

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125349Orig1s000

OTHER REVIEW(S)



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

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

FINAL LABEL AND LABELING REVIEW

Date: December 10, 2012

Reviewer: Kimberly Rains, Pharm. D.
Office of Biotechnology Products,
Immediate Office

Through: David Frucht, MD
Product Reviewer
Division of Monoclonal Antibodies (DMA)

Patrick Swann, Ph.D.
Deputy Director
Division of Monoclonal Antibodies (DMA)

Application: BLA 125349

Product: Raxibacumab

Applicant: Human Genome Sciences, Inc.

Submission Date(s): June 17, 2009, June 15, 2012, September 5, 2012, December 7, 2012

Executive Summary

The carton and container labels for Raxibacumab were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 35-NF 30 (8/1/12-11/30/12). Labeling deficiencies were identified, mitigated, and resolved. Comments are listed in the conclusions section. The carton and container labels submitted on December 7, 2012 are acceptable.

Background and Summary Description

STN 125349 for Raxibacumab is a Biologic License Application (BLA) indicated for the treatment of patients with inhalation anthrax due to *B. anthracis*. The product is

STN 125349/0

currently held in the Strategic National Stockpile (SNS) under IND and is labeled with agency approved exemptions. The BLA contains commercial labels and overlabels that will be applied to the approved IND labeled product upon approval. The product is supplied as 1700 mg/ 34 mL (50mg/ml) single-use glass vials. The application received a Complete Response on November 14, 2009. Revised labels were submitted with resubmitted data for review.

Materials Reviewed:

Raxibacumab

Container labeling-commercial label and overlabel for SNS stock

Carton –unit (b) (4)

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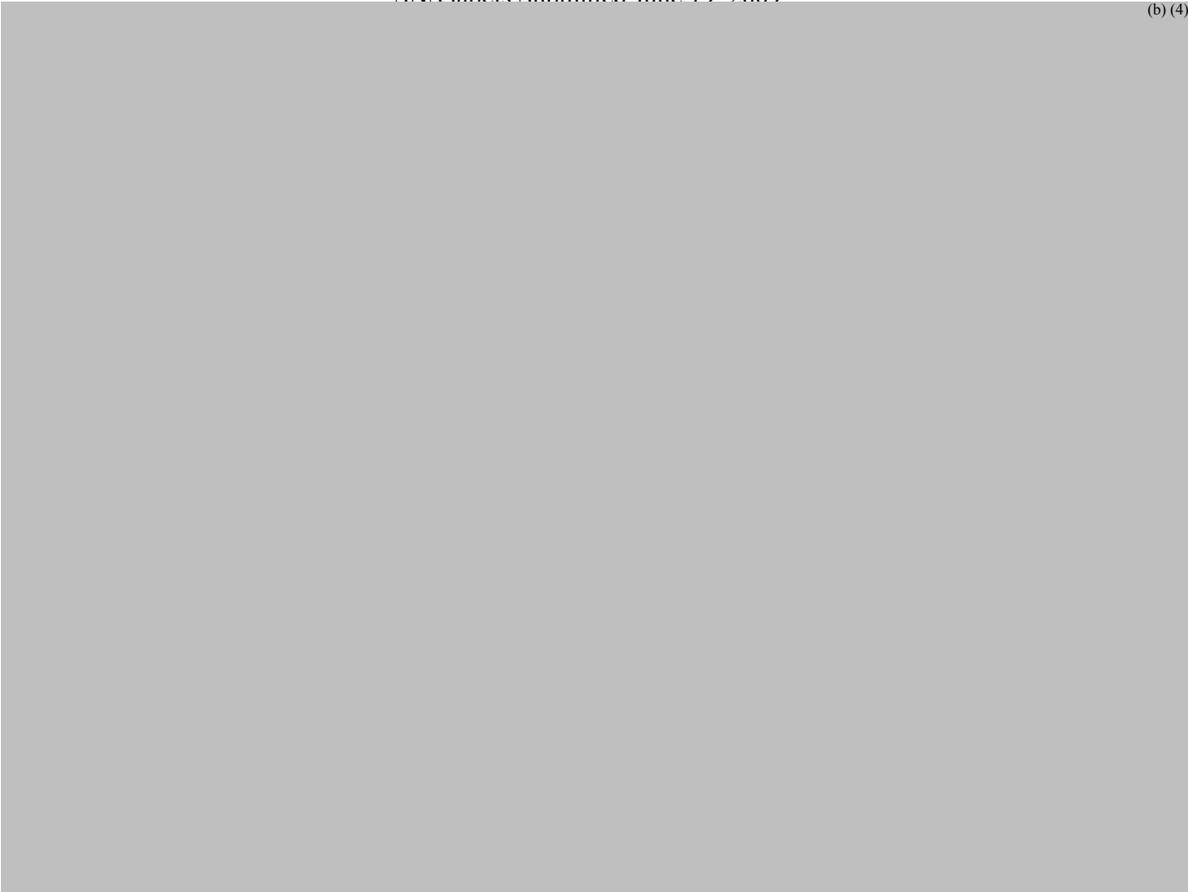
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Start of Sponsor Material

SNS labels Submitted June 19, 2009

(b) (4)



Proposed Commercial label Submitted June 15, 2012

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I. Container

A. 21 CFR 610.60 Container Label (Commercial)

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name of the product – Raxibacumab – is displayed as Raxibacumab (b)(4) without a proprietary name, (trade name). **This does not conform to the regulation. Remove the (b)(4) from the name.**
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The following presentation is displayed on the side panel: U.S. License No is listed as XXXX (b)(4) Manufactured by Human Genome Sciences, Inc, Rockville, MD 20850. This conforms to the regulation.
 - c. The lot number or other lot identification – Is not displayed. **This does not conform to the regulation.**
 - d. The expiration date – Is not displayed. **This does not conform to the regulation.**
 - e. The recommended individual dose, for multiple dose containers – This is a single use vial. A statement appears on the label to this effect.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – Exempted from this requirement. This section does not apply.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear

on the container label. – The container is enclosed in a package (carton). This section does not apply.

3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This section does not apply.
 4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.
 5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – **This does not conform to the regulation. Need info.**
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on label. This conforms to the regulation.
- C. 21 CFR 201.5 Drugs; adequate directions for use – No statement appears on the label. **This does not conform to the regulation.**
- D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proper name. This conforms to the regulation.
- E. 21 CFR 201.10 Drugs; statement of ingredients – This conforms to the regulation.
- F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”, “Do not Freeze”, and storage conditions) are prominent and do not overlap. This conforms to the regulation.
- G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not displayed on the label. **This does not conform to the regulation.**
- H. 21 CFR 201.25 Bar code label requirements – A bar code does appear on the label. This conforms to the regulation.

- I. 21 CFR 201.50 Statement of identity – The proper name is listed as Raxibacumab (b) (4) is stated on the label. There is no proprietary name, (trade name) for the product. **This does not conform to the regulation.**
- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents (34 mL Single Use Vial) is declared on the label. This conforms to the regulation.
- K. 21 CFR 201.55 Statement of dosage – The statement “Single Use Vial” is displayed on the label. This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, other pertinent information, but does not list a lot number and expiration date. **This does conform to the regulation.**

Start of Sponsor Material

Submitted June 19, 2009

(b) (4)



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End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Carton/Package Label – Commercial Unit (b) (4) Carton

- a. The proper name of the product – Raxibacumab – is displayed as Raxibacumab (b) (4) without a proprietary name, (trade name). **This does not conform to the regulation. Remove the (b) (4) from the name.**
- b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The following presentation is displayed on the side panel: U.S. License No is listed as XXXX (b) (4) Manufactured by Human Genome Sciences, Inc, Rockville, MD 20850. This conforms to the regulation.
- c. The lot number or other lot identification – The lot number is not listed. **This does not conform to the regulation.**
- d. The expiration date – The expiration date is not listed below the lot number on the carton. **This does not conform to the regulation.**

- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the side panel of the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one single-use vial per carton. The statement, “(b) (4) Single-Use Vial”. This conforms to the regulation.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration. The statement, “1700 mg/ 34 mL (50 mg/mL).”
- h. The recommended storage temperature – The statement (b) (4) is displayed on the side panel of the carton. This conforms to the regulation.
- i. The words “PROTECT FROM LIGHT”, “REFRIGERATE” or the equivalent, as well as other instructions, when indicated by the character of the product is displayed on the carton. This conforms to the regulation.
- j. The recommended individual dose (b) (4) (b) (4) appears on the rear of the unit (b) (4) carton. This conforms to the regulation.
- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For Intravenous (b) (4)” is located on the front and rear panels of the carton.
- l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information – None listed. This conforms to the regulation.

- m. The type and calculated amount of antibiotics added during manufacture – None listed. This conforms to the regulation.
 - n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information – listed on carton and Prescribing Insert. This conforms to the regulation.
 - o. The adjuvant, if present – None listed. This conforms to the regulation.
 - p. The source of the product when a factor in safe administration – None listed. This conforms to the regulation.
 - q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None listed. This conforms to the regulation.
 - r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. Standard of Potency has been prescribed, the words “No U.S. Standard of Potency” – Displayed on side panel. This conforms to the regulation.
 - s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the front and back of the carton. This conforms to the regulation.
 - t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – This conforms to the regulation.
- B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2©(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*] – The proper name, Raxibacumab, is the only name on the label. This conforms to the regulation.

- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – Human Genome Sciences, Inc. is the only manufacturer listed on the label. This conforms to the regulation.
- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”. “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. – There is no distributor listed on the carton. This conforms to the regulation.
- E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the front and back panels of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states (b) (4)
 This conforms to the regulation.
- I. 21 CFR 201.6 Drugs; misleading statements – The name shown on the carton label is Raxibacumab. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – This conforms to the regulation.
- K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”, “DO NOT FREEZE”, and storage conditions) are prominent and do not overlap. This conforms to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not displayed under the lot identification number as required by 610.61 on the carton label. **This does not conform to the regulation.**

- M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The proper name, Raxibacumab, is stated on the label and no proprietary name, (trade name) is listed. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The label states (b) (4)
 This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, storage conditions, and reference to the package insert. The statement “PROTECT FROM LIGHT”, “DO NOT FREEZE”
The required identifying lot number and expiration date is not displayed.
This does not conform to the regulation.

III.





IV. Conclusions and Recommendations

The following deficiencies were noted in the initial review of the container and carton labels:

- A. 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. **Change made and acceptable with June 15, 2012.**
 - 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. **Information submitted and acceptable with June 15, 2012.**
- B. Commercial Cartons
 - 1. 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). **Change made and acceptable with June 15, 2012 submission.**
 - 2. 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. **A place holder has been identified on the bottom of the container with the June 15, 2012 submission.**
- C. Commercial Carton and Container

1. 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. **Change made and acceptable with June 15, 2012 submission.**
2. 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

Change made and acceptable with June 15, 2012 submission.

3. Please revise the presentation of the statement, “(b) (4) Single –Use Vial” to “Single-Use Vial” to prevent redundancy. Relocate the (b) (4) statement to the primary panel (b) (4)
Change made and acceptable with June 15, 2012 submission.
4. 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.

Change made and acceptable with June 15, 2012 submission.

5. 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.

Change made and acceptable with June 15, 2012 submission.

- D. SNS container, unit carton ^{(b) (4)} labels with the addition of the overlabs have the following deficiencies:
1. The manufacturer is listed incorrectly per the definition of manufacturer listed in 21 CFR 600.3(t). The statement,



The correct statement is listed on the commercial labels as:
“Manufactured by
Human Genome Sciences, Inc.
Rockville, MD 20850”

Change made and acceptable with September 5, 2012 submission.

2. The proper name, “Raxibacumab ^{(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). Change made and acceptable with September 5, 2012 submission.
3. 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. Change made and acceptable with September 5, 2012 submission.
4. The statement, “Rx Only”, is not displayed on the ^{(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. . Change made and acceptable with September 5, 2012 submission.

Amendment

Labels and labeling were resubmitted on December 7, 2012 with changes requested by the Division of Medication Error Prevention and Analysis (DMEPA). The labels submitted on December 7, 2012 are acceptable.

The following revisions were submitted:

1. Commercial Vial Label
 - The quantity, 34 mL, has been added to the bottom left section of the vial label.

- The NDC number has been relocated above the product name and the blue bar.
 - The customary preferred statement “Must Be Diluted Prior To Use” has been added to the vial label directly below “For Intravenous Infusion”.
2. SNS Vial Over-Label
- The quantity, 34 mL, has been added to the bottom left section of the vial over-label. The NDC number has been relocated above the product name and the blue bar. The customary preferred statement “Must Be Diluted Prior To Use” has been added to the vial over-label directly below “For Intravenous Infusion”.
 - The statement “For Strategic National Stockpile Use Only” has been added to the bottom left section of the vial over-label.
 - HGS requests clarification regarding the assignment of a different NDC number to the SNS and commercial products. One way to accomplish this is to assign a different product code to each vial (as shown on the labels). Since the product code represents specific strength, dosage form, and formulation and these attributes are identical between the SNS and commercial products, it is not certain that SPL will accept this difference in NDC numbers. (b) (4)
3. Commercial Unit Carton Labeling
- The quantity, 34 mL, has been added to the bottom section of the unit carton principal display panels.
 - The customary preferred statement “Must Be Diluted Prior To Use” has been added to the principal display panels directly below “For Intravenous Infusion”.
 - The HGS company logo has been relocated to the side panel. HGS has been acquired by GlaxoSmithKline; therefore, the Manufactured by statement has been revised to define HGS as a subsidiary of GlaxoSmithKline. In addition, the company logo for GlaxoSmithKline has been added to the side panel.
4. SNS Unit Carton Labeling
- The quantity, 34 mL, has been added to the bottom section of the unit carton principal display panels. The statement “For Strategic National Stockpile Use Only” has been added to the bottom section of the unit carton principal display panels. A different NDC number, 49401-104-01, has been added to the SNS unit carton to distinguish it from the commercial unit carton (49401-103-01). HGS requests clarification on assignment of different NDC numbers (see response to B3 above). The HGS company logo has been relocated to the side panel. HGS has been acquired by GlaxoSmithKline; therefore, the Manufactured by statement has been revised to define HGS as a subsidiary of GlaxoSmithKline. In

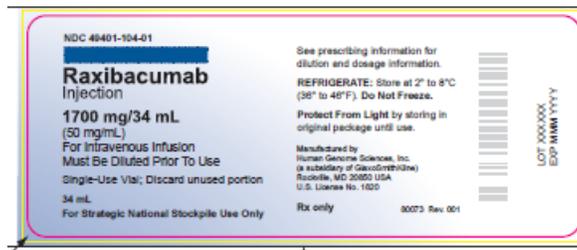
addition, the company logo for GlaxoSmithKline has been added to the side panel. Deferred to DMEPA safety evaluator.

- The customary preferred statement “Must Be Diluted Prior To Use” has been added to the principal display panels directly below “For Intravenous Infusion”.

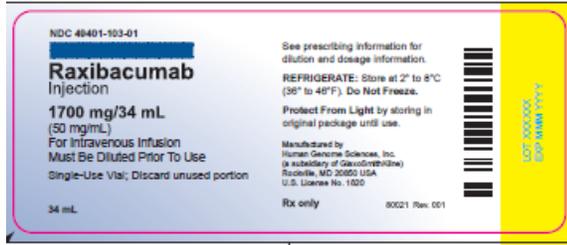


(b) (4)

SNS Vial Label



Commercial Vial Label



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

/s/

KIMBERLY M RAINS
12/10/2012

DAVID M FRUCHT
12/10/2012

PATRICK G SWANN
12/13/2012

PMR/PMC Development Template

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

NDA/BLA #	125349
Product Name:	Raxibacumab
PMR/PMC Description #1:	Conduct a field study to evaluate the efficacy, pharmacokinetics and safety of raxibacumab use for <i>Bacillus anthracis</i> in the United States.
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>6/15/2013</u>
	Study/Trial Completion: <u>To be determined should an event occur</u>
	Final Report Submission: <u>To be determined should an event occur</u>
	Other: <u>N/A</u>

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

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

This study is a required postmarketing study as the approval is under the Animal Rule, where the applicant is required to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical, e.g. during or following an anthrax bioterrorism event.

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

Raxibacumab is being approved under the Animal Rule. Adequate and well controlled efficacy studies in animal models of inhalational anthrax were conducted in lieu of the clinical trials. Safety evaluation of raxibacumab was performed in healthy adult volunteers. The goal of this study to evaluate adverse event (AE) profiles, clinical response, and PK of raxibacumab when the product is used in the treatment of suspected or confirmed inhalational anthrax.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

BLA #	125349
Product Name:	Raxibacumab
PMR/PMC Description #2:	Conduct a Phase 4 Study to evaluate the effect of raxibacumab on immunogenicity of AVA vaccine
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>11/1/2014</u>
	Study/Trial Completion: <u>10/1/2016</u>
	Final Report Submission: <u>10/1/2017</u>
	Other: _____ <u>N/A</u>

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

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

Raxibacumab is an anti-PA monoclonal antibody that could potentially interfere with efficacy of AVA vaccine if administered concomitantly. AVA vaccine and raxibacumab could potentially be administered as part of anthrax postexposure prophylaxis regimen. Raxibacumab will be approved for the indication of treatment of inhalational anthrax and concomitant administration with AVA vaccine is unlikely to be warranted in such scenario, however, raxibacumab is thought to have a favorable benefit-risk profile as postexposure prophylaxis measure particularly in the situations where *B. anthracis* is deemed or found to be multi-drug resistant.

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

The goal of the study is to establish the effect of raxibacumab on immunogenicity of AVA vaccine when administered simultaneously.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

A prospective randomized double blind study to evaluate the effect of raxibacumab on the immunogenicity of AVA vaccine when administered concomitantly relative to AVA vaccine alone.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

BLA #/Product Name: 125349 (raxibacumab)

PMR/PMC Description #3: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/29/2013</u>
	Study/Trial Completion:	<u>11/30/2013</u>
	Final Report Submission:	<u>12/15/2013</u>
	Other:	<u>N/A</u>

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

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

The study will be performed using in-process material obtained during the next manufacturing campaign, which is scheduled to begin in the 3rd quarter of 2012. Therefore, the study cannot be completed prior to BLA approval. The study is appropriate as a PMC because there are bioburden controls for the drug substance manufacturing process.

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

The goal of the study is to evaluate whether endotoxin detection is inhibited during LAL testing of undiluted bulk drug substance samples. This data will supplement the standard LAL method suitability data that was provided in the BLA.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

To 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.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

Reviewer's comment: The sponsor has agreed to perform the study and has provided a timeline, but study design will be discussed further during a teleconference with the review team on 21-Nov-2012.

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 125349
Product Name: raxibacumab

PMR/PMC Description #4: Develop and validate a new (b) (4) assay that has improved sensitivity and capability to detect a greater range of potential (b) (4) contaminants compared to the current assay and to provide this information as a prior approval supplement to the BLA by 6/30/15.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/31/2014
	Study/Trial Completion:	04/30/2015
	Final Report Submission:	06/30/2015
	Other:	N/A

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

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

(b) (4)

(b) (4) We are requesting that HGS improve the sensitivity of their (b) (4) assay such that it can detect more potential (b) (4) contaminants.

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

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Development of an improved (b) (4) assay
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

JANE A DEAN
12/13/2012

SUMATHI NAMBIAR
12/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **December 3, 2012**

To: John Farley, M.D., Acting Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BEN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: **DMPP Review of Patient Labeling: Patient Package Insert (PPI)**

Drug Name (established name): raxibacumab

Dosage Form and Route: Injection for Intravenous Use

Application Type/Number: BLA 125349

Applicant: Human Genome Sciences

1 INTRODUCTION

On May 13, 2009, Human Genome Sciences (HGS) submitted a Biologics Licensing Application (BLA) for raxibacumab, a human monoclonal antibody to the protective antigen of *Bacillus anthracis*, for the treatment of inhalation anthrax. Reference is also made to the Complete Response Letter (CRL) that the Applicant received from the FDA on November 14, 2009.

On June 15, 2012, the Applicant submitted a response to Complete Response Letter (CRL) providing responses addressing, but not limited to the deficiencies identified in the CRL. This review is written in response to a request by the Division of Anti-Infective Products (DAIP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for raxibacumab.

2 MATERIAL REVIEWED

- Draft raxibacumab PPI received on July 28, 2012, and revised by the review division throughout the review cycle and sent to DMPP on November 28, 2012.
- Draft raxibacumab Prescribing Information (PI) received July 28, 2012, revised by the Review Division throughout the current review cycle and received by DMPP on November 28, 2012.

3 REVIEW METHODS

Review of new NDA and BLA Patient Package Insert and Medication Guide submissions will reflect changes to previous patient labeling practice. These changes are designed to decrease the length of patient information while maintaining consistency with the Regulations as specified in 21 CFR 208.20.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our review of the PPI we have:

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
12/03/2012

MELISSA I HULETT
12/04/2012

LASHAWN M GRIFFITHS
12/04/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

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

Memorandum

Date: November 30, 2012

To: Jane Dean RN, MSN, Regulatory Project Manager, DAIP

From: Adora Ndu Pharm.D., Regulatory Review Officer, DCDP

Subject: BLA 125349 DCDP comments for RAXIBACUMAB injection for intravenous use Patient Package Insert (PPI)

OPDP has reviewed the proposed PPI for RAXIBACUMAB injection for intravenous use submitted for consult on July 23, 2012, and offers the following comments.

The version of the draft PPI used in this review is entitled, "draft-labeling_v11-28-12.doc".

