukuda, MHA	Project Manager
Karen Higgins, ScD	Statistical Team Leader
Katherine Laessig, MD	Deputy Director
Frances V. LeSane	Chief, Project Management Staff
Terry Miller, PhD	Pharmacology/Toxicology Reviewer
Sumathi Nambiar, MD, MPH	Deputy Director for Safety
Eileen Navarro Almario, MD	Clinical Team Leader
Ryan Owen, PhD	Clinical Pharmacology Reviewer
David Roeder, MS	Associate Director of Regulatory Affairs (Office of Antimicrobial Products)
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Yuliya Yasinskaya, MD	Clinical Reviewer
William Tauber, MD	Clinical Reviewer
Lan Zeng, PhD	Statistical Reviewer

Reference ID: 3116580

Division of Monoclonal Antibodies (DMA):

David Frucht, MD	Chief, Laboratory of Cell Biology
Chen Sun, MD, PhD	Product Quality Reviewer

Office of Counterterrorism and Emergency Coordination (OCTEC):

Brad Leissa, MD	Deputy Director
Susan McDermott, MD	Medical Officer
Gerald Poley, MD	Medical Officer
Andrea Vincent, PharmD, JD	Pharmacist

Division of Bioequivalence and Good Laboratory Practice Compliance (DBGLPC):

Charles Bonapace, PharmD	Acting Branch Chief, Good Laboratory Practice Branch
Michael Skelly, PhD	Pharmacologist
William Taylor, PhD, DABT	Acting Director

Office of Counterterrorism and Emerging Threats:

Alan Liss, PhD	Director of Public Health and Security Action Team

SPONSOR ATTENDEES

Human Genome Sciences, Inc.:

Sally Bolmer, PhD, RAC	Senior Vice President, Development and Regulatory Affairs
Jim Davis, PhD, JD	Executive Vice President, Government Affairs (contract negotiations)
William Freimuth, MD, PhD	Vice President, Clinical Research
Julie Hagan	Specialist, Regulatory Affairs
Maggie Lewis	Senior Manager, Regulatory Affairs
Craig Malzahn	Director, Supply Chain Manufacturing
Thi Sau Migone, PhD	Vice President, Research
Christine Pannunzio, MAS	Executive Director, Regulatory Affairs-CMC
Brian Porter, MD, PhD, MPH	Associate Director, Clinical Research
John Zhong, PhD	Senior Director, Biostatistics

Battelle Biomedical Research Center (BBRC):

Gabriel Meister, PhD	Manager, Bacteriology and Toxicology group
Daniel Sanford, PhD	Study Director
Daphne Vasconcelos, DVM, PhD, DABT	Pathologist

Reference ID: 3116580

Biomedical Advanced Research and Development Authority, (BARDA):

Thomas Drier, PhD	Non-clinical Subject Matter Expert
Michael Merchlinsky, PhD	Non-clinical Subject Matter Expert
Quentin Scott, PhD	Regulatory Specialist
Chia-Wei Tsai, PhD	Project Officer
Debra Yeskey, PharmD	Director, Regulatory and Quality Affairs Division

1.0 BACKGROUND

Human Genome Sciences, Inc. (hereafter referred to as HGS) submitted a meeting request January 17, 2012. The purpose of the meeting was to receive input from the Agency on the adequacy of their planned resubmission of their Biologic License Application (BLA) for raxibacumab. The BLA was originally submitted on May 13, 2009. The Agency sent a Complete Response letter on November 14, 2009 which outlined the deficiencies and the recommended solutions. Their meeting request was granted and scheduled for March 19, 2012. HGS submitted their briefing document February 15, 2012. The Agency's preliminary comments, sent to HGS via email on March 9, 2012, are appended to these meeting minutes (Attachment 1). HGS reviewed the Agency's responses and found there were only two points of discussion to focus on for the meeting. All other responses were acceptable to HGS.

2. DISCUSSION

Questions were included throughout the briefing document and identified by the title of the section it was in and the page number where the question could be found. Using this convention, HGS responded on March 15, 2012, to the preliminary comments stating their acceptance and understanding of most of the Agency's responses. Where further clarification was needed, HGS referenced the page number and repeated the question. They also included the Agency's response and followed it with their question. The email with their question is appended to these meeting minutes (Attachment 2).

2.1. Proposed Indication

Page 64:
Original Sponsor question: Does the Agency agree that the data to be presented in the BLA and the BLA resubmission support this indication for raxibacumab?

Follow-up discussion for the meeting: Can the Agency provide further guidance/clarification regarding their thoughts on the addition of a statement regarding meningitis to the label? For example, does the Agency recommend that we include a statement such that raxibacumab is not effective in the brain, while there is no evidence that raxibacumab has a toxic effect on the brain?

Reference ID: 3116580

Can the Agency provide further guidance/clarification regarding their recommendation for raxibacumab co-administration with antibiotics in the label? We agree that adding wording on co-administration should be included, but would like to hear the Agency's thoughts regarding the use of raxibacumab in combination with antibiotics.

Page 65:
Follow-up discussion for the meeting: Can the Agency provide their current thinking on the possible toxic effects of raxibacumab in the brain (i.e., potential mechanism of action) vs thoughts that raxibacumab fails to benefit the brain, given it does not cross the blood:brain barrier until the animal is otherwise compromised.

The Agency's response to these three questions is incorporated in the discussion that follows.

FDA Response: The histopathology findings in the brains of raxibacumab-treated animals that succumb to anthrax could possibly be related to the limited penetration of raxibacumab into the brain, hindering its ability to clear the infection. The rabbit CNS study showed that raxibacumab is unable to penetrate the blood: brain barrier in the absence of meningitis, as survivors had normal histopathology and negative immuno-staining of the brain for raxibacumab. The Agency expressed concern regarding the ability of raxibacumab to penetrate the blood: brain barrier at sufficient levels in a setting of meningitis. The absence of dose-response in the intensity and frequency of brain findings and negative brain tissue cross-reactivity make direct brain toxicity of raxibacumab less likely. However, the histopathology findings could be a sign of indirect toxicity of raxibacumab in the setting of anthrax meningitis. Indirect toxic effect may be related to the raxibacumab's anti-toxin mechanism of action. This hypothesis is based on research indicating that lethal toxin has an immunosuppressive effect. Theoretically, it is possible, that at low levels achieved in the brains of animals with meningitis, raxibacumab is unable to clear the infection, but is able to achieve sufficient inhibition of lethal toxin immunosuppressive effect leading to exaggerated inflammatory response. The Agency added that in some settings involving neurological infection and inflammation, immunosuppression can provide clinical benefit. The Agency would like to see histopathology data from the CNS and added benefit studies. CNS findings in raxibacumab treated non-survivors and their implications for raxibacumab administration in patients with anthrax meningitis should be addressed by HGS.

The Agency recommended that HGS provide their best recommendations and labeling for the use of raxibacumab monotherapy versus combination therapy with antibiotics in their resubmission of the BLA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no other issues that required further discussion.

Reference ID: 3116580

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Agency will send meeting minutes to HGS within 30 days	FDA	April 18, 2012
HGS will resubmit the BLA incorporating the Agency's recommendations	HGS	June 2012

5.0 ATTACHMENTS AND HANDOUTS

Attachment 1: March 9, 2012 email of preliminary responses sent to HGS
Attachment 2: March 15, 2012 email of HGS response to the preliminary comments

Reference ID: 3116580

From: Dean, Jane
Sent: Friday, March 09, 2012 10:54 AM
To: 'Sally Bolmer'
Subject: BLA 125349 (raxibacumab) - preliminary comments to the 3/19/12 meeting questions

Hi, Sally, included in this email are the responses to your meeting questions submitted in your February 15, 2012, meeting package. Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment at the scheduled meeting. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

In preparation for our upcoming meeting, please be advised that the official advice and recommendations of this division will be communicated during the formal dialogue of our upcoming meeting. Any conversations before or after the official meeting will not reflect the decisions or agreements of the division and thus will not be reflected in the official meeting minutes. If follow-up or clarification on a particular issue is required, those issues should be discussed during the meeting or can be pursued through the formal meetings process in a subsequent meeting or teleconference.

If you wish to change this meeting to a telecon, please contact your Project Manager. If you wish to cancel this meeting, the following responses will become part of the administrative record. Submit your cancellation by letter to your application and contact your Project Manager.

If you wish to discuss another application, the official meeting process should be followed as outlined in the May 2009 "*Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*".

Efficacy & Safety

Page 16:
Does the FDA agree that the added benefit study is sufficient to demonstrate that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial alone arm and supports resubmission of the BLA?

FDA Response: We note that you have conducted an added benefit study according to the protocol agreed upon by the review Division. The complete study report and associated listings and analysis datasets should be included in the resubmission of your BLA. The adequacy of this study in supporting raxibacumab approval will be assessed during the resubmission review.

Page 28:

Does the FDA agree that the CNS study performed is sufficient to address the requirement the CRL to evaluate the effect of raxibacumab on the CNS in an animal model of inhalational anthrax and supports resubmission of the BLA?

FDA Response: You note that you have conducted a study assessing CNS effects of raxibacumab according to the protocol agreed upon by the review Division. The complete study report and associated listings and analysis datasets should be included in the resubmission of your BLA. The adequacy of this study in supporting raxibacumab approval will be assessed during the resubmission review.

Clinical Pharmacology

Page 36:
a. Does the Agency agree that no additional raxibacumab human PK studies or analyses are required to support resubmission of the BLA?

FDA Response: We agree.

b. Based on the equivalence of the results in the original and modified assays in the 3 human clinical studies, does the Agency agree that the reassay of the PK samples from animal studies 682-G005758 in rabbits and 724-G005829 in monkeys is not necessary to support resubmission of the BLA?

FDA Response: We agree. The decision on whether or not to reassay the nonclinical raxibacumab concentrations was dependent on whether a difference was observed between the two methods on the human samples. Since no such difference was observed, the reassay of nonclinical samples for raxibacumab concentrations is not necessary.

c. Does the Agency confirm that reassay of the PK samples from plasma toxicokinetic samples for raxibacumab from the nonclinical toxicology Study 6962-140 and Study 6962-173 is not necessary to support resubmission of the BLA?

FDA Response: We agree (see response to Question b).

Page 40:
d. Does the Agency agree that no additional ciprofloxacin human PK studies or analyses are required to support resubmission of the BLA?

FDA Response: We agree.

e. Does the Agency agree that the reassay of the PK samples from animal study 789-G923702 in monkeys is not necessary to support resubmission of the BLA?

FDA Response: We agree.

Product Quality

Page 41:
a. Does the Agency agree that the endotoxin specification is acceptable to support resubmission of the BLA?

FDA Response: Yes.

Page 44:
a. Does the Agency agree that the scope of the information to be provided for the product quality requests is adequate to support resubmission of the BLA?

FDA Response: Yes.

Page 49:
a. Does the Agency agree that it is acceptable to include this new/updated quality information in the resubmitted BLA?

FDA Response: Yes, it is acceptable to include the updated quality information in the resubmitted BLA.

b. Does the Agency want an updated lot history table and the batch analyses data for all (b) (4) BDS lots and all (b) (4) FDP lots manufactured since the original BLA filing?

FDA Response: Yes, please include an updated lot history table and the batch analyses data for all (b) (4) BDS lots and all (b) (4) FDP lots.

a. Since an earlier version of the batch records was included in the initial BLA does the Agency desire to have the latest version of the executed batch records included in the resubmitted BLA?

FDA Response: If manufacturing changes introduced since the initial BLA submission required significant modifications to manufacturing process parameters or additional process validation, then provide the latest version of the executed batch record.

Safety Update

Page 60:
Does the Agency agree that no safety update is required in the BLA resubmission?

FDA Response: We agree.

Labeling

Page 61:
Does the Agency have any additional comments on resubmission of proposed labeling?

FDA Response: Please refer to our answer to the question regarding proposed indication below.

Organization of the BLA Resubmission in eCTD Format

Page 62:
Does the Agency confirm that the resubmission be supplied as an amendment to the original BLA?

FDA Response: Yes.

Does the Agency agree with the HGS proposal to include summaries of the rabbit efficacy, and PK and histopathology results in the Clinical Efficacy and Clinical Pharmacology sections of Module 2, respectively, and to include the respective study reports in Module 5, given that these data are providing the demonstration of clinical efficacy of raxibacumab under the Animal Rule?

FDA Response: We agree.

Does the Agency agree with the datasets and listings proposed for submission for the new animal studies?

FDA Response: We agree.

Proposed Indication

Page 64:
Does the Agency agree that the data to be presented in the BLA and the BLA resubmission support this indication for raxibacumab?

Raxibacumab is a human monoclonal antibody that binds the protective antigen (PA) of Bacillus anthracis (B. anthracis). Raxibacumab is indicated for the treatment of patients with inhalational anthrax due to B. anthracis.
Important limitations:

- *The effectiveness and safety of raxibacumab have not been tested in humans with inhalational anthrax.*
- *The effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax.*
- *Raxibacumab serum concentrations achieved in humans serve as a surrogate endpoint likely to predict clinical benefit and is the basis for approval of this indication.*

FDA Response: The adequacy of data submitted to support raxibacumab approval for the proposed indication will be assessed during the resubmission review.

You should consider revision of the third bullet point to reflect that raxibacumab exposures at the approved therapeutic dose in humans are similar to those achieved at the dose found to be efficacious in animals and are likely to predict clinical benefit.

We recommend you consider including another limitation of available data on raxibacumab efficacy/safety for the treatment of patients with anthrax meningitis as it pertains to CNS findings in animal efficacy studies.

We recommend you consider whether raxibacumab co-administration with antibiotics should also be included in the indication/limitations of raxibacumab use.

Other Advice

Page 65:
Does the Agency have any other advice or guidance on the BLA resubmission?

FDA Response: Please include in your BLA resubmission recommendations for and modeling/simulation results supporting dosing of raxibacumab in pediatric patients.

The summary data available indicate that raxibacumab penetration into CNS (brain and CSF) is limited only to animals with meningitis: positive immunohistochemistry in raxibacumab treated non-survivors and negative in raxibacumab treated survivors. Therefore, it is important to include in your submission a discussion and additional data if

available on whether exaggerated inflammatory changes in the brain of animals treated with raxibacumab are due to failure of raxibacumab to cure progressive meningitis or in part due to the toxic effects of raxibacumab.

Jane

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
FDA/CDER

Office: 301-796-1202
Fax: 301-796-9881
Rm. 6397, Bdg. 22

Email address: jane.dean@fda.hhs.gov

consider the environment before printing this e-mail

From: Julie Hagan [mailto:Julie_Hagan@hgsi.com]
Sent: Tuesday, March 13, 2012 2:22 PM
To: Dean, Jane
Cc: Sally Bolmer; Maggie Lewis
Subject: HGS BLA 125349 - raxibacumab FDA meeting

Hi Jane –

HGS has 2 key questions/comments following our review of the Agency's preliminary feedback for which we would like to focus our discussion on during the 19 March 2012 face-to-face meeting. All other questions, including clinical pharmacology and product quality, were addressed adequately and we require no further discussion at the meeting.

Please reference the comments for which we would like to discuss further during the meeting below (FDA responses are shown in blue and red text highlights the issues for which we seek further clarification). We realize that the proposed labeling is a review issue, but we would welcome the opportunity to understand FDA's current thinking about the CNS data and concomitant use of antibiotics so that HGS can adequately address these concerns in the BLA. We also acknowledge that the complete results and data sets have not yet been made available to or reviewed by the Agency, and that decisions on adequacy of the data for licensure and labeling will be made after the BLA has been resubmitted. We do very much appreciate the discussion that this meeting provides.

Proposed Indication

Page 64:
Does the Agency agree that the data to be presented in the BLA and the BLA resubmission support this indication for raxibacumab?

Raxibacumab is a human monoclonal antibody that binds the protective antigen (PA) of Bacillus anthracis (B. anthracis). Raxibacumab is indicated for the treatment of patients with inhalational anthrax due to B. anthracis.
Important limitations:
- *The effectiveness and safety of raxibacumab have not been tested in humans with inhalational anthrax.*
- *The effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax.*
- *Raxibacumab serum concentrations achieved in humans serve as a surrogate endpoint likely to predict clinical benefit and is the basis for approval of this indication.*

FDA Response: The adequacy of data submitted to support raxibacumab approval for the proposed indication will be assessed during the resubmission review.

You should consider revision of the third bullet point to reflect that raxibacumab exposures at the approved therapeutic dose in humans are similar to those achieved at the dose found to be efficacious in animals and are likely to predict clinical benefit.

We recommend you consider including another limitation of available data on raxibacumab efficacy/safety for the treatment of patients with anthrax meningitis as it pertains to CNS findings in animal efficacy studies.

- Follow-up discussion for meeting: Can the Agency provide further guidance/clarification regarding their thoughts on the addition of a statement regarding meningitis to the label? For example, does the Agency recommend that we include a statement such that raxibacumab is not effective in the brain, while there is no evidence that raxibacumab has a toxic effect on the brain?

We recommend you consider whether raxibacumab co-administration with antibiotics should also be included in the indication/limitations of raxibacumab use.

- Follow-up discussion for meeting: Can the Agency provide further guidance/clarification regarding their recommendation for raxibacumab co-administration with antibiotics in the label? We agree that adding wording on co-administration should be included, but would like to hear the Agency's thoughts regarding the use of raxibacumab in combination with antibiotics.

Other Advice

Page 65:
Does the Agency have any other advice or guidance on the BLA resubmission?

FDA Response: Please include in your BLA resubmission recommendations for and modeling/simulation results supporting dosing of raxibacumab in pediatric patients.

The summary data available indicate that raxibacumab penetration into CNS (brain and CSF) is limited only to animals with meningitis: positive immunohistochemistry in raxibacumab treated non-survivors and negative in raxibacumab treated survivors. Therefore, it is important to include in your submission a discussion and additional data if available on whether exaggerated inflammatory changes in the brain of animals treated with raxibacumab are due to failure of raxibacumab to cure progressive meningitis or in part due to the toxic effects of raxibacumab.

- Follow-up discussion for meeting: Can the Agency provide their current thinking on the possible toxic effects of raxibacumab in the brain (ie, potential mechanism of action) vs thoughts that raxibacumab fails to benefit the brain given it does not cross the blood:brain barrier until the animal is otherwise compromised.

We will also send you an updated list of HGS attendees shortly.
Thank you and we look forward to seeing you on Monday!

Julie K Hagan, MS
Specialist, Regulatory Affairs
Human Genome Sciences, Inc.
14200 Shady Grove Road | Rockville, MD 20850
WORK 240-314-4400 x2290 **FAX** 240-238-2803
EMAIL julie_hagan@hgsi.com

HUMAN GENOME SCIENCES

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

/s/

JOHN J FARLEY
04/13/2012

7 Page(s) has been Withheld in Full immediately following this page as duplicate copy of an attachment from 4.13.12 Meeting Minutes on previous page

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: November 13, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349 for raxibacumab – Labeling for Packaging

Total no. of pages including cover: 2

Comments:

Concurrence:

David Frucht, M.D., Product Quality Reviewer, Division of Monoclonal Antibodies

Kimberly Rains, Pharm.D., Project Manager, Office of Biotechnology Products/OPS

Scott Dallas, Pharm.D., Safety Evaluator, DMEPA/OSE

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

Based on the initial review of the container and carton labels, we have the following comments:

Commercial Container Label

1. Per 21 CFR 610.61(c)(d) and 21 CFR 201.100, please add the lot and expiration date to the container label.

2. Per 21 CFR 610.60, please provide information to describe how the label has been affixed to the container to permit visual inspection of the vial contents.

3. Relocate the bar code to appear only on the side panel in order to increase the amount of space on the principal display panel for other important information. Ensure the bar code can be easily read by bar coding equipment. If it is not easily read then we suggest displaying the bar code in a vertical format.

4. Ensure the prominence of other information, such as the NDC number, License number, and Manufactured by, on the principal display panel is less prominent than the proper name and expression of strength. Additionally, the "Manufactured by" statement should not be in bold font on the container label.

5. Suggest decreasing the size of the graphic to the left of the principal display panel in order to provide more space and improve the readability of the information on the label.

Commercial Cartons

6. Per USPC Official 8/1/09-12/1/09, USP 32/NF27, <1091> "Labeling of Inactive Ingredients," please list the names of all inactive ingredients in alphabetical order. Consider the following format in alphabetical order: inactive ingredient (amount).

