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*APPLICATION NUMBER:*

**125349Orig1s000**

**CHEMISTRY REVIEW(S)**

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

## Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date:

OND's goal date for taking action on this BLA is 29-Nov-2012.

The PDUFA date is 15-Dec-2012.

Applicant Name: Human Genome Sciences

U.S. License #: 1820

STN(s): 125349

Product(s): raxibacumab

Short summary of application: BLA resubmission in response to CR letter dated 14-Nov-2009. Raxibacumab is indicated for the treatment of inhalation anthrax.

---

## FACILITY INFORMATION

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Drug product (DP) manufacturing. Some DP release testing. DP inspecting, labeling, and packaging. Short term DP storage. Preparation of DP for shipment.

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Inspected by (b) (4) and classified VAI. Although the VAI classification is listed as initial in FACTS, the final VAI classification has been confirmed with (b) (4). The inspection included comprehensive GMP surveillance coverage. The BTP, SVS, and SVL profiles were updated and are acceptable.

Manufacturing Location: (b) (4)  
 Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility testing for DP stability studies.

Inspected by (b) (4) and classified NAI. The CTX profile was updated and is acceptable.

Manufacturing Location: (b) (4)  
 Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)

Short summary of manufacturing activities performed: Container closure integrity testing for DP stability studies.

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

Manufacturing Location: Rockville, MD  
 Human Genome Sciences, Inc.  
 Traville Facility  
 14200 Shady Grove Road  
 FEI: 1000303703

Short summary of manufacturing activities performed: corporate headquarters responsible for BDS quality oversight and batch disposition, MCB and WCB storage, equivalency testing of WCB.

The most recent inspection reported under this FEI was conducted by CDER-DMPQ (b) (4) and classified VAI. This was a pre-licensing inspection that was limited to the manufacture of (b) (4) drug substance. In addition, raxibacumab responsibilities at this facility were specifically covered during a September 2009 CDER-led inspection that was classified VAI. Also, this facility was covered October 22 – November 2, 2012 during a BTL-DO surveillance inspection that has been initially classified NAI. That inspection has been recorded under FEI 3003782237. This site is acceptable for the responsibilities listed.

Manufacturing Location: Rockville, MD  
 Human Genome Sciences, Inc.  
 Belward Small Scale Manufacturing Facility  
 9910 and 9911 Belward Campus Drive  
 FEI: 3003782237

Short summary of manufacturing activities performed: BDS manufacturing, storage, release and stability testing (some methods), and shipment to DP manufacturing site; MCB and WCB manufacture; receipt, testing, and storage of raw materials.

Inspected by BLT-DO October 22 – November 2, 2012 and initially classified NAI. This was a comprehensive pre-approval / CGMP inspection for BLA 125349 that found BDS manufacturing operations acceptable. Although the inspection classification is not yet final in FACTS, BLT-DO has confirmed that the final classification will be NAI / acceptable. The TRP profile has been update and is acceptable. DGMFA finds this site acceptable for the purposes of this supplement.

Manufacturing Location: (b) (4)

(b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: unprocessed bulk release testing (b) (4) manufacture and testing of MCB and WCB

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

Manufacturing Location: (b) (4)

(b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: (b) (4)

Inspected by (b) (4) and classified VAI. Although the classification has not been finalized in FACTS, it has been confirmed as final (via phone) with (b) (4). The CTL profile was updated and is acceptable.

**Overall recommendation:**

There are no pending or ongoing compliance actions that prevent approval of this BLA.

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/s/  
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TIMOTHY J POHLHAUS  
11/28/2012

**Product Quality Review Addendum  
CR letter Response  
BLA 125349.25  
Raxibacumab [Human Genome Sciences (HGS), Inc.]**

**Reviewed by: Chen Sun M.D., Ph.D., Product Quality Reviewer, Division of Monoclonal Antibodies**

**Team Leader: David M. Frucht, M.D., Product Quality Reviewer, Division of Monoclonal Antibodies**

**Division Director: Kathleen A. Clouse, Ph.D., Director, Division of Monoclonal Antibodies**

**Submission Date: June 15, 2012**

**Decision Date: December 15, 2012**

**Executive Summary:** Raxibacumab is a recombinant, human, IgG1 $\lambda$  monoclonal antibody that binds the protective antigen (PA) of *Bacillus anthracis* (*B. anthracis*) with high affinity and inhibits PA binding to anthrax toxin receptors, thereby protecting cells from anthrax toxin-mediated effects. Raxibacumab is indicated (b) (4)

The Biologics Licensing Application (BLA) for raxibacumab was originally submitted on 13 May 2009 by HGS, and a Complete Response Letter (CRL) was sent to the Sponsor from FDA on 14 November 2009. In November 2010, the Sponsor's request for a 2-year BLA filing extension was approved by FDA. In this resubmission, HGS provides responses to address the deficiencies identified in the CRL, pediatric dosing per the FDA request dated 23 March 2012, and updated product quality information in the quality sections (table 3). The new/amended text is marked in bold to distinguish it from material previously submitted and reviewed. Reviewer comments are in bold font and italicized.