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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/s/

ADORA NDU
11/30/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

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

Memorandum

Date: November 27, 2012

To: Jane A. Dean, RN, MSN – Regulatory Health Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products

From: Christine Corser, PharmD. – Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: **Raxibacumab injection, for intravenous use**
BLA #125349

As requested in your consult dated July 12, 2012, DPDP has reviewed the draft Package Insert (PI) for Raxibacumab injection, for intravenous use.

DPDP's comments are based on the proposed, marked-up, substantially complete version of the PI sent to OPDP via email by Jane Dean on November 26, 2012.

The Division of Consumer Drug Promotion (DCDP) will be reviewing the patient package insert, and this review will follow under separate cover.

Thank you for the opportunity to provide comments on this PI.

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/s/

CHRISTINE G CORSER
11/27/2012

**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 [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 IgG₁ 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 cultured in serum-free medium. The drug substance is manufactured at Human Genome Sciences in Rockville, MD. The manufacturing process includes [REDACTED] (b) (4). The bulk drug

substance is [REDACTED] (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), [REDACTED] (b) (4) and administered by intravenous infusion. The diluent is not supplied with the drug product.

Facility Information

[REDACTED] (b) (4)

The process includes:

[REDACTED] (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 [REDACTED] (b) (4) a contract manufacturer that produces multiple CDER-approved products [REDACTED] (b) (4)

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

A CGMP inspection of the [REDACTED] (b) (4) site was conducted by [REDACTED] (b) (4) from [REDACTED] (b) (4) to [REDACTED] (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* [REDACTED] (b) (4)

(b) (4)

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

5. *The manufacturing process is* [REDACTED] (b) (4)
[REDACTED] *produced by the establishment.*

The manufacturing process for raxibacumab drug product is [REDACTED] (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

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 19, 2012
Reviewer: Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis
Acting Team Leader: Chi-Ming (Alice) Tu, PharmD
Division of Medication Error Prevention and Analysis
Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis
Drug Name and Strength: Raxibacumab injection, 1700 mg/34 mL (50 mg/mL)
Application Type/Number: BLA 125349
Applicant/sponsor: Human Genome Sciences, Inc.
OSE RCM #: 2012-1432

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the resubmitted proposed vial labels, carton and package insert labeling for Raxibacumab injection, BLA 125349, for areas of vulnerability that could lead to medication errors. This is a priority review with a 6 month PDUFA clock.

1.1 BACKGROUND AND REGULATORY HISTORY

Raxibacumab is not currently available commercially; however the product is part of the strategic national stockpile (SNS). The current submission contains proposed vial labels, carton labeling and package insert labeling for Raxibacumab injection, BLA 125349, which are meant for commercial marketing and to replace the packaging of the product that is currently in the strategic national stockpile. A prior OSE review #2009-1112, dated November 5, 2009, evaluated the proposed labels and labeling (for commercial use and SNS). Most of the recommendations have been implemented by the Applicant.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 4 and September 5, 2012 label and labeling submission.

- Active Ingredients: Raxibacumab
- Indication of Use: Treatment of patients with inhalation anthrax due to *Bacillus anthracis*
- Route of Administration: Intravenous infusion
- Dosage Form: Injection
- Strength: 1700 mg/34 mL (50 mg/mL)
- Dose and Frequency:
 - Adults: 40 mg/kg as a single intravenous infusion
 - Pediatrics weighing greater than 15 kg and less than or equal to 50 kg: 60 mg/kg as a single intravenous infusion
 - Pediatrics weighing less than or equal to 15 kg: 80 mg/kg as a single intravenous infusion
- How Supplied: (b) (4)
- Storage: Refrigerated

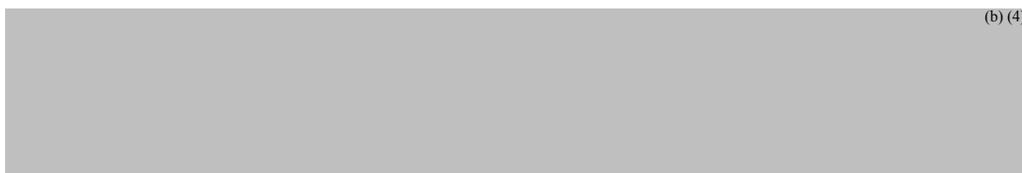
2 METHODS AND MATERIALS REVIEWED

Raxibacumab is not available commercially and is not listed in the FDA FAERS database; therefore DMEPA did not search the database for Raxibacumab medication error reports. We reviewed the proposed Raxibacumab labels and labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Commercial Vial Label submitted September 4, 2012 (Appendix B)
- SNS Vial Over-Label submitted September 4, 2012 (Appendix C)
- Commercial Unit Carton Labeling submitted September 4, 2012 (Appendix D)
- SNS Unit Carton Labeling submitted September 4, 2012 (Appendix E)



- Insert Labeling submitted September 5, 2012
- Recommendations in OSE Review #2009-1112, dated November 5, 2009

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA completed a label and labeling review for Raxibacumab injection, OSE review #2009-1112, on November 5, 2009. Our prior recommendations to revise the strength expression, include the statement “For Intravenous Infusion”, relocate the statement “Single-Use Vial”, add the statement “Discard unused portion”, remove the word (b) (4) relocate the bar code, decrease the prominence of the “manufactured by...” information (b) (4) were implemented. However, in the current submission the Applicant made additional changes beyond what was requested.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The following label and labeling revisions, beyond DMEPA’s recommendations, were noted: the Applicant removed the (b) (4) statement (b) (4) and the statement “For Strategic National Stockpile Use Only” (applicable to SNS labels), relocated the NDC number to a non-customary area on the vial label, added the statement “For Intravenous Infusion (b) (4)” and added the company logo “Human Genome Sciences” (on cartons only). The revisions to the label and labeling have not previously been reviewed and will require alteration due to readability, exclusion of required information, use of non-customary language, and non-customary placement of information.

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

Additionally, in the proposed insert labeling, under the Dosage and Administration section 2.3 Preparation for Administration, the instructions for product preparation are unclear and need further refinement. This section needs to provide the end user with concise and clear step by step directions to prepare the product correctly, our comments are listed below in section 5.1.

Also, Section 8.4, Pediatric Use, (b) (4) and Section 2.2, Dose and Schedule, does not provide dosing directions for children who are under 18 years of age but weigh more than 50 kg. Thus, additional dosing guidance needs to be incorporated into the labeling. This issue was further discussed at a labeling meeting and it was determined that pediatric patients that weigh more than 50 kg should be dosed according to the adult dosing schedule.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to approval of this BLA.

A. Highlights of Prescribing Information Dosage and Administration Section

1. The Dosing and Administration section does not specifically state how to treat pediatric patients that weigh more than 51 kg. Thus, we suggest adding a third pediatric category to read “ (b) (4) 40 mg/kg raxibacumab (preferred) or incorporate this information into Adult dosing section to read (b) (4)
2. In order to avoid the use of overlapping numbers (e.g. 15 kg) and to base the dosing on a whole kilogram numbers, consider revising the sentences (b) (4) to read (b) (4) and (b) (4) to read (b) (4)
3. If it is not appropriate to revise the dosing weight ranges as described in A2 above, then replace the symbols greater than ‘>’, and less than or equal ‘≤’, which are on the Institute for Safe Medication Practices’ (ISMP) list of error-prone abbreviations², with the corresponding description in words “greater than” and “less than or equal” as appropriate.

² Available at: www.ismp.org/tools/errorproneabbreviations.pdf . Accessed October 18, 2012.

B. Full Prescribing Information Dosage and Administration Section

1. Section 2.1, General Information, the statement (b) (4) does not provide clear direction when the prescriber should use the 25 mg dose or the 50 mg or if there is a preferred route of administration. Consider if clinical data support revising this information to provide additional guidance to the practitioner on the preferred dosing and route of administration (e.g. Pediatric patients vs. Adult, and oral vs. intravenous). Or if one dose may be used in all patients then clarify the one appropriate dose and route of administration. This information is also repeated in Section 5.1 and should be revised accordingly.
2. Section 2.2, Dose and Schedule, see A1, A2, and A3 above, additionally consider revising the dosing information for the pediatric patients from the current table format to sentence format similar to the adult dosing statement or bulleted format similar to the Highlights of Prescribing Information.
3. Section 2.3, Preparation for Administration, the first sentence of the first paragraph only specifies the 250 mL volume to be used in the final preparation, (b) (4)

Also the sentence refers only to Sodium Chloride the compatible solution and provides on the adult dose, omitting other compatible solutions and pediatric dosing.

To clarify this information, include reference to all patients and solutions in this section by revising the first sentence:

From:

(b) (4)

Similar to:

The recommended dose of Raxibacumab is weight based, given as an intravenous infusion after further dilution in a compatible solution to a final volume of 250 mL (for adults and children weighing (b) (4) kg or (b) (4) or (b) (4))

4. Section 2.3, Preparation for Administration, the second and third sentences in the first paragraph provide information on (b) (4) compatible (b) (4) solutions in a paragraph format, which may cause confusion or be misread and cause errors. We recommend clarifying this statement by providing the information in a bulleted format (or table), and remove the reference to the (b) (4) to prevent the end user from misreading or misinterpreting this information. Revise the sentence to appear as:

i. Dilute Raxibacumab using one of the following compatible solutions:

- 0.9% Sodium Chloride Injection, USP
- 0.45 % Sodium Chloride Injection, USP

(b) (4)

5. Section 2.3, Preparation for Administration, the last sentence in the first paragraph refers specifically to adult patients. Since we are requesting for this information to be inclusive of all patients, delete the words (b) (4) from the last sentence in the first paragraph, to read: “Follow the steps below to prepare the raxibacumab intravenous infusion solution”.
6. Section 2.3, Preparation for Administration, customarily when providing instructions to end users each step in the preparation process is numbered vs. bulleted as currently proposed. Consider deleting the bullets and instead number each step sequentially. A number sequence of steps is beneficial when referring to a specific step in the preparation process.
7. Section 2.3, Preparation for Administration, the information in the second bullet provides more information than necessary for the end user, which may lead to confusion. At this step, the key information for the reader is the amount of drug (in milliliters) he/she is expected to withdraw from each vial to prepare the dose. To clarify this step, revise the second bullet

From:

(b) (4)

Similar to:

Calculate the required volume in milliliters of raxibacumab injection needed for the dose by dividing the calculated dose in milligrams (from step 1) by the concentration, 50 mg/mL. Each single-use vial allows delivery of 34 mL raxibacumab.

8. Section 2.3, Preparation for Administration, the third bullet specifically refers to (b) (4)

The key information for the reader at this step is to select the appropriate bag, withdraw from the bag the volume equal to the volume calculated in the step above and to discard the withdrawn solution. To clarify this step, revise the third bullet:

From:

(b) (4)

[Redacted] (b) (4)

Similar to:

[Redacted] (b) (4)

9. Section 2.3, Preparation for Administration, the fifth bullet specifically refers to [Redacted] (b) (4)

[Redacted] The key information for the reader at this step is to withdraw the calculated amount of drug and then mix it in the bag. To clarify this step, revise the fifth bullet:

From:

[Redacted] (b) (4)

Similar to:

Transfer the required volume of Raxibacumab injection to the [Redacted] (b) (4)
[Redacted] Gently invert the bag to mix the solution. Do not shake.

C. Full Prescribing Information Dosage Forms and Strengths

1. The presentation of the information in Section 3 is inconsistent with the information in the Highlights of Prescribing Information. We recommend revising this information to state: “This product is available as a single use vial which contains 1700 mg/34 mL (50 mg/mL) of Raxibacumab injection [see Description (11) for details].

D. Full Prescribing Information How Supplied Section

1. Section 16 customarily describes all the packaging configurations for the product. In this case [Redacted] (b) (4) the corresponding NDC number is not listed. We recommend adding this information to the section.

5.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to the approval of this BLA.

A. Commercial Vial Label

1. Add the quantity statement (34 mL) as per 21 CFR 201.51 to bottom section of the principal display panel. This statement was present in the previous submission in a different location but was incorrectly removed in the current submission.
2. Relocate the NDC number to the customary area, at the top one-third of the principal display panel as per 21 CFR 207.35(b)(3). We recommend relocating the NDC number above the product name and the blue bar. The NDC number was present on the commercial vial in this customary location in the previous submission but was incorrectly relocated in the current submission.
3. Change the statement “For Intravenous Infusion (b)(4)” to the customary preferred statement “Must Be Diluted Prior To Use”.

B. SNS Vial Over-Label

1. See A1, A2 (NDC number was not present in the previous submission), and A3 above.
2. Add the statement “For Strategic National Stockpile Use Only” to the bottom of the label. This statement was present in the previous submission but was removed in the current submission.
3. Ensure the NDC number for the SNS product is different than the commercial product.

C. Commercial Unit Carton Labeling

1. See A1 above.
2. See A3 above and relocate the statement below “For intravenous Infusion”.
3. The company logo “Human Genome Sciences” competes for prominence with the name and strength presentation. Decrease the prominence of the logo by decreasing the size and debolding it or relocating it to the side panel.

D. SNS Unit Carton Labeling

1. See A1, B2, B3 and C3 above.
2. See A3 above and relocate the statement below “For intravenous Infusion”.

(b)(4)

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

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APPENDICES

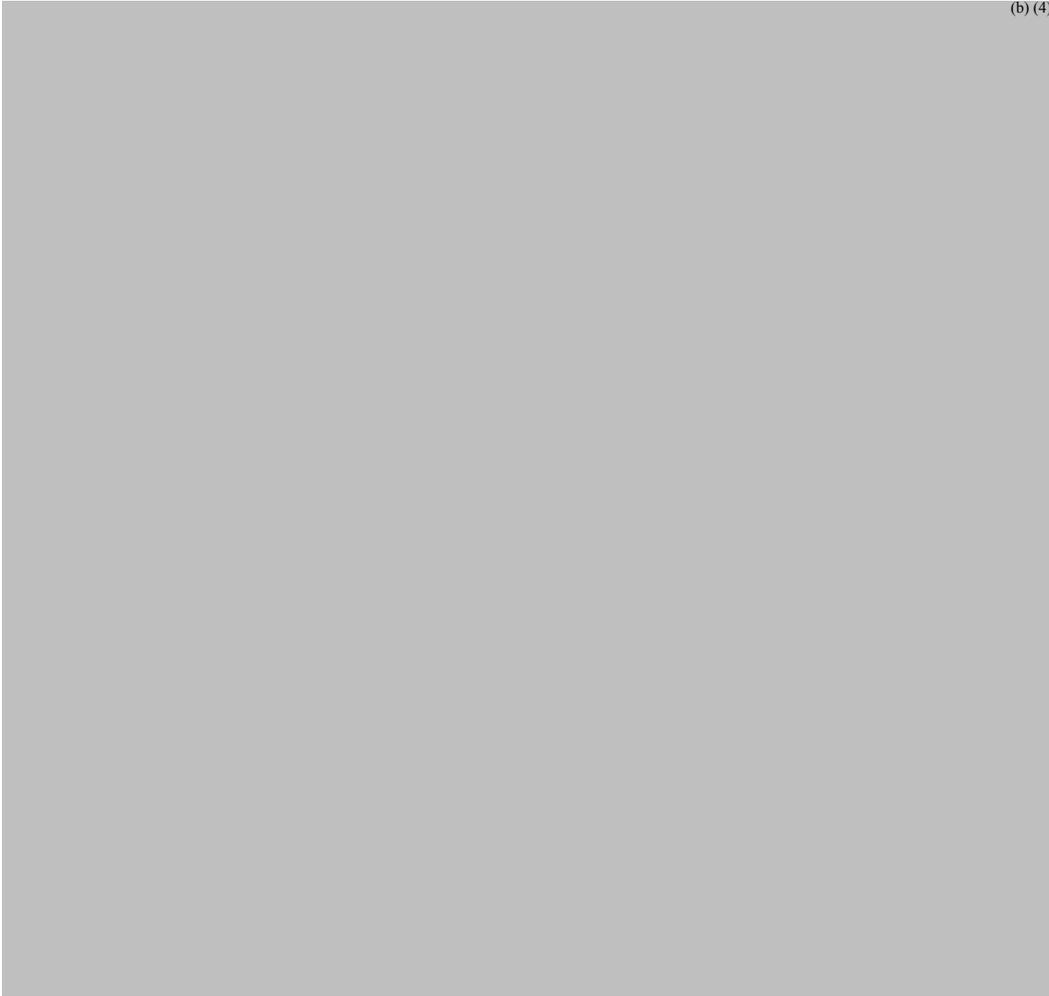
Appendix A. Database Descriptions

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

(b) (4)



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/s/

ALEKSANDER P WINIARSKI
11/19/2012

CHI-MING TU
11/19/2012

SCOTT M DALLAS
11/19/2012



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

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

FINAL LABEL AND LABELING REVIEW

Date: November 9, 2012

Reviewer: Kimberly Rains, Pharm. D.
Office of Biotechnology Products,
Immediate Office

Through: David Frucht, MD
Product Reviewer
Division of Monoclonal Antibodies (DMA)

Patrick Swann, Ph.D.
Deputy Director
Division of Monoclonal Antibodies (DMA)

Application: BLA 125349

Product: Raxibacumab

Applicant: Human Genome Sciences, Inc.

Submission Date(s): June 17, 2009, June 15, 2012, September 5, 2012

Executive Summary

The carton and container labels for Raxibacumab were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 35-NF 30 (8/1/12-11/30/12). Labeling deficiencies were identified, mitigated, and resolved. Comments are listed in the conclusions section. The carton and container labels submitted on September 5, 2012 are acceptable.

Background and Summary Description

STN 125349 for Raxibacumab is a Biologic License Application (BLA) indicated for the treatment of patients with inhalation anthrax due to *B. anthracis*. The product is currently held in the Strategic National Stockpile (SNS) under IND and is labeled with

STN 125349/0

agency approved exemptions. The BLA contains commercial labels and overlabels that will be applied to the approved IND labeled product upon approval. The product is supplied as 1700 mg/ 34 mL (50mg/ml) single-use glass vials. The application received a Complete Response on November 14, 2009. Revised labels were submitted with resubmitted data for review.

Materials Reviewed:

Raxibacumab

Container labeling-commercial label and overlabel for SNS stock

Carton – (b) (4)

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/s/

KIMBERLY M RAINS
11/09/2012

DAVID M FRUCHT
11/14/2012

PATRICK G SWANN
11/14/2012

MEMORANDUM

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

DATE: Oct 26, 2012

TO: John Farley, M.D.
Director, Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR covering BLA 125-349, Raxibacumab, from
Human Genome Sciences

At the request of the Division of Anti-Infective Products (DAIP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an inspection of the analytical portion of the following study, specifically for ciprofloxacin measurements:

HGS1021-C1064: "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."

The bioanalysis of ciprofloxacin for study HGS1021-C1064 was conducted at [REDACTED] (b)(4)

[REDACTED] This was a re-analysis of samples from Study HGS1021-C1064 for ciprofloxacin. The original analysis was conducted at [REDACTED] (b)(4)

The inspection by OSI at [REDACTED] (b)(4) identified a number of

significant deficiencies in the study. Subsequently, the sponsor contracted with (b)(4) to re-assay all study samples for ciprofloxacin using a new assay developed by (b)(4). The purpose of this inspection was to confirm data quality and integrity for the re-assayed samples.

The audit was conducted by ORA investigator, (b)(4), and DBGC/OSI scientist, Seongeun Julia Cho, from (b)(4). The audit included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

Following the inspection, Form FDA-483 containing two inspectional observations was issued (**Attachment 1**). The firm's response has not been received as of this review. If correspondence is received, DBGC will evaluate it, inform DAIP, and amend the review as appropriate. The Form FDA-483 observations and our evaluation follow:

1) Failure to conduct the following validation studies for the LC/MS/MS method used to analyze ciprofloxacin in study plasma samples:

- Freeze/thaw stability
- Processed sample stability/Reinjection reproducibility
- Blank matrix selectivity

During the original validation, (b)(4) established 3-cycle freeze-thaw stability and blank matrix selectivity in human plasma containing sodium heparin as an anticoagulant. Because Study HGS1021-C1064 collected plasma samples with K3-EDTA, (b)(4) is in the process of conducting freeze-thaw stability and matrix selectivity testing using human plasma containing K3-EDTA. (b)(4) is also conducting processed sample stability and reinjection reproducibility testing, under conditions consistent with the study procedures and conduct. DAIP and OCP should evaluate these additional data when the sponsor submits them.

2) Failure to implement electronic system access control to ensure data security.

Specifically, the policy for using AB Sciex Analyst software which was in place at the time of this study did not prohibit personnel from making changes to electronic documents without signing in as the owner of the changes. Although Analyst required a unique user name and password, during data acquisition, the computers were accessible by a common account and password shared by (b)(4) employees.

(b)(4) informed us that (b)(4) current practice is that instrument computers connected to LC/MS/MS are accessible by employees via a common account and a password, which are shared among all (b)(4) employees. This was instituted because of an incident in which logging-out of the acquisition software Analyst during analytical runs caused a disruption of the run. (b)(4) stated that they are aware of data security concerns with this practice and will further try to improve data security and the computer log-in practice.

While the firm's practice on electronic data access control is objectionable, we did not find evidence that data integrity for the audited study was compromised, and therefore this observation would not likely have impact on study outcome.

In addition to inspectional observations cited in Form FDA-483, the review division also should note that the long-term frozen storage stability of ciprofloxacin in human plasma with K3 EDTA anticoagulant covers 239 days as of this writing. (b)(4) stated that long-term stability testing in human plasma with K3 EDTA matrix, covering the entire sample storage period for study HGS1021-C1064, will be completed in June, 2013, and that the data will be submitted to the sponsor.