7. Per 21 CFR 610.61(c)(d) and 21 CFR 201.100, please add the lot and expiration date to the unit (b) (4) cartons.

Commercial Carton and Container

8. Please revise the proper name, "Raxibacumab (b) (4)" to "Raxibacumab" to conform to the definition of proper name per 21 CFR 600.3(k) and to match the applicant information listed on the 356h.

9. Per the United States Pharmacopeia, 8/1/09-12/1/09, USP 32/NF27, General Chapter, Injection <1>, 21 CFR 201.10, and 21 CFR 201.51 please revise the prominence of the strength presentation of, "1700 mg/34 mL (50 mg/mL)" to:

   1700 mg/34 mL
   50 mg/mL

10. Please revise the presentation of the statement, "(b) (4) Single –Use Vial" to "Single-Use Vial" to prevent redundancy. Relocate the statement "Single-Use Vial" away from the proper name and expression of strengths. Please ensure that this statement is less prominent than the proper name and expression of strength. Relocate the (b) (4) statement away from the primary expression of strength on the primary panel (b) (4)

11. Revise the label to include the statement "Discard unused portion." This statement should appear in conjunction with the statement "Single-Use."

12. Please revise the primary presentation of the proper name, dosage form, and route of administration to the following:

    Raxibacumab
    Injection
    1700 mg/ 34 mL
    (50mg/mL)
    For Intravenous Infusion

    The agency is working toward standardizing the presentation of the trademark, proper name or established name, dosage form, and route of administration.

13. Consider relocating the license number below the manufacturer information using the following format:

    Human Genome Sciences, Inc.
    Rockville, MD 20850
    U.S. License No. XXXX

    This is the agency preferred format.

SNS Container, Unit Carton [redacted] (b) (4) *Labels with the addition of the Overlabels:*

14. The manufacturer is listed incorrectly per the definition of manufacturer listed in 21 CFR 600.3(t). The statement,

    [redacted] (b) (4)

    The correct statement should be listed on the commercial labels as:

    Manufactured by
    Human Genome Sciences, Inc.
    Rockville, MD 20850

15. The proper name, "Raxibacumab [redacted] (b) (4)" does not conform to the definition of proper name per 21 CFR 600.3(k). "Raxibacumab" is the correct proper name per 21 CFR 600.3(k).

16. The statement, "No Preservative" is not displayed on the carton per 21 CFR 610.61 (e). It may be added to an overlabel to comply with the requirement.

17. The statement, "Rx Only," is not displayed on the [redacted] (b) (4) carton per 21 CFR 610.61(s) and 21 CFR 201.100. It may be added to the overlabel to meet this requirement.

18. Revise the expiration date so that it is presented in a consistent manner on all labeling including the overwrap labels. The month should be presented with at least 3 three letters and the year with 4 digits, not two digits as currently proposed. (e.g., 12 Jul 2014)

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: November 6, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349 for raxibacumab – Recommendations to resolve DSI findings

Total no. of pages including cover: 4

Comments:

Concurrence:

John Lazor, Ph.D., Director, DCP-4/OCP

Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology Team Leader, DCP-4/OCP

Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer, DCP-4/OCP

C.T. Viswanathan, Ph.D., Associate Director-Bioequivalence, Division of Scientific Investigations/CDER

Martin Yau, Ph.D., Acting Team Leader-Bioequivalence, DSI/CDER

Jacqueline A. O'Shaughnessy, Ph.D., Acting Team Leader-GLP, DSI/CDER

Michael Skelly, Ph.D., Pharmacologist, DSI/CDER

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

Please also refer to the inspection findings during the audit conducted by the Division of Scientific Investigations (DSI) for clinical studies HGS1021-C1063 and HGS1021-C1064 (dated September 9, 2009 – September 21, 2009), the teleconference with DSPTP held on October 20, 2009, and your correspondence dated October 29, 2009 (BLA 125349/017) containing the revised assay validation report, assay qualification report, and standard operating procedure (SOP), CLI-2879, for quantitation of raxibacumab in human serum.

We agree that the pharmacokinetic samples from study HGS1021-C1064 should be re-assayed; however, the revised assay validation, qualification, and SOP documents do not fully address the inspection issues identified in the Form FDA-483. Thus, before samples are re-assayed, the following comments should be addressed as they pertain to the methods proposed for quantitation of raxibacumab in human serum:

1. The calibration (standard) curve should consist of a minimum of six acceptable standard points. Calibration standards should be serum-based, and the calibration curve should have calibrator samples at the upper limit of quantitation (ULOQ) and at the lower limit of quantitation (LLOQ) to cover the expected study sample concentration range. We recommend that you select appropriate dilution factors so that ULOQ and LLOQ are on the linear segment of the ECL versus concentration plot.

2. Estimation of raxibacumab concentrations in unknown samples by extrapolation of standard curves below the LLOQ or above the ULOQ is not acceptable. Instead, the standard curve should be redefined or samples with higher concentration should be diluted to be within the calibration range and re-assayed.

3. Quality control (QC) samples in duplicate at three concentrations (one near the LLOQ, one in midrange, and one close to the ULOQ) should be incorporated in each assay run. All QCs should be serum-based.

4. The acceptance of analytical runs for the back-calculated concentrations should be based on the limits of accuracy (%RE) and precision (%CV). For the calibration standards in each run, a minimum of 75% of the back-calculated values (including the ULOQ) should fall within ±20%, except for LLOQ and ULOQ, where it can be ±25% of the nominal value. A minimum of 66% of the back-calculated QC concentrations, and at least 50% at each concentration, should fall within ±20% of the nominal concentrations. The nominal concentrations, and not indirectly determined values, should be used.

5. Incurred sample reproducibility should be evaluated during the analytical runs.

6. The evaluation of stability/recovery for at least three freeze/thaw cycles should be repeated, documenting actual dates and times of each freeze/thaw cycle.

7. Following incorporation of our aforementioned comments and recommendations into the revised procedures, the pharmacokinetic samples from human studies HGS1021-C1063, HGS1021-C1064, and HGS1021-C1069 should be re-assayed using the revised procedures. Pharmacokinetic parameters for raxibacumab from these re-analyses should be re-calculated in humans following re-assay of the samples. Depending on the outcome of these re-analyses, additional pharmacokinetic studies may be required.

8. Because of the outstanding issues with the assay of raxibacumab in human serum, we have now become concerned about the reliability of the pharmacokinetic data that was generated from the animal efficacy studies in New Zealand White rabbits and Cynomolgus macaque monkeys, which used similar bioanalytical procedures as that for the human studies. Therefore, the pharmacokinetic samples from animal studies 682-G005758, 724-G005829, 781-G923701, and 789-G923702 should be re-assayed using the revised procedures, and with incorporation of our comments and recommendations mentioned above. Pharmacokinetic parameters for raxibacumab from these re-analyses should be re-calculated in rabbits and monkeys following re-assay of the samples. Depending on the outcome of these re-analyses, additional pharmacokinetic studies may be required.

We request that you submit complete documentation (i.e. a complete bioanalytical report) of the analytical results for the above experiments. This documentation should be in accordance with the FDA Guidance for Industry – Bioanalytical Method Validation (section VII. Documentation, C. Application for Routine Drug Analysis) dated May 2001. It is important to note that previously submitted "validation and qualification" reports and SOPs do not constitute adequate documentation of bioanalytical methods used in these studies. Future submissions must also include a full, written "bioanalytical" report for the analysis of samples obtained in each study. This report needs to address the components outlined in the section of the guidance mentioned above.

In addition, we agree that the ciprofloxacin pharmacokinetic samples from study HGS1021-C1064 should be re-assayed for ciprofloxacin concentrations using a revised analytical method that adequately addresses the DSI Form 483 findings for the ciprofloxacin assay. Because of the outstanding issues with the assay of ciprofloxacin in human plasma, we have now become concerned about the reliability of the pharmacokinetic data that was generated from the combination animal efficacy study in Cynomolgus macaque monkeys, which used the same bioanalytical laboratory as that for the human studies. Thus, the plasma samples obtained from the Cynomolgus macaque monkey study 789-G923702 should be re-assayed for ciprofloxacin concentrations using a revised analytical method that adequately addresses the DSI Form 483 findings for the ciprofloxacin assay. Pharmacokinetic parameters for ciprofloxacin from these re-analyses should be re-calculated in both humans and monkeys following re-assay of the samples. Depending on the outcome of these re-analyses, additional pharmacokinetic studies may be required.

To further discuss these issues and come to a mutual understanding and agreement on a plan to move forward, a teleconference with DSI and OCP has been coordinated on November 12, 2009 at 2:00 p.m. EST.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: 3 November 2009
To: Administrative File, STN 125349/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/MAPCB/BMT PFH 11/3/09
Subject: New BLA
Applicant: Human Genome Sciences, Inc.
Mfg Facilities: **Drug substance:** Human Genome Sciences, Inc., Belward Small Scale Manufacturing Facility, Rockville, MD (FEI 3003782237)
Drug Product: [redacted] (b) (4)
Product: Raxibacumab (no trade name provided)
Dosage: Sterile liquid in a glass vial for intravenous injection, 1700 mg/34 mL vial
Indication: Treatment of inhalation anthrax
Due Date: 13 November 2009

Recommendation for Approvability

CMC Microbiology:

Because the BLA application will not be approved from a clinical pharmacology perspective (communication with the OND RPM, Rebecca McKinnon, 11/2/2009), it is recommended that the PMR and the PMCs originally identified in the primary reviews of the application be communicated as CMC microbiology deficiencies in the complete response letter to the sponsor. Therefore, the application is not recommended for approval from a CMC microbiology perspective.

The CMC microbiology deficiencies are as follows:

1. Conduct a validation study that supports the hold time of [redacted] (b) (4) at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA.

2. Conduct a validation study that supports the proposed hold times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a retrospective analysis of at-scale production runs, but the analysis should include verifiable information such as batch run numbers and hold conditions.

3. Re-assess (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials.

4. Implement in-process bioburden testing of the bulk drug product (b) (4) . Alternatively, perform full-scale validation of the time limit (b) (4)

5. Re-assess (b) (4) the bacterial endotoxin specification for raxibacumab final drug product. The re-assessment should consider the endotoxin contribution from the saline solution used to dilute raxibacumab drug product prior to administration. The revised specification should reflect the current manufacturing process capabilities and provide a safety factor (e.g., 2-4 fold) when the endotoxin limits from both the saline and the drug product are considered.

6. Update the stability testing protocol to include endotoxin testing at expiry.

7. Develop and validate a container closure integrity test to be used in lieu of sterility testing for samples on stability. The dye ingress method described in the BLA is not validated and therefore not suitable for use in lieu of sterility testing. Conduct sterility testing instead of container closure integrity testing for samples on stability until a validated ingress test method is developed and implemented.

CGMP Acceptability of Establishments:

The manufacturing and testing facilities listed in the BLA are currently in compliance with CGMP requirements and there are no pending compliance actions that would prevent approval of this BLA from a CGMP perspective.

Summary

Human Genome Sciences, Inc., has submitted a BLA for raxibacumab, a human monoclonal antibody that specifically binds to the protective antigen (PA) protein produced by *Bacillus anthracis*. Raxibacumab is produced from recombinant NS0 mouse myeloma cells (b) (4) The drug substance is manufactured at the Belward Small Scale Manufacturing facility of HGS in Rockville, MD.

The raxibacumab drug substance CMC section of the BLA contains several deficiencies which were communicated to the sponsor during the review of this application. Three issues remain to be resolved, although the firm has communicated its intention to address the deficiencies (amendment dated 14 Sep 2009). The sponsor should complete a study

investigating the appropriateness of its (b) (4) expiration date (b) (4) The sponsor should conduct a validation study supporting the proposed hold times for in-process materials and should re-assess (b) (4) endotoxin and bioburden limits for in-process materials to reflect the current drug substance manufacturing process.

An inspection of the HGS drug substance facility was conducted by CDER reviewers (from OBP/DMA and OC/BMT) on September 2-10, 2009. A two-item Form FDA 483 was issued to HGS, citing deficiencies in the production and materials management system. The inspection was classified as Voluntary Action Indicated (VAI) and the facility currently has an acceptable CGMP compliance status.

Raxibacumab drug product is a sterile, preservative-free liquid for intravenous infusion. The drug product is supplied in a single-dose 50 mL USP (b) (4) glass vial and the vial is sealed with a (b) (4) 20 mm (b) (4) stopper and a 20 mm flip-off cap. Each vial contains a target fill of 35.1 mL to ensure delivery of 34 mL product. The proposed shelf-life is (b) (4) at 2-8°C protected from light.

The drug product is manufactured (b) (4) at the contract manufacturing facility, (b) (4) This facility was inspected by FDA district inspectors on (b) (4) and the facility was classified as acceptable. Therefore, the pre-license inspection was waived.

Conclusions:

I. The BLA is not recommended for approval from a microbiology product quality perspective. The following CMC microbiology deficiencies should be communicated to the sponsor:

1. Conduct a validation study that supports the hold time of (b) (4) at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA.

2. Conduct a validation study that supports the proposed hold times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a retrospective analysis of at-scale production runs, but the analysis should include verifiable information such as batch run numbers and hold conditions.

3. Re-assess (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials.

4. Implement in-process bioburden testing of the bulk drug product (b) (4) . Alternatively, perform full-scale validation of the time limit (b) (4)

5. Re-assess (b) (4) the bacterial endotoxin specification for raxibacumab final drug product. The re-assessment should consider the endotoxin contribution from the saline solution used to dilute raxibacumab drug product prior to administration. The revised specification should reflect the current manufacturing process capabilities and provide a safety factor (e.g., 2-4 fold) when the endotoxin limits from both the saline and the drug product are considered.

6. Update the stability testing protocol to include endotoxin testing at expiry.

7. Develop and validate a container closure integrity test to be used in lieu of sterility testing for samples on stability. The dye ingress method described in the BLA is not validated and therefore not suitable for use in lieu of sterility testing. Conduct sterility testing instead of container closure integrity testing for samples on stability until a validated ingress test method is developed and implemented.

II. Information and data in the CMC sections of the BLA not related to microbiology product quality should be assessed by OBP/DMA reviewers.

III. A pre-approval inspection of the drug substance manufacturing and testing site, HGS, on Belward Campus Drive in Rockville, MD (FEI 3003782237) was conducted on September 2-10, 2009 and the compliance status of the facilities is acceptable. The pre-approval inspection of the contract manufacturer, (b) (4) was waived and the compliance status of the facility is acceptable from a CGMP perspective.

CC: WO, Bldg 51, Hughes
WO, Bldg 51, Thomas
WO, Bldg 51, Farbamn
WO, Bldg 51, Dillon
WO, Bldg 22, McKinnon
WO, Bldg 51, e-CTD files (STN 125349)

Archived files: S:\archive\BLAs\125349\125349.0.rev.mem.TL.BLA.11-3-2009.doc

RMS/BLA - Facility Information Sheet for TBP

Complete One Sheet Per Facility

STN: 125349 /0 **Reg. Project Mgr:** Rebecca McKinnon

Facility Status Effective Date: 2 Nov 09

Primary Business Name (name of facility) Human Genome Sciences, Inc

Product raxibacumab

ProprietaryName none

Domestic Reg. # _____ Foreign Reg. # _____

Field Establishment ID # 3003782237

Domestic & Foreign Registration # issued by FDA (If unknown, leave blank; FEI used for inspection and registration purposes (as of 10-1-2000, the FEI replaced the Central File Registration Number)

Facility Address:

Contract Manufacturer - ☐ Yes ☑ No Annual Facility Fee Required? ☐ Yes ☐ No

In Care of: _____ Domestic Phone #: _____

Address Human Genome Sciences, Inc Foreign Phone #: _____

Belward Small Scale Manufacturing Facility

9910 Belward Campus Drive

City: Rockville State or Province: MD Country: USA

Zip Code: 20850 Receive Mail: ☑ Yes ☐ No

List of Valid Values

Facility Activities

☐ **Biological Source Material Manufacturer**

- ☐ Animal Source Material Collection and Processing - Natural
- ☐ Animal Source Material Collection and Processing - Transgenic
- ☐ Cell Bank Production
- ☐ Hybridoma Technology
- ☐ Plant Source Material Collection and Processing - Natural
- ☐ Plant Source Material Collection and Processing - Transgenic
- ☐ Recombinant DNA procedures
- ☐ Storage of Source Materials
- ☐ Testing - Source Material

Continued on back page

Human Genome Sciences, Inc

Facility Information Sheet

Listing of Valid Values

Facility Activities - continued

☑ **Cell Growth & Harvesting**

- ☑ Bioreactor
- ☐ Batch Culture
- ☑ Cell Culture Production - Mammalian (Human, CHO, Murine)
- ☐ Cell Culture Production - Bacterial (Spore-formers)
- ☐ Cell Culture Production - Yeast
- ☐ Cell Culture Production - Fungal
- ☐ Cell Culture Production - Insect
- ☐ Cell Culture Production - Plant
- ☐ Cell Culture Viral (Viral vaccines, viral vectors)
- ☐ Continuous Culture
- ☐ Roller Bottle Culture
- ☑ Testing - Bulk Culture Harvest

☑ **Manufacture Bulk Drug Substance**

- ☑ Adventitious Agent Inactivation/Clearance
- ☐ Chemical Modification (pegylation, conjugation with toxin)
- ☑ Purification - Recombinant Product
- ☐ Purification - Natural Product
- ☐ Purification - Synthetic Peptide
- ☐ Purification - Viral
- ☐ Radiolabeling
- ☑ Testing - Bulk Drug Substance

☐ **Manufacturer Final Drug Product - (Bulk Material to Final Product)**

- ☐ Filling of Final Containers
- ☐ Lyophilization
- ☐ Product Formulation
- ☐ Sterilization

☑ Testing - Product Release

DATA ENTRY - ENTER UNDER TEST PERFORMED

- ☐ Alternative Sterility Testing Methodology
- ☐ Bulk sterility performed on first filled final container
- ☐ Pyrogen Testing
- ☐ General Safety Testing
- ☐ Sterility Test
- ☐ BDS & DP lot release test methods (Maintain current lot release protocols in DARP BLA files)
- ☑ LAL Testing

- ☐ Labeling
- ☐ Packaging of Final Containers
- ☐ Distribution
- ☐ Storage of Final Product for Distribution

Date Entered _____ Entry Initials _____ Date Verified _____ Verify Initials _____

RMS/BLA - Facility Information Sheet for TBP

Complete One Sheet Per Facility

STN: 125349 /0 **Reg. Project Mgr:** Rebecca McKinnon

Facility Status Effective Date: 2 Nov 09

Primary Business Name (name of facility) (b) (4)

Product raxibacumab

ProprietaryName none

Domestic Reg. # _____ Foreign Reg. # _____

Field Establishment ID # (b) (4)

Domestic & Foreign Registration # issued by FDA (If unknown, leave blank; FEI used for inspection and registration purposes (as of 10-1-2000, the FEI replaced the Central File Registration Number)

Facility Address:

Contract Manufacturer - ☑ Yes ☐ No Annual Facility Fee Required? ☐ Yes ☐ No

In Care of: _____ Domestic Phone #: _____

Address (b) (4) Foreign Phone #: _____

City: (b) (4) State or Province: (b) (4) Country: (b) (4)

Zip Code: (b) (4) Receive Mail: ☑ Yes ☐ No

List of Valid Values

Facility Activities

☐ **Biological Source Material Manufacturer**

- ☐ Animal Source Material Collection and Processing - Natural
- ☐ Animal Source Material Collection and Processing - Transgenic
- ☐ Cell Bank Production
- ☐ Hybridoma Technology
- ☐ Plant Source Material Collection and Processing - Natural
- ☐ Plant Source Material Collection and Processing - Transgenic
- ☐ Recombinant DNA procedures
- ☐ Storage of Source Materials
- ☐ Testing - Source Material

Continued on back page

Hospira, Inc

Facility Information Sheet

Listing of Valid Values

Facility Activities - continued

Cell Growth & Harvesting

- ☐ Bioreactor
- ☐ Batch Culture
- ☐ Cell Culture Production - Mammalian (Human, CHO, Murine)
- ☐ Cell Culture Production - Bacterial (Spore-formers)
- ☐ Cell Culture Production - Yeast
- ☐ Cell Culture Production - Fungal
- ☐ Cell Culture Production - Insect
- ☐ Cell Culture Production - Plant
- ☐ Cell Culture Viral (Viral vaccines, viral vectors)
- ☐ Continuous Culture
- ☐ Roller Bottle Culture
- ☐ Testing - Bulk Culture Harvest

Manufacture Bulk Drug Substance

- ☐ Adventitious Agent Inactivation/Clearance
- ☐ Chemical Modification (pegylation, conjugation with toxin)
- ☐ Purification - Recombinant Product
- ☐ Purification - Natural Product
- ☐ Purification - Synthetic Peptide
- ☐ Purification - Viral
- ☐ Radiolabeling
- ☐ Testing - Bulk Drug Substance

Manufacturer Final Drug Product - (Bulk Material to Final Product)

- ☑ Filling of Final Containers
- ☐ Lyophilization
- ☑ Product Formulation
- ☑ Sterilization

☑ Testing - Product Release

DATA ENTRY - ENTER UNDER TEST PERFORMED

- ☐ Alternative Sterility Testing Methodology
- ☑ Bulk sterility performed on first filled final container
- ☐ Pyrogen Testing
- ☐ General Safety Testing
- ☑ Sterility Test
- ☐ BDS & DP lot release test methods (Maintain current lot release protocols in DARP BLA files)
- ☐ LAL Testing

- ☑ Labeling
- ☑ Packaging of Final Containers
- ☐ Distribution
- ☐ Storage of Final Product for Distribution

Date Entered _____ Entry Initials _____ Date Verified _____ Verify Initials _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 28 Oct 2009
To: Administrative File, STN 125349
From: Colleen Thomas, Ph.D., Microbiology Reviewer, OC/DMPQ/MAPCB/BMT CT 30 Oct 09
Through: Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PHut 11/3/09

Subject: New Biologic License Application
US License: 1820
Applicant: Human Genome Sciences, Inc. (Rockville, MD)
Facility: Drug Product: (b) (4)
Product: Raxibacumab
Dosage: Sterile liquid in a glass vial. The required volume of product for a 40 mg/kg dose is diluted to 250 ml with normal saline and administered by intravenous infusion.
Indication: Treatment of inhalation anthrax
Due date: 14 Nov 2009

Recommendation for Approvability: BLA 125349, as amended, is recommended for approval from a CMC sterility assurance and microbiology product quality perspective. One post-marketing requirement and three post-marketing commitments are listed at the end of this review and should be communicated to the sponsor.