**New Data Included In This Re-submission (As summarized from the BLA supplement):**

**3.2S.1.1 Nomenclature**

The updated NDC number is 49401-103-01

**3.2S.2.1 Manufacturer(s)**

HGS has added the information regarding the contract testing organization (CTO) that is responsible for viral clearance studies of raxibacumab drug substance.

Contract Testing Organization  
(Establishment Registration No.):

Address:

Responsibility:

Name of Contact Person:

Telephone Number for Contact Person:

E-mail Address for Contact Person:

Fax Number for Contact Person:

(b) (4)

HGS changed the CTO for genetic stability and identity tests of raxibacumab (from (b) (4) to (b) (4)). In addition, updated contact information for manufacturers (b) (4) is included. Corrections to typographical errors have also been made.

(b) (4)

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/s/  
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CHEN SUN  
11/15/2012

DAVID M FRUCHT  
11/15/2012

KATHLEEN A CLOUSE STREBEL  
11/15/2012

**BLA 125349 Chemistry Assessment [Raxibacumab, Human Genome Sciences (HGS), Inc.]**

**CTD Module 3.2 and immunogenicity assays**

**Reviewed by:**

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

**Team Leader:**

**Kathleen A. Clouse, Ph.D., Director, Division of Monoclonal Antibodies**

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## Introduction

Raxibacumab is a recombinant, fully human, IgG<sub>1</sub>λ monoclonal antibody with a molecular weight of ~146 kilodaltons (kDa) that binds the protective antigen (PA) of *Bacillus anthracis* (*B. anthracis*) with high affinity and inhibits PA binding to anthrax toxin receptors, thereby protecting cells from anthrax toxin-mediated effects. The Sponsor of raxibacumab is Human Genome Sciences, Inc. (HGS). Raxibacumab is expressed in the NS0 mouse myeloma cell line, secreted into culture media, and purified by a series of chromatography and filtration steps. The proposed commercial final drug product for raxibacumab is provided as a sterile, liquid formulation of 35.1 mL for single use in 50 mL, (b) (4) glass vials, sealed with a rubber stopper and a flip-off seal, and stored at 2-8°C. Each vial contains 50 mg/mL raxibacumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5.

Raxibacumab is indicated (b) (4)

(b) (4) The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. HGS proposes that raxibacumab can be administered alone or in combination with antimicrobials. Raxibacumab is intended to be administered as soon as a presumptive diagnosis of inhalation anthrax has been made. A premedication regimen of diphenhydramine administered within 1 hour prior to raxibacumab treatment is recommended for the prevention of infusion and hypersensitivity reactions.

The mechanism of action of anthrax toxin has been well characterized and widely reported. Briefly, the anthrax toxin is a protein complex consisting of the enzymatic moieties, lethal factor (LF) and edema factor (EF), and a binding moiety, PA. The PA protein binds target cells of the host via the anthrax toxin receptors, anthrax toxin receptor-1 (ATR) and capillary morphogenesis gene-2 (CMG2). The PA-ATR interaction results in a conformational change whereby LF and/or EF bind and are internalized. The EF and LF proteins are ultimately translocated to the cytosol where they exert toxic effects, including disruption of cellular homeostasis leading to edema (via EF) and specific cleavage and inactivation of key signal transduction molecules, the mitogen activated protein kinase kinases by LT. Inhibition of PA binding to its cellular receptor can abrogate the downstream deleterious effects the anthrax toxin. Thus, the association between PA and its receptor represents a critical molecular junction in the progression of anthrax disease. Raxibacumab inhibits the anthrax toxin-mediated effects by preventing PA from binding to its receptor. Nonclinical studies demonstrate that raxibacumab specifically recognizes the PA toxin produced by *B. anthracis*, potently inhibits binding of PA to its receptors, and prevents PA-mediated cytotoxicity.

Because evaluation of new treatment options for inhalational anthrax is not possible in controlled clinical trials in humans for ethical concerns, raxibacumab efficacy was evaluated in 2 animal models (New Zealand white rabbits and cynomolgus monkeys) selected because they were thought likely to predict the effect in humans. Because these studies provide the primary efficacy support for licensure, they were designed and performed at a level expected for Phase 3 human clinical trials. Protocols and analytical plans pre-specified the study design and data analysis and were reviewed by the Food and Drug Administration (FDA). The efficacy studies were conducted under Good Laboratory Practice (GLP). Both studies met their pre-specified primary endpoint analyses: a single dose of 20 mg/kg or 40 mg/kg raxibacumab conferred a statistically significant increase in overall survival rate compared with placebo. In separate studies, the effect of the addition of raxibacumab to antimicrobial regimens was assessed for a therapeutic efficacy. The conclusions of these studies were unclear. In both animal models, the survival in the antibiotic alone arm was so high that a survival benefit was impossible to demonstrate. In addition, animals that received raxibacumab, but still died, showed higher levels of fibrino-neutrophilic inflammation in the brain. **The etiology and significance of these CNS findings are unknown, but**