With respect to the history of sample shipment, it was learned through a correspondence between (b)(4) and Human Genome Sciences that among the total of 1812 samples analyzed by (b)(4) for this study, 219 samples were previously shipped to (b)(4) as a part of the original analysis. Human Genome Sciences has provided (b)(4) with the list of samples shipped to (b)(4) and the number of thaws for each sample (Attachments 2 and 3). It should be noted that Human Genome Sciences did not have freeze/thaw information for the above mentioned 219 samples for the period they were at (b)(4) lab. We recommend that **the OCP reviewer evaluate the significance of the lack of this information on the accuracy of the reported data and the bioequivalence assessments.**

Summary and Conclusion:

- 1. Lack of data on freeze/thaw stability, blank matrix selectivity, long-term matrix stability, and processed sample stability/reinjection reproducibility**

The firm should submit data of these validations to the Agency. The review division should confirm the accuracy of reported data in the submission when these validation data become available and evaluate the potential impact on study outcome.

2. Failure to implement electronic system access control to ensure data security.

Although it is objectionable that the security of electronic records and acquisition systems did not comply with 21 CFR Part 11 requirements, it is this reviewer's opinion that this observation did not negatively affect integrity of data in the audited study.

3. Lack of sample tracking information on 219 samples during the custody period at (b)(4) lab.

In the opinion of this reviewer, there are two possible options that the review division may consider: (1) Reanalyze study data after excluding results from the 219 samples; or (2) Have the firm conduct stability testing with additional freeze-thaw cycles to cover the possibility of undocumented events at (b)(4) lab.

Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI: (b)(4)

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Biswas/Dejernet/CF
OCP/DCP4/Lazor/Reynolds/Ryan Owen/Kimberly Bergman
OND/OAP/DAIP/John Farley/ Jane Dean
ORA/ (b)(4)

Draft: SC 10/26/2012
Edit: MFS 10/26/2012;SHH 11/07/2012
OSI: BE6357; O:\Bioequiv\EIRCover\125349.cov.cip.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good

Page 5 - BLA 125-349, Raxibacumab

Laboratory Practice Compliance/Electronic Archive/BEB
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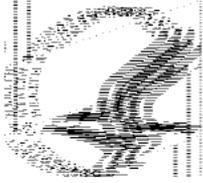
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/s/

SEONGEUN CHO
11/07/2012

SAM H HAIDAR
11/07/2012

WILLIAM H TAYLOR
11/08/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Pediatric and Maternal Health Staff Memorandum

Date: October 23, 2012 Consult Date: August 8, 2012

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Sachs, MD, Team Leader – Pediatrics
Pediatric and Maternal Health Staff

Lynne Yao, MD, Acting OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

PMHS PM: George Greely

To: Division of Anti-Infective Products (DAIP)

BLA: 125349

Drug: Raxibacumab injection, for intravenous injection

Sponsor: Human Genome Sciences

Drug Class: Human monoclonal antibody against the protective antigen protein of
Bacillus anthracis

Consult Request: The Division of Anti-Infective Products (DAIP) requests guidance on the inclusion of pediatric dose-modeling data in Raxibacumab labeling in the absence of pediatric data, which cannot be collected without the occurrence of a counterterrorism event.

INTRODUCTION

On June 15, 2012, Human Genome Sciences submitted a Complete Response submission for Raxibacumab, BLA 125349, for the treatment of inhalation anthrax. The BLA was initially submitted on May 13, 2009, under 21 CFR 601, Subpart H (Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible, (also known as the “Animal Rule”)) and received a Complete Response on November 14, 2009. Orphan designation was granted on November 12, 2003.

The Division of Anti-infective Products (DAIP) consulted the Pediatric and Maternal Health Staff (PMHS) – Pediatrics for guidance on the inclusion of pediatric dose-modeling data in Raxibacumab labeling in the absence of pediatric data, which cannot be collected without the occurrence of a counterterrorism event.

BACKGROUND

Raxibacumab is a human monoclonal antibody to the protective antigen (PA) of *Bacillus anthracis*. Raxibacumab is available as a single-dose intravenous infusion that should be administered as soon as a diagnosis of inhalation anthrax is suspected or made. Efficacy studies were conducted under the Animal Rule (21 CFR 601, Subpart H) in rabbits and monkeys, as efficacy studies in humans were not ethical or feasible. Pharmacokinetic and safety data was collected in both animals and in healthy adults. Human Genome Sciences developed pediatric dose recommendations by simulating pediatric drug exposures from the available animal and human adult pharmacokinetic data using various dose modeling methods and information found in published literature.¹ It should be noted that FDA independently established dosing recommendations for children based on these modeling and simulation methods and that these doses were comparable to the doses identified by the applicant.

DISCUSSION

Under 21 CFR 601, Subpart H, FDA may grant marketing approval for a biological product for which safety has been established and the results of adequate and well controlled studies in animals demonstrate that the product is likely to have clinical benefit in humans. 21 CFR 601, Subpart H applies to certain biological products that have been studied for their safety and efficacy in ameliorating or preventing serious and life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. Definitive efficacy studies cannot be conducted in humans because it is not ethical or feasible to expose healthy adults to any of these potentially lethal and/or disabling substances. Approval under 21 CFR 601, Subpart H is subject to three requirements:

1. Postmarketing studies, such as field studies, must be conducted to verify and describe the biological product’s clinical benefit and to assess its safety when used as indicated when studies are ethical and feasible (e.g., accidental or hostile exposure). The plan for postmarketing studies must be included with the BLA submission.

¹ See Summary of Clinical Pharmacology Studies, submitted June 15, 2012

Reviewer Comment: The Applicant has submitted a phase four post-marketing protocol

(b) (4)

2. Approval with restrictions to ensure safe use:

- Distribution restricted to certain facilities or to healthcare practitioners with special training or experience
- Distribution conditioned on the performance of specified medical procedures, including medical follow-up
- Distribution conditioned on specified record-keeping requirements

3. Provision of patient information

Pediatric Assessment

A pediatric assessment requires dosing, safety, and efficacy data in order to grant a pediatric indication for a drug or biological product. Lacking safety and efficacy data, pediatric dosing information is generally not included in a product's labeling. Medical countermeasure products, such as Raxibacumab pose a labeling dilemma because it is not ethical or feasible to obtain dosing, safety, and efficacy data in the absence of an event; however, if an event occurs, the product is likely to be used in pediatric patients and clinicians using the product need access to available information to inform their use of the product.

Reviewer Comment: Because of the inability to obtain pediatric data on raxibacumab, lacking an event, PMHS believes it is important to include dose-modeling information in labeling to adequately inform clinical use, as the product will likely be used in pediatric patients following an accidental or intentional exposure to anthrax. There are no other potential uses for raxibacumab because of its specific mechanism of action, and the product will be available only through the Strategic National Stockpile (SNS).

Pediatric Use Labeling

The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. 21 CFR 201.57(c)(9)(iv) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Reviewer Comment: Subsection 8.4 Pediatric Use should clearly describe raxibacumab has not been studied in the pediatric population; pediatric dosing information has been derived through modeling and simulation; and a description of pediatric dosing and administration. Lacking a pediatric indication, this information should not appear in

section 2 DOSAGE AND ADMINISTRATION or SECTION 12 CLINICAL PHARMACOLOGY. It would be acceptable to place cross-references to subsection 8.4 in these two sections to direct the clinician to the complete raxibacumab pediatric use information.

CONCLUSIONS AND RECOMMENDATIONS

On September 18, 2012, a teleconference was held with participants from DAIP, PMHS, and the Office of Pediatric Therapeutics/Pediatric Ethics. All participants agreed that the pediatric dose-modeling data should be placed in Raxibacumab labeling in order to inform use of the product in the pediatric population in the event of an Anthrax event (accidental or intentional). This information should be placed only in subsection 8.4 *Pediatric Use*. While it is not usual to provide pediatric dosing information without an indication; this approach is being used to provide important information to prescribers. PMHS, OPT, and DAIP all agree that pediatric dosing recommendations are based on modeling and simulation, and not based on clinical data. Therefore, it would be inappropriate to provide an indication in children or dosing information in section 2.2, though it is arguable that this approach is not completely satisfactory. Nevertheless, in the event of a public health emergency, any dosing information in children would be of benefit because of the high likelihood that this product would be used in children. A field study to collect safety and efficacy data in adult and pediatric patients will be conducted in the event of accidental or intentional anthrax exposure.

Raxibacumab was also discussed at PeRC on October 10, 2012 and PeRC members concurred with placing pediatric dosing information in labeling.

Pediatric Use Labeling Recommendations

See Appendix A for the DAIP proposed Raxibacumab pediatric use labeling. PMHS has made revisions to this proposed pediatric use labeling as listed below. All pediatric use information should be placed in subsection 8.4 Pediatric Use, and not placed in other sections of labeling.

2 DOSAGE AND ADMINISTRATION Section

2.2 Dose and Schedule

[REDACTED] (b) (4)

[REDACTED] (b) (4)

8.4 Pediatric Use

[REDACTED] (b) (4)

[REDACTED] (b) (4)

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/s/

JEANINE A BEST
10/23/2012

HARI C SACHS
10/24/2012
I agree with these recommendations.

LYNNE P YAO
11/05/2012



MEMORANDUM TO FILE

Office of Pediatric Therapeutics
Office of the Commissioner
10903 New Hampshire Ave, WO32-5126
Silver Spring, MD 20993-002
Tel (301) 796-8665; FAX (301) 847-8619

Date: October 9, 2012

From: Robert M. Nelson, M.D., Ph.D., Senior Pediatric Ethicist/Deputy Director
Michelle D. Roth-Cline, M.D., Ph.D., Pediatric Ethicist/Health Scientist
Office of Pediatric Therapeutics, OC

Through: M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics, OC

To: John Alexander, M.D., Lead Medical Officer
Division of Anti-Infective Products, CDER

Re: **BLA 125,349—Raxibacumab Pediatric Dosing**

Background

Raxibacumab is a fully humanized monoclonal antitoxin product developed for the therapeutic treatment of patients with inhalational anthrax due to *Bacillus anthracis*. It is currently being considered for an approval action in adults based on the animal rule. The Animal Rule (21 CFR 314.600, subpart I; 21 CFR 601.90) requires that safety has been established and that efficacy is demonstrated in adequate and well-controlled animal studies. The BLA package includes a safety and pharmacokinetic study of 326 adult volunteers as well as several studies using animal models of anthrax disease.

According to the division, raxibacumab demonstrated efficacy in a monotherapy study using an appropriate animal model. A study looking at the added benefit of raxibacumab to the use of appropriate antibiotics showed a trend in the direction of added efficacy. A study of possible neurological toxicity showed no direct toxicity from the experimental product. As the sponsor will not be able to evaluate the product in children other than those with anthrax, FDA's Office of Clinical Pharmacology helped to model a pediatric dose based on adult data to be used in support of a possible Emergency Use Authorization (EUA). The sponsor has proposed to include this dosing in the product labeling, even though the product has never been given to a child. Raxibacumab for this indication was granted an Orphan Designation, and thus an approval action for this indication does not trigger required pediatric studies under the Pediatric Research Equity Act (PREA). An advisory committee meeting is scheduled for November 2.

One of the requirements following approval under the animal rule is a postmarketing field study to verify benefit and assess safety. The sponsor has submitted a phase four post-marketing protocol that would include both adult and pediatric patients who are treated with raxibacumab for inhalational anthrax in the event of a bioterror attack in which patients were exposed. The primary endpoint of the protocol is to evaluate survival, and a secondary purpose is to obtain pharmacokinetic data that would validate the modeling of the pediatric dose.

Questions

1. Is there a way to label raxibacumab pharmacometric modeled dosing for pediatric patients in the absence of pediatric data, which will not be collected until the counterterrorism event occurs?
2. Can a field study required after approval under the Animal Rule regulations that includes pediatric subjects be considered as an equivalent of a dedicated pediatric study to confirm modeled PK and collect safety and efficacy data on raxibacumab for the treatment of anthrax in pediatric patients?
3. What are the alternative ways to inform healthcare provider in the field about the modeled pediatric dosing?

Discussion:

Generally, it is unusual to put pediatric dosing information in a label absent an approved pediatric indication and absent clinical trial data in support of the pediatric dosing information. However, in this case there are considerations that argue in favor of placing pediatric dosing in the label in spite of the absence of clinical confirmation of the modeled dose. First, the inclusion of the modeled pediatric dosing in the label would establish the requirement that the dosing be confirmed in a phase four postmarketing protocol. Absent this requirement, FDA may be unable to obtain clinical data in support of the modeled pediatric dose since the adult indication has been granted orphan status and thus PREA is not triggered. Secondly, once the product is approved, clinicians will be able to use the product “off-label” in children whether or not any dosing information is provided. As a practical matter, the product may only be available through the Strategic National Stockpile, which would create a centralized mechanism by which the use of the product could be tracked and monitored. Such tracking would be essential if we are to obtain opportunistic pharmacokinetic data in order to verify the modeled pediatric dosing. Finally, the availability of the modeled pediatric dosing in the approved label would assist in the dissemination of appropriate dosing guidelines for use by clinicians in the event of an anthrax outbreak.

The product would not have an approved pediatric indication. Accordingly, all modeled pediatric dosing information should be contained in section 8.4 of the product label rather than in the dosing section. We recommend this step to avoid confusing practitioners given the lack of any clinical data in support of the modeled pediatric dose. The language in section 8.4 should make it clear that the dosing recommendation is based on modeling, that there are no pediatric clinical data, and that the modeled dose needs to be confirmed in the clinical setting. We may want to describe the requirement for post marketing verification of the pediatric dosing, and encourage clinicians to inquire about the appropriate protocol that must be in place to obtain the required data if an anthrax event were to occur.

The distribution and administration of raxibacumab to pediatric patients may not require an EUA. The evidentiary standard for establishing an EUA is that it is “reasonable to believe [that the product] may be effective” and that the “benefits outweigh the risks.” In addition, there must be no adequate approved alternatives. Given the absence of any clinical pediatric data, it is unclear to us that the product would meet this evidentiary standard. As this product is intended for the treatment of established anthrax disease, raxibacumab would most likely be administered by hospital personnel (i.e., physicians and/or nurses working under the supervision of physicians) who would be licensed and /or authorized to use the product for any indication (including off-label pediatric use). As such, it is unclear that an EUA is needed to allow for “unapproved use of an approved product”, as the off-label

pediatric use of the approved product would likely fit within the clinical discretion afforded appropriately licensed medical personnel.

We know the difficulties associated with conducting a clinical trial in the setting of an actual anthrax event. As such, considerable flexibility should be allowed in the implementation and conduct of the clinical protocol. This may be especially true for the pharmacokinetic portion of the study. Scavenged samples or sparse sampling may be options for maximizing the opportunity to obtain pharmacokinetic samples. Presumably, the clinical benefit of the product can be verified using an endpoint of all-cause mortality. (b) (4)



Finally, we have considered whether it would be appropriate to study the pharmacokinetics of raxibacumab to validate the modeled pediatric dosing in children who do not have inhalational anthrax. Single-dose pharmacokinetic studies have been conducted under 21 CFR 50.53 using children that do not currently have the disease but are considered to be at risk for the disease. This category of research requires that the risks of administration of the experimental product be no more than a minor increase over minimal risk, and that the information collected must be important to either understand or ameliorate the child's condition of being "at-risk" for the disease. In other words, the risk of administering raxibacumab to a child must be only slightly greater than the risks of visiting their pediatrician for routine health care, or of routine activities that a parent may permit during daily life.

We did not review the safety data in order to make an independent assessment of whether the administration of raxibacumab to pediatric subjects would meet this minor increase standard. Without such a review, it is unclear to us whether safety data on 326 healthy adult volunteers is sufficient to support the judgment that the risk of administering this product to a child without anthrax disease is only slightly more than the risk of visiting their pediatrician for routine health care. In addition, we are unable to comment on whether experience with the use of other monoclonal antibodies would inform this risk assessment. Given the public attention garnered by the recent proposal to do a pre-event pediatric study of anthrax vaccine, we anticipate that any proposal to study the pharmacokinetics of raxibacumab in the absence of an anthrax event would be similarly controversial. In addition, good scientific and/or practical justification would be needed as to why such data must be obtained in a pre-event setting. One potential justification might include a lack of confidence in the modeled pediatric doses, such that additional PK data would be necessary in a pre-event setting to ensure that children would receive an adequate dose in the event of an attack. However, absent significant scientific uncertainty about the dose, we would find it hard to justify a pre-event study.

Summary Recommendations

- The modeled pediatric dosing recommendations should be included in the approved label, along with the caveat that these recommendations are not based on any clinical data. This step would

enable FDA to require the verification of the pediatric dosing recommendations in a postmarketing pediatric study.

- We recommend that the administration of raxibacumab in a postmarketing setting should be done outside of any protocol (i.e., off-label). The required postmarketing studies should be designed to include only clinical data collection and opportunistic pharmacokinetic sampling to facilitate rapid IRB review and approval. Pharmacokinetic data may be obtained using scavenged samples or sparse sampling, and routine clinical follow-up data may be obtained per standard of care. This approach would be similar to the opportunistic collection of pharmacokinetic data that has been proposed for other medications that have extensive off-label pediatric use.

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/s/

MICHELLE ROTH-CLINE
11/08/2012

ROBERT M NELSON
11/08/2012

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125349

Name of Drug: raxibacumab (injection)

Applicant: Human Genome Sciences, Inc.

Labeling Reviewed

Submission Date: September 5, 2012

Receipt Date: September 5, 2012

Background and Summary Description:

Raxibacumab is submitted for the treatment of patients with inhalational anthrax due to *B. anthracis*. The original new application was submitted on May 13, 2009. Human Genome Sciences (HGS) received a Complete Response Letter (CRL) from the FDA on November 14, 2009. Permission was granted by the FDA on November 17, 2010, for a 2-year BLA filing extension. HGS submitted their resubmission as a complete response on June 15, 2012.

On August 10, 2012, an email was sent to HGS apprising them of minor formatting changes that were needed to their label in order to be compliant with the Physician's Labeling Rule. This amendment corrects the deficiencies.

Review

The submitted labeling was reviewed in accordance with the Physician's Labeling Rule (PLR) formatting requirements.

Recommendations

All SRPI format deficiencies of the PI that were communicated to HGS via email on August 10, 2012, were corrected. This resubmitted PI will be used for further labeling review.

Jane A. Dean, RN, MSN
Regulatory Project Manager

July 6, 2012
Date

Frances V. LeSane
Chief, Project Management Staff

Date

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/s/

JANE A DEAN
09/07/2012

FRANCES V LESANE
09/12/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125349

Application Type: Resubmission of BLA after a Complete Response Letter

Name of Drug: raxibacumab (injection)

Applicant: Human Genome Sciences

Submission Date: June 15, 2012

Receipt Date: June 15, 2012

1.0 Regulatory History and Applicant's Main Proposals

Raxibacumab is submitted for the treatment of patients with inhalational anthrax due to *B. anthracis*. The original new application was submitted on May 13, 2009. Human Genome Sciences (HGS) received a Complete Response Letter (CRL) from the FDA on November 14, 2009. Permission was granted by the FDA on November 17, 2010, for a 2-year BLA filing extension. HGS submitted their resubmission as a complete response on June 15, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Appendix 4.0.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant via email. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 1, 2012. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
- NO** 2. 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 granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Comment: HIGHLIGHTS OF PRESCRIBING INFORMATION section is more than one half page.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

- YES** 4. White space must be present before each major heading in HL.

- NO** 5. 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).

Comment: 1st bullet under **DOSAGE AND ADMINISTRATION** does not have the numerical identifier.

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

Selected Requirements of Prescribing Information (SRPI)

- RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Highlights Limitation Statement

NO 9. 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).**”

Comment: Drug product name is in lower case in both instances.

Product Title

YES 10. Product title in HL must be **bolded**.

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Boxed Warning

N/A 12. All text must be **bolded**.

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

18. Must be listed in the same order in HL as they appear in FPI.

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year)

Selected Requirements of Prescribing Information (SRPI)

format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

- N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Indications and Usage

- NO 21. 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)].”

Comment: Statement is broken into two sentences.

Dosage Forms and Strengths

- N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Contraindications

- YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.
24. Each contraindication is bulleted when there is more than one contraindication.

N/A

Adverse Reactions

- YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Patient Counseling Information Statement

- YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Revision Date

- YES 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Contents: Table of Contents (TOC)

GENERAL FORMAT

Selected Requirements of Prescribing Information (SRPI)

- YES** 28. A horizontal line must separate TOC from the FPI.
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
- YES** 34. When a section or subsection is omitted, the numbering does not change.
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
- YES** 37. All section and subsection headings and numbers must be **bolded**.
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information (SRPI)

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

- NO** 39. 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.

Comment: It is included as 17.4

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it

Selected Requirements of Prescribing Information (SRPI)

is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Patient Counseling Information

- NO** 48. 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)”

Comment: Missing information in the parentheses

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/s/

JANE A DEAN
08/17/2012

FRANCES V LESANE
09/07/2012

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125349

Name of Drug: raxibacumab (injection)

Applicant: Human Genome Sciences, Inc.

Labeling Reviewed

Submission Date: June 15, 2012

Receipt Date: June 15, 2012

Background and Summary Description:

Raxibacumab is submitted for the treatment of patients with inhalational anthrax due to *B. anthracis*. The original new application was submitted on May 13, 2009. Human Genome Sciences (HGS) received a Complete Response Letter (CRL) from the FDA on November 14, 2009. Permission was granted by the FDA on November 17, 2010, for a 2-year BLA filing extension. HGS submitted their resubmission as a complete response on June 15, 2012.

Review

The submitted labeling was reviewed in accordance with the Physician's Labeling Rule (PLR) formatting requirements.

Recommendations

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 1, 2012. The resubmitted PI will be used for further labeling review.