Review Summary

Human Genome Sciences, Inc. submitted BLA 125349 to license raxibacumab and the associated drug substance and drug product manufacturing processes. Raxibacumab is a fully human monoclonal antibody that specifically binds to the protective antigen (PA) of *Bacillus anthracis*. The proposed indication is treatment of inhalation anthrax.

Fast Track Status and Orphan Drug Designation were granted on 15 August 2003 and 13 November 2003, respectively. The referenced IND number is 11069. BLA 125349 is an electronic submission in CTD format. This review covers the drug product manufacturing process from a microbial control and sterility assurance perspective. Review of product quality issues other than microbial control and sterility assurance is deferred to OBP.

The following amendments related to microbiology CMC were reviewed:

- Sequence 0012, 14 September 2009: stability data
- Sequence 0015, 23 September 2009: response to drug product CMC information request
-

Sequence 0012 is reviewed in section P.8. Responses to CMC inquiries regarding microbial control and sterility assurance of the drug product are all contained in sequence 0015.

The drug product manufacturing facility [redacted] (b) (4) was inspected by the District on [redacted] (b) (4) and deemed acceptable (NAI). This comprehensive GMP inspection included biologic product manufacturing. Therefore, the pre-license inspection was waived. An inspection waiver memo is attached.

Review Narrative

1. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Raxibacumab drug product is a sterile, preservative-free liquid for intravenous infusion. Bulk drug substance is diluted with [redacted] (b) (4) excipients to form bulk drug product with 50 mg/ml raxibacumab. The drug product components are listed in the table below. The drug product is supplied in a single-dose 50 ml USP [redacted] (b) (4) glass vial [redacted] (b) (4) with a 35.1 ml target fill volume to ensure delivery of 34 ml product. The vial is sealed with a [redacted] (b) (4) 20 mm [redacted] (b) (4) stopper [redacted] (b) (4) and a 20 mm flip-off aluminum cap [redacted] (b) (4). [redacted] (b) (4) The proposed shelf life is [redacted] (b) (4) at the recommended storage conditions (2-8 °C protected from light).

Raxibacumab Drug Product Composition

Component	Concentration (mg/mL)	Amount Per Vial (mg/vial)[1]	Function	Grade
Raxibacumab	50	1700	API[2]	HGS Specification
Citric acid [redacted] (b) (4)	0.13	[redacted] (b) (4)		
Sodium citrate [redacted] (b) (4)	2.8			
Sucrose	10			
Glycine	18			
Polysorbate 80	0.2			
[redacted] (b) (4)	[redacted] (b) (4)			

1 Amount listed is deliverable amount.

2 API: Active Pharmaceutical Ingredient

3 According to supplier's definition, multicompendial grade includes full compendial testing as appropriate to USP or National Formulary (NF), European Pharmacopoeia (EP), British Pharmacopoeia (BP), and Japanese Pharmacopoeia (JP).

4 According to supplier's definition, multicompendial grade includes full compendial testing as appropriate to USP/NF, EP, and JP.

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2. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

Vial labels, unit cartons, [redacted] (b) (4) specify that the product is sterile. The package insert includes a statement regarding visual examination of parenteral products prior to administration. The application includes a plan for relabeling [redacted] (b) (4) the raxibacumab inventory stored in the Strategic National Stockpile to include commercial labeling information.

Environmental Assessment

A claim for categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31 is provided by the applicant on the grounds that no extraordinary circumstances exist that that would require an environmental assessment.

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the submitted sites. There are no pending or ongoing compliance actions to prevent approval of BLA 125349 at this time. The status for the sites is the following:

From: Stock, Marisa
Sent: Wednesday, October 14, 2009 11:50 AM
To: Farbman, Mary; CDER-TB-EER
Subject: RE: New BLA 125349 from HGS

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the list below to find the updated compliance status of each facility.

Human Genome Sciences, Inc. - corporate headquarters, quality oversight, batch disposition, release testing, storage of MCB and WCB, and equivalency testing of WCB
14200 Shady Grove Road
Rockville, MD
FEI: 1000303703
A DSI-led sponsor/monitor/CRO inspection was conducted July 29-31, 2009 and classified NAI. This site is not profiled. Although this site was not specifically covered for GMP compliance, this site is considered to be acceptable for the purposes of this BLA.

Human Genome Sciences, Inc. - drug substance manufacture, storage, and release testing, MCB/WCB manufacture and storage, receipt, testing, and storage of raw materials, stability testing, and shipment of drug substance to fill-finish site
9910-9911 Belward Campus Drive
Rockville, MD
FEI: 3003782237
A pre-approval inspection for raxibacumab was conducted September 2-10, 2009 and initially classified VAI. The TRP profile was covered, however a final classification has not yet been made.

[redacted] (b) (4) - viral release testing of unprocessed bulk MCB and WCB
Malvern, PA
FEI: [redacted] (b) (4)
Inspected [redacted] (b) (4) and classified NAI. The CTL profile was covered and is acceptable.

(b) (4) - (b) (4)
(b) (4)
FEI: (b) (4)
Inspected (b) (4) and classified VAI. The CTL profile was covered and is acceptable. An inspection assignment will be issued for this site.

(b) (4). - storage of MCB and WCB
(b) (4)
FEI: (b) (4)
Inspected (b) (4) and classified VAI. The CTL profile was covered and is acceptable.

(b) (4)
;
FEI: (b) (4)
Inspected (b) (4) and classified NAI. The BTP profile was covered and is acceptable.

(b) (4) - stability testing
(b) (4)
FEI: (b) (4)
Inspected (b) (4) and classified NAI. The CTL profile was covered and is acceptable.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

Conclusion

I. The BLA was reviewed from a sterility assurance perspective and microbiology product quality perspective only and is recommended for approval with one post-marketing requirement and three post-marketing commitments.
II. The supplement should be reviewed by an OBP/DMA reviewer for product quality issues other than microbial control and sterility assurance.
III. No additional inspection follow-up items were identified.

Cc: OND/OAP/DSPTP, WO Bldg 22, McKinnon
OC/DMPQ/BMT, WO Bldg 51, Hughes
OC/DMPQ/BMT, WO Bldg 51, Thomas
OC/DMPQ/BMT, WO Bldg 51, Dillon
OPS/OBP/DMA, HFD-123, Frucht
OC/DMPQ/BMT, WO Bldg 51, Blue Files (STN 125349)

Archived File: S:\archive\BLAs\125349\125349.0.rev.mem.BLA.10-28-09.doc

CMC Microbiology PMR for Raxibacumab Drug Product

1. Re-assess (b) (4) the bacterial endotoxin specification for raxibacumab final drug product. The re-assessment should consider the endotoxin contribution from the saline solution used to dilute raxibacumab drug product prior to administration. The revised specification should provide a safety factor (e.g., 2-4 fold) when the endotoxin limits from both the saline and the drug product are considered. *Final report submission: December 2009.*

CMC Microbiology PMCs for Raxibacumab Drug Product

1. Implement in-process bioburden testing of the bulk drug product (b) (4) . Alternatively, perform full-scale validation of the time limit (b) (4) *Protocol and final report submission: December 2009.*

2. Update the stability testing protocol to include endotoxin testing at expiry. *Revised protocol submission: December 2009.*

3. Develop and validate a container closure integrity test to be used in lieu of sterility testing for samples on stability. The dye ingress method described in the BLA is not validated and therefore not suitable for use in lieu of sterility testing. Conduct sterility testing instead of container closure integrity testing for samples on stability until a validated ingress test method is developed and implemented. *Container closure test protocol and validation report and revised stability protocol: December 2009.*

Memo of Teleconference
Human Genome Sciences, Inc.
October 26, 2009

Time: ~3:15-3:30 p.m. and 4:00-4:05 p.m.

FDA participant: David Frucht
HGS participant: Alicia Gilbert

It was clarified that this was an information request meeting (i.e., not decisional). The following information requests were discussed:

I requested that HGS clearly state which stability protocols would support bulk drug substance (BDS) and final drug product (FDP) stability. Alicia Gilbert provided the following breakdown:

BDS:
Stability study #M2106011: Lots 410101, 410102, 410110, and 410116
Stability study #M2109002: Commercial protocol for new lots (annual)

FDP:
Stability study #M210614: Lots 71044, 71051, 71066, 71067, and 71068
Stability study #M210712: Lots 71044 and 71051 (restart due to light exposure issue)
Stability study #M2109001: Commercial protocol for new lots (annual)
Stability study #17: Lot AB50409-M38, developmental (proposed Nov. supplement)
Stability study #19: Lot AB50409-M41, developmental (proposed Nov. supplement)

Alicia Gilbert stated that all protocols were in the protocol, except for stability studies #17 and 19 for FDP stability extension. I (DF) stated that in order to pre-approve the expiry extension based on acceptable data from these studies, FDA would need to review the detailed protocols for stability studies #17 and 19.

Action Items:

Alicia Gilbert stated that stability study protocols #17 and 19 will be submitted as a BLA amendment. In addition, HGS will provide a table summarizing each of the other stability studies proposed to extend BDS and FDP, identifying which lots are covered under these protocols (as listed above), and providing the location where detailed summaries of these protocols can be found in the BLA submission.

Minutes Preparer:

David Frucht, M.D. David M. Frucht
Product Quality Reviewer, Division of Monoclonal Antibodies

Date: 12 Nov 2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: 19 October 2009
To: Administrative File, STN 125349/0
From: Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT MEF 19 Oct 09
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PFH 20 Oct 09
Subject: New BLA
Applicant: Human Genome Sciences, Inc.
Mfg Facility: Human Genome Sciences, Inc., Belward Small Scale Manufacturing Facility, Rockville, MD (FEI 3003782237)
Product: Raxibacumab (no trade name provided)
Dosage: Liquid for intravenous injection, 1700 mg/34 mL
Indication: Treatment of inhalation anthrax
Due Date: 13 November 2009

Recommendation for Approvability

The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective. Three post-marketing commitments (PMCs) are recommended. A list of PMCs is attached to this memo.

Summary

Human Genome Sciences, Inc., has submitted a BLA for raxibacumab, a human monoclonal antibody against the protective antigen protein of *Bacillus anthracis*. The drug substance is manufactured at HGS in Rockville, MD.

An amendment (125349/0/13) in response to a drug substance microbiology information request was provided to the FDA on 14 September 2009; this amendment is also reviewed below.

An inspection of the drug substance facility occurred September 2-10, 2009. A two-item Form FDA 483 was issued to HGS, citing deficiencies in the production and materials management system. The inspection was classified as VAI.

The following post-marketing commitments (PMCs) should be communicated to the sponsor:

1. Conduct a validation of the hold time of [redacted] (b) (4) for microbial control at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA. *Protocol and Final Report Submission: December 2009.*

2. Conduct a validation study that supports the proposed hold times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a retrospective analysis of at-scale production runs, but the analysis should include verifiable information such as batch run numbers and hold conditions. *Protocol and Final Report Submission: December 2009.*

3. Re-assess [redacted] (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials. *Final Report Submission: December 2009.*

The application is recommended for approval with the caveat that the PMCs be completed by December 2009.

Assessment

3.2.S. DRUG SUBSTANCE
3.2.S.1. GENERAL INFORMATION

Raxibacumab is a recombinant monoclonal antibody of ~146 kDa produced in NS0 mouse myeloma, secreted into cell culture media, purified via chromatography and filtration, and processed into a sterile liquid drug product. Raxibacumab's primary mode of action is binding the protective antigen (PA) of *Bacillus anthracis*, thereby preventing the antigen from binding anthrax toxin receptors; the protein thus inhibits potent anthrax-toxin mediated effects on cells. The proposed dosage of the protein is a single intravenous administration of 40 mg/kg.

3.2.S.1.1. NOMENCLATURE

The chemical name of the API is immunoglobulin G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), disulfide with human monoclonal PA γ-chain, dimer. The firm refers to the protein as HGS1021, PA mAB, and ABthrax. The USAN is raxibacumab.

This section will be reviewed by OBP.

3.2.S.1.2. STRUCTURE

The molecular formula for raxibacumab is [redacted] (b) (4) and its molar mass is ~145.9 kDa. The protein consists of two identical light chains and two identical heavy chains. [redacted] (b) (4)

(b) (4)

This section will be reviewed by OBP.

3.2.S.1.3. GENERAL PROPERTIES

This section will be reviewed by OBP and is not discussed here.

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURER(S)

Each of the firms listed in the table below was submitted for an establishment evaluation; the results of this evaluation are provided on pp. 18-19 of this review memo.

Firm	Responsibility
Human Genome Sciences, Inc. Traville Facility 14200 Shady Grove Rd. Rockville, MD 20850 FEI 1000303703	Corporate headquarters Quality oversight Batch disposition Release testing (select methods) Storage of MCB and WCB Equivalancy testing of WCB
Human Genome Sciences, Inc. Belward Small Scale Manufacturing (SSM) Facility 9910 Belward Campus Drive Rockville, MD 20850 FEI 3003782237	Drug substance manufacture Drug substance storage MCB and WCB manufacture MCB and WCB storage Drug substance release testing (select methods)
Human Genome Sciences, Inc. Belward Large Scale Manufacturing (LSM) Facility 9911 Belward Campus Drive Rockville, MD 20850 FEI 3003782237	Receipt, testing, and storage of raw materials Drug substance release testing (select methods) Stability testing Shipment of drug substance to contract fill-finish site
(b) (4)	Viral release testing of unprocessed bulk MCB and WCB testing
	(b) (4) (b) (4)
	Storage of MCB and WCB

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(b) (4)

Environmental Assessment

HGS has stated that raxibacumab qualifies for a categorical exclusion under 21 CFR 25.31(c) and has stated that to its knowledge, no extraordinary circumstances exist. Citing 21 CFR 25.15(d), the firm did not submit an environmental assessment.

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the message below to find the update compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of new BLA 125349 at this time.

Human Genome Sciences, Inc. - corporate headquarters, quality oversight, batch disposition, release testing, storage of MCB and WCB, and equivalency testing of WCB
14200 Shady Grove Road
Rockville, MD
FEI: 1000303703

A DSI-led sponsor/monitor/CRO inspection was conducted July 29-31, 2009 and classified NAI. This site is not profiled. Although this site was not specifically

covered for GMP compliance, this site is considered to be acceptable for the purposes of this BLA.

Human Genome Sciences, Inc. - drug substance manufacture, storage, and release testing, MCB/WCB manufacture and storage, receipt, testing, and storage of raw materials, stability testing, and shipment of drug substance to fill-finish site
9910-9911 Belward Campus Drive
Rockville, MD
FEI: 3003782237

A pre-approval inspection for raxibacumab was conducted September 2-10, 2009 and classified VAI. The TRP profile was covered and is acceptable.

(b) (4) - viral release testing of unprocessed bulk MCB and WCB
(b) (4)
FEI: (b) (4)

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

(b) (4)
(b) (4)
FEI: (b) (4)

Inspected (b) (4) and classified VAI. The CTL profile was covered and is acceptable. An inspection assignment will be issued for this site.

(b) (4) storage of MCB and WCB
(b) (4)
FEI: (b) (4)

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

Conclusions

I. The BLA is recommended for approval from a microbiology product quality perspective. Three post-marketing commitments (PMCs) are recommended. A list of PMCs is attached to this memo.

II. Information and data in the CMC portion of the BLA not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. A pre-approval inspection of HGS, the drug substance manufacturer, was conducted on September 2-10, 2009. DMPQ has determined that the compliance status of the firm is acceptable.

cc:

Rebecca McKinnon (rebecca.saville@fda.hhs.gov), OND/OAP/DSPTP
Mary Farbman, OC/DMPQ/MAPCB/BMT
Laura Dillon, OC/DMPQ/MAPCB/BMT
David Frucht, OPS/OBP/DMA

List of Microbiology-Related PMCs for Raxibacumab Drug Substance

1. Conduct a validation of the hold time of [redacted] (b) (4) for microbial control at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA. *Protocol and Final Report Submission: December 2009.*

2. Conduct a validation study that supports the proposed hold times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a retrospective analysis of at-scale production runs, but the analysis should include verifiable information such as batch run numbers and hold conditions. *Protocol and Final Report Submission: December 2009.*

3. Re-assess [redacted] (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials. *Final Report Submission: December 2009.*

Farbman, Mary

ɔm: Stock, Marisa
Sent: Monday, October 19, 2009 11:44 AM
To: Farbman, Mary; CDER-TB-EER
Subject: RE: New BLA 125349 from HGS

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the message below to find the update compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of new BLA 125349 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Stock, Marisa
Sent: Wednesday, October 14, 2009 11:50 AM
To: Farbman, Mary; CDER-TB-EER
Subject: RE: New BLA 125349 from HGS

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the list below to find the updated compliance status of each facility.

ɹman Genome Sciences, Inc. - corporate headquarters, quality oversight, batch disposition, release testing, storage of MCB and WCB, and equivalency testing of WCB
14200 Shady Grove Road
Rockville, MD
FEI: 1000303703
A DSI-led sponsor/monitor/CRO inspection was conducted July 29-31, 2009 and classified NAI. This site is not profiled. Although this site was not specifically covered for GMP compliance, this site is considered to be acceptable for the purposes of this BLA.

Human Genome Sciences, Inc. - drug substance manufacture, storage, and release testing, MCB/WCB manufacture and storage, receipt, testing, and storage of raw materials, stability testing, and shipment of drug substance to fill-finish site
9910-9911 Belward Campus Drive
Rockville, MD
FEI: 3003782237
A pre-approval inspection for raxibacumab was conducted September 2-10, 2009 and classified VAI. The TRP profile was covered and is acceptable.

(b) (4) - viral release testing of unprocessed bulk MCB and WCB
(b) (4)
FEI: (b) (4)
Inspected (b) (4) and classified NAI. The CTL profile was covered and is acceptable.

(b) (4)
FEI: (b) (4)
Inspected (b) (4) and classified VAI. The CTL profile was covered. Although the compliance status of this site is ᵓutdated, it is considered acceptable for the purposes of this BLA, and an inspection assignment will be issued.

(b) (4) storage of MCB and WCB
(b) (4)
FEI: (b) (4)

Inspected [redacted] (b) (4) and classified VAI. The CTL profile was covered and is acceptable.

[redacted] (b) (4)
[redacted]
FEI [redacted] (b) (4)
Inspected [redacted] (b) (4) and classified NAI. The BTP profile was covered and is acceptable.