**could represent a direct effect of raxibacumab on CNS tissues vs. evidence of protective immune reconstitution secondary to the blockade of immunosuppressive LT activity by raxibacumab.**

The safety of raxibacumab has been evaluated in over 400 healthy human volunteers, including 326 subjects treated with the proposed dose (40 mg/kg) with product manufactured (M11) and formulated (21-A) by the same process proposed for licensure. Raxibacumab was safe and well tolerated and non-immunogenic with single or repeat dosing in humans. Concomitant administration of raxibacumab with antibiotics in animals did not significantly alter antibiotic efficacy, nor did it alter the safety or pharmacokinetics of either antibiotic or raxibacumab in humans. In human clinical trials, administration of 40 mg/kg raxibacumab achieved serum levels of raxibacumab comparable with serum levels observed in rabbits and monkeys that provided maximal survival benefit. Raxibacumab is proposed to be administered in a single dose of 40 mg/kg IV over 2 hours.

Established pre- and post-exposure prophylaxis for anthrax involves the use of anthrax vaccine adsorbed (AVA) and antibiotics. Vaccination requires weeks to establish protective immunity and would not be effective in the event of acute exposure to anthrax spores. Limitations of antibiotics include the lack of activity against anthrax toxin, poor patient compliance, and inactivity against bioengineered antibiotic resistant strains of *B. anthracis*. Given the current prophylactic options, a mass exposure scenario is estimated to generate a death toll orders of magnitude greater than that realized in 2001. Therefore, the U.S. Government has made the development of a direct antitoxin a priority for civilian defense. Indeed, HGS has been awarded a contract for raxibacumab by the US Government, and this antibody has already been included in the U.S. Strategic National Stockpile (SNS) as an investigational agent for use in the event of an emergency. By directly targeting the anthrax toxin itself, raxibacumab provides a therapeutic intervention strategy that is complementary to antibiotic and vaccine-mediated prophylaxis.

3.2.S.1.1 Nomenclature

Recommended International Nonproprietary Name (INN):	Not applicable (see USAN)
Trade name:	Not applicable
Chemical name(s):	Immunoglobulin G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), difulvide with human monoclonal PA λ-chain, dimer
Company or laboratory code:	HGS1021, PA mAb, Abthrax™
Other non-proprietary name(s) (USAN):	raxibacumab
Chemical Abstracts Service (CAS) registry number:	565451-13-0
NDC	NDC number will be requested during BLA review

3.2.S.1.2 Structure

Raxibacumab is a fully human IgG<sub>1</sub> lambda (λ) antibody comprising two identical light chains and two identical heavy chains. Raxibacumab has (b) (4)

4

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/s/  
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DAVID M FRUCHT  
11/15/2012

KATHLEEN A CLOUSE STREBEL  
11/15/2012

## Product Quality Review Addendum

**Reviewed by:**

David M. Frucht, M.D., Product Quality Reviewer, Division of Monoclonal Antibodies *David M. Frucht*  
12 Nov 09

**Team Leader:**

Kathleen A. Clouse, Ph.D., Director, Division of Monoclonal Antibodies *K. Clouse*  
11/12/2009

**Product:** Raxibacumab, anti-anthrax protective antigen for treatment of inhalation anthrax

**Date:** 4 November 2009

**Summary:**

On 14 Sept 2009, HGS submitted an amendment to the BLA that included a proposal to (b) (4) expiry period for FDP to (b) (4) based on the submission of real-time data for 2 GMP lots (M11 process, full (b) (4) scale) and 2 developmental lots (M11 process, but (b) (4) scale) in a Changes Being Effected (CBE) supplement in November 2009. Specifically, HGS proposed to (b) (4) the expiry date based on the real-time stability data from Lots 71044 and 71051 in the upright position (commercial lots), and Lots AB50409-M38 and AB50409-M41 in the inverted position (developmental lots). In subsequent conversations, it was clarified that the stability of the two developmental lots was established under two additional stability studies designated studies #17 (AB50409-M38) and #19 (AB50409-M41). HGS stated that these studies included the following testing parameters: appearance, pH, protein concentration, reduced SDS-PAGE, SE-HPLC, CE-HPLC, osmolality, and potency: cAMP-based assay. The acceptability of using stability protocols M2106014, M2107012, M2109001, study #17, and study #19 to support (b) (4) expiry should be conveyed in the approval letter, with the stipulation that study #17 and study #19 protocols are submitted to the BLA and confirmed to conform to the description as outlined by HGS during these communications.