Jane A. Dean, RN, MSN
Regulatory Project Manager

July 6, 2012

Date

Frances V. LeSane
Chief, Project Management Staff

Date

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/s/

JANE A DEAN
08/17/2012

FRANCES V LESANE
09/07/2012

MEMORANDUM

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

DATE: August 28, 2012

TO: Director, Investigations Branch

(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority PDUFA BLA, Pre-Approval Data
Validation Inspection** Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: BLA 125-349
DRUG: Raxibacumab
SPONSOR: Human Genome Sciences
14200 Shady Grove Road
Rockville, MD 20850, USA

This memo requests that you arrange for inspection of the analytical portion of the following bioanalytical study. **A DBGLPC scientist with specialized knowledge will participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC upon receipt of this assignment to arrange scheduling of the inspection. Following the identification of the investigator, background materials will be forwarded directly. The inspection should be completed before October 1, 2012.**

Clinical Study Number: HGS1021-C1064

Bioanalytical Report#: 8224813

Study Title: "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."

Analytical Site:

(b) (4)

Sample Analysis:

(b) (4)

Contact Person:

(b) (4)

Methodology:

LC/MS-MS

Extraction Method:

(b) (4)

Analytes Assayed:

Ciprofloxacin

Internal Standard used:

(b) (4)

Special Conditions:

Sensitive to light

Matrix:

Human Plasma

Anticoagulant:

K₃EDTA

Please note that this is a follow-up inspection for confirmation of data integrity. The original bioanalysis was performed at

(b) (4)

Subsequently, a new method to measure ciprofloxacin concentrations in human plasma was developed by (b) (4) to reassay samples from Study HGS1021-C1064 and to address the deficiencies listed below, which were identified during the previous DBGLPC inspection of the original bioanalytical site:

1. Failure to demonstrate the accuracy and precision of the assay method used for ciprofloxacin analysis and to validate matrix effect, selectivity, extraction recovery, anti-coagulant effect between EDTA and CPD, and stability experiments such as stock solution, auto-sampler and processing of analytes in matrix.
2. Failure to demonstrate assay reproducibility.
3. Failure to follow the study SOP to reject batches when QCs did not meet the acceptance criteria.

4. Failure to use separate stock solutions for preparation of QCs and calibration standards used in the validation and analytical runs.

5. Failure to establish adequate written procedures to ensure the accuracy and integrity of study conduct.

6. Failure to fully document all aspects of study conduct like sample processing, sample movement from freezer and study related correspondence

Please examine the data from (b)(4) and confirm that the above listed deficiencies were not repeated. Please also comment on or address the following items during the inspection:

- All materials related to the analytical method used for the measurement of ciprofloxacin concentrations in human plasma.
- The accuracy of the sponsor's data submitted with the study.
- The analytical data provided in the BLA submissions should be compared with the original documents at the site.
- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC accuracy and precision, at least one demonstration of accuracy and precision of standards and QCs prepared from separate stock solutions, subject samples were analyzed within the established storage stability**
- **Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.**
- **Preparation of quality control samples (QCs) and calibration standards in matrix with same anticoagulant as the study samples.**
- **Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered stability of reanalyzed subject samples.**

In addition to the standard investigation involving the source documents, the files of correspondence between the analytical sites and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, additional study specific instructions and questions may be provided by DBGLPC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further follow-up instructions before the inspection regarding any data anomalies or questions noted during review of study reports. The ORA investigator should contact the DBGLPC POC for inspection related questions or clarifications.

Please FAX/Email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, the violations appear to warrant an OAI classification, please notify the assigned DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written responses as soon as you receive to Sam Haidar and DBGLPC POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC Point of Contact: Gopa Biswas, Ph.D.
(301) 796-4167
Email: gopa.biswas@fda.hhs.gov

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Biswas/Dejernett/CF

(b) (4)

OND/OAP/DAIP/Dean, Jane/Farley, John J.
Draft: GB 08/17/2012
Edit: AD 08/23/2012, WAH 08/28/2012
OSI: BE6357; O:\BE\assigns\bla125349.doc
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
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/s/

GOPA BISWAS

08/28/2012

Dr. Taylor signing on behalf of Dr. Haidar

WILLIAM H TAYLOR

08/28/2012

MEMORANDUM

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

DATE: July 27, 2012

TO: Director, Investigations Branch

(b)(4)

FROM: Charles R. Bonapace, Pharm.D.
Acting Chief, Good Laboratory Practice (GLP) Branch
Division of Bioequivalence and Good Laboratory
Practice Compliance (DBEGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance (OC)

SUBJECT: FY 2013, **PDUFA GLP Directed Inspection**, Bioresearch
Monitoring, Human Drugs, CP 7348.808

RE: BLA-125349

DRUG: Raxibacumab (HGS 1021, ABthrax™, PA mAb, Human
Monoclonal Antibody Against the Protective
Antigen Protein of *Bacillus anthracis*)

SPONSOR: Human Genome Sciences, Inc. (HGS)
14200 Shady Grove Road
Rockville, MD 20850

The Division of Anti-Infective Products (DAIP) requests that arrangements be made for conducting inspections of the following two GLP studies subject to both GLP regulations (21 CFR Part 58) and the Animal Efficacy Rule [Federal Register 67(105): 37988-37998, 5/31/02; 21 CFR 314.600], conducted by the Battelle Biomedical Research Center (West Jefferson, OH, in-life facility) and by the Battelle Memorial Institute (Columbus, OH, histopathology). DAIP wants these studies inspected to verify compliance with 21 CFR Part 58 and to confirm the data integrity. Since there is no clinical trial data available demonstrating the efficacy of raxibacumab against anthrax in humans, DAIP will be relying on the inspected nonclinical data from these GLP studies to support this indication in humans. These studies are considered pivotal to support the BLA under review at CDER. **The inspections should be completed prior to October 26, 2012.**

Preannouncement of our intent to inspect should not be made.

STUDY #1:

1103-G923704: "Evaluation of Raxibacumab as a Therapeutic Treatment against Inhalation Anthrax in the New Zealand White Rabbit Model"

Study Initiation Date: June 7, 2010

Final Report Date: February 21, 2012

Battelle Study Director: Daniel C. Sanford, Ph.D.

STUDY #2:

1141-CG920871: "Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model"

Study Initiation Date: January 10, 2011

Final Report Date: May 21, 2012

Battelle Study Director: Gabriel T. Meister, Ph.D.

The in-life portions of both these studies were conducted at:

Battelle Biomedical Research Center (BBRC)
1425 State Route 142
West Jefferson, OH 43162-9647
(FEI Number: 1000220376)

The histopathology portions of both studies were conducted at:

Battelle Memorial Institute (BMI)
505 King Avenue
Columbus, OH 43201
(FEI Number: 1523658)

Three CDER scientists (two OSI Pharmacologists and a Veterinary Pathologist) will participate in this inspection to provide scientific and technical expertise. Please contact OSI for background materials and to coordinate the inspection schedule.

The inspection conducted at Battelle's West Jefferson, OH facility should focus on the primary measures of these studies:

- Verification of exposure to *B. anthracis* challenge (aerosol characteristics and dosimetry)
- Toxemia

- Bacteremia (counts of *B. Anthracis* in the blood and identification in cultures)
- Identification of tissue/cell distribution of inhaled *B. anthracis*
- Identification of surviving *B. anthracis* and raxibacumab sensitivity (minimal inhibitory concentrations [MIC]) in specimens from rabbits found dead and sacrificed prior to and at the end of each study
- Pharmacokinetics of raxibacumab and Protective Antigen in the absence (Study 1103-G923704) and presence (Study 1141-CG920871) of levofloxacin in New Zealand White Rabbits
- Pharmacokinetics of levofloxacin in New Zealand White Rabbits (for Study 1141-CG920871)

The inspection conducted at Battelle's King Avenue facility in Columbus, OH should focus on the audit of the histopathology portion of Study 1103-G923704. The CDER Veterinary Pathologist should read the slides from Study 1103-G923704 and compare the findings to source records and pathology reports to find out if there are any discrepancies in observations.

In addition, the CDER Veterinary Pathologist should scrutinize pertinent Standard Operating Procedures (SOPs) and inspect the actual conduct of the training program for histology technicians to all procedures of technical conduct within the histology laboratory, including its histopathology services.

Procedures of technical conduct in the histology laboratory that should be inspected include:

- Preparation records for critical reagents (e.g. fixative, dehydrant, decalcifier, stains) used in the histology lab
- Operation, maintenance and calibration of automated fixation machinery, tissue processor, sonicator, paraffin and cryostat microtome, autostainer and autocoverslipping equipment
- Procedures for the trimming, dehydrating, infiltrating and embedding of tissues and sectioning of paraffin tissue blocks or frozen sectioning
- Treatment of brittle tissue paraffin blocks
- Hematoxylin and Eosin (H & E) staining and special staining of tissue sections
- Immunohistochemical and autoradiography methods and in-situ hybridization

- Histology post-review procedures (e.g. microscopic slide quality review and slide/block matching of stained tissue slides)
- Boxing, verification and disposition of tissue blocks
- Histology work request to order special stain, pathology recuts, and specific tissue slides to be delivered for review
- Histology lab procedures for tissues of study animals dying during chronic studies
- Record keeping and record keeping procedures of the histology laboratory

Histopathology services that should be inspected include:

- Records of receiving and shipment of pathology specimens
- Study pathologist - qualifications, personnel record and training (and refresher) program
- Recut request procedures
- Macro- and microphotography techniques (routine and digital, equipment maintenance)
- Quality Control of slides and their corresponding histopathology worksheet by the study pathologist
- Pathology reports and tables for each study
- Microscopic examination
- Data entry and use of pathology forms (hard copies and electronic forms)
- Operation and maintenance of image analyzers, digital image-storing systems, and antigen retrieval equipment
- Review, boxing and verification of tissue blocks, slides and data records for archiving by the study pathologist
- Peer review procedure of microscopic findings
- Histopathology data reporting and editing
- Glossary maintenance and diagnostic criteria used in automated data entry system

All pertinent items related to HGS Studies 1103-G923704 and 1141-CG920871 should be examined and the sponsor's data should be audited. For each study, the protocol and actual study conduct, QAU monitoring, maintenance and calibration of pertinent equipment, and the archives should be examined. The SOPs for the various procedures, such as the ones for various aspects of histology work, need to be scrutinized. In addition to the standard investigation involving source documents, the correspondence files pertaining to HGS Studies 1103-G923704 and

1141-CG920871 should be examined for sponsor-requested changes, if any, to the study data or report. Applicable exhibits (e.g., SOPs, raw data sheets) should be collected for all findings to assess the impact of the findings.

The EIR should document answers to the following questions:

- What was the procedure to determine the sequence and day on which rabbits were challenged with inhalational anthrax? Was the order of anthrax challenge random or by treatment group?
- How many rabbits were challenged at a time with anthrax?
- How were the Sponsor, the Battelle Study Directors and staff blinded to the animal group assignments?

The following issues must also be addressed during the inspection of each of the two Battelle facilities and discussed in the EIR:

- What percentage of the facility's total workload is subject to Part 58? What percentage of the facility's GLP workload is related to human drugs?
- Does the facility outsource any study phases, e.g., analysis of dosing formulations and histopathologic evaluations? Document how QAU oversight is assured for the outsourced phases. Does the final report identify the facility that conducted the outsourced phases? Please collect and exhibit in the EIR a list of all firms used for outsourced phases.
- Did the study director sign and date protocol amendments on or before the day when procedures were actually changed?
- Were the results of test article characterization and dosing formulation analyses reported to the study director and included in the final report?
- Were signed and dated contributing scientists' reports attached to the final report?

Headquarters Contact Person: Abhijit Raha, Ph.D.
301-796-3708
abhijit.raha@fda.hhs.gov

cc:

HFR-CE4525/Mishelle Harriger (BIMO)
HFR-CE440/Mark Parmon (Acting DIB)
OSI/DBEGLPC/Taylor/Bonapace/ChenZ/Matthews/Raha/CF
OND/DNP/Luann McKinney
Draft: AR 7/23/2012; 7/25/2012; 7/27/2012
Edit: ZC 7/24/2012
Edit: CB 7/27/12
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GLP File No. 0825
FACTS: 1427896

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/s/

ABHIJIT RAHA
07/27/2012

ZHOU CHEN
07/27/2012

CHARLES R BONAPACE
07/27/2012

OSI Consult	
Request for Biopharmaceutical Inspections	
Date	July 17, 2012
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	Office of Antimicrobial Products/Division of Anti-Infective Products
Project Manager	Jane Dean, x61202
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NDA <input checked="" type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	BLA 125349
Drug Product	raxibacumab
Sponsor Name	Human Genome Sciences
Sponsor Address	14200 Shady Grove Road Rockville, MD 20850
US Agent (if applicable)	
US Agent Address	
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date	December 15, 2012
Action Goal Date	December 15, 2012
OSI Review Requested By	October 26, 2012

Inspection Request Detail (All fields should be fill out completely)	
Study #1	
Study Number	Bioanalytical Study: Reference Report 8224813 (for clinical study HGS1021-C1064)
Study Title	Bioanalytical Study: Determination of Ciprofloxacin in Human Plasma Samples from HGS1021-C1064 by HPLC with MS/MS Detection For Clinical Study: 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
Study Type	<input type="checkbox"/> In vivo BE <input type="checkbox"/> In vitro BE <input type="checkbox"/> Permeability <input checked="" type="checkbox"/> Others (in vivo PK)
<input type="checkbox"/> Inspection Request - Clinical	<input checked="" type="checkbox"/> Inspection Request - Analytical Site
Facility #1 Name: Address: (Tel) (Fax)	Facility #1 Name: (b) (4)

	(b) (4)
Clinical Investigator: (email)	Principal Analytical Investigator: (email) (b) (4)
Facility #2 Name: (if applicable) Address: (Tel) (Fax)	Facility #2 Name: (if applicable) Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input type="checkbox"/> Study Report: (location, eg., 5.3.1.2)	<input checked="" type="checkbox"/> Validation Report: (eg., 5.3.1.2) <input checked="" type="checkbox"/> Bioanalytical Report: (eg., 5.3.1.4)

Study #2				
Study Number				
Study Title				
Study Type	<input type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Others (specify)
<input type="checkbox"/> Inspection Request - Clinical Site	<input type="checkbox"/> Inspection Request - Analytical Site			
Facility Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility Name: (or indicate if same as above) Address: (Tel) (Fax)			
Clinical Investigator: (email)	Principal Analytical Investigator: (email)			
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause			
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>				
<input type="checkbox"/> Study Report: (location, eg., 5.3.1.2)	<input type="checkbox"/> Validation Report: (eg., 5.3.1.2) <input type="checkbox"/> Bioanalytical Report: (eg., 5.3.1.4)			

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection

Purpose of inspection: follow-up inspection for confirmation of data integrity. The original bioanalysis was performed at (b) (4). Subsequently, a method for the determination of ciprofloxacin was developed by (b) (4) to reassay human plasma samples from Study HGS1021-C1064 to address deficiencies identified during OSI inspection of the original bioanalytical site.

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

/s/

JANE A DEAN
07/17/2012

OSI Consult Request for Nonclinical Inspections

Date:	July 17, 2012
Subject:	Request for Nonclinical Inspections (GLP)
Addressed to:	William H. Taylor, PhD, DABT Acting Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division:	Office of Antimicrobial Products/Division of Anti- Infective Products
Project Manager:	Jane Dean, x61202
Application Type:	<input type="checkbox"/> IND <input type="checkbox"/> NDA <input checked="" type="checkbox"/> BLA
Application Number(s):	BLA 125349
Product Name:	raxibacumab
Trade Name:	n/a
Sponsor Name:	Human Genome Sciences
Sponsor Address:	14200 Shady Grove Road Rockville, MD 20850
Electronic Submission:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date:	December 15, 2012
Action Goal Date:	December 15, 2012
Date OSI Review Requested:	October 26, 2012

Inspection Request Detail (All fields should be filled out completely)

Site #1	
Study Number:	1103-G923704
Study Title:	Evaluation of raxibacumab as a therapeutic treatment agent against inhalation anthrax in the New Zealand White rabbit model
Study Type:	<input checked="" type="checkbox"/> GLP <input type="checkbox"/> Non-GLP
Facility Type:	<input checked="" type="checkbox"/> In-life <input type="checkbox"/> Bioanalytical <input type="checkbox"/> Histopath <input type="checkbox"/> Other (specify)
Site Name: Battelle Biomedical Research Center (BBRC) Address: 505 King Ave., JM-8-1-086, Columbus, OH 43201 Phone: 614-424-7836 FAX: 614-458-7836	
Contact Name: Gabriel T. Meister, PhD Address: 505 King Ave., JM-8-1-086, Columbus, OH 43201 Phone: 614-424-7836 FAX: 614-458-7836 Email: MeisterG@battelle.org	
Location of study report/Data listings (electronic submission link): < http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680b18ff3 >	

Site #2	
Study Number:	1141-CG920871
Study Title:	Added benefit of raxibacumab with levofloxacin vs. levofloxacin as post-exposure treatment in the new Zealand white rabbit inhalational anthrax model
Study Type:	<input checked="" type="checkbox"/> GLP <input type="checkbox"/> Non-GLP
Facility Type:	<input checked="" type="checkbox"/> In-life <input type="checkbox"/> Bioanalytical <input type="checkbox"/> Histopath <input type="checkbox"/> Other (specify)
Site Name: Battelle Biomedical Research Center (BBRC)	
Address: 505 King Ave., JM-8-1-086, Columbus, OH 43201	
Phone: 614-424-7836	
FAX: 614-458-7836	
Contact Name: Gabriel T. Meister, PhD	
Address: 505 King Ave., JM-8-1-086, Columbus, OH 43201	
Phone: 614-424-7836	
FAX: 614-458-7836	
Email: MeisterG@battelle.org	
Location of study report/Data listings (electronic submission link):	
< http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680b18ff3 >	

Note: International inspection requests require sign-off by the OND Division Director.

Specific Review Concerns or Items To be Addressed During the Inspection
There are no specific concerns about these sites. Need confirmation of GLP and data integrity.

Contact Person if Additional Information is Required
Contact Name: Jane Dean, RN, MSN
Title: Regulatory Health Project Manager
Phone: 301-796-1202



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

Date: November 12, 2009

To: Renata Albrecht, MD, Director
Division of Special Pathogen and Transplant Products (DSPTP)

Through: Mary Willy, PhD, Deputy Director *Mary Willy*
Division of Risk Management (DRISK)

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

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

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Raxibacumab Injection for Intravenous Use

Application Type/Number: BLA 125349

Applicant/sponsor: Human Genome Sciences

OSE RCM #: 2009-1112

1 INTRODUCTION

This review is written in response to a request by the Division of Division of Special Pathogen and Transplant Products (DSPTP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert for Raxibacumab.

Raxibacumab is a BLA being submitted under 21 CFR 601, Subpart H. Raxibacumab is a fully human monoclonal antibody to the Protective Antigen (PA) of *bacillus anthracis*, for the treatment of inhalation anthrax. Raxibacumab is currently being stored in the Strategic National Stockpile (SNS).

Please let us know if DSPTP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Raxibacumab Prescribing Information (PI) submitted June 24, 2009 and revised by the Review Division throughout the current review cycle.
- Draft Raxibacumab Patient Package Insert (PPI) submitted June 24, 2009 and revised by the review division throughout the review cycle.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.



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

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

Label Review

Application Number: STN 125346/0
Name of Drug: Raxibacumab
Sponsor: Human Genome Sciences, Inc.
Material Reviewed: Raxibacumab carton and container labels
Submission Date: May 13, 2009
OBP Receipt Date: June 17, 2009

Background:

STN 125349 for raxibacumab is a Biologic License Application (BLA) indicated for the treatment of patients with inhalation anthrax due to *B. anthracis*. The product is currently held in the Strategic National Stockpile (SNS) under IND and is labeled with agency approved exemptions. The BLA contains commercial labels and overlabs that will be applied to approved IND labeling upon approval. The product is supplied as 1700 mg/ 34 mL (50mg/ml) single-use glass vials.

Labels Reviewed:

Raxibacumab

Carton Labels

SNS unit carton [REDACTED] (b) (4) with overlabs

Commercial unit carton [REDACTED] (b) (4)

Container label

Current SNS Vial label

Overseal labels for SNS

Review

I. Container

A. 21 CFR 610.60 Container Label (Commercial)

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 1. The proper name of the product – Raxibacumab – is displayed as Raxibacumab (b) (4) without a proprietary name, (trade name). This does not conform to the regulation. Remove the (b) (4) from the name.
 2. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The following presentation is displayed on the side panel: U.S. License No is listed as XXXX (b) (4) Manufactured by Human Genome Sciences, Inc, Rockville, MD 20850. This conforms to the regulation.
 3. The lot number or other lot identification – Is not displayed. This does not conform to the regulation.
 4. The expiration date – Is not displayed. This does not conform to the regulation.
 5. The recommended individual dose, for multiple dose containers – This is a single use vial. A statement appears on the label to this effect.
 6. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 7. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – Exempted from this requirement. This section does not apply.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.

3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This section does not apply.
 4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.
 5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This does not conform to the regulation. Need info.
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on label. This conforms to the regulation.
 - C. 21 CFR 201.5 Drugs; adequate directions for use – No statement appears on the label. This does not conform to the regulation.
 - D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proper name. This conforms to the regulation.
 - E. 21 CFR 201.10 Drugs; statement of ingredients – This conforms to the regulation.
 - F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”, “Do not Freeze”, and storage conditions) are prominent and do not overlap. This conforms to the regulation.
 - G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not displayed on the label. This does not conform to the regulation.
 - H. 21 CFR 201.25 Bar code label requirements – A bar code does appear on the label. This conforms to the regulation.
 - I. 21 CFR 201.50 Statement of identity – The proper name is listed as Raxibacumab (b)(4) is stated on the label. There is no proprietary name, (trade name) for the product. This does not conform to the regulation.

- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents (34 mL Single Use Vial) is declared on the label. This conforms to the regulation.
- K. 21 CFR 201.55 Statement of dosage – The statement “Single Use Vial” is displayed on the label. This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, other pertinent information, but does not list a lot number and expiration date. This does conform to the regulation.



II. **Carton**

- A. 21 CFR 610.61 Carton/Package Label – Commercial Unit (b) (4)
Carton
 - a. The proper name of the product – Raxibacumab – is displayed as Raxibacumab (b) (4) without a proprietary name, (trade name). This does not conform to the regulation. Remove the (b) (4) from the name.
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The following presentation is displayed on the side panel: U.S. License No is listed as XXXX (b) (4) Manufactured by

Human Genome Sciences, Inc, Rockville, MD 20850.
This conforms to the regulation.

- c. The lot number or other lot identification – The lot number is not listed. This does not conform to the regulation.
- d. The expiration date – The expiration date is not listed below the lot number on the carton. This does not conform to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the side panel of the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one single-use vial per carton. The statement, “(b) (4) Single-Use Vial”. This conforms to the regulation.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration. The statement, “1700 mg/ 34 mL (50 mg/mL).”
- h. The recommended storage temperature – The statement (b) (4) is displayed on the side panel of the carton. This conforms to the regulation.
- i. The words “PROTECT FROM LIGHT”, “REFRIGERATE” or the equivalent, as well as other instructions, when indicated by the character of the product is displayed on the carton. This conforms to the regulation.
- j. The recommended individual dose (b) (4)
(b) (4)
(b) (4) appears on the rear of the unit (b) (4) carton. This conforms to the regulation.

- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For Intravenous (b)(4)” is located on the front and rear panels of the carton.
- l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information – None listed. This conforms to the regulation.
- m. The type and calculated amount of antibiotics added during manufacture – None listed. This conforms to the regulation.
- n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information – listed on carton and Prescribing Insert. This conforms to the regulation.
- o. The adjuvant, if present – None listed. This conforms to the regulation.
- p. The source of the product when a factor in safe administration – None listed. This conforms to the regulation.
- q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None listed. This conforms to the regulation.
- r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. Standard of Potency has been prescribed, the words “No U.S. Standard of Potency” – Displayed on side panel. This conforms to the regulation.
- s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the front and back of the carton. This conforms to the regulation.
- t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the

required statement may be placed on the package label –
This conforms to the regulation.

- B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2©(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*] – The proper name, Raxibacumab, is the only name on the label. This conforms to the regulation.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – Human Genome Sciences, Inc. is the only manufacturer listed on the label. This conforms to the regulation.
- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. – There is no distributor listed on the carton. This conforms to the regulation.
- E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the front and back panels of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states

_____ This conforms to the regulation. (b) (4)
- I. 21 CFR 201.6 Drugs; misleading statements – The name shown on the carton label is Raxibacumab. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – This conforms to the regulation.

- K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”, “DO NOT FREEZE”, and storage conditions) are prominent and do not overlap. This conforms to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not displayed under the lot identification number as required by 610.61 on the carton label. This does not conform to the regulation.
- M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The proper name, Raxibacumab, is stated on the label and no proprietary name, (trade name) is listed. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The label states (b) (4)
” This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, storage conditions, and reference to the package insert. The statement “PROTECT FROM LIGHT”, “DO NOT FREEZE”
The required identifying lot number and expiration date is not displayed. This does not conform to the regulation.

3 Page(s) of Draft Labeling has been Withheld in Full as
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IV. Conclusions and Recommendations

The following deficiencies were noted in the initial review of the container and carton labels:

- A. 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.
- B. Commercial Cartons
1. 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).
 2. 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.
- C. Commercial Carton and Container
1. 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.
 2. 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
 3. Please revise the presentation of the statement, “(b)(4) Single –Use Vial” to “Single-Use Vial” to prevent redundancy. Relocate the (b)(4) statement to the primary panel (b)(4)
 4. 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

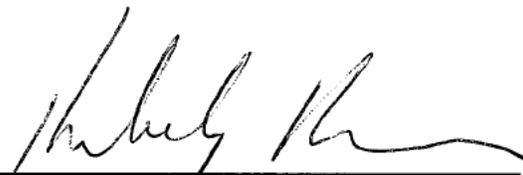
The agency is working toward standardizing the presentation of the trademark, proper name or established name, dosage form, and route of administration.

5. 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

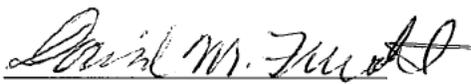
This is the agency preferred format.

- D. SNS container, unit carton (b)(4) labels with the addition of the overlayers have the following deficiencies:
 1. The manufacturer is listed incorrectly per the definition of manufacturer listed in 21 CFR 600.3(t). The statement, (b)(4)
(b)(4)
(b)(4)
(b)(4)
The correct statement is listed on the commercial labels as:
“Manufactured by
Human Genome Sciences, Inc.
Rockville, MD 20850”
 2. The proper name, “Raxibacumab (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).
 3. 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.
 4. The statement, “Rx Only”, is not displayed on the (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.

 11/10/09

Kimberly Rains, Pharm. D.
Regulatory Project Manager
CDER/OBP/IO

Concurrence/Comments:



David Frucht,
Product Reviewer
CDER/OPS/OBP/DMA



Patrick Swann
Deputy Division Director
CDER/OPS/OBP/DMA



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

Date: November 5, 2009

To: Renata Albrecht, MD, Director
Division of Special Pathogen and Transplant Products,
HFD-590

Thru: Carol Holquist, RPh, Director *Carol Holquist 5 Nov 09*
Division of Medication Errors and Prevention and Analysis,
HFD-420

From: Scott Dallas, RPh, Safety Evaluator *Scott Dallas 5 Nov 2009*
Division of Medication Errors and Prevention and Analysis,
HFD-420

Subject: DMEPA Raxibacumab Label Review

Drug Name(s): Raxibacumab Injection
1700 mg/34 mL
(50 mg/mL)

Application Type/Number: BLA 125349

Applicant: Human Genome Sciences, Inc.

OSE RCM #: 2009-1112

1 INTRODUCTION

This review was written in response to a request from the Division of Special Pathogen and Transplant Products (DMIHP) to evaluate the proposed container label, carton and insert labeling for Biologics License Agreement, BLA 125349, raxibacumab from a medication error safety perspective. Under an Emergency Investigational New Drug agreement a supply of raxibacumab injection has been placed in the Strategic National Stockpile (SNS). Therefore, the applicant, Human Genome Sciences, Inc. has submitted additional proposed labeling (overlabels) to be affixed to the labels and labeling of the product in the SNS upon approval of the BLA. DMEPA has also evaluated the applicants' proposed overlabels.

1.1 PRODUCT INFORMATION

Raxibacumab is a human monoclonal antibody which binds the protective antigen of *Bacillus anthracis*. Raxibacumab is seeking an indication (b) (4)

The effectiveness of raxibacumab has not been tested in humans, since it would be unethical or feasible to conduct a controlled clinical study. The effectiveness has been based solely on efficacy studies in animal models of inhalational anthrax. Serum concentrations achieved in humans serve as a surrogate endpoint likely to predict clinical benefit.

The recommend dosage of raxibacumab is 40 mg/kg as a single dose infusion administered intravenously over 2 hours. The dose should be diluted with normal saline to a final volume of 250 mL. A prophylactic dose of 25 mg to 50 mg diphenhydramine should be administered prior to the administration of the raxibacumab infusion solution.

2 MATERIAL REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Failure Mode and Effects Analysis (FMEA) in our evaluation of the labels and labeling. DMEPA has reviewed the following:

- Container (Vial) Label (Appendix A)
- Carton Labeling for Single Use Vial (Appendix B)
- (b) (4)
- SNS Container (Vial) Label (Appendix D)
- SNS Carton Labeling for Single Use Vial (Appendix E)
- (b) (4)

3 DISCUSSION

Our evaluation of the proposed label and labeling indicates that the proposed text, presentation and design may be vulnerable to confusion that could lead to medication errors. Therefore, DMEPA has provided label and labeling comments to enhance the understandability and readability of important information, and to present statements in a manner consistent with other approved products while satisfying the biologics labeling requirements found in 21 CFR 610.

3.1 PACKAGE INSERT LABELING

During an internal wrap-up meeting on October 5, 2009, DMEPA expressed concern that the proper name for the product appeared to be inconsistent with other similar biologic products. DMEPA was informed that the correct proper name for the product would be determined by the Office of Pharmaceutical Sciences, Office of Biotechnology Products (OPS/OBP). It was also decided that DMEPA should collaborate with OPS/OBP to review the package insert labeling that would be available on October 6th and comment on sections of the labeling that related to our expertise. The intent was for the DSPTP to consolidate all recommendations from various disciplines and forward a revised package insert to the applicant the week of October 11th. On October 7th, DMEPA emailed revisions for the package insert labeling to OPS/OBP who edited and forwarded the revised labeling to the DSPTP. At this time the terminology “deliverable” was introduced into the package insert labeling. DMEPA expressed concern with this terminology, because this terminology is not generally seen with drug products. Thus, DMEPA was concerned how healthcare provider would interpret this terminology and how it will affect future drug applications. On October 14th, OPS/OBP incorporated additional language with the term “deliverable” to present the over fill in the bottle while expressing the total drug content and product strength. OPS/OBP proposed the language “contains 35.1 mL of raxibacumab solution at a concentration of 50 mg/mL (to allow delivery of 1700mg/34mL). DMEPA thought this wording may be acceptable for the Description and How Supplied section, but not for the Highlights or Dosage and Administration section. The proposed wording was incorporated into the labeling and forwarded to the applicant on October 15, 2009. DMEPA was also concerned that the proper method for administration of the product should be addressed and included in the labeling. Healthcare providers will need to know as much information as possible about the proper method to administer the product. Individuals exposed to inhalational anthrax may receive both raxibacumab and an antibiotic. However, the package insert labeling does not indicate if raxibacumab and antimicrobials can be administered concomitantly, or if the agents should be administered through the same or different intravenous lines. This concern was also forwarded to the applicant to address in the October 15th communication with the applicant. Selected sections of DMEPA’s proposed insert labeling wording were included as Appendix G.

3.2 CONTAINER LABELS AND CARTON LABELING

DMEPA has included container and carton labeling comments in the Recommendations section of this review. On October 28, 2009 DMEPA met with representatives from the Office of Pharmaceutical Sciences, Office of Biotechnology Products (OPS/OBP) to discuss potential revisions with the labels and labeling. At the meeting representatives from OPS/OBP and DMEPA were in agreement with the proposed label and labeling recommendations in order to satisfy both the regulatory requirements and promote the safe use of the product.

3.3



4 RECOMMENDATIONS

Our evaluation of the proposed container label, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 4.1 contains comments to the Division concerning the review of the labels and labeling. Section 4.2 contains our recommendations to be communicated to the Applicant prior to approval. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Nitin M. Patel, Project Manager, at 301-796-5412.

4.1 COMMENTS TO THE DIVISION

DMEPA has provided recommendations to the DSPTP during various meetings and through emails from October 7th through October 14th, and will continue to work collaboratively with OPS/OBP on the labels and labeling. Selected sections of the insert labeling that DMEPA has revised or provide comments on are included in Appendix G

4.2 COMMENTS TO THE APPLICANT

A. Container Labels

1. Increase the prominence of the primary expression of strength. The proper name should have the greatest prominence on the principal display panel, followed in prominence by the expression of strength statements. We recommend that the presentation of the strength statements follow the standard in the United States Pharmacopeia, General Chapter <1> Injections, USP 32/NF 27 that reads in part “the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses.” This USP standard became effective February 1, 2009. We suggest that the expressions of strength are presented on two different lines similar to:

1700 mg/34 mL
(50 mg/mL)

2. Relocate that the total volume statement, 34 mL, away from the primary expression of strength, 1700 mg/34 mL. The total volume statement should have less prominence on the principal display panel than the primary expression of strength.
3. We recommend that the route of administration statement should be presented as a stand alone statement and not part of the proper name. We note that the labels and labeling submitted for inclusion in the Strategic National Stockpile use the wording “For Intravenous Infusion (b)(4)”. We recommend that all labels and labeling should use the same route of administration statement. We prefer the statement “For intravenous Infusion (b)(4)” over the statement “For Intravenous (b)(4)”.
4. 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 strengths.
5. Revise the label to include the statement “Discard unused portion”. This statement should appear in conjunction with the statement “Single-Use Vial”.

6. Remove the word (b)(4) from the label. This statement is unnecessary and adds clutter to the principal display panel.
7. 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.
8. 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 be debolded on the container label.
9. 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.

B. Carton Labeling

Revise the carton labeling in accordance with container label comments, see Section A1 through A6 above.

C. Overwrap Labels for Relabeling of SNS Product

Revise the expiration date so that it is presented in a consistent manner on all labeling. 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)

8 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

INTRODUCTION

Human Genome Sciences submitted an original BLA (125349) on May 19, 2009, for raxibacumab injection for intravenous use for the treatment of inhalation anthrax. Fast Track Status and Orphan Drug Designation were granted to raxibacumab for the treatment of inhalation anthrax on 15 August 2003 and 13 November 2003, respectively.

The Division of Special Pathogens and Transplant Products consulted the Maternal Health team (MHT) to review the Pregnancy and Nursing Mothers subsections of raxibacumab labeling.

BACKGROUND

Raxibacumab

Raxibacumab is a fully human monoclonal antibody to the Protective Antigen (PA) of *Bacillus anthracis* for the treatment of inhalation anthrax infection. Raxibacumab targets anthrax toxins after they are released by the bacteria into the blood and tissues, specifically binds PA, interferes with the binding of PA to anthrax toxin receptors, and prevents killing of macrophages by anthrax lethal toxin. Raxibacumab does not have direct antimicrobial activity and is usually co-administered with antimicrobials in the treatment of inhalation anthrax. Because of feasibility and ethical concerns, no efficacy studies were conducted with raxibacumab in humans. Efficacy studies for raxibacumab were conducted in two species using the criteria in 21 CFR 601 Subpart H under the Animal Rule. Raxibacumab was administered to healthy human volunteers to establish dosing and safety; however, findings at site inspections raised concerns about the quality and reliability of pharmacokinetics data about raxibacumab absorption, distribution and metabolism by the human body. The review division plans to issue a Complete Response (CR) for raxibacumab this review cycle.

An Advisory Committee meeting was held on October 27 to discuss the animal studies conducted to establish efficacy of raxibacumab in the treatment of inhalation anthrax. The panel voted that that Human Genome Sciences should submit more evidence to show whether adding raxibacumab to antimicrobial treatment of anthrax improves clinical outcomes, because antimicrobials alone are highly effective against anthrax infection.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT's suggested revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of Raxibacumab injection for intravenous use labeling.

SUBMITTED LABELING

Proposed Pregnancy and Nursing Mothers Labeling (October 22, 2009 revised version)



CONCLUSIONS

The MHT is structuring the Pregnancy and Nursing Mothers label information in a way that complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

MHT's recommended pregnancy and nursing mothers labeling revisions for raxibacumab are provided below on pages 4-5 of this review. Appendix A of this review also provides a track changes version of labeling.

MATERNAL HEALTH TEAM LABELING RECOMMENDATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION



(b) (4)

8.3 Nursing Mothers

(b) (4)

[Redacted text block]

Reviewer Comment: For more information on the transfer of immunoglobulins in human milk see Van de Perre P. Transfer of antibodies via mothers milk. Vaccine 2003; 21: 3374-76.

ADDITIONAL MATERNAL HEALTH TEAM COMMENT

MHT would appreciate the opportunity to be re-consulted on the pregnancy and nursing mothers section of raxibacumab labeling when the Sponsor submits a Complete Response for the application.

Appendix A - MHT Tracked-Changes Labeling Revisions

24 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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

Memorandum

Date: October 30, 2009
To: Rebecca McKinnon, Regulatory Project Manager,
Division of Special Pathogen and Transplant Products (DSPTP)
From: Sharon Watson, Regulatory Review Officer,
Division of Drug Marketing, Advertising, and Communications (DDMAC)
Katie Klemm, Regulatory Review Officer, DDMAC *Katie Klemm*
CC: Marci Kiester, DTC Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC
Subject: BLA 125349
DDMAC labeling comments for raxibacumab injection for intravenous use

DDMAC has reviewed the proposed product labeling (PI) and patient labeling for raxibacumab injection for intravenous use submitted for consult on October 14, 2009, and offers the following comments.

The version of the draft PI and patient labeling used in this review is titled, "SEALD 22OCT09 edits to DRAFT – FDA CLEAN revised BLA 125349 raxi labeling 10-14-09.doc" which was sent via email from Rebecca McKinnon on October 22, 2009.

AC's comments are provided directly on the marked up version of this document, attached below.

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

If you have any questions on the comments for the patient labeling, please contact Sharon Watson at 301.796.3991 or Sharon.Watson@fda.hhs.gov. If you have any questions on the comments for the PI, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

(b) (4)



MEMORANDUM

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

DATE: October 7, 2009

TO: Renata Albrecht, M.D.
Director
Division of Special Pathogen And Transplant Products
(DSPTP)

FROM: John A. Kadavil, Ph.D.
Hyojong Kwon, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Yant-K. Yau 10/7/09*
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering BLA 125,349, Raxibacumab i.v.,
Sponsored by Human Genome Sciences, Inc.

At the request of DSPTP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following pharmacokinetic studies supporting BLA 125,349:

Study Number: HGS1021-C1063
Study Title: "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"

Study Number: HGS1021-C1064
Study Title: "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"

The clinical portions of studies HGS1021-C1063 and HGS1021-C1064 were conducted at Covance CRU, Inc., Daytona Beach, FL and Covance CRU, Inc. Austin, TX. The analytical portions were

conducted at Human Genome Sciences, Inc., Rockville, MD (Raxibacumab) and at [REDACTED] (b)(4) [REDACTED] (ciprofloxacin).

Following the inspection at Covance CRU, Austin (8/3-10/2009), no Form FDA-483 was issued. Following the inspections at Covance CRU, Daytona Beach (8/10-19/2009), Human Genome Sciences (9/9-21/2009), and [REDACTED] (b)(4) [REDACTED]), Forms FDA-483 were issued. The observations and our evaluation are as follows:

Human Genome Sciences, Rockville, MD (Raxibacumab)
(Findings are for the quantitation of raxibacumab in human serum.)

- 1. In Study HGS1021-C1064, the firm inappropriately accepted 22 assay plates based on the performance of only the mid (PC2) and low (PC3) quality controls (QCs). For these 22 plates, the high QC (PC1) was excluded from assay acceptance/rejection criteria.**

A minimum of duplicate QCs at three concentrations, representing the entire range of the standard curve, should be evaluated in each assay. At least 67% (4 out of 6) and half (1 of 2) at each concentration should be within the firm's *a priori* acceptance criteria. Since the firm assessed only two QC concentrations in the aforementioned assay plates, the accuracy of raxibacumab measurements in these runs is not assured. See Appendix for subject sample listing.

For 5 of these runs, the firm excluded the high QC from run acceptance/rejection due to the high QC failing (see Appendix). For the remaining 17 runs, only mid and low QC concentrations were assessed as no high QC was used.

- 2. The firm failed to demonstrate the calibration range using fixed points of concentrations with accuracy. Instead, some points were outside the assay range and extrapolated.**

The firm reported upper and lower limits of quantification as 70 and 0.03 ng/mL, respectively, although the calibration curve used throughout qualification, validation, and the study never included standard points at these concentrations. Instead, the following standards were used: 75, 18.75, 4.688, 1.172, 0.293, 0.073, 0.018 and 0.0047 ng/mL. The points at 75, 0.018 and 0.0047 ng/mL were outside the calibration range and were used only as "anchor points" in fitting the calibration function.

Thus, subject sample results with concentrations reported above 18.75 ng/mL or below 0.073 ng/mL were extrapolated values. Similarly, the high QC at 49 ng/mL (HGS 1021-C1063), the high QC at 70 ng/mL (HGS 1021-C1064) and the dilution QC at 600 µg/mL (diluted 1:24,000, to 25 ng/mL) were extrapolated.

It should be noted that the calibration curve only had 5 non-zero calibration standards within the firm's defined assay range, instead of the usual minimum of 6.

3. **The firm failed to use acceptance criteria for calibration standards in the SOP based on accuracy. Instead, standards were accepted solely on %CV.**

The firm's calibration curve acceptance criterion, provided in SOP CLI-2879, is insufficient as it does not require assessment of accuracy of calibration standards. Calibration standards throughout pre-study qualification, validation, as well as studies HGS1021-C1063 and HGS1021-C1064, were accepted solely on precision (%CV) and accuracy was not assessed. Therefore, accuracy for the calibration points was not assured.

4. **Assay qualification and assay validation reports failed to document performance parameters such as precision and accuracy for the calibration standards.**

The Assay Qualification Report and Assay Validation Report failed to discuss the performance (precision and accuracy) of standards on the calibration curve. Instead, the curve was assessed on the performance of separate spiked samples ("accuracy spikes") that were back-calculated against the standard curve. **These accuracy spikes included samples to determine the ULOQ and LLOQ.**

5. **The firm had insufficient documentation to verify the following:**
 - a) **The actual number of freeze/thaw cycles that freeze/thaw stability samples, used for pre-study assay qualification, underwent**
 - b) **The lot # for the human serum pool used to make stability samples and dilution QCs used during pre-study assay qualification**
 - c) **The condition upon receipt of PK and immunogenicity samples**

In particular, this lack of documentation does not assure that freeze/thaw (F/T) stability samples underwent the required

number of F/T cycles prior to analysis. Therefore, the firm's F/T stability assessment is questionable. The integrity of the PK and immunogenicity samples is also questionable since the condition of these samples upon receipt was not documented sufficiently.