[redacted] (b) (4)) - stability testing
[redacted] (b) (4)
FEI: [redacted] (b) (4)
Inspected [redacted] (b) (4) and classified NAI. The CTL profile was covered and is acceptable.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Farbman, Mary
Sent: Tuesday, October 13, 2009 2:34 PM
To: CDER-TB-EER
Subject: FW: New BLA 125349 from HGS

Hello,
Can you please provide an updated establishment evaluation for the establishments in the TB-EER below? The application in question is 125349/0, raxibacumab, with PDUFA date of 13 November 2009. The GRMP primary review adine is 14 Oct 2009, and the secondary review deadline is 19 Oct 2009.

Thanks for your assistance with this short turn-around!

--Mary

From: Kiel, Hea S
Sent: Tuesday, June 16, 2009 12:15 PM
To: Lolas, Anastasia
Cc: CDER-TB-EER
Subject: FW: New BLA 125349 from HGS

Anastasia,

The Manufacturing Assessment and Preapproval Compliance Branch has completed the review and evaluation of the Compliance Check request below. There are no pending or ongoing investigations or compliance actions to prevent approval of BLA125349 at this time. The following are the current status for the submitted sites:

Establishment	FEI	Inspection Date	Classification	Profile
1) Human Genome Sciences, Inc. 14200 Shady Grove Road Rockville, MD	1000303703	8/26 ~ 9/4/2008 Registered	VAI	Not profilable Non Clinic Lab

* Initial Inspection as a GLP Facility was done. The Inspection covered HGS's conduct of portions of two GLP studies- No corrective actions to verify.

) Human Genome Sciences, Inc. Not in Data- No Inspection and Registration
9910 Belward Campus Drive
Rockville, MD

3) Human Genome Sciences, Inc.
11 Belward Campus Drive
ckville, MD

Not in Data- No Inspection and Registration

(b) (4)

(b) (4)

·aSuk Kiel
ɔnsumer Safety Officer
FDA/CDER/OC/DMPQ/HFD-323
Phone: 301-796-3246
Fax: 301-847-8741

From: Lolas, Anastasia
Sent: Friday, June 05, 2009 1:51 PM
To: CDER-TB-EER
Cc: Dillon, Laura; Farbman, Mary; Thomas, Colleen
Subject: New BLA 125349 from HGS

A new BLA STN 125349 was submitted on 13-May-2009 by Human Genome Sciences for ABthrax (raxibacumab) for the treatment of inhalation anthrax. HGS has requested priority review but I don't think it has been granted yet. If it does, this will be a 6-month review cycle with a PDUFA of ~13-Nov-2009.

Please conduct a preliminary establishment evaluation for the following facilities:

Human Genome Sciences, Inc.
& release
Traville Facility
14200 Shady Grove Road
Rockville, MD 20850
operational number): 1000303703

Corporate headquarters, QA oversight for DS & DP manufacture

Storage of MCB and WCB, Release & stability testing of DP

FEI to be determined (I looked it up and I think this is the

Human Genome Sciences, Inc.
ɜlward Small Scale Manufacturing Facility (SSM)
ɜ10 Belward Campus Drive
Rockville, MD 20850
status is)

Manufacture and storage of MCB, WCB and DS
DS release and stability testing

FEI to be determined (pending, I'm trying to find out what the

Human Genome Sciences, Inc.
Belward Large Scale Manufacturing Facility (LSM)
9911 Belward Campus Drive
Rockville, MD 20850

Receipt, testing and storage of raw materials
DS & DP release & stability testing
Unprocessed bulk release testing
Shipment of DS to DP site

FEI to be determined (pending)

(b) (4)

Unprocessed bulk release testing (in vitro viral), manufacture &

FEI (b) (4)

Transmission electron microscopy testing of MCB, WCB &

FEI (b) (4) (I looked this one up, no # provided)

(b) (4)

FEI (b) (4) (I looked this one up, no # provided)

Storage of MCB & WCB

(b) (4)

FEI (b) (4)

genetic stability & identity of MCB

FEI (b) (4) (I looked this one up, no # provided)

Receipt, testing & storage of raw materials
DP manufacture, labeling, packaging & release testing

FEI (b) (4)

sterility testing for DP stability

FEI (b) (4)

Thank you,

Anastasia

Anastasia G. Lolas, M.S.
Microbiologist
Biotech Manufacturing Team/MAPCB/DMPQ
Office of Compliance, CDER
White Oak Bldg 51, Room 4216
301-796-1566

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: October 14, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349 for raxibacumab (submitted May 13, 2009)

Total no. of pages including cover: 2

Comments:

Concurrence:

Yuliya Yasinskaya, M.D., Acting Medical Team Leader, DSPTP

Sue Lim, M.D., Medical Officer, DSPTP

Patricia Hughes, Ph.D., Team Leader, BMT

Mary Farbman, Ph.D., Chemist, BMT

Ozlem Belen, M.D., Deputy Director for Safety, DSPTP

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to your BLA 125349 for raxibacumab submitted on May 13, 2009.

To assist with the completion of the review of BLA 125349, we are notifying you of potential postmarketing requirements (PMR) and postmarketing commitments (PMC):

- Regarding the PMRs, submit any comments or issues for discussion.

- Regarding PMCs, please submit to the BLA separately, as an official submission, your stated agreement to each of the PMCs identified below. In your agreement, address each PMC specifically and completely.

Include timetables for completing each PMR or PMC. Please be aware, that due to time constraints involved in this BLA review, we ask you submit a complete, official response no later than November 5, 2009.

Postmarketing Requirement under Subpart I Confirmatory Trial

1. Develop a protocol for a clinical trial to address the requirement to conduct postmarketing trials, such as field trials, to verify and describe raxibacumab's clinical benefit and to assess its safety when used as indicated for inhalational anthrax when such trials are feasible and ethical (i.e., if an event should occur) in cooperation with U.S. (Centers for Disease Control and Prevention) and/or international public health agencies. Additional data to be collected should include: cerebrospinal fluid raxibacumab concentrations in all patients; brain tissue raxibacumab concentrations in non-survivors; immunohistochemical staining of brain and meninges in non-survivors; complete neurologic exams to be performed by a neurologist at baseline (if possible) and at pre-specified timepoints after raxibacumab administration for a minimum of 6 months. FDA is willing to meet and discuss the design of the protocol prior to submission.

   The time table << insert date>> states that you will conduct this trial according to the following timetable:

   Protocol Submission: June 2010
   Trial Start Date: In the event of an emergency
   Final Report Submission: To be determined

Postmarketing Requirement

2. Conduct a cross-reactivity study or submit existing data to demonstrate the presence or absence of cross-reactivity between animal (rabbit and cynomolgus monkey) and human meninges.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Final protocol Submission:
   Study Completion Date:
   Final Report Submission:

Postmarketing Commitments

3. Conduct a study to evaluate the efficacy contribution of raxibacumab to the antimicrobial when a suitable (well-characterized) animal model of inhalational anthrax is available.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Final Protocol Submission:
   Study Completion Date:
   Final Report Submission:

4. Conduct a study in a suitable animal model of inhalational anthrax to further evaluate the efficacy, safety/tolerability, pharmacokinetics and dose-response of intravenous raxibacumab at 40 mg/kg compared to doses of 60 mg/kg and greater (e.g. 80 mg/kg) in order to collect additional data at higher doses.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Final Protocol Submission:
   Study Completion Date:
   Final Report Submission:

5. Conduct a validation of the hold time of [redacted] (b) (4) for microbial control at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Protocol and Final Report Submission: December 2009

6. Conduct a validation study that supports the proposed hold-times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a retrospective analysis of at-scale production runs but the analysis should include verifiable information such as batch run numbers and hold conditions.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Protocol and Final Report Submission: December 2009

7. Re-assess [redacted] (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials.

   The time table << insert date>> states that you will conduct this study according to the following timetable:

   Final Report Submission: December 2009

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Memo of Teleconference
Human Genome Sciences, Inc.
October 6, 2009

Time: 4:40 p.m.-4:45 p.m.

FDA participant: David Frucht
HGS participant: Christine Pannunzio

It was clarified that this was an information request meeting (i.e., not decisional). The following information requests were discussed:

(1) I requested that HGS provide a rationale for why the viral clearance [redacted] (b) (4) studies were performed [redacted] (b) (4)

(2) I requested that information regarding flow-rates and contact times be provided for each of the above chromatography steps.

Follow-up:

Christine Pannunzio phoned back and spoke to me (DF) from 4:53-4:57 and stated that this information could be found in report PVP-21-025R, which was linked to the [redacted] (b) (4) validation report. [redacted] (b) (4)

Minutes Preparer:

David Frucht, M.D.
Product Quality Reviewer, Division of Monoclonal Antibodies

Date: 10/20/09

Memo of FDA Teleconference
Human Genome Sciences, Inc.
September 28, 2009

Time: 1:55 p.m.-2:00 p.m.

FDA participant: David Frucht
HGS participant: Christine Pannunzio, Alicia Gilbert

It was clarified that this was an information request meeting (i.e., not decisional). The following information requests were discussed:

(1) I (DF) requested information regarding the two sterilization assays indicated on FDP stability protocol M2109001. HGS clarified that the first (release) is conducted by (b) (4) under their testing SOP. The annual sterility checks, on the other hand, are conducted by another contract testing facility.
(2) I (DF) inquired why protocol #M210712 had not been updated to reflect numerical limits (b) (4). HGS clarified that the version currently in the BLA was outdated (#3). The current version will be sent by email and submitted as a formal amendment to the BLA.
(3) I (DF) inquired whether HGS' plan to submit data supporting (b) (4) expiry for FDP (discussed at the time of the HGS facility inspection) had been submitted as an amendment to the BLA. HGS informed me that this plan had been submitted as amendment sequence #12.

Follow-up:

Alicia Gilbert left a phone message on 28 September 2009 indicating that the updated version of protocol #M210712 had been already incorporated into the BLA. I confirmed this in the link from amendment serial #12.

Minutes Preparer:

David Frucht, M.D.
Product Quality Reviewer, Division of Monoclonal Antibodies

Date:

Memo of FDA Teleconference
Human Genome Sciences, Inc.
September 21, 2009

Time: 10:45 and follow-up at 11:05 a.m.-11:06 a.m.

FDA participant: David Frucht
HGS participant: Christine Pannunzio

I requested the qualification report [redacted] (b) (4) HGS first ascertained that the information was not present in the BLA. HGS then committed to sending me the report by email, with an amendment with the identical information to be submitted to the BLA in a rapid manner. HGS stated that the reason that this information was not provided in the original BLA was that there were no positive immunogenic responses in human receiving raxibacumab.

Minutes Preparer:

David Frucht, M.D.
Product Quality Reviewer, Division of Monoclonal Antibodies

Date:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

September 14, 2009

Pamela Hodges
Senior Director Quality Assurance
14200 Shady Grove Road
Rockville, MD 20850

Dear Ms. Hodges:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between July 29 and 31, 2009, Ms. Cynthia A. Harris representing the FDA, met with you and your staff to review your responsibilities in the conduct of the following two clinical investigations of the investigational drug raxibacumab, performed for Human Genome Sciences, Inc:

> Protocol# HGS1021-C1063, entitled "A Randomized, Single-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Raxibacumab (Human Monoclonal Antibody to *B. anthracis* Protective Antigen) in Healthy Subjects", and
>
> Protocol# HGS1021-C1064, entitled "An Open-Label Study to Evaluate the Pharmacokinetics and Safety of Raxibacumab (Human Monoclonal Antibody to *B. anthracis* Protective Antigen) Administered in Combination with Ciprofloxacin in Healthy Subjects".

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the monitoring practices of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Harris during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/Tejashri Purohit-Sheth/
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5358
10903 New Hampshire Avenue
Silver Spring, MD 20993

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: September 10, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349 for raxibacumab (submitted March 13, 2009)

Total no. of pages including cover: 2

Comments:

Concurrence:

Philip Colangelo, Pharm.D., Clinical Pharmacology Team Leader

Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

The Clinical Pharmacology Review Team has the following request:

- Please provide quality control/assay performance information for the analytical runs for determination of raxibacumab serum concentrations in Studies HGS1021-C1063, HGS1021-C1064, and HGS1021-C1069 (i.e. results for the positive control samples from each analytical run). If this information has already been submitted, please provide the location (submission number, date, and files) where this information can be located.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: September 10, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349 for raxibacumab (submitted March 13, 2009)

Total no. of pages including cover: 2

Comments:

Concurrence:

Shukal Bala, Ph.D., Microbiology Team Leader

Maureen Davidson, Ph.D., Microbiology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

The Microbiology Review Team has the following request:

- Your protocol for Study 290-N005433 states that serum was collected for determination of PA concentrations at one week prior to aerosol exposure to *B. anthracis* spores (Study day -7); at 0, 7, 14, and 28 days post infection, and, if possible, also from animals that were found dead or were euthanized. We could not locate these data in the study report. Please provide these data, or their location within the BLA application, for our review.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: September 8, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Patricia Hughes, Ph.D., Director, CDER/OC/DMPQ/BMT

Colleen Thomas, Ph.D., CMC Reviewer, CDER/OC/DMPQ/BMT

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

The Biotechnology Manufacturing Team in the Division of Manufacturing and Product Quality/Office of Compliance has the following requests regarding the drug product:

1. Please clarify whether any live vaccines or potent toxins are produced in the same manufacturing area as raxibacumab. Describe controls that are in place to ensure that cross-contamination does not occur.

2. Please clarify whether the stability protocol includes container closure integrity testing. We recommend performing a validated container closure integrity test initially, annually, and at expiry to verify integrity (and therefore product sterility) over the shelf-life of the product. This can be done in lieu of sterility testing.

3. Regarding the microbial ingress test for container closure integrity, please provide the following information:

    a. Concentration of *B. diminuta* at the beginning and end of the test.
    b. Positive and negative controls, including preparation of the positive controls.
    c. Growth promotion testing of the media.
    d. Study parameters including immersion time, temperature, and pressure.

4. Regarding the dye ingress test for container closure integrity, please provide the following information:

    a. Positive and negative controls, including preparation of the positive controls.
    b. Study parameters including immersion time, temperature, and the pressure challenge.
    c. Detection limit of the dye (test sensitivity) and the method used for dye detection.
    d. Comparison of the dye ingress test sensitivity to the microbial ingress test sensitivity.

5. Regarding the hold time validation studies, please provide the following information:

    a. Hold time validation data for bulk drug substance thawing, pooling, and hold with respect to microbial control.
    b. Actual temperatures measured during the studies.
    c. Scale of the hold time validation studies. Hold time validation with respect to microbial control should be done at full scale.

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

g. Whether (b) (4) classification standards refer to (b) (4) conditions.
h. Whether the (b) (4) meets USP specifications.

18. Regarding shipping validation, please provide the following information:

a. Minimum and maximum shipment sizes.
b. Validation data indicating that the case shippers can maintain the required product temperature under worst-case conditions.
c. Whether container closure integrity testing is done during shipping validation studies.

We are providing the above information by email for your convenience. We would appreciate a response by September 18, 2009. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Memorandum to File

BLA 125349
Raxibacumab

The following email exchange occurred between Dr. David Frucht, FDA's Product Quality Reviewer and HGS Regulatory Chemistry team, the applicant of BLA 125349 for raxibacumab, submitted on March 13, 2009. In summary, Dr. Frucht requested additional product quality information, and HGS submitted this information formally to the BLA on September 4, 2009.

Rebecca D. McKinnon, Pharm.D.
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
September 4, 2009

From: Frucht, David
Sent: Friday, August 28, 2009 3:50 PM
To: "Alicia_Gilbert@hgsi.com'
Subject: RE: Fw: BLA STN 125349 – Request for Information

Hi Alicia,

Thank you for your prompt response. Please submit the entirety of these clarifications and additional data as an amendment to the BLA.

Thanks,

David

From: Alicia_Gilbert@hgsi.com [mailto:Alicia_Gilbert@hgsi.com]
Sent: Friday, August 28, 2009 9:36 AM
To: Frucht, David
Subject: RE: Fw: BLA STN 125349 - Request for Information

Hi David,

AB50409-M13 is the BDS lot number and it was formulated in (b) (4) sodium citrate, (b) (4) glycine, and (b) (4) sucrose. Lot AB50409-M13-R (b) (4) was produced from BDS Lot AB50409-M13. (b) (4) BDS Lot AB50409-M13 was also used to produced nonclinical FDP Lot 02A21109.

Please let me know if any further clarifications are needed.

Thanks,
Alicia

"Frucht, David" <David.Frucht@fda.hhs.gov>

08/27/2009 02:55 PM

To Alicia_Gilbert@hgsi.com

cc

Subject RE: Fw: BLA STN 125349 - Request for Information

Hi Alicia,

Could you clarify if AB50409-M13 and AB50409-M13-R only differ in formulation. Were they derived from the same Drug Substance lot?

Thanks,

David

From: Alicia_Gilbert@hgsi.com [mailto:Alicia_Gilbert@hgsi.com]
Sent: Wednesday, August 26, 2009 5:14 PM
To: Frucht, David
Cc: christine_pannunzio@hgsi.com
Subject: Re: Fw: BLA STN 125349 - Request for Information

Hi David,

The early nonclinical lots, AB504-02 K1, AB504-08 K1, and AB50409-K1, were not tested for potency using the Ribidium or the cAMP induction assays. HGS has potency data for 2 of the lots requested, AB50409-M13-R and AB50409-M9 (see table below). The Ribidium assay was replaced with the cAMP induction assay in May 2003 (at the time of IND submission, 22 May 2003); therefore, the release of lots from the M10 and M11 manufacturing process used the cAMP assay.

Table-1 Data from Rubidium and cAMP induction potency assays

	Nonclinical Lot Number	
Potency Assay	**AB50409-M13-R[1]**	**AB50409-M9**
Rubidium assay	(b) (4)	
cAMP induction assay		

Please let me know if you need any additional information.

Kind regards,
Alicia

Alicia Gilbert

Assoc. Director, Regulatory Affairs
Human Genome Sciences, Inc.
P - 240-314-4400 x6561
F - 301-309-0311

Christine Pannunzio/Hgsi

08/21/2009 12:31 PM

To Alicia Gilbert/Hgsi@HGSI
cc

Subject Fw: BLA STN 125349 - Request for Information

----- Forwarded by Christine Pannunzio/Hgsi on 08/21/2009 12:31 PM -----

"Frucht, David" <David.Frucht@fda.hhs.gov>

08/21/2009 12:12 PM

To christine_pannunzio@hgsi.com
cc

Subject RE: BLA STN 125349 - Request for Information

Hi Christine,

Could you clarify whether or not there exists cAMP induction assay potency data for AB50409-K1, AB50409-M9, AB50409-K1, AB50402 K1, and AB50409-M13? Also, could you clarify if there exists rubidium release potency assay results for M10 and M11 process material, to which the potency assay results for AB50409-M13 could be directly compared?

Thanks,

David

From: christine_pannunzio@hgsi.com [mailto:christine_pannunzio@hgsi.com]
Sent: Friday, August 07, 2009 1:32 PM
To: Frucht, David
Cc: Alicia_Gilbert@hgsi.com
Subject: BLA STN 125349 - Request for Information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: August 21, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Patricia Hughes, Ph.D., Director, CDER/OC/DMPQ/BMT

Mary Farbman, Ph.D., CMC Reviewer, CDER/OC/DMPQ/BMT

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

The Biotechnology Manufacturing Team in the Division of Manufacturing and Product Quality/Office of Compliance has the following requests:

(b) (4)

[redacted]

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

10. Regarding Analytical Assays (3.2.S.4.2, 3.2.S.4.3):

a. Please provide validation/qualification documentation demonstrating that the in-process samples tested using the LAL assay do not interfere with the assay's ability to detect bacterial endotoxin in those samples.
b. Please provide validation/qualification documentation demonstrating that the in-process samples tested using the microbial plate count bioburden assay do not interfere with the assay's ability to detect objectionable organisms in those samples.

We are providing the above information by email for your convenience. We would appreciate a response by September 11, 2009. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Memo of FDA Teleconference
Human Genome Sciences, Inc.
4 August 2009

Time: 1:55 p.m.-2:05 p.m.

FDA participant: David Frucht
HGS participants: Christine Pannunzio

It was clarified that this was an information request meeting (i.e., not decisional). The following information request was discussed:

I (David Frucht) stated that it was problematic that the number of particulates present in the DP was not provided in the Certificates of Analysis or in the stability analysis (only that the lots complied with USP). For this reason, trending analysis could not be performed. To address this problem, Christine Pannunzio committed to the following:

(1) HGS will provide particulate number data for each of the DP lots as an amendment to the BLA.
(2) HGS will amend the DP Certificates of Analysis to include the actual number of particulates in the DP.
(3) HGS will provide DP particulate number data for the stability lots in their planned September stability update amendment.