#### IV. ADMINISTRATIVE

##### A. Reviewer's Signature

Product Quality Reviewer: David Frucht, M.D. *David M. Frucht 19 Oct 2009*

##### B. Endorsement Block

Product Division Team Leader: Kathleen A. Clouse, Ph.D. *Kathleen A. Clouse  
10/19/2009*

Product Division Deputy Director: Patrick Swann, Ph.D. *Patrick Swann 10/19/2009*

Product Division Director: Kathleen A. Clouse, Ph.D. *K.A. Clouse  
10/19/2009*

##### C. CC Block

OBP Office Director: Steven Kozlowski, M.D.

Clinical Deputy Division Director: Eileen Navarro, M.D. (Acting)

Clinical Division Director: Renata Albrecht, M.D.

Clinical Office Director: Ed Cox, M.D.

Division of Monoclonal Antibodies File: BLA STN 125268

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

## Instructions:

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- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

---

## APPLICATION INFORMATION

PDUFA Action Date:

OND's goal date for taking action on this BLA is 29-Nov-2012.

The PDUFA date is 15-Dec-2012.

Applicant Name: Human Genome Sciences

U.S. License #: 1820

STN(s): 125349

Product(s): raxibacumab

Short summary of application: BLA resubmission in response to CR letter dated 14-Nov-2009. Raxibacumab is indicated for the treatment of inhalation anthrax.

---

## FACILITY INFORMATION

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Drug product (DP) manufacturing. Some DP release testing. DP inspecting, labeling, and packaging. Short term DP storage. Preparation of DP for shipment.

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Manufacturing Location: (b) (4)  
Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility testing for DP stability studies.

Manufacturing Location: (b) (4)  
Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: Container closure integrity testing for DP stability studies.

Manufacturing Location: Rockville, MD  
Human Genome Sciences, Inc.  
Traville Facility  
14200 Shady Grove Road  
FEI: 1000303703

Short summary of manufacturing activities performed: corporate headquarters responsible for BDS quality oversight and batch disposition, MCB and WCB storage, equivalency testing of WCB.

Manufacturing Location: Rockville, MD  
Human Genome Sciences, Inc.  
Belward Small Scale Manufacturing Facility  
9910 and 9911 Belward Campus Drive  
FEI: 3003782237

Short summary of manufacturing activities performed: BDS manufacturing, storage, release and stability testing (some methods), and shipment to DP manufacturing site; MCB and WCB manufacture; receipt, testing, and storage of raw materials.

Manufacturing Location: (b) (4)  
(b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: unprocessed bulk release testing (in vitro viral), manufacture and testing of MCB and WCB

Manufacturing Location: (b) (4)  
(b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: (b) (4)

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/s/  
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JANE A DEAN  
11/08/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Science  
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123  
29B Lincoln Drive, Bethesda, MD 20892

## The Quality Team Leader’s Executive Summary

**From:** David M. Frucht, M.D., Product Quality Team Leader  
Division of Monoclonal Antibodies (DMA)

**Through:** Kathleen A. Clouse, Ph.D., Director, DMA

**BLA Number:** 125349 (Original Submission in 2009, Complete  
Response in 2012)

**Product:** Raxibacumab

**Sponsor:** Human Genome Sciences, Inc.

**Date of Review:** October 11, 2012

# Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of raxibacumab is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents and is sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use from a product quality perspective (under conditions specified in the package insert).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable (language subject to ongoing negotiation)

HGS commits to developing and validating a new <sup>(b) (4)</sup> assay that has improved sensitivity and capability to detect a greater range of potential <sup>(b) (4)</sup> contaminants compared to the current assay and will provide this information as a prior approval supplement to the BLA by 30 June 2015.

## II. Summary of Quality Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

- Raxibacumab is a recombinant, human, IgG<sub>1</sub>λ monoclonal antibody with a molecular weight of ~146 kilodaltons (kDa) that binds the protective antigen (PA) of *Bacillus anthracis* (*B. anthracis*) with high affinity and inhibits PA binding to anthrax toxin receptors. <sup>(b) (4)</sup>

- Raxibacumab specifically recognizes the protective antigen (PA) protein produced by *B. anthracis*, and its mechanism of action is to inhibit PA binding to its receptors, thereby preventing PA-mediated cellular cytotoxicity. The biological effects of anthrax toxin have been well characterized and widely reported. The anthrax toxin is a protein complex consisting of the enzymatic moieties, lethal factor (LF) and edema factor (EF), and a

binding moiety, PA. The PA protein binds to target cells of the host via the anthrax toxin receptors, anthrax toxin receptor-1(ATR) and capillary morphogenesis gene-2 (CMG2). The PA-ATR interaction results in a conformational change, whereby LF and/or EF bind and are internalized. The EF and LF proteins are ultimately translocated to the cytosol where they exert toxic effects, including disruption of cellular homeostasis leading to edema (via EF) and specific cleavage and inactivation of key signal transduction molecules, the mitogen activated protein kinase kinases, by LT. Inhibition of PA binding to its cellular receptor can abrogate the downstream deleterious effects mediated by anthrax toxin. Thus, the association between PA and its receptor represents a critical molecular junction in the progression of anthrax disease. Nonclinical studies demonstrate that raxibacumab inhibits the anthrax toxin-mediated effects by preventing PA from binding to its receptor.