6. The firm failed to evaluate the incurred sample reproducibility (ISR) of the electrochemiluminescence method for raxibacumab in Study HGS1021-C1063.

By not conducting any reanalyses of incurred samples, the firm did not assure accuracy of subject sample measurements through assay reproducibility. Study HGS1021-C1063 was conducted from June to August 2008.

At the close of the inspection, the firm indicated that they would provide a written response to the agency to address Observations 1-6. The response has not arrived at DSI as of this writing.

(b)(4)

1. Failure to demonstrate the accuracy and precision of the assay method used to analyze ciprofloxacin samples of study HGS1021-C1064 in that numerous validation experiments were not conducted.

- For example, inter- and intra-day precision and accuracy for the calibration range of 10-5000 ng/mL, matrix effect, selectivity, extraction recovery, anti-coagulant effect between EDTA and CPD, and stability experiments such as stock solution, auto-sampler and processing of analytes in matrix.

(b)(4) evaluated precision and accuracy within the calibration range of 10 to 1000 ng/mL. However, the upper limit of quantification (ULOQ) was increased to 5000 ng/mL following analysis of the first batch of study samples. (b)(4) failed to conduct validation experiments to assess assay performance with the new calibration range of 10 to 5000 ng/mL.

The stability validation was not done adequately in that only one concentration was assessed for stability. The firm also failed to evaluate assay selectivity, extraction recovery, and anti-coagulant effect during method validation. Different anti-coagulants were used for collecting study samples (EDTA) and

preparing QCs and calibrators (CPD; citrate-phosphate-dextrose). (b)(4) did not evaluate the effects of different anti-coagulants and dilution of CPD plasma (approximately 22%) on ciprofloxacin assay accuracy, precision, extraction recovery, and stability. We note that ciprofloxacin is approximately 40% bound to proteins in plasma.

2. Failure to demonstrate assay reproducibility.

- In study HGS1021-C1064, 26 ciprofloxacin samples were re-assayed per the sponsor's request and about 46% (11 out of 26) of the re-assayed sample results exhibited more than 20% difference from the original results.

After (b)(4) completed analysis of all samples in study HGS1021-C1064, the sponsor (HGS) requested that (b)(4) re-assay 26 samples with aberrant PK results. There was no investigation or resolution of the aberrant original results for these samples, all from accepted analytical runs. These samples were re-assayed without objective justification. Following reanalysis, 46% of those samples differed from their original results by more than 20%. DSI is of the opinion that the original values should be used for pharmacokinetic evaluation.

3. Failure to follow the study SOP to reject batches when QCs did not meet the acceptance criteria.

- For example, more than 50% of LQCs of batches B, F, I, S, and W failed to meet acceptance criteria but these batches were not rejected.

Batches B, F, I, S and W did not meet acceptance criteria due to failure of more than 50% of LQCs. However all samples in these batches were accepted and the concentration results were reported (Appendix 5 in the final report). These batches should have been rejected and re-assayed.

4. Failure to use separate independent stock solutions for the preparation of QC samples and calibration samples used in the validation and analytical runs.

(b)(4) should have prepared independent stock solutions for QCs and calibration samples to adequately monitor the assay performance during validation runs. Independent stock solutions for calibrators and QCs used during the studies would have confirmed accuracy during production.

5. Failure to establish adequate written procedures to ensure the accuracy and integrity of study conduct.

- Lack of reporting procedure
 - a) No validation report was prepared for the ciprofloxacin method.
 - b) Not all re-assayed samples and data were included in the report for Study HGS1021-C1064, in that batches U and V were rejected and re-assayed but these results were not disclosed as re-assayed results in the study report.
- Lack of SOP for incurred sample re-analysis
- Lack of objective criteria for manual re-integration

There was no validation report and the re-assayed results table (Appendix 3 in the final study report) is not accurate, as it did not include data from samples in reassayed batches U and V.

Some calibrators or QCs were manually re-integrated without established objective criteria. Although inconsistent integration within a batch is objectionable, DSI found that both the original and manual integrations provided comparable results. During the inspection, selected original chromatograms (especially for the QC and calibrator samples) were compared to the manual integrations; the manual integrations did not affect run acceptance.

6. **Failure to fully document all aspects of study conduct and study related correspondence.**
- No record of duration (start/end time) of sample processing in all sample processing worksheets, and times of freezer removal and replacement of all samples in the freezer-log book
 - Study related correspondence was not maintained with source documents in the archive.

Records for duration of sample processing and handling are required to ensure that calibrators, QCs, and study samples were stable during analysis. The accuracy of study data cannot be assured because there was no documentation to confirm that study samples were handled in the same way as QCs or calibrators, and no validation experiments demonstrated sample stability at various conditions (See Form 483 Item 1 issued to (b)(4)).

Not all the study-related correspondence was archived with source documents and readily available for inspection.

Covance CRU, Daytona Beach, FL

1. Failure to follow the protocol.

The firm failed to follow their exclusion criteria in that Subject #49 was enrolled although the subject was diagnosed with squamous cell carcinoma in 2004. The protocol states that subjects with a history of malignancy within the last 5 years should not be enrolled.

Additionally, sample processing logs for raxibacumab PK samples (Group 1 - Days 5, 6 and 12) document centrifuge durations, speeds, and temperatures that deviate from protocol requirements.

2. Failure to assure appropriate study conduct

For Study HGS1021-C1063, the husband and daughter of the study coordinator were enrolled in the study (Subject #50 and Subject #33, respectively), and study records reveal entries made by the study coordinator for these subjects. The firm's policy states that an employee can not be directly involved in the study if family members are enrolled.

3. Failure to maintain accurate records.

Infusion volume of the test article on Day 0 for subjects #47 and #10 could not be ascertained due to incomplete documentation.

The infusion pump verification records for pumps used in Study HGS1021-C1064 document equipment verifications on 5/23/2007, even though the pumps were delivered on 5/31/2007. Therefore, the verification records are questionable.

The firm failed to report to the sponsor adverse events on 5/3/2008 and 6/11-12/2008 for Subject #59, following the use of Aleve. The use of Aleve on 6/11-12/2008 was not documented in the Concomitant Medications Log.

Although the deficiencies in items 1-3 deserve correction, they should have negligible impact on study outcomes.

Conclusions:

Raxibacumab assays

DSI recommends that raxibacumab data for subject samples assayed in the 22 runs cited in Item 1 (see also Appendix) should be excluded from pharmacokinetic assessment for study HGS1021-C1064.

Items 2-4 reveal the firm's failure to demonstrate the accuracy of raxibacumab assays over the reported calibration range used for subject sample analyses. DSI recommends that concentrations results above 18.75 ng/mL or below 0.073 ng/mL should be excluded from pharmacokinetic analyses

Ciprofloxacin assays

DSI recommends that the accuracy of ciprofloxacin concentrations cannot be assured due to lack of documentation that study samples were handled in the same way as QCs (Item 6), and incomplete assay method validation (Item 1). DSI recommends that the data for ciprofloxacin in Study HGS1021-C1064 are not acceptable. An SOP for incurred sample reproducibility (ISR) should be established and implemented for current/future studies.

After you have reviewed this transmittal memo, please append it to the original BLA submission.



John A. Kadavil, Ph.D.
Pharmacologist



Hyojong Kwon, Ph.D.
Staff Fellow

Final Classifications:

Covance CRU, Austin, TX - NAI
Covance CRU, Daytona Beach, FL - VAI
Human Genome Sciences, Inc. - VAI

(b) (4)

CC:

HFD-45/RF

HFD-48/Kadavil/Kwon/Kaufman/CF

OND OAP DSPTP/Yasinskaya/McKinnon

HFR-CE250/Harris (ORA investigator at HGS)

HFR-SW250/ (b)(4))

HFR-SE2570/Carmichael (ORA investigator at Covance, Daytona)

Draft: HK 9/24/09; JAK 10/2/09, 10/6/09

Edit: MKY 10/5/09, 10/6/09; MFS 10/6/09

DSI: 5981; O:\BE\EIRCover\125349hgs.rax.doc

FACTS 1068681

Run ID	Subject Samples
19JUL07_eboyd_HGS1021-C1064_2879_pl1*	US001-000001, -000002, -000003
26JUL07_kpieri_HGS1021-C1064_2879_p2*	US003-000002, -000004, -000005, -000006, -000007 (5 min, 1d, 21d), -000008 (PD)
01AUG07_kpieri_HGS1021-C1064_2879_p2*	US003-000025 (7-21d), -000026 (5min-14d) -000027 (5min-14d), -000028 (PD, 5min, 8h, 7-21d) -000029 (PD-14d)
02AUG07_eboyd_HGS1021-C1064_2879_pl1*	US003-000013, -000014 (1-21d), -000015 (PD, 5min, 1-14d), -000016, -000017 (PD)
02AUG07_eboyd_HGS1021-C1064_2879_pl2*	US003-000017 (5min-21d) -000018 (PD, 5min, 8h, 21-56d) -000019 (PD, 5min, 8h, 3-14d), -000020
08AUG07_eboyd_HGS1021-C1064_2879_p1	US003-000047 (14d, 21d), -000048 (PD-21d) -000049 (1, 3, 14-28d), -000050 (PD, 5min-7d) -000051, -000052 (PD, 5min)
08AUG07_eboyd_HGS1021-C1064_2879_p3	US003-000056 (7-28d), -000057 (5min-14d) -000058 (PD-7d), -000059 (PD, 8h, 1, 3, 14d) -000060 (PD-1d, 7, 21d), -000061 (PD-8h)
08AUG07_kpieri_HGS1021-C1064_2879_p1	US003-000030 (PD-21d), -000031 (PD, 1-28d) -000032, -000033 (PD-14d)
10AUG07_eboyd_HGS1021-C1064_2879_p1	US003-000052 (8h-21d), -000053 (5min-21d) -000054 (5min-28d), -000055 (5min-21d) -000056 (PD-3d)
10AUG07_eboyd_HGS1021-C1064_2879_p2	US003-000038 (21d), -000039 (PD-21d) -000040 (PD, 1-21d), -000041 (PD-7d) -000042 (8h-21d), -000043 (PD-1d)
10AUG07_eboyd_HGS1021-C1064_2879_p3	US003-000043 (3-21d), -000044 (PD-21d), -000045 (PD-21d), -000046 (PD-21d), -000047 (PD-7d)
27AUG07_eboyd_HGS1021-C1064_2879_p1	US001-000018 (56d), -000019 (42-56d), -000020 (14d), US002-000002 (7d, 28-56d), -000003 (28-56d), -000005 (7d), -000006 (7-56d), -000007 (7d, 28-56d), -000008 (7-56d), -000009 (7-42d)
27AUG07_eboyd_HGS1021-C1064_2879_p2	US002-000009 (56d), US003-000002 (14, 28d) -000004 (7, 28, 56d), -000005 (21-42d) -000007 (7-56d), -000012 (56d), -000015 (56d) -000016 (42-56d), -000017 (42d), -000019 (42d) -000020 (42-56d), -000021 (28-56d) -000023 (28-56d), -000024 (42-56d) -000025 (28-56d), -000026 (42d)
27AUG07_eboyd_HGS1021-C1064_2879_p3	US003-000026 (56d), -000027 (28-56d) -000028 (28-56d), -000029 (28-56d) -000030 (28, 56d), -000031 (42d), -000032 (42-56d) -000033 (42-56d), -000034 (42-56d) -000035 (42-56d), -000037 (28-56d) -000038 (28-56d), -000039 (28d) -000040 (28-56d), -000041 (42-56d)
28AUG07_eboyd_HGS1021-C1064_2879_p1	US001-000010 (14-56d), -000011, -000012, -000013

* Runs in which the firm excluded the failing high QCs from run acceptance

28AUG07_eboyd_HGS1021-C1064_2879_p2	US003-000042 (28-56d), -000043 (28-56d) -000044 (28-56d), -000045 (28-56d) -000046 (28-56d), -000047 (28-56d), -000048 (7d), -000049 (7, 42-56d), -000051 (42d), -000052 (28-56d), -000053 (42d) -000054 (42-56d), -000055 (28-42d), -000056 (56d) -000057 (42-56d)
28AUG07_eboyd_HGS1021-C1064_2879_p3	US001-000002 (PD, 28d), -000003 (5min) -000005 (5min, 56d), -000008 (3-7d), -000009 (8h) -000015 (3d, 28d), -000019 (5min, 7d) US002-000003 (56d), -000007 (14d) US003-000004 (3d, 14d), -000005 (14d) -000009 (1-3d), -000011 (5min) -000014 (5min, 8h), -000015 (8h) -000059 (21-42d), -000060 (14, 28-42d) -000061 (7-42d)
29AUG07_eboyd_HGS1021-C1064_2879_p1	US003-000015 (42d), -000018 (7-14d) -000019 (1, 21d), -000021 (PD), -000022 (PD, 3-7d) -000023 (21d), -000026 (PD, 21-28d), -000027 (PD) -000028 (3d), -000031 (5min, 56d), -000032 (5min) -000034 (PD), -000035 (5min, 1d), -000037 (3d) -000040 (5min, 8h), -000041 (8h), -000042 (5min) -000044 (14d), -000045 (21d), -000046 (1d) -000047 (8h)
29AUG07_eboyd_HGS1021-C1064_2879_p2	US003-000049 (5min, 8h), -000050 (8h) -000053 (PD), -000054 (PD, 21d), -000055 (8h) -000057 (21-28d), -000059 (5min, 7d)
05SEP07_eboyd_HGS1021-C1064_2879_p2	US003-000004 (8h), -000005 (PD) -000006 (PD, 8h), -000007 (PD, 8h, 3d) -000013 (1d), -000014 (PD), -000018 (1-3d) -000024 (1d), -000025 (1d), -000027 (21d) -000028 (1d), -000029 (5min, 8h, 1-3d), -000031 (8h), -000042 (PD), -000052 (1d) -000055 (PD), -000057 (PD), -000060 (3d) -000061 (1-3d)
06SEP07_kpieri_HGS1021-C1064_2879_p2	US001-000003 (1d), -000007 (14d), -000008 (28d) -000010 (5min, 7d), -000011 (5min, 8h) -000015 (21d), -000017 (5min, 8h) -000018 (5min, 8h), US002-000004 (14-56d) -000006 (7, 56d), -000007 (28d) US003-000007 (21d), -000021 (5min, 8h) -000022 (8h), -000031 (5min), -000042 (5min) -000059 (5min)
11SEP07_kpieri_HGS1021-C1064_2879_p1	US003-000017 (56d), -000053 (56d), -000059 (56d) -000060 (56d), -000061 (56d)

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do NOT send this page with draft letter.

Application #(s):	BLA 125349/0
DSI Electronic Archive	BLA 125349/0
FEI/CFN:	1000303703
Field Classification:	NAI
Headquarter's Classification:	NAI (No Action Indicated) (Monitor)
If headquarters classification is different from field classification, please explain why:	
Deficiencies Noted:	None
Deficiency Code(s):	N/A
Drafted by and dates:	YP: 8/26/09; 9/2/09
Reviewed by and dates:	ST: 8/31/09
Reviewed by and dates:	TPS: 9/3/09
Meeting dates:	
Finalized:	YP: 9/14/09
Filename:	O:\Thompson\Human Genome Sciences.doc
Case Closed :	Yes. Send copy to HFR-CE240 DCB- Kirk Sooter – release EIR per FMD-145
DFS Key Words:	DSI Staff Letters – Sponsor/CRO/Monitor Program
CC:	<p><u>CST, please scan letter and submit an electronic copy to the following:</u> DSPTP/Review Division/MO/Yuliya Yasinskaya/Sue Lim/Renata Albrecht DSPTP/Review Division/PM/Rebecca McKinnon DSI/Branch Chief/Tejashri Purohit-Sheth DSI/GCP Reviewer/Susan Thompson DSI/GCP Branch CST/Joseph Peacock/Kimberly Gifford DSI/Database PM/Dana Walters/Christina Thompson HFR-CE250/DIB/Christine Smith HFR-CE250/BIMO/Stephanie Shapley HFR-CE250/Field Investigator/Cynthia Harris HFR-CE240/DCB/Kirk Sooter- release EIR per FMD-145</p> <p><u>CST place paper copy in File:</u> DSI Doc. Rm. GCP File #13102</p> <p><u>CST enter in Electronic Archive #</u> BLA 125349/0</p>

**DSI note to Review
Division**

This CRO/monitor inspection was issued to review the monitoring practices of clinical studies conducted in support of BLA 125349/0 raxibacumab in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program. The purpose of the inspection was to verify enrollment of large numbers of study subjects.

The inspection audited two clinical Trials, 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" with a focus on clinical investigators Frank Farmer Jr. (Dayton Beach, FL) and David C. Carter (Austin, TX).

The inspection confirmed that study C1063 was conducted at six clinical sites, with 322 subjects enrolled. A comparison of source records for 159 subject records (49.4% of total) against data line listings submitted to FDA by the sponsor revealed no discrepancies related to adverse events, concomitant medications, eligibility criteria, or performance of study procedures. Study C1064 was conducted at three clinical sites, with 90 subjects enrolled. A comparison of source records for all subject records (100% of total against data line listings submitted to FDA by the sponsor) revealed no discrepancies related to adverse events, concomitant medications, eligibility criteria, or performance of study procedures. Although the monitoring for the C1064 study appeared adequate and of appropriate frequency, there was no protocol specified monitoring plan. The Human Genome Sciences representatives stated that they will ensure that all appropriate staff members are educated on implementation of the SOPs for monitoring. The inspector also noted that protocol violations and deviations, as well as data clarification requests could be reviewed and tracked to determine if corrective actions by the sponsor are warranted.

The inspection revealed that the assay method used was validated and the primary efficacy endpoint data were verifiable for the subjects reviewed. No objectionable conditions were observed during the inspection. No Form FDA 483 was issued. No refusals were encountered and no samples were collected during the inspection.

The studies appear to have been conducted adequately, and the data generated appear acceptable in support of the respective indication.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 6, 2009

TO: Rebecca McKinnon, Regulatory Project Manager
Yuliya Yasinskaya, M.D., Medical Officer
Division of Special Pathogen and Transplant Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Jean M. Mulinde, M.D. *Jmm 10/17/09*
Acting Team Leader
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: BLA STN # 125349

APPLICANT: Human Genome Sciences
14200 Shady Grove Road
Rockville, MD 20850

DRUG: Raxibacumab (no proprietary name)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: 1. Treatment of inhalational anthrax

CONSULTATION REQUEST DATE: October 7, 2009

DIVISION ACTION GOAL DATE: November 13, 2009

PDUFA DATE: November 14, 2009

I. BACKGROUND:

Anthrax is caused by infection with *Bacillus anthracis*, a Gram-positive, spore-forming rod. Anthrax spores are easily aerosolized and their size allows inhalation and eventual location in the lower respiratory tract. Infection is initiated by the inhalation of anthrax spores, which are taken up and subsequently germinate within the macrophages as they are transported to the draining mediastinal lymph nodes. Multiplication of the bacteria results in a high organism count in the blood, and production of bacterial toxins with the rapid onset of septicemia. Although bacterial replication can be controlled by antibiotics, the bacterial toxin continues to exert deleterious effects. In many patients, massive pleural effusions and hemorrhagic meningitis develop; pneumonitis is not usually present. Death is universal in untreated cases and occurs in as many as 95% of treated cases if therapy is begun more than 48 hours after the onset of symptoms. The current recommendation for anthrax treatment or post-exposure prophylaxis is antibiotics administered for 60 days. However, antibiotics have no activity against bacterial toxin and patient compliance with a 60 day treatment regimen is problematic. Anthrax Vaccine Adsorbed (AVA) is the current FDA-approved form of anthrax vaccine which contains a noninfectious, attenuated strain of *B. anthracis* absorbed to an adjuvant. The main protein component of the AVA vaccine is the protective antigen (PA), and antibodies generated against PA through vaccination protect susceptible animals from inhalational anthrax. However, the vaccine would not be effective in the event of an acute exposure; in addition, the multiple injections over 18 months plus annual boosters are required for protection using the AVA vaccine.

The anthrax toxin is a tripartite toxin that contains enzymatic and binding A and B moieties, respectively. The lethal factor (LF) and edema factor (EF) proteins function as the enzymatic A moieties of the toxin, while the protective antigen (PA) protein functions as the B, or binding, moiety. The bound EF and LF proteins are translocated from the endosome to the cytosol via the pore where they exert their toxic effects. Inhibition of PA binding to its cellular receptor can abrogate the downstream toxin mediated deleterious effects of the anthrax toxin. Raxibacumab is a fully human monoclonal antibody that blocks binding of the PA protein to its cell surface receptor and protects cells from the lethal effects of the anthrax toxin. Single prophylactic or immediate post-exposure administration of raxibacumab to rabbits exposed to a highly lethal spore burden showed a significant prolongation in time to death at all doses evaluated. A survival benefit has also been demonstrated with raxibacumab used as a post-exposure/prophylactic therapeutic treatment after the onset of symptomatic anthrax in rats and rabbits. Raxibacumab levels that accorded protection against lethality in these relevant animal models were used to define the human target antibody concentrations and provided the basis for the dose ranges evaluated in the Phase 1 clinical trial.