Minutes Preparer:

David M. Frucht

David Frucht, M.D.
Product Quality Reviewer, Division of Monoclonal Antibodies

Date:
9/16/09

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: July 30, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Philip Colangelo, Pharm.D., Clinical Pharmacology Team Leader

Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab and to your submission dated May 13, 2009.

The Clinical Pharmacology Review Team has the following request:

- Please provide complete datasets and analysis files for the population PK study HGS1021-POP01, including but not limited to the complete working PK analysis dataset 'dat_0001.txt'. These files should be provided in electronic format. If these files have already been submitted, please provide the location (submission number and date) where these files can be located.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Memo of FDA Teleconference
Human Genome Sciences, Inc.
16 July 2009

Time: 2:00 p.m.-2:35 p.m.

FDA participant: David Frucht
HGS participants: Christine Pannunzio, Sally Bolmer, Alicia Gilbert, David Kahn, and Tom Spitznagel

It was clarified that this was an information request meeting (i.e., not decisional). The following information requests were discussed:

1. Please provide data that demonstrate that your current endotoxin assay is equivalent to the rabbit pyrogen test.

HGS has shown one lot of FDP to be non-pyrogenic by the rabbit pyrogen test. Side-by side results with the LAL test will be provided in the filing letter response to be submitted prior to July 20, 2009.

2. The medium used (b) (4) contains (b) (4). Please provide a description of the (b) (4) process and validation (b) (4) processing of the Drug Substance.

HGS will provide (b) (4) test results for several lots of the BDS, along with calculations for the input levels (b) (4) clearance will be calculated. In addition, HGS will provide information regarding the theoretical clearing capacity of the major (b) (4) processing steps. In addition, HGS will provide a toxicological assessment the levels (b) (4) that would be predicted to be toxic compared to those present in the BDS. These data will be provided by July 20, 2009.

3. Please provide a comprehensive list of each of the product classes for those products manufactured at (b) (4). All monoclonal antibodies should be listed with isotype and subclass.

HGS will contact (b) (4) and request that this information be provided.

4. Please confirm that raxibacumab is nearly completely degraded during (b) (4) storage at RT under (b) (4) conditions.

HGS confirms this to be true.

5. Please address how you will comply with 21 CFR 610.12(a) sterility requirements for DS.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administratior
Rockville, MD 20857

FILING COMMUNICATION
PRIORITY REVIEW DESITNATION

BLA 125349

JUL 1 3 2009

Human Genome Sciences, Inc.
Attn: Sally Bolmer, Ph.D.
Senior Vice President, Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

This letter is in regard to your biologics license application (BLA), dated May 13, 2009, received May 14, 2009, and submitted under section 351 of the Public Health Service Act, for raxibacumab.

We have completed a preliminary review of your application to determine its acceptability for filing and have determined that your application is sufficiently complete to permit a substantive review. Therefore, under 21 CFR 601.2(a), we filed your application today. The review classification for this application is priority; as a result, the user fee goal date is November 14, 2009. 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 include 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 review process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and postmarketing commitment requests by October 14, 2009. We have tentatively scheduled raxibacumab to be discussed at the Anti-Infective Drugs Advisory Committee (AIAC) meeting for October 27, 2009.

During our filing review of your application, we identified the following potential review issues:

A. Issues identified by the Product Quality reviewers.

1. Please provide data that demonstrate that your current endotoxin assay is an equivalent alternative to the rabbit pyrogen test.

2. The medium used for [redacted] (b) (4) contains [redacted] (b) (4) Multiple citations in published literature (e.g., McCan *et al.*, IAI, 73:6340, 2005) show that beta glucans, a component of the yeast cell wall, can trigger an inflammatory response. Please provide a description of the [redacted] (b) (4) process and validation [redacted] (b) (4) of the Drug Substance.

3. Please provide a comprehensive list of each of the product classes for those products manufactured at [redacted] (b) (4) All monoclonal antibodies should be listed with isotype and subclass.

B. Issues identified by the Microbiology reviewers, conveyed to you in our electronic communication dated June 3, 2009.

4. The lot numbers of raxibacumab used for several studies were omitted from some of your study reports and from the tables indicating the lot histories for the various preparations of raxibacumab. The information contained within Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2 is required for our review of the following studies: AB50409.INF.0.004, AB50409.INF.0.005, AB50409.INF.0.006, AB50409.INF.0.007, and TR-21-08-044. Please provide similar information on the 5H3 monoclonal antibody used in the published study by Cui, *et al.*

C. Issues identified by the Clinical and Microbiology reviewers, conveyed to you in our two electronic communications dated June 9, 2009.

5. You have submitted technical reports for studies TR-21-07-066, TR-21-08-037 and TR-PD-21-03-008 and have referenced the supporting Standard Operating Procedures (SOPs; CLI-2979, CLI-3033 and 01EL1-BA-21-1966, respectively). However, the SOPs are not included in the submissions. Additionally, the relevant line data are not available. Please provide the SOPs and line data pertinent to each report for our review.

6. You have submitted the final study report for Study HGS1021-C1064. Although the cover of this study report includes a watermark indicating that the report was amended, we were unable to locate a summary of changes from the version you submitted on April 30, 2008 to IND 11,069. Please provide a summary of the changes.

7. Please refer to the *Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements* and also to http://www.fda.gov/cder/regulatory/physLabel/default.htm

for fictitious examples of labeling in the Physician Labeling Rule (PLR) format for the appropriate formatting requirements and revise your content of labeling for the package insert.

D. Issues identified by the Clinical and Microbiology reviewers, conveyed to you in our electronic communication dated June 12, 2009.

8. Linking the product used for nonclinical studies with that used for the pivotal efficacy studies is important. Raxibacumab lot numbers AB504-02 K1, AB50409-K1, and AB50409-M13-R do not have release data or certificates of analysis included in the BLA submission. Please submit the certificates of analysis for our review, or if submitted, please describe their location in your BLA.

9. You have certified that some study reports submitted in the BLA are identical to specific reports that have been previously reviewed in the IND for the placement of raxibacumab into the Strategic National Stockpile. Please also certify that the datasets for these studies are identical to those previously submitted to IND 11,069.

10. You have submitted the final study report for Study 901-G005829 in your BLA. The draft version of the study report was submitted to IND 11,069 in N-093 on December 24, 2008. We are unable to locate a summary of changes in the BLA from the draft version. Please provide a summary of the changes or certify that this report is exactly the same as you submitted on December 24, 2008.

11. For all clinical Studies PAM-NH-01, HGS1021-C1064, HGS1021-C1063, and HGS1021-C1069, please submit case report forms for all subjects who experienced serious adverse events and adverse events that resulted in study drug discontinuations.

12. For animal studies 789-G923702 and 781-G923701, please submit the subject data listings to your BLA application.

13. Notify the Agency as soon as you receive your DS facility registration number.

E. Labeling issues conveyed to you in our electronic communication dated June 12, 2009.

14. Please revise the content of labeling for your package insert, particularly the **INDICATIONS AND USAGE** section, according to the letter you received granting orphan drug status for raxibacumab. Your **CLINICAL STUDIES** section of the package insert should describe your animal efficacy studies that support your proposed indication.

15. You have submitted annotated labeling but some of the hyperlinks do not link directly to study reports but instead link to summaries of the studies or other parts of the package insert. When submitting your revised annotated labeling, please correct the hyperlinks so that the annotation goes to the study reports.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not have time to review your response before we take an action on your application. Following a review of the application and consideration of the advice from the AIAC, we will advise you in writing of our action.

We acknowledge receiving your responses to the items listed in B, C, D, and E on June 8, 2009, June 16, 2009, June 18, 2009, and June 24, 2009. Please provide responses to the items listed in A by July 20, 2009.

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, call Rebecca D. McKinnon, Pharm.D., Regulatory Project Manager, at 301-796-1600.

Sincerely,

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

JUL 13 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: June 30, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Karen Higgins, Sc.D., Statistics Team Leader

Lan Zeng, Ph.D., Statistics Reviewer

Document to be mailed: YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009. The Statistics Team has the following requests regarding Studies 781-G923701 and 789-G9237021:

1. Please provide SAS programs used to generate tables and figures in the study reports.

2. The "txtimes.xpt" file does not contain variables indicating study populations such as mITT and as-treated. Please provide.

3. Please clarify whether the following are represented in "txtimes.xpt". If so, please specify variable names.

    a. Toxemia and bacteremia at or before treatment initiation;
    b. Toxemia and bacteremia at the time of treatment initiation;
    c. Toxemia and bacteremia at anytime;

    d. Toxemia and/or bacteremia at or before treatment initiation;
    e. Toxemia and/or bacteremia at the time of treatment initiation;
    f. Toxemia and/or bacteremia at anytime;

    g. Bacteremia without toxemia at or before treatment initiation;
    h. Temperature increased but with no PA toxemia or bacteria at or before treatment initiation;

    i. Time to PA detection (quantitative ECL or ELISA);
    j. Time to PA detection (screening).

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: June 12, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349: Missing information from application

Total no. of pages including cover: 3

Comments:

Concurrence:

Yuliya Yasinskaya, M.D., Acting Medial Team Leader

Sue Lim, M.D., Medical Officer

Susan McCune, M.D., Medical Team Leader, OCTEC

Shukal Bala, Ph.D., Microbiology Team Leader

Maureen Davidson, Ph.D., Microbiology Reviewer

Lynette Berkeley, Ph.D., Microbiology Reviewer

Document to be mailed: YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009.

To assist with our filing determination, the Review Team has the following requests that will need to be addressed by June 19, 2009:

1. Linking the product used for nonclinical studies with that used for the pivotal efficacy studies is important. Raxibacumab lot numbers AB504-02 K1, AB50409-K1, and AB50409-M13-R do not have release data or certificates of analysis included in the BLA submission. Please submit the certificates of analysis for our review, or if submitted, please describe their location in your BLA.

2. You have certified that some study reports submitted in the BLA are identical to specific reports that have been previously reviewed in the IND for the placement of raxibacumab into the Strategic National Stockpile. Please also certify that the datasets for these studies are identical to those previously submitted to IND 11,069.

3. You have submitted the final study report for Study 901-G005829 in your BLA. The draft version of the study report was submitted to IND 11,069 in N-093 on December 24, 2008. We are unable to locate a summary of changes in the BLA from the draft version. Please provide a summary of the changes or certify that this report is exactly the same as you submitted on December 24, 2008.

   As requested on June 9, 2009, you have submitted the final study report for Study HGS1021-C1064. Although the cover of this study report includes a watermark indicating that the report was amended, we were unable to locate a summary of changes from the version you submitted on April 30, 2008 to IND 11,069. Please provide a summary of the changes.

4. For all clinical Studies PAM-NH-01, HGS1021-C1064, HGS1021-C1063, and HGS1021-C1069, please submit case report forms for all subjects who experienced serious adverse events and adverse events that resulted in study drug discontinuations.

5. For animal studies 789-G923702 and 781-G923701, please submit the subject data listings to your BLA application.

6. As requested on June 9, 2009, you have submitted technical reports for studies TR-21-07-066, TR-21-08-037 and TR-PD-21-03-008 and have referenced the supporting Standard Operating Procedures (SOPs; CLI-2979, CLI-3033 and 01EL1-BA-21-1966, respectively). However, the SOPs are not included in the submissions. Additionally, the relevant line data are not available. Please provide the SOPs and line data pertinent to each report for our review.

The Review Team also has the following additional requests:

7. Notify the Agency as soon as you receive your DS facility registration number.

8. Please revise the content of labeling for your package insert according to the letter you received granting orphan drug status for raxibacumab. Your **CLINICAL STUDIES** section of the package insert should describe your animal efficacy studies that support your proposed indication.

9. You have submitted annotated labeling but some of the hyperlinks do not link directly to study reports but instead link to summaries of the studies or other parts of the package insert. When submitting your revised annotated labeling, please correct the hyperlinks so that the annotation goes to the study reports.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: June 9, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Shukal Bala, Ph.D., Microbiology Team Leader, DSPTP

Lynette Berkeley, Ph.D., Microbiology Reviewer, DSPTP

Document to be mailed: YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009. The Microbiology Review Team has the following request:

- You have submitted technical reports for studies TR-21-07-066, TR-21-08-037 and TR-PD-21-03-008 and have referenced the supporting Standard Operating Procedures (SOPs; CLI-2979, CLI-3033 and 01EL1-BA-21-1966, respectively). However, the SOPs are not included in the submissions. Additionally, the relevant line data are not available. Please provide the SOPs and line data pertinent to each report for our review.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: June 9, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Yuliya Yasinskaya, M.D., Acting Medial Team Leader

Document to be mailed: YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009. The Clinical Review Team has the following requests:

- You have submitted the final study report for Study HGS1021-C1064 entitled "An Open-Label Study to Evaluate the Pharmacokinetics and Safety of Raxibacumab (Human Monoclonal Antibody to *B. anthracis* Protective Antigen) Administered in Combination with Ciprofloxacin in Healthy Subjects." Although the cover of this study report includes a watermark indicating that the report was amended, but we are unable to locate a summary of changes from the version you submitted on April 30, 2008 to IND 11,069. Please provide a summary of the changes.

- Please refer to the *Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements* and also to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the Physician Labeling Rule (PLR) format for the appropriate formatting requirements and revise your content of labeling for the package insert. We have also attached two examples of approved package insert, one in PLR format and one as an example of the type of content that should be included.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: June 3, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Shukal Bala, Ph.D., Microbiology Team Leader, DSPTP

Maureen Davidson, Ph.D., Microbiology Reviewer, DSPTP

Document to be mailed: YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009. The Microbiology Review Team has the following request:

- The lot numbers of raxibacumab used for several studies were omitted from some of your study reports and from the tables indicating the lot histories for the various preparations of raxibacumab. The information contained within Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2 is required for our review of the following studies: AB50409.INF.0.004, AB50409.INF.0.005, AB50409.INF.0.006, AB50409.INF.0.007, and TR-21-08-044. If possible, please provide similar information on the 5H3 monoclonal antibody used in the published study by Cui, *et al.*

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BLA ACKNOWLEDGEMENT

Our STN: BLA 125349/0

MAY 2 8 2009

Human Genome Sciences, Inc.
Attn: Sally Bolmer, Ph.D.
Senior Vice President, Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

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

Name of Biological Product:	raxibacumab
Date of Application:	May 13, 2009
Date of Receipt:	May 14, 2009
Our Submission Tracking Number (STN):	125349/0
Proposed Use:	Treatment of inhalation anthrax

If you haven't 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 301-796-1600.

Sincerely,

RMcKinnon

Rebecca D. McKinnon, Pharm.D.
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

MAY 2 8 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Antimicrobial Products

TRANSMITTAL SHEET

DATE: May 21, 2009

To: Maggie Lewis, MS, RAC Senior Regulatory Affairs Specialist	**From:** Rebecca McKinnon, Pharm.D.
Company: Human Genome Sciences, Inc.	Division of Special Pathogen and Transplant Products
Fax number: 301-309-0311 **Email:** Maggie_Lewis@hgsi.com	**Fax number:** 301-796-9881
Phone number: 240-314-4400	**Phone number:** 301-796-1600

Subject: BLA 125349

Total no. of pages including cover: 2

Comments:

Concurrence:

Yuliya Yasinskaya, M.D., Acting Clinical Team Leader, DSPTP

Document to be mailed: YES ☑ NO

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Dear Ms. Lewis:

Please refer to BLA 125349 for raxibacumab submitted on May 13, 2009. In your cover letter, you request a Priority Review for the application as follows:

Given that inhalation anthrax remains a major bioterror threat, that raxibacumab represents a novel approach to the unmet need for a therapeutic treatment of anthrax, and that a statistically significant survival benefit has been demonstrated with raxibacumab treatment of symptomatic inhalation anthrax in 2 animal species in accordance with the Animal Rule (21 CFR 601 Subpart H), HGS requests that the BLA for raxibacumab for the treatment of inhalation anthrax be considered for Priority Review.

According to the CDER Manual of Policies and Procedures (MaPP) Review Classification Policy: Priority (P) and Standard (S) [6020.3], a determination for priority review should be based on whether the drug product provides safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement compared to marketed products in treating, preventing, or diagnosing disease.

To assist in our determination of the review designation of raxibacumab, please provide additional information to address your assertion that raxibacumab provides a significant improvement compared to marketed products. Significant improvement can be interpreted to mean:

1. Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease
2. Elimination or substantial reduction of a treatment-limiting drug reaction
3. Documented enhancement of patient compliance
4. Evidence of safety and effectiveness in a new subpopulation.

Evidence to support your justification can come from clinical trials or animal efficacy studies comparing a marketed product(s) with raxibacumab or from other scientifically valid information.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Rebecca D. McKinnon, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

RMS/BLA - Product Information Sheet for TBP

STN: 125349 / 0 **Reg. Coordinator:** Rebecca Saville-McKinnon

Document Date: 5/13/09 FDA Rcvd Date: 5/14/09 CBER Rcvd Date: 5/14/09

Applicant Human Genome Sciences, Inc.

Product Raxibacumab

Proprietary/Trade Name(s) n/a

Complete a box for each indication

Indication Treatment of inhalation anthrax

Dose 1700 mg/34 mL (40 mg/Kg)

Age groups - check all that apply

☒ Adult 18+ ☐ All ☐ Child 3-12 ☒ Geriatric 65+ ☐ Pediatric 0-3 ☐ Young Adult 13-18 ☐ Other _____

Indication Product Use - check all that apply

☐ Ancillary ☒ Diagnostic/Therapeutic ☐ Therapeutic ☐ Prophylaxis ☐ Other _____

☐ Further Manufacturing Injectable ☐ Further Manufacturing Non Injectable

Indication _____

Dose _____

Age groups - check all that apply

☐ Adult 18+ ☐ All ☐ Child 3-12 ☐ Geriatric 65+ ☐ Pediatric 0-3 ☐ Young Adult 13-18 ☐ Other _____

Indication Product Use - check all that apply

☐ Ancillary ☐ Diagnostic/Therapeutic ☐ Therapeutic ☐ Prophylaxis ☐ Other _____

☐ Further Manufacturing Injectable ☐ Further Manufacturing Non Injectable

Guidance for completion of this form

Indication/Usage -- As stated in the P.I. This should also go into the short summary under the submission screen

Dose – From the "Dosage and Administration" section of P.I. – This is what the patient actually gets.

Dosage/Physical Form Details – From the "How Supplied" section of P.I. – Enter final dosage strengths; Potency & Units are important for user fee information

Product Information Sheet - Dosage/Physical Form

Complete one sheet for each physical form, potency, and fill size.