- (b) (4)  
The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. HGS proposes that raxibacumab be administered alone or in combination with designated antimicrobials. It is intended to be administered as soon as a presumptive diagnosis of inhalation anthrax has been made. A premedication regimen of diphenhydramine administered approximately 1 hour prior to raxibacumab treatment is recommended for the prevention of infusion and hypersensitivity reactions.
- Raxibacumab final drug product (FDP) is supplied as a sterile, preservative-free liquid formulation in vials. Each vial of raxibacumab is intended for single use and is packaged in an individual Unit Dose Carton to provide protection from light. (b) (4)  
A protocol to re-package product in the Strategic National Stockpile (SNS) has been reviewed and deemed acceptable. These lots will be labeled and packaged to reflect their licensed status.
- Raxibacumab should be stored at 2-8°C, protected from light. It does not contain preservatives; therefore, unused portions of raxibacumab should be discarded.
- Each raxibacumab FDP vial is filled with 35.1 mL of a 50 mg/mL raxibacumab solution (34 mL or 1700 mg deliverable) in a formulation containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5. Each vial contains 34 mL deliverable raxibacumab with a 1.1 mL overfill to ensure that the 34 mL deliverable can be fully recovered from the vial. The container closure for raxibacumab FDP is a 50 mL USP (b) (4) glass vial (b) (4), a 20 mm gray (b) (4) rubber stopper (b) (4), and a 20 mm flip-off aluminum seal (b) (4)
- The excipients used in the formulation of raxibacumab, as noted above, are citric acid, sodium citrate, sucrose, glycine, and polysorbate 80. The stability of raxibacumab is affected by pH, as determined by studying thermal transitions of the protein at various pH

levels using differential scanning calorimetry (DSC) and fluorescence, but there was no major impact on biological activity. Minimum degradation is observed (b) (4) and FDP is formulated at pH 6.5 with a lot release acceptance criterion of (b) (4) providing adequate stability. Citric acid and sodium citrate (b) (4) Glycine is included (b) (4), and sucrose is added (b) (4) Polysorbate 80 is added (b) (4)

- Studies performed to identify the properties relevant to the performance of FDP revealed that, in addition to pH, protein concentration is an important parameter for protein stability (aggregation) and viscosity. The proposed protein concentration acceptance criterion for commercial FDP is (b) (4). Excipient robustness studies show that protein concentrations ranging from (b) (4) do not impact FDP stability; syringe use studies show that FDP at 3 times the target concentration can be delivered in less than 10 seconds using a 26G ½ inch needle. Thus, protein concentrations (b) (4) have negligible impact on performance and manufacturability.
- The extinction coefficient for raxibacumab used for calculation of the final protein concentration was determined to be (b) (4) using the Edelhoch method as described by Pace, et. al. (1995). The concentration of raxibacumab is determined by measuring the absorbance wavelength at 280 nm and calculated using the Beer-Lambert law with the extinction coefficient noted previously. To lend confidence that the Edelhoch method for extinction coefficient determination was accurate, the concentration of raxibacumab was determined (b) (4). The reported difference (b) (4) between these two methods is (b) (4) thereby providing confidence in the accuracy of this method.
- The compatibility of raxibacumab with the container closure system was evaluated by performing stability studies of FDP in the upright and inverted position. The stability trajectory was found to be acceptable for long-term storage of the product at intended storage conditions. No differences were observed when raxibacumab was stored in the upright or inverted position, indicating that the product is compatible with both the (b) (4) glass vial and the stopper used in the container closure system. In addition, the Sponsor provided data from leachables and extractables studies, which were deemed acceptable from a product-risk perspective.
- Raxibacumab is delivered intravenously and diluted with normal saline prior to administration. The compatibility of raxibacumab with intravenous (IV) bags containing normal saline and administration sets was evaluated by diluting raxibacumab at 20 and 40 mg/kg doses at patient weights bracketing the lowest and highest doses. The effect of using an inline filter during administration was also evaluated. The quality of the samples, analyzed by SEC-HPLC, IE-HPLC, SDS-PAGE and potency showed that the quality of raxibacumab was not affected when infused at normal or very slow rates of infusion. In addition, adsorption of the protein to the IV bag or administration set was not observed. There were no differences in product quality or protein concentration when raxibacumab was delivered with or without an in-line filter. It is recommended that



performed to evaluate the effects of stress conditions on raxibacumab stability, evaluate the ability of release and characterization methods to monitor degradation products formed under the stress conditions, identify the degradation products formed under these stress conditions, and evaluate the effect of the degradation on raxibacumab bioactivity. The stress conditions evaluated included exposure to oxidants, high temperature and pH, wide pH range, metals, and thermal cycling. Degradation pathways observed in raxibacumab under the different stress conditions and the methods capable of detecting these pathways include (b) (4)

[Redacted]

These studies also documented that raxibacumab is light-sensitive.