Raxibacumab was well tolerated by healthy volunteers in a Phase 1 study. In a raxibacumab/ciprofloxacin interaction study, the safety and PK of raxibacumab (40 mg/kg) administered IV in combination with oral and/or IV ciprofloxacin was examined. One of 32 subjects with a previous psychiatric history who received PO ciprofloxacin/IV raxibacumab experienced a SAE of schizophrenia. A total of 8 subjects experienced adverse events of rash that were Grade 1 (mild) or Grade 2 (moderate) in severity; 4 of the 8 events were observed within the 1st day of raxibacumab administration. Two of the subjects received only partial

infusions due to mild generalized urticaria. Rashes occurred in 6 of the initial 25 subjects dosed with raxibacumab. Premedication of subsequent subjects with diphenhydramine prior to administration of raxibacumab significantly reduced the occurrence of rash and only 2 out of 61 subjects developed a rash (1 considered related to raxibacumab) after diphenhydramine premedication. There were no clinically significant laboratory abnormalities. There was no consistent or meaningful impact of ciprofloxacin exposure on raxibacumab PK.

The BLA for raxibacumab was submitted for the indication of treatment of inhalational anthrax on May 14, 2009 and will undergo Priority Review, with a PDUFA date of November 14, 2009.

A brief synopsis of the protocols which the review division requested to be inspected is given below.

Protocol HGS1021-C1063: 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

This was a randomized, single-blind, placebo-controlled study of raxibacumab conducted between March 12 and July 22, 2008. Subjects were enrolled at 6 active centers in the United States. The primary objective of the study was to evaluate the safety and tolerability of intravenously (IV) administered raxibacumab in healthy subjects. The secondary objective was to determine serum raxibacumab concentrations for use in a population PK analysis. Eligible subjects were healthy adults > 18 years of age. Exclusionary criteria included history of acute or chronic disease, prior immunization against or prior treatment for anthrax, history of Type I hypersensitivity to food or drugs, history of urticaria, history of drug or alcohol addiction, previous exposure to raxibacumab, and participation in other clinical trials of an investigational compound within 60 days of initiating dosing in the current study. Subjects who had a history of malignancy, positive test for HIV, Hepatitis B surface antigen, or Hepatitis C antibody or had clinically significant abnormalities in an electrocardiogram were also to be excluded. Subjects, investigators, and clinical site staff were blinded to subject treatment assignments, while Human Genome Sciences, Inc. and the Safety Monitoring Board were not. Subjects were randomized to 1 of 2 raxibacumab groups (40 mg/kg double dose or 40 mg/kg single dose) or to 1 of 2 matching placebo groups at a ratio of 3:1 (raxibacumab:placebo). Subjects were stratified at randomization by age (< age 65 or ≥ age 65) with a target distribution of approximately 15% of the subjects in the single-dose cohorts ≥ age 65. Subjects in the double-dose cohorts received doses of raxibacumab or placebo on Days 0 and 14, while subjects in the single-dose cohorts were administered their dose on Day 0. Screening was to occur up to 28 days prior to dosing and included informed consent, performance of medical history, physical examination to include weight and vital signs, EKG, laboratory studies including hematology and clinical chemistry, urinalysis, pregnancy testing, and recording of concomitant medication. Study agent was administered on Day 0 after randomization, and laboratory testing, urinalysis, physical examination, EKG, pregnancy testing, PK sampling, immunogenicity testing, and recording of concomitant medications and adverse events. Follow-up visits occurred on Days 1, 2, and 7 and consisted of vital signs, laboratory testing, urinalysis, recording of concomitant medications, and adverse event monitoring. On Day 14, subjects on the double dose schedule received the second dose of

raxibacumab in addition to a physical examination, laboratory testing, urinalysis, PK sampling, immunogenicity testing, pregnancy testing, recording of concomitant medications, and adverse event monitoring. Subjects in the single dose group had the same study events on Day 14, with the exception of immunogenicity and pregnancy testing. Follow up visits occurred on Day 15, 16, 21, 28, 42, 56, and 70 in the double dose group, and on Day 28, 42, and 56 in the single dose group. At these visits, vital signs, laboratory studies, urinalysis, recording of concomitant medications, and adverse event monitoring were conducted. At selected visits delineated in the protocol, PK sampling, immunogenicity testing, and physical examinations were performed. A Safety Monitoring Board monitored the study. The first review occurred after 100 subjects were dosed and evaluated through Day 7, and the second review was conducted after 200 cumulative subjects were dosed and completed through Day 7 in the study. Safety and laboratory data were reviewed as they were received by the Human Genome Sciences monitor. The safety of raxibacumab was assessed by evaluation of the type, frequency, severity, and duration of adverse events, changes in laboratory parameters, physical examinations, monitoring of vital signs, and a determination of the immunogenicity of raxibacumab. Descriptive statistics were used to summarize the adverse events, routine laboratory parameters, vital signs and immunogenicity. All safety parameters were compared between the placebo and raxibacumab treatment groups.

Brief Summary of Results

A total of 700 subjects were screened to provide 322 randomized subjects for the study. Of the 322 randomized subjects, 320 subjects were treated (72 in the placebo single-dose group, 8 in the placebo double-dose group, 216 in the raxibacumab single-dose group, and 24 in the raxibacumab double-dose group). Raxibacumab-treated subjects did not have a higher incidence of adverse events, related adverse events, serious adverse events, or severe adverse events relative to subjects treated with placebo. Subjects in the double-dose group had a similar incidence of adverse events, related adverse events, or serious adverse events relative to subjects in the raxibacumab single-dose group. One subject in the placebo double-dose group died from injuries sustained in a motor vehicle accident; the event was considered not to be related to study agent. One subject in the raxibacumab double-dose group had a Grade 3 event of cholecystitis recorded as possibly related to raxibacumab; the adverse event began 10 days after the subject's 2nd raxibacumab infusion. In the raxibacumab single-dose group, 6/217 (2.8%) and in the placebo single-dose group 1/74 (1.3%) had a Grade 3 or higher laboratory abnormality. Diphenhydramine treatment was well tolerated. The incidence of rash was similar among raxibacumab-treated subjects (2.5%) and placebo-treated subjects (2.5%). All rashes were mild, 4 were related to study drug (all transient), and 2 were ongoing at the end of the study (all not related). No subjects developed an anti-raxibacumab antibody response, and none had a Grade 3 or higher laboratory abnormality.

Protocol HGS1021-C1064: 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

This was an open-label study to evaluate the safety and PK of combined administration of raxibacumab and ciprofloxacin in healthy adult male and female subjects. Subjects were enrolled at 3 United States centers between January 26 and August 28, 2007. Eligible subjects were healthy adults age 18 to 64 years with BMI 18 to 30 kg/m². Exclusionary criteria

included history of acute or chronic disease, prior immunization against or prior treatment for anthrax, history of hypersensitivity to food or drugs, history of urticaria, use of medications (other than birth control and vitamins), history of drug or alcohol addiction, and previous exposure to raxibacumab. Subjects who had a history of malignancy, positive test for HIV, Hepatitis B surface antigen, or Hepatitis C antibody were also to be excluded. Three treatment groups were evaluated. Group 1 received PO ciprofloxacin (500 mg q12h, Days 0 to 7), with a single raxibacumab (40 mg/kg) dose IV on Day 5. Group 2 received a single raxibacumab (40 mg/kg) dose IV on Day 0. Group 3 received a single IV ciprofloxacin (400 mg) dose on Day 0 immediately followed by a single IV raxibacumab (40 mg/kg) dose, a 2nd ciprofloxacin (400 mg) dose 12 hours later, and then PO ciprofloxacin (500 mg q12h, Days 1 to 7) for a total of 13 doses. The study phases included screening (subject eligibility and baseline assessments, Days -28 to -1), inpatient (study agent dosing and pre- and post-dose assessments, Days 1 to 7), and outpatient (follow-up) assessments on Days 8 to exit (final assessments, Day 61 for Group 1; Day 56 for Group 2 and Group 3).

Safety was assessed by the evaluation of the type, frequency, and severity of adverse events, changes in clinical laboratory parameters (hematology and clinical chemistry), immunogenicity, physical examinations, and monitoring of vital signs over time. The frequency and rate of adverse events were summarized based on MedDRA System Organ Class and preferred term.

Brief Summary of Results

A total of 90 subjects were randomized, 88 were treated, and 70 completed the study. Of the subjects who completed the study, 26 were in Group 1, 22 were in Group 2, and 22 were in Group 3. Raxibacumab was safe and well tolerated when administered at a dose of 40 mg/kg alone or in combination with 500 mg PO or 400 mg IV ciprofloxacin or both. Six subjects (6.8%) experienced infusion-related rashes considered related to raxibacumab during the study. Most subjects (60 of 61; 98.4%) who were premedicated with PO diphenhydramine did not develop a raxibacumab-related infusion reaction. There was no evidence of systemic hypersensitivity or anaphylactoid reaction in subjects with rash. No subject treated with raxibacumab had an anti-raxibacumab antibody response. Exposure to ciprofloxacin had no consistent or meaningful impact on raxibacumab PK.

The sites were selected based on number of subjects enrolled; the sites selected below enrolled over 43% of the total number of subjects in the BLA safety database for raxibacumab. The review team noted in their consult that initial brief review of the submission did not reveal specific concern regarding data integrity. This BLA application is the first for a monoclonal antibody to be considered for approval under the Animal Rule. Efficacy data for this application was obtained from animal model studies of inhalational anthrax treatment. Protocols HGS 1021-C1063 and HGS 1021-C1064 provide clinical safety data for the BLA, and the safety data from these studies is what is covered in the current assignment. **These two studies also obtained pharmacokinetic data; a separate GLP/Bioequivalence Assignment will be issued for inspectional coverage of the pharmacokinetic portion of these two studies.**

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects:	Inspection Date	Interim Classification	Final Classification
H. Frank Farmer Jr., MD, PhD, CPI 1900 Mason Ave., Ste. 140 Covance CRU, Inc. Daytona Beach, FL 32117	Protocol HGS1021-C1063, Site #US001: 70 subjects Protocol HGS1021-C1064, Site# US002: 9 subjects	8/10/09-8/19/09	VAI	Pending
David C. Carter, MD 313 East Anderson Lane Austin, TX 78752	Protocol HGS1021-C1063, Site #US002: 39 subjects Protocol HGS1021-C1064, Site# US003: 61 subjects	8/3/09-8/10/09	NAI	Pending
Human Genome Sciences 14200 Shady Grove Road Rockville, Maryland 20850	Protocol HGS1021-C1063 Protocol HGS1021-C1064	7/29/09-7/31/09	NAI	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. H. Frank Farmer Jr., MD, PhD 555 Winderley Placc, Suite 200 Maitland, FL 32751

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Protocol HGS1021-1064, there were 27 subjects screened and 9 subjects were enrolled into the study; 7 subjects completed the study and 2 were lost to follow-up. The informed consents for all subjects were reviewed during the inspection. Dosing and pharmacokinetic data were verified, and charts were reviewed for past medical history, inclusion and exclusion criteria, adverse events, and ECGs. For Protocol HGS1021-1063, there were 170 subjects screened and 70 subjects were enrolled; 67 subjects

completed the study, 1 subject was lost to follow-up, 1 withdrew due to job responsibilities, and 1 discontinued due to death in a motorcycle accident. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, and Dr. Farmer's written response dated September 14, 2009. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

- b. **General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

1. In Protocol HGS1021-1063 Exclusion Criterion #7 states that "evidence of active or suspected malignancy or history of malignancy within the last 5 years (with the exception of adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix)" is an exclusion criterion. Subject #49 was enrolled having had a squamous cell carcinoma removed in 2004.

Recordkeeping Violations [21 CFR 312.62(b)]

1. For Protocol HGS1021-C1064, the six infusion pumps used in this study to deliver study drugs were delivered to the site on 5/31/07. However, the Infusion Pump Verification Record completed by Dr. Farmer's staff, documents 5/23/07.
Medical Officer's Comment: In Dr. Farmer's written response, he acknowledges the incorrect date listed for Infusion Pump Verification and states that recording 5/23 was an error. There is no citation from the investigator regarding incorrect operation of the Infusion Pump. Therefore, it is unlikely that this violation affected data integrity.
2. For Protocol HGS1021-C1064, five sample processing logs (for Group 1 – including Study Days 5, 6, & 12) display a speed, duration, and/or temperature that do not correlate with those centrifuge parameters set forth in the protocol for the raxibacumab PK sample preparation.
Medical Officer's Comment: Dr. Farmer's written response states that confusion resulted from failure to maintain two separate logs for two analytes requiring different preparations for PK determination; the single sample log contained parameters pertinent to one analyte. Dr. Farmer states that it was the site's standard practice to follow the instructions provided by the sponsor contained in the Study Procedures Manual. Therefore, it is unlikely that this violation affected data integrity.
3. For Protocol HGS1021-C1064, the Study Day 12 log contains a late entry for a sample for Subject 05 collected and processed on 6/19/07, one day after the other four samples had been prepared. There was no notation that the centrifuge parameters were again verified prior to processing.
Medical Officer's Comment: Dr. Farmer's written response states that the subject missed the scheduled visit on 6/18/09; rather than use a new log to record subject

information, a notation was made regarding the missed visit and information was recorded in the log from 6/18/07 with a note explaining the missed visit.

4. For Protocol HGS1021-C1063, the infusion volume of the test article on Day 0 for Subjects 10 and 47 could not be determined due to a pump/malfunction/change.

Medical Officer's Comment: In Dr. Farmer's written response, he acknowledges that the infusion volume could not be determined from the read out on the pump.

However, the CRF for these two subjects was completed indicating that the total prepared dose was given the subjects. Therefore, although there was a recordkeeping violation, the subjects did receive the appropriate dose of study drug.

5. For Subject 59, the concomitant medication Aleve was administered on 5/3/08 (for headache) and on 6/11-6/12/08 (unknown indication), but the precipitating adverse event was not recorded. The use of Aleve on 6/11/08 was not recorded in the Concomitant Medications Log, although it was recorded in the source document.

- c. **Assessment of data integrity:** Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors significantly impacted safety outcomes of the study. The data from this site appear acceptable for use in support of the NDA.

2. **David C. Carter, M.D.**
313 E. Anderson Ln. Ste 200
Austin, TX 78752-1225

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Protocol HGS1021-1064, there were 137 subjects screened and 59 subjects were enrolled into the study; 43 subjects completed the study. The informed consent documents of all subjects were reviewed during the inspection and 20 subject records were reviewed in detail. For Protocol HGS1021-1063, there were 39 subjects enrolled and 35 subjects completed the study. The informed consent documents of all subjects were reviewed during the inspection and 13 subject records were reviewed in detail. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR, and the review division will be notified expeditiously.
- b. **General observations/commentary:** This inspection has been completed, and no Form FDA 483 was issued. As a Form FDA 483 was not issued at this site, it is unlikely that significant violations affecting data integrity occurred at this site.
- c. **Assessment of data integrity:** At this time, the data from this site appear acceptable for use in the NDA. If conclusions change when the EIR is reviewed, a CIS addendum will be generated and the review division notified.

3. **Human Genome Sciences**
14200 Shady Grove Rd
Rockville, MD 20850-7464

- a. **What was inspected:** The FDA investigators reviewed Human Genome Sciences procedures and records for Protocols HGS1021-C1063 and HGS1021-1064. The sponsor inspection occurred between July 29 and July 31, 2009. The observations noted are based on communications with the FDA field investigator and the EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** The inspection confirmed that Study HGS1021-C1063 was conducted at six clinical sites, with 322 subjects enrolled. A comparison of source records for 159 subject records against data line listings submitted to the FDA by the sponsor revealed no discrepancies related to adverse events, concomitant medications, eligibility criteria, or performance of study procedures. Study HGS1021-C1064 was conducted at three clinical sites, with 90 subjects enrolled. A comparison of source records for all subject records against line listings submitted to the FDA by the sponsor revealed no discrepancies related to adverse events, concomitant medications, eligibility criteria, or performance of study procedures. There were no objectionable observations for this inspection, and no Form FDA-483 was issued. There was a single issue discussed with regulatory management at the conclusion of the inspection regarding the lack of specificity in the firm's SOP for monitoring, in that there was no written description of the responsibility or format for preparing protocol-specific monitoring plans. However, the inspector noted in the EIR that study monitoring appeared to have been adequate.
- c. **Assessment of data integrity:** The data collected and maintained at the sponsor's site, as it pertains to the two clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810 appear consistent with that submitted to the agency as part of and in support of BLA 125349. It is unlikely that the observation noted above will impact data integrity or the final outcomes of the studies.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. There were no significant regulatory violations documented at Dr. Carter's site for Protocols HGS 1021-1064 and HGS 1021-1064. The inspections documented minor regulatory violations at Dr. Farmer's site regarding protocol and recordkeeping violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

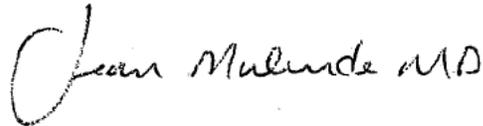
The data collected and maintained at the sponsor's site, as it pertains to the two clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810, appear consistent with that submitted to the agency as part of and in support of BLA 125349. **Please note that further recommendations will be forthcoming from the GLP/Bioequivalence Branch of DSI regarding the GLP portion of these inspections, as well as an additional GLP inspection in (b) (4).**

Follow-Up Actions: The observations noted above for Drs. Farmer, and Carter are based on preliminary communications with the FDA field investigators and the Form FDA 483 issued at Dr. Farmer's site, as well as Dr. Farmer's written response dated September 14, 2009 to the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.



Susan D. Thompson, M.D.
Medical Officer, Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:



Jean M. Mulinde, M.D.
Acting Team Leader
Good Clinical Practice Branch II
Division of Scientific Investigations

**Memorandum**

Date: September 25, 2009

From: M.Walton M.D. PhD. *MWA 10/2/09*

Subject: Consult on BLA 125349/0

To: Y.Yasinskaya, MD, Acting Team Leader, DSPTP/OAP

Synopsis of Consult Circumstances

This consult was requested on the basis of M.Walton's prior experience in review, development and regulation of monoclonal antibody products, including this product when the IND was first submitted. DSPTP is also requesting, among others, a formal neurology consult from DNP/ODE1.

Raxibacumab is a humanized monoclonal antibody directed against the anthrax protein PA, and important protein in the bacterium's pathological effects on an infected host, and is being developed for treatment of anthrax infection. Due to the nature of this indication, safety and efficacy studies cannot be done in the actual clinical indication setting, and the product has been developed with approval under the 'Animal Rule' as the goal. Clinical safety studies have been performed in healthy volunteers, and efficacy studies in animal models of infection in rabbit and in cynomolgus macaque monkey. Raxibacumab demonstrated efficacy in both of these animal studies. Human safety studies did not reveal any findings of sufficient concern to offset the significant potential for efficacy.

The basis for this consult is that in both of these studies an important, potentially safety related, observation was made. In short, in animals that were treated with raxibacumab but nonetheless did not survive, meningitis was observed more frequently than in the control animals, all of whom died and underwent necropsy. This raises the concern regarding the cause of the meningitis, and whether the antibody is directly contributing to meningitis.

Summary of Information Submitted to the BLA

Submissions from the sponsor and review documents of DSPTP were considered in preparing this memorandum.

The healthy human and monkey studies did not raise concerns for any CNS pathology. The concerns arise from the animal disease model efficacy studies.

In the rabbit study 17-19 animals in each of three groups were given aerosol challenge of B. anthracis at day 0 and treated with 0, 20mg/kg, or 40mg/kg of raxibacumab at designated timing related to onset of symptoms or serum PA levels. Treatment occurred typically approximately 1 day after anthrax challenge (range 20-36 hours). Survival results showed 0/17 placebo rabbits, 5/18 20mg/kg rabbits, and 8/18 40mg/kg rabbits survived, clearly demonstrating the efficacy of

raxibacumab in this model (ITT analysis; FDA primary analysis has fewer animals due to discounting of animals not clearly conforming to planned model, but same trend shown).

Animals found moribund were euthanized. Animals euthanized or found dead underwent necropsy (16 placebo, 12 at 20mg/kg, and 11 in 40mg/kg groups). Most pathologic findings were either similar or more severe in the placebo group. The notable exception is the CNS findings. CNS pathology, particularly reported as meningitis, was observed in 4/16 of the placebo group, 12/12 in the 20 mg/kg group, and 8/11 in the 40mg/kg group. The sponsor's analysis states that the animals in the placebo group died more quickly than the animals in the raxibacumab treated groups, as well as that the animals that showed CNS pathology died later than those that did not irrespective of treatment group. The sponsor interprets this to mean that CNS pathology is merely a late appearing aspect of anthrax infection, and only animals that survive somewhat longer will exhibit this pathology. DSPTP has done careful examination of the study data and determined that the study design had observation of the animals too infrequently for the time of death of the animals found dead to be precisely known as compared to the rate of the disease progression and the apparent differences between groups to be reliably analyzed and interpreted. Additionally, the 'time of death' for the euthanized animals is not fully comparable to those found dead. The available data are not inconsistent with the sponsor's hypothesis, but cannot be deemed as strongly supporting it.

In the cynomolgus monkey study 40 monkeys were randomized and treated with placebo (n=12) or raxibacumab (n=14 at 20mg/kg, n=14 at 40mg/kg). Animals were treated when PA protein was detected in a serum assay, and observed q6 hours. Efficacy results showed survival in 0/12 placebo group animals, 7/14 animals in the 20mg/kg group, and 9/14 animals in the 40mg/kg group, affirming the efficacy of raxibacumab in this animal model (ITT analysis; the FDA primary analysis discounting for non-bacterimic animals eliminated several animals from the analysis, but showed the same trend). Although observation was planned q6hrs, there were nonetheless animals found dead, while other animals found moribund were euthanized, and all these underwent necropsy.