STN: [/] **Reg. Coordinator:** _____

Dosage/Physical Forms Injection (See back page for Valid Values)

Dosage

Potency (measurement of activity or strength) 1700 mg **Units** 34mL (See back page for Valid Values)

Duration (length of time dosage will remain stable) _____ (months)

Temperature 2-8°C

Container Type

☐ Ampule (Glass) ☐ Ampule (Plastic) ☐ Bag Bulk ☐ Bottle ☐ Pump Spray

☐ Other** _____ ☐ Syringe ☐ Tube ☒ Vial

Container Closure

☐ Heat Seal ☐ Plunger ☐ Screw Cap Closure ☐ Stopper (Dry Natural Rubber)

☐ Stopper (Synthetic) ☒ Stopper (Unknown) ☐ Other

Container Fill Size 34 mL (Volume)

Route of Administration IV (See back page for Valid Values)

Dosage/Physical Forms N/a (See back page for Valid Values)

Dosage

Potency (measurement of activity or strength) _____ **Units** _____ (See back page for Valid Values)

Duration (length of time dosage will remain stable) _____ (months)

Temperature _____

Container Type

☐ Ampule (Glass) ☐ Ampule (Plastic) ☐ Bag Bulk ☐ Bottle ☐ Pump Spray

☐ Other** _____ ☐ Syringe ☐ Tube ☐ Vial

Container Closure

☐ Heat Seal ☐ Plunger ☐ Screw Cap Closure ☐ Stopper (Dry Natural Rubber)

☐ Stopper (Synthetic) ☐ Stopper (Unknown) ☐ Other

Container Fill Size _____ (Volume)

Route of Administration _____ (See back page for Valid Values)

Product Information Sheet - Dosage/Physical Form

Listing of Valid Values

Dosage/Physical Forms

- ❑ Inhalant Solution
- ❑ Injectable Solution
- ❑ Injectable Solution Concentrate
- ❑ Injectable Suspension
- ❑ Lyophilized Powder for In Vitro Test
- ❑ Lyophilized Powder for Injectable Solution
- ❑ Lyophilized Powder for Injectable Suspension
- ❑ Lyophilized Powder for Scarification
- ❑ Lyophilized Powder to be suspended for Instillation
- ❑ Nasal Spray Suspension
- ❑ Powder for Reconstitution
- ❑ Solution
- ❑ Solution for In Vitro Test
- ❑ Suspension for In Vitro Test
- ❑ Spray
- ❑ Tablet
- ❑ Powder for Injectable Solution
- ❑ Powder and Solvent for Suspension for Injection
- ❑ Repository Injection
- ❑ Other _____

Potency Units

❑ AU/.5mL	❑ mg/.8 mL	❑ dil.	❑ mg/vial	❑ ug/.4mL
❑ AU/mL	❑ other	❑ g	❑ Percent	❑ ug/.5mL
❑ BAU/mL	❑ TCID	❑ g/tube	❑ u/.5mL	❑ ug/.6mL
❑ IU/.1 mL	❑ TU/mL	❑ mL	❑ u/2mL	❑ ug/g
❑ IU/mL	❑ U/.75mL	❑ mg	❑ u/mL	❑ ug/mL
❑ IU/vial	❑ cell/mL	❑ mg/0.5 mL	❑ u/tube	❑ ug/vial
❑ Lf/.5mL	❑ cfu/mL	❑ mg/2 mL	❑ u/vial	
❑ MIU/mL	❑ cfu/tab	❑ mg/5 mL	❑ ug	
❑ MIU/vial	❑ conc.	☒ mg/mL	❑ ug/.3mL	

Route of Administration

- ❑ Dental
- ❑ Implantation
- ❑ Inhalation
- ❑ Intracoronary
- ❑ Intradermal
- ❑ Intralesional
- ❑ Intralymphatic
- ❑ Intramuscular
- ❑ Intranasal
- ❑ Intraperitoneal
- ❑ Intrathecal
- ❑ Intratracheal
- ❑ Intravenous
- ❑ Intravesical
- ❑ Nasal Spray
- ❑ Other _____
- ❑ Needle Free Injection
- ❑ Oral
- ❑ Percutaneous
- ❑ Prick Test
- ❑ Scratch Test
- ❑ Spinal
- ❑ Subcutaneous

Product Information Sheet - Components

STN: [/] **Reg. Coordinator:** _____

Name _____

Component Type

❑ Formulation Ingredient ❑ Product ❑ In Process Ingredient ❑ Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

❑ Active ❑ Additive ❑ Diluent ❑ Preservative ❑ Stabilizer

Source _____ **Subsource** _____

Name _____

Component Type

❑ Formulation Ingredient ❑ Product ❑ In Process Ingredient ❑ Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

❑ Active ❑ Additive ❑ Diluent ❑ Preservative ❑ Stabilizer

Source _____ **Subsource** _____

Name _____

Component Type

❑ Formulation Ingredient ❑ Product ❑ In Process Ingredient ❑ Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

❑ Active ❑ Additive ❑ Diluent ❑ Preservative ❑ Stabilizer

Source _____ **Subsource** _____

Susan McCune

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NHP studies

NDA/BLA Number: **Applicant:** HGS **Stamp Date:** 5/14/09

Drug Name: Raxibaumab **NDA/BLA Type:** Original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		✓		Need PLR format Clarify indication Remove prophylaxis info
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?				
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			✓	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	✓			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 NHP monoclonal alone Indication: Ex of Inhalation anthrax	✓			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 NHP - monoclonal + Cipro Indication: Rx of inhalation anthrax	✓			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			✓	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			✓	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✓	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			✓	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			✓	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✓	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			✓	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			✓	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			✓	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
34.	Are all datasets to support the critical safety analyses available and complete?			✓	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		✓		
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		✓		Would like all CRFs if possible. At a minimum all deaths.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			✓	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			✓	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Susan McCune 6/10/09

Reviewing Medical Officer Date

Yuliya Yasinskaya 6/10/09

Clinical Team Leader Date

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125,349 **Applicant: HGS** **Stamp Date: May 13, 2009**

Drug Name: Raxibacumab (ABthrax) **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		Not PLR, have already requested sponsor resubmit
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5.6 of "2.5 Clinical Overview"
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Dec 07 and July 06 – FDA agreed to 300
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		X		Cannot locate
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _ Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Application is fileable but the sponsor must submit CRFs for all deaths, SAEs and AEs leading to study discontinuation.

Sue Lin	June 10/09
Reviewing Medical Officer	Date
[illegible]	6/10/09
Clinical Team Leader	Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Sally Bolmer	Senior Vice President, Development and Regulatory Affairs
FIRM / ORGANIZATION Human Genome Sciences, Inc.	
SIGNATURE	DATE 20 Apr 09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PSC Graphics (301) 443-1090 EF

Attachment to Form FDA 3454

Clinical Investigators

Protocol PAM-NH-01

Site Number	Name of Clinical Investigator
001	(b) (4) [redacted]
001	
001	
001	
001	
001	

Protocol HGS1021-C1063

Site Number	Name of Clinical Investigator
US001	(b) (4) [redacted]
US001	
US001	
US001	
US002	
US002	
US002	
US003	
US003	
US003	
US004	
US004	
US004	
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US005	
US005	
US005	
US005	
US006	
US006	
US006	

Protocol HGS1021-C1064

Site Number	Name of Clinical Investigator
US001	(b) (4)
US001	
US001	
US001	
US001	
US001	
US001	
US002	
US002	
US002	
US003	
US003	
US003	
US003	

Protocol HGS1021-C1069

Site Number	Name of Clinical Investigator
US001	(b) (4)
US001	
US001	
US002	
US002	
US002	

Pivotal Nonclinical Efficacy Studies in Rabbits and Monkeys

Study Numbers	Name of Investigator
682-G005758	Jason Mott
724-G005829	(Battelle Biomedical Research
781-G923701	Center)
789-G923702	

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 11,069

Human Genome Sciences, Inc.
Attn: Sally Bolmer, Ph.D.
Senior Vice President, Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

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

We also refer to the meeting held on October 21, 2008 between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rebecca McKinnon, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Memorandum of Meeting

Meeting Date: October 21, 2008 (2:00 pm EST)

Application: IND 11,069

Drug Name: ABthrax (raxibacumab)

Sponsor: Human Genome Sciences, Inc.

Meeting Type: Type B Pre-BLA Face-to-Face

Attendees:

FDA Participants

Edward Cox, M.D.	Director, Office of Antimicrobial Products (OAP)
Renata Albrecht, M.D.	Director, Division of Special Pathogen and Transplant Products (DSPTP)
Eileen Navarro Almario, M.D.	Clinical Team Leader, DSPTP
Yuliya Yasinskaya, M.D.	Medical Officer, DSPTP
Patrick Archdeacon, M.D.	Medical Officer, DSPTP
William Taylor, Ph.D.	Pharmacology/Toxicology Team Leader, DSPTP
Ying Mu, Ph.D.	Pharmacology/Toxicology Reviewer, DSPTP
Shukal Bala, Ph.D.	Microbiology Team Leader, DSPTP
Maureen Davidson, Ph.D.	Microbiology Reviewer, DSPTP
Lynette Berkeley, Ph.D.	Microbiology Reviewer, DSPTP
Diana Willard	Chief, Project Management Staff, DSPTP
Rebecca McKinnon, Pharm.D.	Regulatory Project Manager, DSPTP
John Lazor, Ph.D.	Director, Clinical Pharmacology
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, OCP
Kimberly Bergman, Pharm.D.	Clinical Pharmacology Reviewer, OCP
Karen Higgins, Sc.D.	Statistics Team Leader, DB-4
Hongling Zhou, Ph.D.	Statistics Reviewer, DB-4
Kathleen Clouse, Ph.D.	Director, Division of Monoclonal Antibodies (DMA)
David Frucht, M.D.	Product Quality Reviewer, DMA
Rosemary Roberts, M.D.	Director, Office of Counterterrorism & Emergency Coordination (OCTEC)
Susan McCune, M.D.	Medical Officer, OCTEC
Gerald Poley, M.D.	Medical Officer, OCTEC
Cheryl Turner	Regulatory Project Manager, OCTEC
Marc Cavaille-Col, M.D., Ph.D.	Medical Team Leader, DSPTP
Hala Shamsuddin, M.D.	Medical Officer, DSPTP
Joseph Stalder	PharmD Candidate, DSPTP

HGS Participants

Sally Bolmer, Ph.D.	Senior Vice President, Development & Regulatory Affairs
Alfred Corey, BS	Senior Pharmacokineticist II, Pathology, Pharmacokinetics

	& Toxicology
Maggie Lewis, M.S., RAC	Manager, Regulatory Affairs
Julie Hagan	Senior Associate, RA
Thi Migone, Ph.D.	Senior Director, Clinical Immunoassay
David Stump, M.D.	Executive Vice President, Research & Development
Mani Subramanian, M.D., Ph.D.	Senior Director Clinical Research, Infectious Diseases
John Zhong, Ph.D.	Director, Biostatistics
Janelle Zimmerman	Clinical Project Manager, Clinical Operations
Nicole Baker, M.S.	Associate Director, Global Project Management
Jim Davis, Ph.D.	Executive V.P., Government Affairs
Alicia Gilbert	Associate Director, RA CMC
Matt Devalaraja, DVM, Ph.D.	Director, Pharmacology, Pharmacokinetics & Toxicology
Letha Healey, M.D.	Associate Director, Clinical Research, Infectious Diseases
Craig Malzahn	Team Leader and Director, Supply Chain Manufacturing
LuAnne Novello	Director, Clinical Operations
Christine Pannunzio, MAS	Executive Director, RA CMC
Tom Spitznagel, Ph.D.	VP, Biopharmaceutical Product Development
David Kahn	Director, Purification Sciences

Battelle Biomedical Research Center (Consultants for HGS)

Gabriel T. Meister, Ph.D.	Senior Research Scientist
Jason Mott, DVM, Ph.D.	Associate Director

HHS/Biomedical Advanced Research and Development Authority (BARDA)

Stephen Morris, Ph.D.	Project Officer
Terri Richards, MLFSC	Project Officer
Robert Stevenson, BS	Regulatory Affairs Advisor
Quentin Scott, Ph.D.	Regulatory Specialist, Regulatory and Quality Affairs
Alan Liss, Ph.D.	Deputy Director for Regulatory and Quality Affairs

CDC (via teleconference)

Hye-Joo Kim, Pharm.D.	Chief, Regulatory Affairs, SSPU/CCID
Yon Yu, Pharm.D.	Deputy Chief, Regulatory Affairs, OD/CCID
Theresa Smith, MD, MPH	Epidemiology Team Lead, Bacterial Zoonoses Branch, NCZVED/CCID

Background:

BB-IND 11,069 for raxibacumab is a monoclonal antibody directed against the protective antigen (PA) virulence factor of *Bacillus anthracis*, the causative agent of anthrax. Human Genome Sciences (HGS) is the sponsor of IND 11,069, which was established on May 22, 2003. HGS is developing raxibacumab for the treatment of inhalational anthrax and intends to seek licensure of the product under the Animal Rule. In early 2008, HGS submitted final study reports and data under their IND for DSPTP review in consideration of a recommendation to include raxibacumab in the Strategic National Stockpile (SNS) for use under Emergency Use Authorization in the event of anthrax exposure.

On September 9, 2008, HGS requested to meet with DSPTP and OAP to discuss the upcoming submission of their Biologic Licensing Application (BLA), planned for early 2009. A background package for this pre-BLA meeting was submitted on September 19, 2008. In a facsimile sent on October 17, 2008, DSPTP addressed the questions listed in the HGS background package. During the meeting, the discussion focused on clarification of specific questions that HGS had regarding the DSPTP's correspondence. HGS also presented the findings of additional histological studies they conducted in response to DSPTP's September 9, 2008 request, and provided an overview of results of two studies, one conducted in monkeys and another in rabbits, to evaluate potential interference between antimicrobials (ciprofloxacin or levofloxacin, respectively) and raxibacumab when administered in combination.

Summary of Discussion:

In response to questions listed in the September 19, 2008 meeting background package, DSPTP's responses were sent to HGS on October 17, 2008. The format below provides the sponsor's questions in **bold** font followed by DSPTP's responses in *italicized* font. Additional comments from the meeting are in regular font and indicated with headings. Following this discussion, HGS presented additional histopathology data from the studies in monkeys and rabbits, as noted above and discussed in the additional comments for Question #5.

Toxicology

1. **Does the Agency agree that these studies are sufficient to file the BLA and support licensure?**

   FDA Response: The Division agrees that these toxicology studies are sufficient to file your BLA.

   Meeting Comment: No additional discussion.

Efficacy

2. **Does the Agency agree that the therapeutic efficacy studies performed in animals with systemic anthrax disease at the time of raxibacumab treatment are sufficient to file the BLA and support licensure?**

   FDA Response: The Division agrees that the therapeutic efficacy studies performed in animals with systemic anthrax disease at the time of raxibacumab treatment are sufficient to file your BLA. Whether or not the studies support licensure will be determined during our review of the BLA.

   Meeting Comment: No additional discussion.

Clinical Safety

3. **Does the Agency agree that the proposed safety database is sufficient to file the BLA and support licensure?**

   FDA Response: The Division agrees that the proposed safety database is sufficient to file your BLA. Whether or not the database supports licensure will be determined during our review of the BLA.

   Meeting Comment: No additional discussion.

4. **Does the Agency agree that the proposed formats are adequate to present the safety data in the integrated safety summary (ISS)?**

   FDA Response: The Division agrees with a separate presentation of the M10 and M11 safety data; however, we recommend that you also present the safety data of the single doses in its totality of 326 subjects receiving the M11 product while presenting safety of the double dose with and without washout separately.

   Meeting Comment: No additional discussion.

Dose Selection

5. **Does the Agency agree that the efficacy, safety and PK data support the dose of raxibacumab proposed for licensure?**

   FDA Response: The Division will determine whether the efficacy, safety, and PK data support the 40 mg/kg dose of raxibacumab for licensure upon completing our review of the BLA. Upon review of your meeting package, we are concerned that raxibacumab appears to negatively affect the efficacy of antimicrobial in your NHP antimicrobial-raxibacumab combination study. Please explain this finding and discuss the potential implications of this finding on raxibacumab safety and use in the setting of anthrax disease in humans. In addition, we note in your studies involving antimicrobials with or without raxibacumab, the survival rates are higher than in the studies evaluating raxibacumab alone and would like you to discuss these results.

   Meeting Comments: During the review of HGS' two animal efficacy studies (Study 724-G005829 in monkeys and Study 682-G005758 in rabbits), DSPTP requested additional histopathology on all preserved tissues from monkeys that died in Study 724-G005829; the request was made on September 9, 2008. Additional information requests, including additional analyses of histopathology findings and an independent peer review of all the histopathology slides from both studies, were sent to HGS on September 30, 2008. HGS presented an overview of their histopathology findings during this meeting (see Attachment 1. HGS' Slide Presentation). HGS responded to the information requests in a written communication submitted on October 10, 2008, and during this meeting, stated that the independent review by Battelle was still ongoing. HGS believes

that the histopathology data is consistent between the two studies, and a report of their additional analyses will be submitted within a few weeks.

During this meeting, HGS also presented additional information regarding the raxibacumab and antimicrobial (levofloxacin or ciprofloxacin) interaction studies that they conducted in rabbits and monkeys, respectively (see Attachment 1. HGS' Slide Presentation). Following each presentation, the following items were discussed:

- DSPTP noted that HGS' results from the raxibacumab/levofloxacin interaction study in rabbits demonstrate a survival rate of approximately 95% for levofloxacin alone and for the combination. DSPTP inquired as to the relevance of this model to human efficacy, when compared to the survival observed in the 2001 anthrax exposures. It is anticipated that a survival rate that more closely mirrors the human outcomes would demonstrate the added benefit of raxibacumab over antibiotics alone. HGS responded that a pilot levofloxacin rabbit model study, submitted to the FDA, had a 100% survival rate for levofloxacin. A hollow fiber PK study was conducted beforehand to determine the appropriate levofloxacin dose that would result in the exposures equivalent to the human exposure at an approved dose. Treatment intervention was performed at a time when the rabbits became symptomatic (elevation in temperature) for anthrax disease post-challenge. Thus, HGS noted that a demonstration of added benefit by raxibacumab was not possible; however, a potential negative interaction could be demonstrated. According to a representative from Battelle, a similarly designed study conducted by Battelle, under contract by another organization, also demonstrated approximately 90% survival rate.

  HGS further explained that when antimicrobial treatment is initiated at 6 – 12 hours post-challenge and prior to symptoms, approximately 50% of the rabbits died after antimicrobial discontinuation. An increased survival rate of 95% can be achieved by delaying treatment until the rabbits were symptomatic. They concluded that levofloxacin is not effective against toxin and spores present in the rabbit when treated prior to symptoms (too early). If treatment is delayed until the rabbits are symptomatic and all bacteria were synchronized in a vegetative state, a higher survival rate will be seen with levofloxacin. Therefore, HGS concluded that raxibacumab must be administered as soon as PA was observed to achieve higher levels of survival.

  HGS stated that they did not conduct a similar pilot study using ciprofloxacin in non-human primates because they believe it was not needed when adequate published literature exists to support correct ciprofloxacin doses in non-human primates that correlate to human exposure.

- To clarify how the progression of bacterial spores to vegetative bacteria would affect the concomitant dosing of raxibacumab and antimicrobials, HGS indicated that although a large number of individuals will be treated with antimicrobials immediately after an expected exposure, additional treatment with the monoclonal

antibody might reduce tissue damage, reduce toxin levels, and address possible antimicrobial resistant anthrax stains and anthrax disease in the individuals who are unable to tolerate antimicrobials.

- When asked how raxibacumab demonstrates an advantage over current therapies, and whether developing further animal models to model the expected 50% human survival rate of antimicrobials was explored, HGS responded that their primary goal had been to develop a novel therapy as contracted with HHS. HGS' goal was obtaining licensing approval for raxibacumab based on safety and efficacy compared to placebo, not superiority or added benefit to antimicrobial, and they believe that raxibacumab has a novel mechanism of action, is efficacious as monotherapy, and provides a tool for combating antimicrobial resistant strains. HGS emphasized that the interaction studies conducted so far were designed per DSPTP guidance. (b) (4).

- To clarify whether improved survival rates for raxibacumab when used alone could be achieved using doses higher than 40 mg/kg (conducting more dose-ranging studies), HGS indicated that they didn't believe so because the raxibacumab levels achieved at 40 mg/kg dose are higher than the maximum plasma concentration of PA. Even in the interaction studies with antimicrobials, PA concentrations in treated animals were not higher than the raxibacumab levels at 40 mg/kg dose. HGS has not yet submitted these quantitative data. HGS added that 100% of PA was being bound at both the 20 mg/kg and 40 mg/kg doses and that the dose increase beyond 40 mg/kg would provide only marginal improvement.

- DSPTP inquired if HGS, in their BLA application, could demonstrate an advantage of raxibacumab plus antimicrobial therapy over antimicrobial alone based on histopathology data, i.e. reduced tissue damage, hemorrhage, and inflammation, and perhaps also by improvements in CRP and creatinine levels. HGS responded that necropsy/histopathology was performed on all study animals regardless of survival status only in the raxibacumab plus levofloxacin interaction study in rabbits because the NHPs were not sacrificed for ethical reasons in the raxibacumab plus ciprofloxacin study. They agreed to look into DSPTP's inquiry.

- DSPTP emphasized that patients will be treated with antimicrobials immediately if an anthrax exposure occurs. DSPTP noted that HGS may be able to demonstrate superiority using a better animal model that approximates the 50% human survival. HGS responded that they originally considered administering ciprofloxacin in a post-exposure prophylaxis setting followed by the administration of raxibacumab in a treatment setting; however, after discussion

with DSPTP, agreed that raxibacumab should be evaluated only in a treatment setting. DSPTP inquired what would happen if treatment with raxibacumab is delayed because patients have been symptomatic for an extended period of time. HGS' animal models were designed only for raxibacumab intervention soon after symptoms are observed. HGS responded that antimicrobials alone would not decrease toxin concentrations and early or late raxibacumab administration would not be a problem. HGS indicated that they would like to have a recommendation for raxibacumab to be acquired by the Strategic National Stockpile as soon as possible and emphasized they believe they have enough evidence demonstrating support of the safety and efficacy of raxibacumab. DSPTP responded that their questions were being asked to understand the benefit and practical use of raxibacumab. Having animal data to demonstrate benefit over antimicrobial alone would be helpful, and so far, HGS' data doesn't demonstrate any additional benefit.