- The *in vitro* potency assay is based on the ability of raxibacumab to bind to *B. anthracis* PA, thereby preventing PA from shuttling another anthrax toxin component, EF (a bacterial adenylate cyclase), into targeted CHO cells. (b) (4)

[Redacted]

- Raxibacumab is expressed in NS0 murine myeloma cells stably transfected with expression constructs for the antibody heavy and light chains. The cell bank system consists of a Master Cell Bank (b) (4) and a Working Cell Bank (b) (4)

[Redacted]

- Raxibacumab is manufactured using [REDACTED] (b) (4)
- The [REDACTED] (b) (4) impurities validated to be effectively cleared during manufacturing include [REDACTED] (b) (4)
- Major modifications to the raxibacumab drug substance and drug product manufacturing processes occurred only once during clinical development [REDACTED] (b) (4)

## B. Description of How the Drug Product is Intended to be Used

- Raxibacumab is indicated [REDACTED] (b) (4)
- Raxibacumab drug product is provided as a sterile, preservative-free liquid formulation in vials. Each vial contains 35.1 mL of a 50 mg/mL raxibacumab solution in a formulation containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5. Each vial contains a 1.1 mL overfill to ensure that the 34 mL deliverable drug product can be fully recovered from the vial. Each vial of raxibacumab is intended for single use and is packaged in an individual carton to provide protection from light.
- Recommended storage of raxibacumab is at 2-8°C, protected from light. Raxibacumab is packaged as a single use presentation. Formulation does not include preservatives, so any unused portion remaining in the vial must be discarded immediately.

- The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. HGS proposes that raxibacumab be administered alone or in combination with designated antimicrobials, but it is intended to be administered as soon as a presumptive diagnosis of inhalation anthrax has been made. A premedication regimen of diphenhydramine administered approximately 1 hour prior to raxibacumab treatment is recommended for the prevention of infusion and hypersensitivity reactions. Pediatric dosing recommendations have not been finalized, but it should be emphasized that the raxibacumab vials are intended for single use, as the formulation contains no preservatives.

### C. Basis for Approvability

- Raxibacumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Raxibacumab is manufactured consistently, leading to a safe and effective product for the intended indication; sufficient product quality data support its licensure.
- The approval letter should indicate that the HGS proposal to extend the expiration date for the final drug product to 60 months, based on data from two full-scale GMP lots and two (b) (4) developmental lots is acceptable. Protocol No. M2109001 (Version 3.0) should be approved as the stability protocol for commercial FDP. Protocol No. M2109002 (Version 4.0) should be approved as the stability protocol for commercial BDS.

### Quality Unit Assessment

#### I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is attached as a separate document that also includes review of the human anti-human antibody immunogenicity assay.

#### II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

##### A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

HGS contends that raxibacumab qualifies for a categorical exclusion under 21 CFR 25.31(c), and to their knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). We concur with this conclusion.

There is minimal impact expected of Raxibacumab manufacturing on the environment.

### **III. LIST OF DEFICIENCIES TO BE COMMUNICATED**

Not applicable.

#### IV. ADMINISTRATIVE

##### A. Reviewer's Signature

Product Quality Reviewer: Chen Sun, M.D., Ph.D

##### B. Endorsement Block

Product Division Team Leader: David Frucht, M.D.

Product Division Director: Kathleen A. Clouse, Ph.D.

##### C. CC Block

DMA Deputy Director: Patrick Swann, Ph.D.

OBP Office Director: Steven Kozlowski, M.D.

Clinical Team Leader: John Alexander, M.D.

Clinical Division Director: John Farley, M.D.

Clinical Office Director: Ed Cox, M.D.

Division of Monoclonal Antibodies File: BLA STN 125349

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/s/  
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DAVID M FRUCHT  
11/15/2012

KATHLEEN A CLOUSE STREBEL  
11/15/2012

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

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Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date: December 15, 2012

Applicant Name: Human Genome Sciences, Inc

US License: 1820

STN(s): 125349

Product(s): Raxibacumab

Short summary of application: This is resubmission of BLA 125349 responding to the CR letter dated 14-November-2009.

---

## FACILITY INFORMATION

#1.

Firm Name: Human Genome Sciences, Inc.

Traville Facility

Address: 14200 Shady Grove Road

Rockville, MD 20850

FEI: 1000303703

Responsibility: Corporate headquarters with corporate responsibility for BDS manufacture, quality oversight, BDS and cell bank storage, and BDS batch disposition, BDS release testing (select methods), Storage of master cell bank (MCB) and working cell bank (WCB), and Equivalency testing of WCB.

Inspected by CDER-DMPQ from [REDACTED] (b) (4) and classified VAI. This was a pre-licensing inspection that was limited to the manufacture of [REDACTED] (b) (4) drug substance.

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

While the inspection focused on operations for another product, the inspectional coverage is sufficient to find the site acceptable for the responsibilities listed.