In this study the CNS was again the only organ with more severe pathologic findings in the raxibacumab groups than the placebo group. CNS pathology in brain and meninges was seen in animals from 3/12 placebo group, 6/7 in the 20mg/kg group, and 3/5 in the 40mg/kg group. The gross pathology findings lead to further detailed examination of the CNS tissue. Raxibacumab treated animals had greater incidence and severity of lesions (inflammation, hemorrhage, necrosis), and more numerous and widespread bacteria compared to the placebo group animals, where bacteria were more often confined to blood vessels and immediate perivascular space. An independent pathology assessment emphasized the severity, particularly in meninges, is greater in raxibacumab treated animals. OCTEC/DSPTP analysis of the available data shows that the data do suggest that there is trend of longer survival time in the ultimately succumbing raxibacumab treated animals compared to the placebo animals, and that in all groups, animals who showed inflammation had longer disease courses than those that did not show inflammation. This was also the case for the presence of hemorrhage and necrosis. These data may also have limitations due to some animals being found dead (time of death not known within 6 hours) and issues of time-comparability for those who were euthanized (natural time of death not known). Among the surviving monkeys in the raxibacumab treated groups, no residual neurologic symptoms were observed in their general behavior.

The full study report for the tissue cross reactivity study showed no cross reactivity of raxibacumab with brain of rabbit, monkey or human brain tissue.

Assessment

Anthrax meningitis is a less common, but well recognized feature of anthrax infection in humans. Thus it is plausible that the CNS pathology observed here is related to the infection, and not to the antibody. However, the between group differences in incidence, in both animal models, clearly raises the concern that the antibody either directly causes the CNS pathology or interacts with the disease in a manner to enable such to occur. Direct causality would most likely be related to antigen specific portion of the antibody. There are a variety of other humanized monoclonal antibodies in marketed use, with extensive human exposure for many of them. There have been a limited number of reports of various kinds of clinical CNS adverse events reported as post-marketing events, however these have been comparatively rare, and generally are unclear in the actual relationship between the monoclonal antibody product and the CNS event.

Antibody direct causality

With regards to the concern for direct causality, no CNS pathology was seen in healthy animals exposed to raxibacumab, or CNS symptoms in healthy human volunteers. Given the substantial frequency of the CNS findings in the disease model studies, the absence of findings in the healthy animal and human studies decreases concern for direct causality in so far as the antibody gained exposure to the relevant tissue. However, it should be borne in mind that in a healthy animal or human the antibody will be largely excluded from the CNS, including the interior surface of the meninges. The tissue cross-reactivity studies did allow for exposure of the antibody to CNS tissue, and did not show significant binding.

In relation to this, while including brain parenchyma, the reported CNS lesions were highlighted as meningitis. In the tissue cross-reactivity study, the tissue reported was 'brain'. It is not stated whether or not any meninges were included within the tested tissue. It may be worthwhile to see if that question could be clarified by returning the original slides, a more detailed description of what was on the tested slides (if such exists), or the source of the tissues, to determine clearly if meninges were present or absent from the slides. If meninges were absent from the tissues tested, consideration can be given to retesting cross reactivity to all three species CNS tissues with the definite inclusion of meninges. If meninges is tested and shows no cross-reactivity the concern for direct adverse effect to normal tissues can be deemed remote (unless there were some concern that the preparative method for the tissues might have altered some of the potential tissue binding sites).

Antibody causality only in the presence of anthrax infection

A second question is whether the antibody may be the causative agent of the CNS pathology, but only in the presence of anthrax infection. This can be conceived of by two avenues.

One avenue is that the antibody would bind to brain and/or meninges, but in the healthy animal/human has no access to the binding sites due to the blood brain barrier. However, in the presence of infection, potentially the direct bacterial action and/or the significant inflammatory

responses that occur with that, raxibacumab gains entry into the CNS, binds, and causes increased inflammatory activity and injury. However, this avenue would seem to be evaluable by the above discussed tissue cross reactivity studies. If there were significant residual concern regarding this potential avenue, a rabbit study where healthy rabbits were given raxibacumab followed by one of the agents that causes transient blood brain barrier disruption to allow antibody entry into the CNS could be considered. However, this option would seem of low likelihood to provide additional insight unless there were some reason why the tissue cross-reactivity studies could not be relied upon to provide full sensitivity to the same internally-only facing ligands.

A second avenue is that the antibody is the causative agent, but only when the infection has induced new ligands to be expressed either on the surface of the cells in the CNS or internally (and these internal proteins then made available as the cells lyse from the infection). There is potential that this might be evaluated by doing cross reactivity studies with CNS tissue from disease model animals in the placebo group which are euthanized or necropsied shortly after natural disease caused death. If this were the mechanism, it would be hard to know if the tissue samples were from an animal where the these neo-antigens were expressed, and thus might warrant a number of animals to provide tissues to assay for the development of a new ligand. If further disease model studies are planned, it can be considered to take tissue samples to employ in this manner. The likelihood of this mechanism actually occurring should be considered carefully by experts in cell biology prior to proceeding to create additional disease model animals solely for this purpose, however.

Additionally, for both of these avenues to CNS pathology, it seems likely to be occurring in all infected animals treated with raxibacumab. In that case, CNS lesions would be expected to have occurred even in the animals who ultimately did survive the infectious challenge. The monkeys are reported to have exhibited no residual apparent CNS injury among those who survived. Observations are limited in sensitivity, but do offer some reassurance. Having necropsy examination of the surviving rabbits or monkeys would have provided greater reassurance.

Antibody creates a permissive set of circumstances

Finally, an additional mechanism to consider is the one proposed by the sponsor. Anthrax meningitis is a recognized manifestation of the disease course. The determinants of whether this manifestation occurs are not known. It is plausible that a critical factor is that there is sufficient time after the infection becomes systemic to breach the blood brain barrier and gain access to the restricted CNS compartment prior to demise. However, how long this additional period of infection-exposure must be is not known. If this is the key factor CNS pathology is expected to be seen more frequently in a treated group where the treatment effect slowed the infection's destructiveness on other organs, but was insufficient to allow eradication of the infection. The CNS can be highly sensitive to this type of pathologic process once the blood brain barrier is breached, and it is plausible that only a few hours are needed to transition from no significant CNS lesions to the substantial number of lesions seen in these animals. Thus, the confounding due to the time gaps between observations of the animals and from the incomplete comparability of time of natural disease-death and time of euthanasia, as well as the potential for significant variability from animal to animal in time of transition to exhibiting CNS lesions, may impair discerning the time-relationship. Nonetheless, the data appear to offer some suggestion of this time difference.

The possibility of this being the mechanism for the CNS lesions could potentially be further evaluated in new animal studies with revised design to improve sensitivity to this process through increased frequency of observation, dosing to ensure a significant number of animals with various degrees of ultimately inadequate treatment, and planned evaluation of CNS from surviving animals as well. However, since it is likely that there are a variety of factors that contribute to the variability of this disease model, it may be a difficult study to design and perform so as to have high likelihood of informative results.

Summary

The CNS lesions observed in these disease model studies seem to be similar to known manifestations of anthrax infection. There is not a necessity to conclude that some anthrax-unrelated process has occurred.

A direct and sole causal relationship of the antibody and the CNS lesions appears to be of lower likelihood than other mechanisms, given the good safety experience of the product in healthy animals and humans, the un concerning cross-reactivity studies, and the relative good safety profile of other humanized monoclonal antibody products. Nonetheless, following up on the cross-reactivity studies to confirm there is no cross-reactivity with animal or human meninges is worthwhile.

The possibility of antibody cross-reactivity with CNS/meninges ligands expressed only in presence of anthrax infection should be discussed with personnel with greater expertise in such phenomena prior to pursuing, and may be deemed low likelihood after greater reflection. If not deemed sufficiently unlikely, perhaps cross-reactivity tests in tissue samples from moribund untreated disease-model animals, and examining brain from treated and surviving disease model animals would offer some useful information. If no evidence to support this process were found in these examinations, concern that this is the operative process may be decreased.

The hypothesis that requires the least new and unknown phenomena to explain the CNS findings is that proposed by the sponsor. The sponsor's data are insufficient to be convincing, but have some suggestive elements. It appears that it would be possible, although potentially difficult to provide stronger evidence for this being the process leading to the differing incidence of CNS lesions. If this is the operative process, however, it does not pose a significant new safety issue for use in human infection. The CNS lesions appear to occur only when there is ultimately insufficient treatment to prevent demise, but that the patient would have died sooner without treatment. While certainly not a desired effect, it would not outweigh the clear expectation that the product would offer benefit to a substantial fraction of patients with anthrax infection at high risk of death without treatment.

Memo

Date: 8/18/2009

To: File

From: Barbara J. Wilcox, Ph.D. *BW*
Through: Eric Bastings, M.D. *EB*
Deputy Director, Division of Neurology Products
Lois M. Freed, Ph.D. *LMF*
Supervisory Pharmacologist

Consult #: 12733

Receipt Date: 6/22/2009

Subject: Consult request from the Division of Special Pathogens and Transplant Products regarding BLA125349 (reference IND 11069). Comments requested on brain histopathology findings for raxibacumab

Background:

Raxibacumab is a fully human monoclonal antibody directed against the protective antigen toxin of *B. anthracis*. This product is being developed for treatment of inhalational anthrax. BLA 125349 was submitted under the Animal Rule due to the lack of available human subjects infected with *B. anthracis*. Therefore, efficacy studies were conducted in 2 animal efficacy models:

- "Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model (Study 682-G005758)"
- "Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the *Cynomolgus macaque* (Study 724-G005829)."

The clinical safety data base is comprised of data from more than 300 healthy volunteers who were exposed to raxibacumab at the proposed therapeutic dose of 40 mg/kg or higher.

The results of both animal efficacy studies demonstrated a statistically significant dose related increase in survival of animals treated with raxibacumab relative to the respective placebo control groups. In both studies, the animals that died on study underwent necropsy and tissues were examined microscopically. Surviving animals were not sacrificed in either study. Therefore, no histopathology data in survivors are available for either study.

The gross and histopathology findings in the animals that died on study showed systemic anthrax infection, as evidenced by presence of bacteria and signs of inflammation in multiple tissues. The primary concern for this consult request is the findings of meningitis on both gross and microscopic examination in both species. The incidence and severity of the meningeal involvement was greater in the treated groups relative to the respective placebo groups in each study.

The table below summarizes the survival rate in each of the dose groups for each test species.

Species	Low dose group survival (survivors/total) %	High dose group survival	Control group survival
Rabbit	(4/16) 25%	(6/16) 35%	(0/13) 0%
Monkey	(5/12) 42%	(9/13) 69%	(0/10) 0%

The table below summarizes the incidence of meningitis in the animals that died on study in each dose group for each species.

Species	Low dose group Meningitis incidence	High dose group Meningitis incidence	Control group Meningitis incidence
Rabbit	12/12 (100%)	8/11 (72.5%)	4/16 (25%)
Monkey	6/7 (86%)	3/5 (60%)	3/12 (25%)

Histopathology of other tissues showed no significant differences in incidence and/or severity of lesions among groups in either study.

A discussion of the findings and possible interpretations was held on Friday, August 14, 2009 among representatives from DNP and DSPTP.

Questions:

Raxibacumab treatment provides a statistically significant survival benefit in inhalational anthrax disease in animals. However, the finding of meningeal bacteria, inflammation, and hemorrhage in the rabbits and monkeys treated with a fully-human monoclonal antibody needs to be better understood.

1. What is the plausibility and potential mechanism of monoclonal antibody-disease interactions resulting in the enhanced brain pathology findings in the monoclonal-treated animals compared to placebo animals?

Response:

In animals that died following anthrax exposure, the mechanism(s) underlying the findings of increased incidence and severity of meningitis in raxibacumab-treated animals relative to those treated with placebo is unknown. The concern that the presence of the monoclonal antibody may have facilitated brain infection cannot be ruled out, but the mechanism for such an effect cannot be determined from the data available. One hypothesis would be that raxibacumab provided peripheral protection against blood-borne anthrax, but was not able to penetrate the blood-brain barrier so could not protect against brain infection. Monoclonal antibodies are not thought to cross the blood-brain-barrier easily since the molecular size of these molecules (approximately 150 kDa) limits their volume of distribution to only slightly greater than the vascular space. They do not normally penetrate cellular membranes. Therefore, unless the blood-brain barrier is compromised (or an as yet unknown carrier mechanism is present), the presence of significant amounts of raxibacumab would not normally be expected in the CSF, meninges or CNS tissue. Measurements of drug levels in the CSF of the surviving or sacrificed animals are not available, so it is not known if, or the extent to which,

raxibacumab gained access to the CNS in the efficacy studies. Unless tissue handling and preservation preclude analysis, it may be possible to detect the presence of raxibacumab in retained brain tissue and meninges of the sacrificed animals using immunohistochemistry. The results of such investigations may provide useful data for developing hypotheses regarding the mechanism behind the apparent increase in meningitis in the treated monkeys.

2. What are the implications of brain pathology findings in animals for human safety and risk benefit assessment?

Response:

This question cannot be answered until a thorough assessment has been conducted. It is not clear why histopathology was not conducted in the animals that survived the anthrax infection, as would typically be expected in a pivotal study. If only animals that die from the anthrax infection exhibit evidence of meningitis, it may not be as important to determine the cause of the meningitis, particularly since raxibacumab protected against anthrax-induced lethality. If, however, survivors are similarly affected, then further investigation would certainly be warranted. With the available data, there is no clear way to determine if the brain findings in the animals that died are relevant.

3. Are there ways to mitigate the observed pathology?

Response:

Until the mechanism(s) behind the pathology and relevance can be better defined, it is difficult to determine how the pathology can be mitigated.

Recommendation:

- We recommend that the sponsor repeat the animal efficacy studies.
 - Histopathology should be performed on all study animals, including survivors.
 - In light of the meningitis findings, the repeat studies should include measurements of raxibacumab in CSF and brain tissue.
 - Monitoring for development of anti-drug antibodies should be included in the repeat studies.
 - Animals used in the repeat studies should be verified as treatment naïve and anti-drug antibody naïve prior to initiation of the study.
- We suggest, if possible, immunohistochemical staining of retained tissue samples of brain and meninges from Study # 724-G005829 and 682-G005758 for presence of raxibacumab to address the question of blood brain barrier penetration by the monoclonal antibody.

BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information	
BLA license # 1820	BLA STN # 125349/0
Proprietary Name: none Established/Proper Name: raxibacumab Dosage Form: IV Strengths: 1700 mg/34 mL	
Applicant: Human Genome Sciences, Inc.	
Date of Application: May 13, 2009 Date of Receipt: May 14, 2009 Date clock started after UN: N/A	
PDUFA Goal Date: November 14, 2009	Action Goal Date (if different): November 13, 2009 (Friday)
Filing Date: July 13, 2009 Date of Filing Meeting: June 10, 2009	
Proposed Indication(s): Treatment of inhalation anthrax	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
This BLA was submitted under 21 CFR 601, Subpart H.	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> No	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input checked="" type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
List referenced IND Number(s): 11,069	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Are the proprietary, established/proper, and applicant names correct in tracking system?</p> <p><i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?</p> <p><i>If not, ask the document room staff to make the appropriate entries.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
<p>Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i></p> <p>If yes, explain:</p> <p>If yes, has OC/DMPQ been notified of the submission?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
<p>Form 3397 (User Fee Cover Sheet) submitted</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>User Fee Status</p> <p>Comments:</p>	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<p><i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i></p>	
Exclusivity	
<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments: N/A</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments: N/A</p>	<input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> N/A
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO
Format and Content	
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	<input checked="" type="checkbox"/> N/A
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments: Drug establishment registration number was being determined at time of submission. It was submitted to the FDA on June 18, 2009 (BLA 125349-005).</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p> <p>Comments: Some of the hyperlinks in the labeling do not work, but the applicant agreed to fix on June 18, 2009 (BLA 125349-005).</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments: FDA Form 3542a is not required in BLAs per Section 351 of the Public Health Service Act.</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note:</i> Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/> N/A (electronic submission or no CMC technical section) <input type="checkbox"/> YES <input type="checkbox"/> NO
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note:</i> Financial disclosure is required for bioequivalence studies that are the basis for approval.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Pediatrics

PREA

Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.

Are the required pediatric assessment studies or a full waiver of pediatric studies included?

- Not Applicable
- YES**
- NO

If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?

- YES
- NO

- *If no, request in 74-day letter.*
- **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)

- YES
- NO

Comments: Raxibacumab has an orphan drug designation and does not trigger PREA.

BPCA (NDAs/NDA efficacy supplements only):

Is this submission a complete response to a pediatric Written Request?

- N/A

If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).

- YES
- NO

Comments: N/A

Prescription Labeling

Check all types of labeling submitted.

- Not applicable
- Package Insert (PI)**
- Patient Package Insert**
- Instructions for Use
- MedGuide
- Carton labels**
- Immediate container labels**
- Diluent
- Other (specify)

Comments:

Is electronic Content of Labeling submitted in SPL format?

- YES**
- NO

If no, request in 74-day letter.

Comments:

Package insert (PI) submitted in PLR format?

- YES**
- NO

<p>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments: N/A</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments: HGS was asked to do further work on their labeling and the formatting. DDMAC consult will be sent by month 5.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>REMS consulted to OSE/DRISK?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): July 12, 2006 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): October 21, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 10, 2009

NDA/BLA #: 125349

PROPRIETARY/ESTABLISHED NAMES: raxibacumab

APPLICANT: Human Genome Sciences, Inc. (HGS)

BACKGROUND:

BB-IND 11,069 for ABthrax (raxibacumab) is a fully humanized IgG λ monoclonal antibody directed against the protective antigen on the surface 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, and BLA 125349, which was submitted on May 13, 2009. BLA 125349 was submitted under 21 CFR 601, Subpart H.

Raxibacumab is formulated as an injection for intravenous use. The recommended dose is 40 mg/kg infused over 2 hours after diphenhydramine pretreatment. HGS focused their raxibacumab development program for the treatment of inhalational anthrax under the Animal Rule using primary efficacy studies in monkeys and rabbits. Since the beginning of 2008, HGS submitted data under their IND for DSPTP to 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. DSPTP made this recommendation on January 30, 2009 following the submission and review of the CDC's amended protocol entitled "IND Protocol: Intravenous Administration of Raxibacumab as a Therapeutic Agent for Treatment of Inhalation Anthrax (IND 102964)" submitted January 22, 2009. The first shipment of raxibacumab was delivered to the SNS on February 5, 2009.

The developmental version of the product was referred to as the M10 product, and the drug product used in the rabbit and monkey efficacy studies and human pharmacokinetic and safety studies was the M11 product. The two primary efficacy studies were "Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model (Study 682-G005758)" and "Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the Cynomolgus macaque (Study 724-G005829)." The safety database included over 300 healthy individuals. This product is not expected to be distributed commercially and will be procured by the government for public health preparedness purposes.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Division Leadership	DD	Renata Albrecht	Y
	DDD	Eileen Navarro	Y
	DDS	Ozlem Belen	Y

Regulatory Project Management	RPM:	Rebecca McKinnon	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	Yuliya Yasinskaya		Y
Clinical	Reviewer:	Sue Lim Susan McCune	Y
	TL:	Yuliya Yasinskaya	Y
OSE	Reviewer:	Shawna Hutchins, DRISK Scott Dallas, DMEPA	N Y
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Maureen Davidson Lynette Berkeley	Y
	TL:	Shukal Bala	Y
Clinical Pharmacology	Reviewer:	Kimberly Berman	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Hongling Zhou Lan Zeng	Y Y
	TL:	Karen Higgins (covered by Cheryl Dixon)	N Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ying Mu	Y
	TL:	William Taylor	Y
Statistics, carcinogenicity	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	David Frucht	Y
	TL:	Kathleen Clouse	N
Facility (<i>for BLAs/BLA supplements</i>) OC/DMPQ/BMT	Reviewer:	Mary Farbman (DS) Colleen Thomas (DP)	N Y
	TL:	Patricia Hughes (covered by Anastasia Lolas)	N Y
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (DSI)	Reviewer:	Sue Thompson	Y
	TL:	Tejashri-Purohit Sheth	N

Other reviewers: Pharmacogenomics Pharmacometrics	Shashi Amur, OCP Kevin Krudys, OCP	Y Y
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OTHER ATTENDEES:

Laura Dillon, Project Manager, OC/DMPQ/BMT
 Ginneh Stowe, Public Health Analyst, Maternal and Pediatric Health Team, OND-IO
 John Lazor, Director, OCP
 Darrell Jenkins, PM/TL, OSE
 Cheryl Turner, PM, OCTEC
 Mike Skelley, DSI

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Electronic Submission comments List comments:	<input checked="" type="checkbox"/> N/A
CLINICAL Comments: Case report forms and protocol certification or summary of changes requested and received	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Advisory Committee Meeting needed? Comments: NME and first in class and counterterrorism product for the SNS and public health emergencies If no, for an original NME or BLA application, include the reason. For example: <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public</i> 	<input checked="" type="checkbox"/> YES Date if known: October 27, 2009 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></p>	
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments: Assay SOPs, Lot #s, and dataset certifications requested and received.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (not applicable - BLA)</p>
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Ed Cox, M.D., Director, OAP</p> <p>GRMP Timeline Milestones: GRMP calculator completed</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Patent Information FDA Form 3542A will be requested.</p> <p><input type="checkbox"/> Standard Review</p>

<input checked="" type="checkbox"/>	Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Rebecca McKinnon, PharmD.
 Regulatory Project Manager
 Division of Special Pathogen + Transplant Products
 OAP/OND/CDER/FDA
 July 13, 2009

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

/s/

JANE A DEAN
07/17/2012