Organization and Submission of the BLA

6. **Does the Agency agree with the HGS proposal to include summaries of the rabbit and monkey efficacy and PK results in the Clinical Efficacy and Clinical Pharmacology section of Module 2, respectively, and to include the respective study reports in Module 5, given that these data are providing the demonstration of clinical efficacy of raxibacumab under the Animal Rule?**

   FDA Response: The Division agrees with your proposal.

   Meeting Comment: HGS agreed to clearly specify any changes in the study reports submitted in the BLA submission compared to those submitted and previously reviewed in the IND.

7. **Does the Agency agree with the datasets proposed for submission for the human clinical studies, PAM-NH-01, HGS1021-C1063, HGS1021-C1064, and HGS1021-C1069?**

   FDA Response: The Division agrees with the datasets proposed.

   Meeting Comment: No additional discussion.

8. **Does the Agency agree with the datasets proposed for submission for the animal efficacy and PK studies supporting the indication and for the ancillary animal and PK studies?**

   FDA Response: You state that you will submit raw and analysis datasets with definition files for the GLP raxibacumab/antibiotic interaction studies (Study 781-G923701 and Study 789-G923702) and data listings will be provided with the individual final study reports for the supportive animal studies listed on page 16. This approach seems

reasonable. If questions arise during our review of the supportive studies, we may require raw and analysis datasets and definition files for these studies as well.

Meeting Comment: No additional discussion.

9. **Does the Agency agree that no CRFs for the human clinical studies need to be submitted because there is only 1 death in a placebo-treated subject and no study discontinuations due to AEs?**

   FDA Response: The Division does not agree that CRFs for the human clinical studies do not need to be submitted (see #10 below). Case report form tabulations constructed from the datasets do not have to be submitted.

   Meeting Comment: No additional discussion.

10. **Does the Agency agree with the proposal to provide narratives for the subjects with serious adverse events, but not to provide by-subject CRF tabulations?**

    FDA Response: The Division agrees with your proposal not to submit by-subject CRF tabulations constructed from the datasets; however, the Division disagrees with your proposal to provide only narratives for the subjects with serious adverse events. Please provide narratives and original CRFs for all of these subjects. In addition, early in the review process for a BLA, it is possible a random sample of CRFs may be requested.

    Meeting Comment: No additional discussion.

    Does the Agency agree with the proposal to provide by-animal line listings for raxibacumab/antibiotic interaction studies and the therapeutic efficacy studies?

    FDA Response: The Division prefers that both by-animal line listing and the datasets be in a format similar to the format submitted for the pivotal monkey studies.

    Meeting Comment: No additional discussion.

<u>Fees, Waivers, and Proprietary Name</u>

11. **Does the Agency agree that HGS is not required to submit pediatric data or a plan for acquiring pediatric data, or a request for a waiver with the BLA application for raxibacumab for the treatment of inhalation anthrax?**

    The Division agrees.

12. **Does the Agency agree that HGS is not required to supply additional information in the BLA regarding the name "Raxibacumab" if no proprietary name is being sought for the product?**

The Division agrees; however, we are interested to know why you are not seeking a proprietary name.

Meeting Comment: HGS stated that are not interested in a proprietary name because they do not intend to market raxibacumab to the public and do not want the additional burden and expense of obtaining a proprietary name.

Postmarketing Commitments

13. Does the Agency agree with the proposal to provide a draft protocol, CRF, and patient information in the BLA to support use of raxibacumab in the event of an anthrax attack?

We are unable to respond to this question without consulting the Office of Chief Counsel. We will provide a response at a later time.

Meeting Comment: Animal Rule regulations require the collection of outcome data if raxibacumab is used in patients. DSPTP inquired if HGS would collaborate with the CDC for collection of these data and recommended that HGS consider a protocol and CRF. HGS indicated that they have offered to develop a protocol and CRF for the CDC. HGS plans to continue scientific investigations for raxibacumab and agreed that outcome data should be collected if an event occurs. DSPTP emphasized this information will assist in labeling and patient information during an actual clinical setting.

14. Does the Agency agree that the license that would be granted would be a full approval under the Animal Rule?

We are unable to respond to this question without consulting the Office of Chief Counsel. We will provide a response at a later time.

Meeting Comments: The Division would like to see a plan for postmarketing studies, what kind of data collection would there be, and whether a protocol would be included in the BLA. HGS agreed and are willing to work with the CDC.

Proposed Indication

15. Does the Agency agree that the data to be presented in the BLA support this indication for raxibacumab?

The Division will determine whether or not the data support this indication during our review of the BLA.

Meeting Comment: No additional discussion.

Chemistry

16. Does the Agency agree with the overall format and content of Module 3?

In general, the format of Module 3 is appropriate (with exceptions listed below). However, an assessment of whether the product quality package is fileable will be performed once the BLA is received by FDA.

Meeting Comment: No additional discussion.

17. Does the Agency agree with the placement of the description and qualification/validation results for the various types of analytical methods?

The Division agrees that the description of the analytical methods data should be provided in 3.2.S.4.2, and the methods validation data should be provided in section 3.2.S.4.3.

Meeting Comments: HGS indicated that their Belward Small Scale Manufacturing facility may not be in active production if a pre-approval inspection is conducted during the BLA review cycle. Although the Office of Compliance was not available to answer, FDA believed that HGS could perform dry or mock runs of selected unit operations using water instead of product during the pre-approval inspection.

HGS asked if the proposed locations in the electronic submission for other methods such as the in-process controls and product characterization were acceptable. DSPTP responded that the proposed locations were acceptable as long as they were appropriately hyperlinked from the methods section in Module 3 (3.2.S.4.2).

18. Does the Agency agree that the description of the immunogenicity assays should be included in Section S.4.2 and the validation summaries included in Section S.4.3?

The Division does not agree. Information regarding the immunogenicity assays, along with validation, should be provided in module 5 (section 5.3.5.3.1).

Meeting Comment: HGS asked if the immunogenicity assays could be placed in Section 5.3.1.4. DSPTP indicated that this would be acceptable.

19. Does the Agency prefer to receive a separate Methods Validation Package in Section 3.2.R.2?

Not necessarily, it would be acceptable if these data were provided in section 3.2.S.4.3.

Meeting Comment: A separate methods validation package will not be required. The use of hyperlinks is encouraged.

20. Does the Agency agree with this approach [to submit gels and chromatograms as applicable to support characterization sections, in support of the characterization of

the Reference Standard, and in the BDS and FDP Batch Analysis sections with the release data for the conformance batches]?

This approach is reasonable, but the Division may request additional data during the review cycle if necessary.

Meeting Comment: No additional discussion.

21. **Does the Agency agree that the BLA will contain adequate BDS and FDP stability data to establish commercial expiry dates? Does the Agency agree additional real time stability data can be submitted during the review of the BLA or in response to BLA review question in order to maximize the expiry dates prior to licensure?**

The adequacy of the stability data to establish commercial expiry dating is a BLA review issue. Additional real-time stability data may be submitted during the BLA review cycle. HGS should note, however, that major BLA amendments late in the review cycle will extend the review clock. Please also note that the expiration date will be based on the amount of real-time stability data on file for product produced at the commercial scale.

Meeting Comment: HGS requested clarification on the type and amount of stability data required at the time of filing to maximize the expiry date prior to licensure. At the time of filing, HGS proposed to submit 24 months of real-time stability data for two final drug product (FDP) lots in the upright position, and 18 months of real-time stability data for one FDP lot in the upright position and 3 lots in the inverted position. HGS asked if submission of additional real-time stability data (i.e., 24 months for one FDP lot in the upright position and 3 FDP lots in the inverted position) would be considered a major amendment at 5 months into the review cycle. DSPTP indicated that 5 months into the review cycle was too late for review and could delay his review depending on the amount of additional data. DSPTP asked for clarification of the amount of stability data to be included at the time of BLA submission. HGS summarized the real-time stability for the FDP lots to be included in the initial BLA submission. CP asked if FDA would accept these stability data in addition to 30 to 36 months of supporting, representative development FDP stability data to establish a (b) (4) expiry date. DSPTP stated that the initial stability data may be considered for establishing the (b) (4) expiry date if supported by trending analyses. HGS proposed submitting another package with 2 proposals for submission of FDP stability data for establishing the expiry date: (1) submission of initial 18 to 24 month real-time FDP stability data followed by a BLA amendment during review with 24 month data or (2) submission of initial real-time FDP stability along with trending analyses. DSPTP concurred and emphasized that as much stability information as possible should be included at the time of the BLA submission. HGS agreed, but hopes to reduce the amount of relabeling needed for the product stored in the SNS.

22. **Does the Agency agree with the number and type of release tests and their associated acceptance criteria included in the proposed commercial specifications in Section 7 of this package for BDS and FDP?**

In general, the number and type of release tests appear adequate. However, determination of the adequacy of the proposed acceptance criteria will be assessed during the BLA review.

Meeting Comment: No additional discussion.

23. Does the Agency agree that HGS has performed a comprehensive process validation program and, with adequate results, is sufficient to file the BLA and demonstrate the consistency of manufacture for raxibacumab BDS and FDP?

The sufficiency of the process validation program and supporting data will be determined during the BLA review and/or facility inspection.

Meeting Chair
Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products

Minutes Preparer
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Attachment 1: HGS' Slide Presentation

Human Genome Sciences

Raxibacumab

for Therapeutic Treatment of Inhalation Anthrax

Pre-BLA Meeting

21 October 2008

Rabbit Efficacy Study (682)

- Met its primary endpoint
- Statistically significant improved survival rate
- Statistically significant improved median survival time

	Number (%) Survivors	Median Survival Time (days)
Placebo	0/17 (0%)	2.7
20 mg/kg raxibacumab	5/18 (27.8%)	3.5
40 mg/kg raxibacumab	8/18 (44.4%)	3.8

Rabbit Efficacy Study: Survivors

- Among survivors (all raxibacumab treated)
  - Clinical and laboratory parameters (temperature, hematology, CRP, serum PA) recover
  - No remarkable findings (seizures, loss of balance, loss of coordination) related to CNS effects
    - While on study
    - At the end of the study

Rabbit Efficacy Study: Non-survivors

- All dead/euthanized animals had findings consistent with anthrax disease
- Gross and histopathology qualitatively the same as in the published literature (lung, lymph node, spleen, kidney, brain)
- Incidence of bacteria +/or hemorrhage greater in placebo group for all tissues, except brain

Rabbit Efficacy Study: Non-survivors

Tissue/Observation	Incidence among Non-survivors		
	Placebo (n = 17)	20 mg/kg Raxi (n = 12)	40 mg/kg Raxi (n = 10)
Kidney			
Bacteria	16	4	2
Hemorrhage	8	3	1
Lymph node, bronchial			
Bacteria	16	3	4
Lymph node, mediastinal			
Bacteria	14	3	4
Lung			
Bacteria	15	2	1
Spleen			
Bacteria	15	2	1
Brain			
Bacteria	3	9	7
Hemorrhage	4	10	7

Rabbit Efficacy Study: Non-survivors

- Median time to death was not shorter in raxibacumab treatment groups
  - 2.7 days, placebo
  - 3.0 days, 20 mg/kg raxibacumab
  - 2.9 days, 40 mg/kg raxibacumab
- Median time to death in rabbits with moderate to marked brain inflammation was longer than for rabbits without
  - 2.7 days, without moderate/marked inflammation
  - 4.0 days, with moderate to marked inflammation
  - $p = 0.0017$, Wilcoxon test

Monkey Efficacy Study (724)

- Met its primary endpoint
- Statistically significant improved survival rate
- Statistically significant improved median survival time

	Number (%) Survivors	Median Survival Time (days)
Placebo	0/12 (0%)	3.3
20 mg/kg raxibacumab	7/14 (50.0%)	> 28
40 mg/kg raxibacumab	9/14 (64.3%)	> 28

Monkey Efficacy Study: Survivors

- Among survivors (all raxibacumab treated)
  - Clinical and laboratory parameters (temperature, hematology, CRP, serum PA) recover
  - No remarkable findings (seizures, prostrate, unresponsive) related to CNS effects
    - While on study
    - At the end of the study (additional 30-day follow up)
  - In rechallenge study (374) of survivors from PEP study (290)
    - 21 animals had no signs of emergent CNS effects 11 months after anthrax spore challenge and raxibacumab treatment

Monkey Efficacy Study: Non-survivors

- All dead/euthanized animals had findings consistent with anthrax disease
- Gross and histopathology qualitatively the same as in the published literature
- Incidence of pathology findings on histopathology was the same or greater in placebo group for all tissues, except brain

Monkey Efficacy Study: Non-survivors

Tissue/Observation	Incidence among Non-survivors		
	Placebo (n = 12)	20 mg/kg Raxi (n = 7)	40 mg/kg Raxi (n = 5)
Kidney			
Bacteria	11	3	3
Lymph node, bronchial			
Bacteria	8	2	1
Hemorrhage	5	1	1
Lymph node, mediastinal			
Bacteria	11	5	2
Hemorrhage	7	1	2
Lung			
Bacteria	11	3	4
Hemorrhage	3	1	0
Inflammation	6	2	1
Liver			
Bacteria	11	3	3
Spleen			
Bacteria	10	4	3
Brain			
Bacteria	11	5	5
Hemorrhage	2	6	3
Inflammation	1	6	2

Monkey Efficacy Study: Non-survivors

- Median time to death was numerically greater in raxibacumab treatment groups
  - 3.3 days, placebo
  - 3.9 days, 20 mg/kg raxibacumab
  - 3.7 days, 40 mg/kg raxibacumab
- Median time to death in monkeys with moderate to marked brain inflammation was longer than for monkeys without
  - 3.2 days, without moderate/marked inflammation
  - 4.5 days, with moderate to marked inflammation
  - $p = 0.0171$, Wilcoxon test

Rabbit Raxi/Levo Efficacy Study

- Met its primary endpoint
- Statistically significant improved survival rate
  - Raxibacumab + levofloxacin vs placebo
  - Levofloxacin vs placebo
- Statistically significant improved median survival time

	Number (%) Survivors	Median Survival Time (days)
Placebo	**0/12 (0%)**	**3.3**
Levofloxacin	**20/21 (95.2%)**	**> 28**
Raxibacumab + Levofloxacin	**18/19 (94.7%)**	**> 28**

Raxi/Levo Efficacy Study: Survivors

- Among survivors (all levo +/- raxi treated)
  - 35/38 bacteremic at or after treatment
  - Clinical and laboratory parameters (temperature, hematology, CRP, serum PA) recover
  - No remarkable findings (seizures, loss of balance, loss of coordination) related to CNS effects
    - While on study
    - At the end of the study
  - No abnormal brain findings on gross or histopathology

Raxi/Levo Efficacy Study : Non-survivors

- All placebo-treated rabbits had anthrax disease (all non-survivors)
- 1 Non-survivor (raxibacumab+levo) died of missed gavage
- 1 Non-survivor (levo) died of anthrax
  - No brain involvement on gross or microscopic exam

Raxi/Levo Efficacy Study: Non-survivors

Tissue/Observation	Incidence among Non-survivors		
	Placebo (n = 12)	Levo (n =1)	Levo + Raxi (n = 1)
Kidney			
Bacteria	12	0	0
Lymph node, bronchial			
Bacteria	12	0	0
Hemorrhage	12	0	0
Lymph node, mediastinal			
Bacteria	11	0	0
Hemorrhage	10	0	0
Lung			
Bacteria	12	1	0
Hemorrhage	5	1	1
Inflammation	4	1	1
Liver			
Bacteria	12	0	0
Spleen			
Bacteria	12	0	0
Brain			
Bacteria	8	0	0
Hemorrhage	5	0	0
Inflammation	1	0	0

Monkey Raxi/Cipro Efficacy Study

- Met its primary endpoint
- Statistically significant improved survival rate
  - Raxibacumab + ciprofloxacin vs placebo
  - Ciprofloxacin vs placebo
- Statistically significant improved median survival time

	Number (%) Survivors	Median Survival Time (days)
Placebo	**0/12 (0%)**	**4.2**
Ciprofloxacin	**14/14 (100%)**	**> 28**
Raxibacumab + Ciprofloxacin	**12/14 (85.7%)**	**> 28**

Raxi/Cipro Efficacy Study: Survivors

- Among survivors (all cipro +/- raxi treated)
  - 24/26 bacteremic at or after treatment
  - Clinical and laboratory parameters (temperature, hematology, CRP, serum PA) recover
  - No remarkable findings (seizures, prostrate, unresponsive) related to CNS effects
    - While on study
    - At the end of the study

Raxi/Cipro Efficacy Study : Non-survivors

- All placebo-treated monkeys had anthrax disease (all non-survivors)
- 2 animals (raxibacumab+cipro) died
  - 1 from missed gavage
  - 1 from anthrax
    - Died at 9.9 days
- Pathology findings on gross necropsy in more tissues in placebo group; brain and lymph node in raxibacumab + cipro animal

Raxi/Cipro Efficacy Study: Non-survivors (from anthrax)

	Incidence among Non-survivors		
Gross necropsy/Observation	Placebo (n = 12)	Cipro (n = 0)	Cipro + Raxi (n = 1)
No findings[1]	2	-	-
Adrenal			
Discoloration	1	-	-
Lymph node, enlarged			
Bronchial	6	-	1
Mediastinal	5		-
Axillary	1		-
Mandibular	1		-
Lung			
Discoloration	2	-	-
Liver	1	-	-
Foci			
Brain			
Accumulation/discoloration	4	-	1

[1]Non-survivor without gross findings had microscopic examination: 1 animal (placebo) had bacteria in brain, kidney, liver, spleen and lung;

Propose: Raxibacumab does not induce CNS toxicity in animals with anthrax

- Disease course of inhalation anthrax is lung → lymph nodes, highly vascularized tissue → brain (as epithelial changes to blood brain barrier allow)
- Raxibacumab
  - Does not exacerbate lesions in highly vascularized tissues
    - Bacteria are cleared
  - Prolongs survival and allows for bacteria/toxin to reach brain
    - Bacteria/toxin in the brain are difficult to clear
    - Meningitis associated with high mortality
  - Does not result in CNS effects in bacteremic animals that survive
    - No clinical signs of disability in survivors while on study or in follow up

Propose: Raxibacumab is safe and well tolerated in healthy animals and humans

- No binding to brain/meninges in cross-reactivity studies (human, monkey, rabbit)
- No CNS AEs observed in healthy animal studies
  - Chronic toxicity study
  - Embryo-fetal toxicity study
  - PK studies
- No increase in incidence of nervous system disorders in human clinical trials

	Placebo (N = 105)	Raxibacumab (N = 406)
At least 1 AE in Nervous Systems Disorders	17 (16.2%)	63 (15.5%)

Overall Conclusions

- Raxibacumab
  - Safe and well tolerated in healthy animals and humans
  - Increases survival rate and time to death
  - Non-survivors have pathology qualitatively the same as that reported in the literature
  - Survivors have normalizing laboratory parameters and no signs of CNS involvement