#2

Firm Name: Human Genome Sciences, Inc.  
Belward Large Scale Manufacturing (LSM) Facility  
Address: 9911 Belward Campus Drive  
Rockville, MD 20850  
FEI: 3003782237

Responsibility: Receipt, testing, and storage of raw materials, BDS release testing (select methods), Unprocessed bulk (UPB) release testing (bioburden) Stability testing, Shipment of BDS to contract fill-finish site.

Inspected by CDER-DMPQ from (b) (4) and classified VAI. (b) (4)

While the inspection focused on operations for another product, the inspectional coverage is sufficient to find the site acceptable for the responsibilities listed.

#3

Firm Name: Human Genome Sciences, Inc.  
Belward Small Scale Manufacturing (SSM) Facility  
Address: 9910 Belward Campus Drive  
Rockville, MD 20850  
FEI: 3003782237

Responsibility: Manufacture of BDS using M11 process, Storage of BDS, Manufacture of MCB (b) (4) Manufacture of WCB (b) (4) Storage of MCB and WCB, BDS release testing (select methods), and Stability testing.

Inspected by CDER-DMPQ from (b) (4) and classified VAI. (b) (4)

This facility should be inspected in support of operations listed for BLA 125349. A FACTS assignment -1431868 - was submitted to the BLT-DO on 8/14/12 to perform this inspection.

#4

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility: UPB release testing (b) (4) and Manufacture and testing of MCB and WCB.

Inspected by (b) (4) and classified NAI. This CGMP inspection found the CTL profile updated and acceptable.

#5

Firm Name: (b) (4)

Address: (b) (4)

(b) (4)  
 FEI: (b) (4)  
 Responsibility: (b) (4) testing of MCB, WCB, and UPB.

Inspected by (b) (4) and classified NAI. The inspection covered the firm's GLP operations and the practices of conducting (b) (4) for sponsors under contract. No profiles at this site.

#6  
 Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)  
 Responsibility: UPB release testing (b) (4)

Inspected by (b) (4) and classified NAI. This CGMP inspection found the CTL profile updated and acceptable.

#7  
 Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)  
 Responsibility: Storage of MCB and WCB.

A compliance evaluation is not necessary for the responsibilities listed in regards to this submission. However the facility was inspected by (b) (4) and classified NAI. This CGMP inspection found operations acceptable.

#8  
 Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)  
 Responsibility: Tested the genetic stability and identity by sequencing of MCB.

A compliance evaluation is not necessary for the responsibilities listed in regards to this submission. However the facility was inspected by (b) (4) and classified VAI. This inspection found testing operations acceptable.

Firm Name: (b) (4)  
 Address: (b) (4)  
 FEI: (b) (4)  
 Responsibility: Viral Clearance Studies

A compliance evaluation is not necessary for the responsibilities listed in regards to this submission. However the facility was inspected by (b) (4) and classified VAI. This inspection found testing operations acceptable.

Firm Name: [REDACTED] (b) (4)  
Address: [REDACTED] (b) (4)  
FEI: [REDACTED] (b) (4)

Responsibility: Tested the genetic stability and identity by sequencing of MCB.

A compliance evaluation is not necessary for the responsibilities listed in regards to this submission. This site has no inspectional history.

**Overall recommendation:**

Action on this BLA should not be taken until the inspection at HGS 9910 Belward Campus Drive is completed and evaluated for CGMP compliance.

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/s/  
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MAHESH R RAMANADHAM  
08/14/2012

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

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---

## APPLICATION INFORMATION

PDUFA Action Date: December 15, 2012

Applicant Name: Human Genome Sciences, Inc

US License: 1820

STN(s): 125349

Product(s): Raxibacumab

Short summary of application: This is resubmission of BLA 125349 responding to the CR letter dated 14-November-2009.

---

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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Address: 9911 Belward Campus Drive  
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FEI: 3003782237

Responsibility: Receipt, testing, and storage of raw materials, BDS release testing (select methods), Unprocessed bulk (UPB) release testing (bioburden) Stability testing, Shipment of BDS to contract fill-finish site.

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Firm Name: Human Genome Sciences, Inc.  
Belward Small Scale Manufacturing (SSM) Facility  
Address: 9910 Belward Campus Drive  
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FEI: 3003782237

Responsibility: Manufacture of BDS using M11 process, Storage of BDS, Manufacture of MCB (b) (4) Manufacture of WCB (b) (4), Storage of MCB and WCB, BDS release testing (select methods), and Stability testing.

#4

Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Responsibility: UPB release testing (b) (4) and Manufacture and testing of MCB and WCB.

#5

Firm Name: (b) (4)  
Address: (b) (4)

FEI: I looked this one up, no # provided.

Responsibility: (b) (4) testing of MCB, WCB, and UPB.

#6

Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Responsibility: UPB release testing (b) (4).

#7

Firm Name: (b) (4)  
Address: (b) (4)

FEI: (b) (4)

Responsibility: Storage of MCB and WCB.

#8

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility: Tested the genetic stability and identity by sequencing of MCB.