Raxibacumab/Antibiotic Efficacy Studies

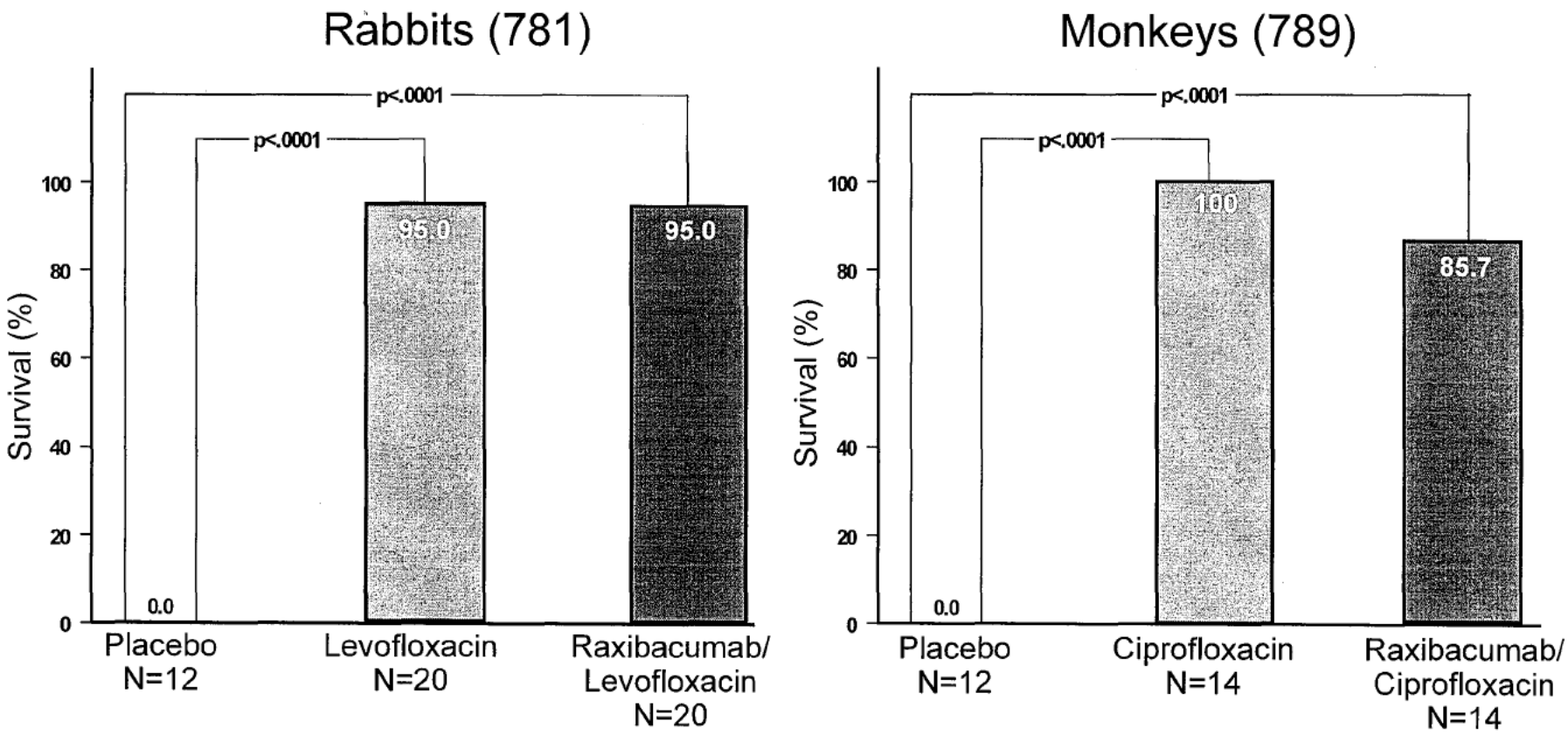
Raxibacumab/Antibiotic Efficacy Study Designs

- Designed to demonstrate effectiveness of antibiotic in combination with raxibacumab
  - Powered to detect reduction in antibiotic effect caused by raxibacumab, if present
  - Not powered to demonstrate added benefit
  - Not designed to demonstrate superiority/non-inferiority of raxibacumab vs antibiotic
- Antibiotic dose to give exposure equivalent to recommended dose in humans
- PK of raxibacumab and antibiotic also analyzed

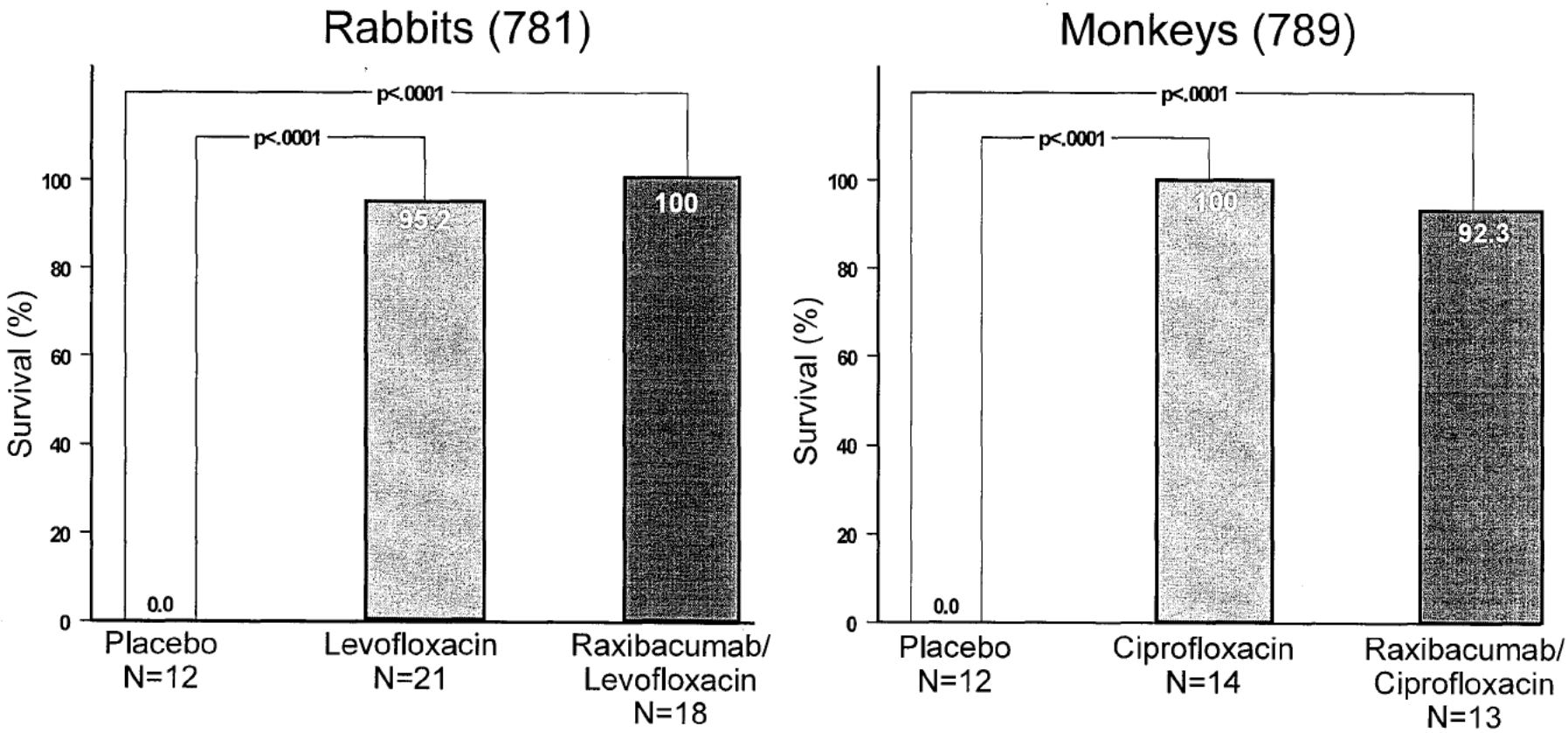
Raxibacumab/Antibiotic Efficacy Study Designs

- Both studies met their primary endpoint
  - Raxibacumab + antibiotic provided statistically significantly greater survival compared with placebo ($p<0.0001$)
    - Antibiotic alone also provided statistically significantly greater survival than placebo ($p< 0.0001$)
    - Survival rates with antibiotic +/- raxibacumab were not significantly different

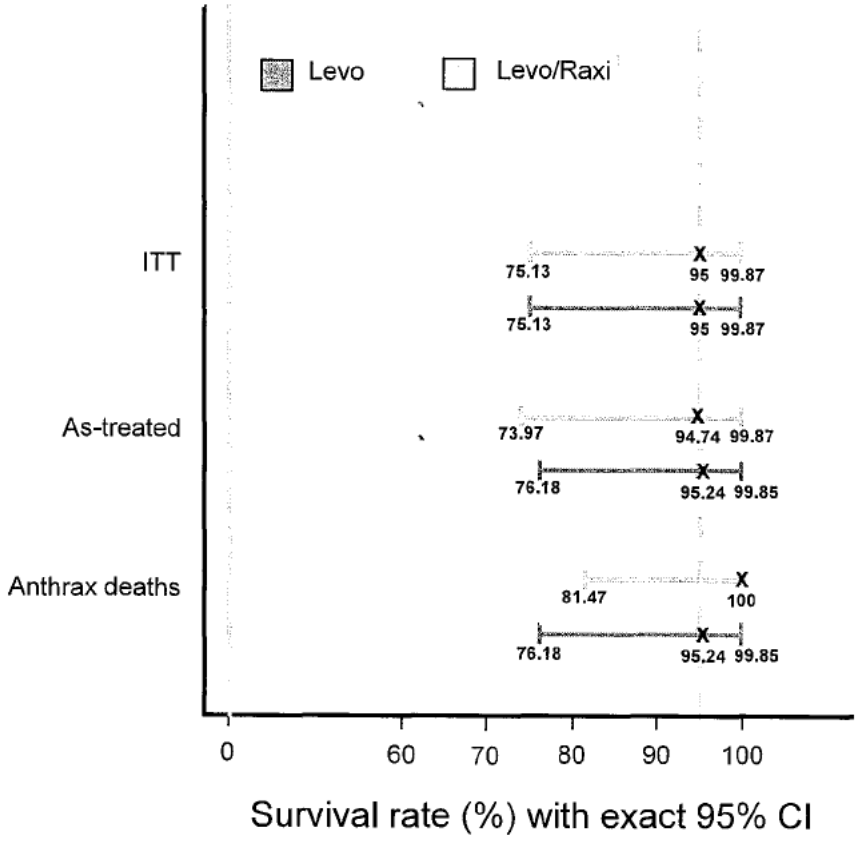
Raxi/Antibiotic Efficacy in 2 Species: Primary Endpoint (ITT)



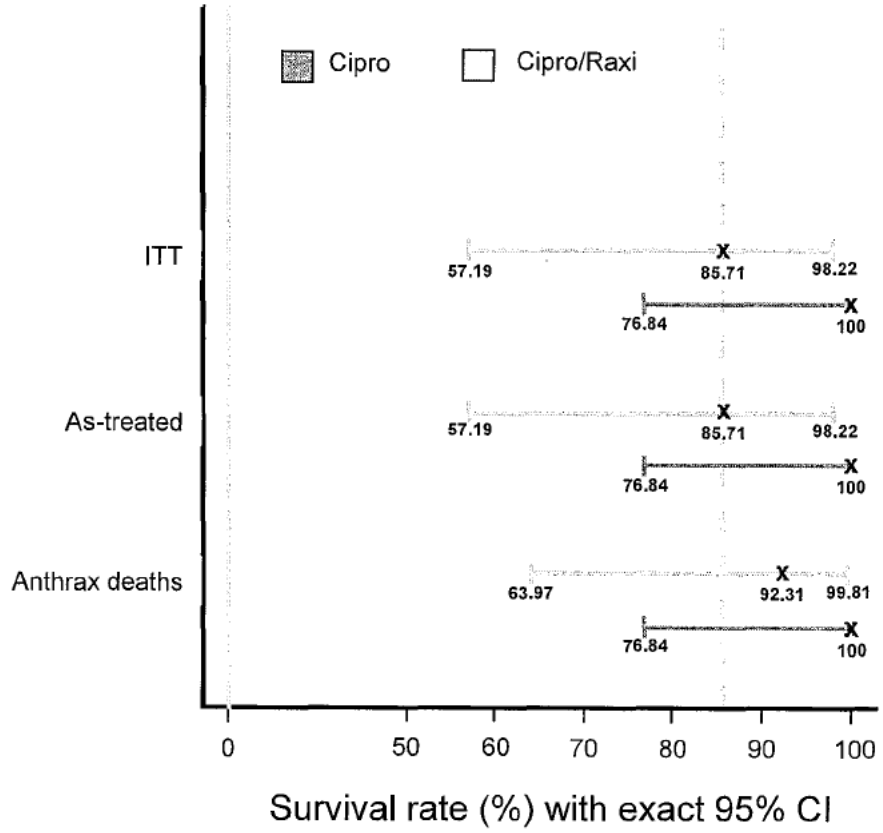
Raxi/Antibiotic Efficacy in 2 Species: Primary Endpoint in As-treated/Anthrax Deaths



Raxi/Antibiotic Efficacy: Primary Endpoint with 95% CI



Rabbits



Monkeys

Raxibacumab/Antibiotic Efficacy: Difference in Survival Rates

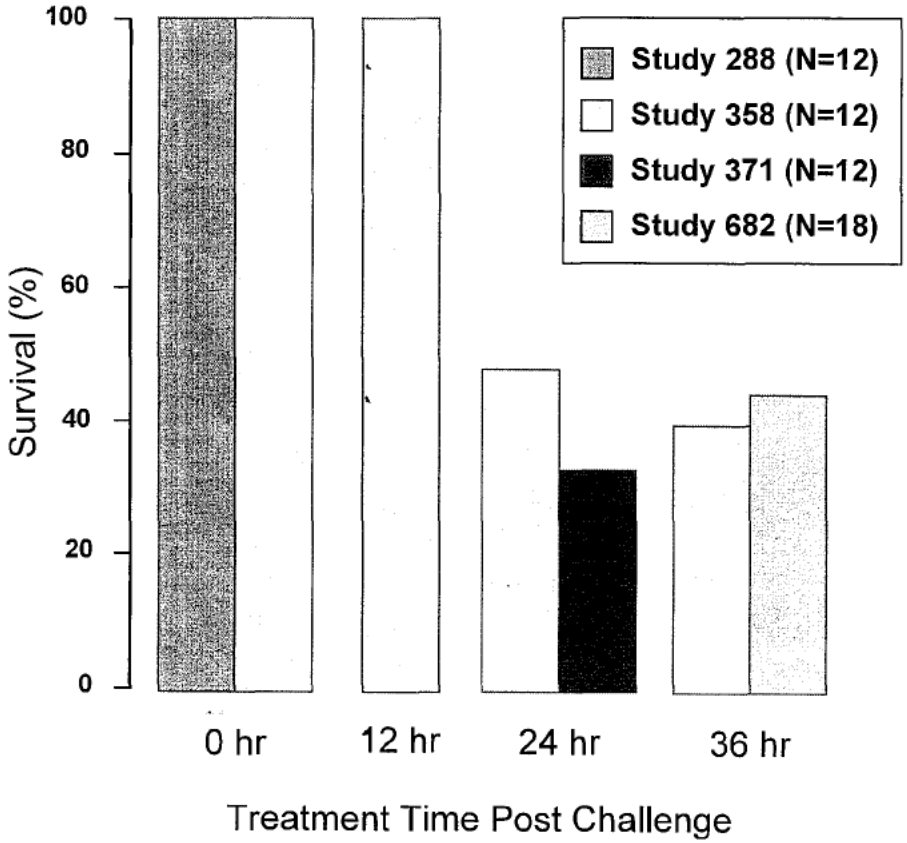
Under Animal Rule, it is necessary to demonstrate safety and effectiveness and translatable PK

- Not added benefit with standard therapy
- Not superior benefit or non-inferiority to current therapy

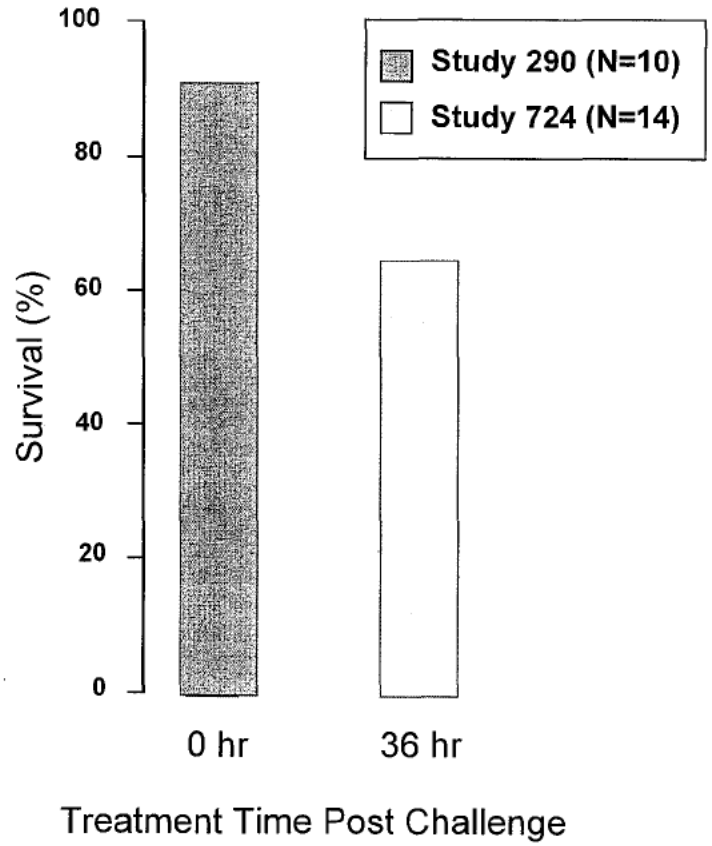
Raxibacumab/Antibiotic Efficacy: Difference in Survival Rates

- Timing of intervention effects efficacy
  - For raxibacumab
    - Earlier intervention (before exponential PA rises) improves efficacy
  - For antibiotics
    - Later intervention (after complete spore germination) improves efficacy

Raxibacumab Efficacy: Survival Rates by Time after Spore Challenge



Rabbits



Monkeys

Raxibacumab Efficacy:

- Raxibacumab
  - Safe and well tolerated in healthy animals and humans
  - Increases survival rate and time to death
    - Met primary endpoint in all trials
  - Non-survivors have pathology qualitatively the same as that reported in the literature
  - Survivors have normalizing laboratory parameters and no signs of CNS involvement

Linked Applications	Sponsor Name	Drug Name
IND 11069	HUMAN GENOME SCIENCES INC	Human Monoclonal Antibody (PA mAb) to Protective Antigen (PA) of Bacillus Anthracis

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

/s/

REBECCA D Mckinnon
11/20/2008

RENATA ALBRECHT
11/20/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RA# 1368 (Master)

November 12, 2003

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850

Attention: Sally Bolmer, PhD
Senior Vice President, Regulatory Affairs

Re: Designation Request # 03-1755

Dear Dr. Bolmer:

Reference is made to your request for orphan-drug designation dated July 29, 2003, of monoclonal antibody against protective antigen protein of *Bacillus anthracis* for the treatment of anthrax infection. Reference is also made to our acknowledgement letter dated August 7, 2003.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bb), your request for orphan drug designation is granted of monoclonal antibody against protective antigen protein of *Bacillus anthracis* for the treatment of anthrax.

Please also note that if the above product receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. § 360cc). Therefore, prior to final marketing approval, we request that you compare the product's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. § 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the product's designated use.

If you need further assistance in the clinical development of your product, please feel free to contact Tan Nguyen, MD, PhD, at (301) 827-3666. Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

John J. McCormick for

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

AUG 15 2003

Our Reference: BB-IND 11069

Human Genome Sciences, Incorporated
Attention: Sally D. Bolmer, Ph.D.
Director, Regulatory Affairs
9410 Key West Avenue
Rockville, MD 20850

Dear Dr. Bolmer:

Reference is made to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody (PA mAb) to Protective Antigen (PA) of *Bacillus anthracis*." We also refer to your submission of June 13, 2003, received on June 16, 2003, requesting designation as a Fast Track Product pursuant to Section 506 of the Food, Drug, and Cosmetic Act.

We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of PA mAb for post exposure prophylaxis and adjunctive therapy of inhalational anthrax disease, and for lessening the severity of inhalational anthrax disease, including disease caused by antibiotic resistant organisms. We acknowledge that your proposed studies related to efficacy will be conducted in animals in accordance with the FDA rule on "Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies are not Ethical or Feasible."

Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program. In this regard, please respond to the issues identified in the August 15, 2003, Advice Information letter addressing your June 13, 2003, submission.

Under the FDA Modernization Act of 1997, designation as a Fast Track product for a new drug or biological product means that FDA will take such actions as are appropriate to expedite the development and review of the application for approval of such product. FDA may also evaluate for filing and commence review of portions of an application for approval of a Fast Track product under certain conditions.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review." This document is available on the internet at http://www.fda.gov/cber/guidelines.htm or may be requested from the Office of Communications, Training, and Manufacturers Assistance, at (301) 827-1800.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence regarding this IND should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
HFM-99, Room 200N
1401 Rockville Pike
Rockville, Maryland 20852-1448

We look forward to working with you to expedite the development and review of this promising proposed use of the product. If you any have questions, please contact Dale Slavin, Ph.D., Division of Application Review and Policy, at (301) 827-5101.

Sincerely yours,

Dale Slavin

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Drug
Evaluation and Research