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/s/  
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MIN TANG  
08/03/2012

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date: 15-Dec-2012

Applicant Name: Human Genome Sciences

U.S. License #: 1820

STN(s): 125349

Product(s): raxibacumab

Short summary of application: BLA resubmission in response to CR letter dated 14-Nov-2009. Raxibacumab is indicated for the treatment of inhalation anthrax.

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## FACILITY INFORMATION

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Drug product (DP) manufacturing. Some DP release testing. DP inspecting, labeling, and packaging. Short term DP storage. Preparation of DP for shipment.

Inspected by (b) (4) and classified VAI. This was a CGMP inspection that found the SVS profile updated and acceptable.

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Manufacturing Location: (b) (4)  
Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility testing for DP stability studies.

Inspected by (b) (4) and classified NAI. This CGMP inspection found the CTX profile updated and acceptable.

Inspected by (b) (4)  
Manufacturing Location: (b) (4)  
Firm Name: (b) (4)  
Address: (b) (4)  
FEI: (b) (4)

Short summary of manufacturing activities performed: Container closure integrity testing for DP stability studies.

Inspected by (b) (4) and classified VAI. This inspection found the SVL profile updated and acceptable.

**OVERALL RECOMMENDATION:**

There are no pending or ongoing compliance actions that prevent approval of this BLA. Please resubmit this TB-EER 15-30 days prior to the planned action date.

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/s/  
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MAHESH R RAMANADHAM  
07/19/2012

**PRODUCT QUALITY (Biotechnology)**  
**FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number:  
**125349**

Applicant:  
**HGS**

Stamp Date:  
**15 June 2012**

Established/Proper Name:  
**Raxi documab**

BLA/NDA Type:  
**BLA**

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Form 356h completed <input checked="" type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	original BLA submission 1/2/14 under 21 CFR 25.31(c)
Comprehensive Table of Contents	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Labeling: <input checked="" type="checkbox"/> PI -non-annotated	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	N/A N/A N/A 7 <sup>32</sup> 2.3.5.1.1
<input checked="" type="checkbox"/> PI -annotated	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> PI (electronic)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> Medication Guide	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> Patient Insert	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> package and container	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input type="checkbox"/> diluent	<input type="checkbox"/> Y <input checked="" type="checkbox"/> N	
<input type="checkbox"/> other components	<input type="checkbox"/> Y <input checked="" type="checkbox"/> N	
<input checked="" type="checkbox"/> established name (e.g. USAN)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> proprietary name (for review)	<input checked="" type="checkbox"/> Y <input checked="" type="checkbox"/> N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> English (or translated into English)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
<input checked="" type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="checkbox"/> Y <input type="checkbox"/> N	
Companion application received if a shared or divided manufacturing arrangement	<input type="checkbox"/> Y <input checked="" type="checkbox"/> N	N/A

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="checkbox"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="checkbox"/> Y N	
Quality overall summary [2.3]	<input checked="" type="checkbox"/> Y N	
<input checked="" type="checkbox"/> Drug Substance	<input checked="" type="checkbox"/> Y N	
<input checked="" type="checkbox"/> Drug Product	<input type="checkbox"/> Y <input checked="" type="checkbox"/> N	<i>Not present, DP already reviewed &amp; except for <sup>new</sup> stability data, this is OK.</i>
<input checked="" type="checkbox"/> Facilities and Equipment	<input checked="" type="checkbox"/> Y N	
<input checked="" type="checkbox"/> Adventitious Agents Safety Evaluation	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Novel Excipients	<input type="checkbox"/> Y <input checked="" type="checkbox"/> N	<i>N/A</i>
<input checked="" type="checkbox"/> Executed Batch Records	<input checked="" type="checkbox"/> Y N	<i>3.2.R</i>
<input checked="" type="checkbox"/> Method Validation Package	<input checked="" type="checkbox"/> Y N	<i>3.2.5.4.3 &amp; 3.2.P.5.3</i>
<input checked="" type="checkbox"/> Comparability Protocols	<input checked="" type="checkbox"/> Y N	<i>3.2.5.2.6</i>

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	<input checked="" type="checkbox"/> Y N	
Drug Substance [3.2.S]		
<input checked="" type="checkbox"/> general info	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input checked="" type="checkbox"/> properties		
<input checked="" type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<input checked="" type="checkbox"/> Y N	
<input checked="" type="checkbox"/> description of manufacturing process and process control	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input checked="" type="checkbox"/> purification		
<input checked="" type="checkbox"/> filling, storage and shipping		
<input checked="" type="checkbox"/> control of materials	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input checked="" type="checkbox"/> cell banking system, characterization, and testing		
<input checked="" type="checkbox"/> control of critical steps and intermediates	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> stability		



**PRODUCT QUALITY (Biotechnology)**  
**FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <li>and sterilization validation</li> <li><input checked="" type="checkbox"/> Validation of aseptic processing (media simulations)</li> <li><input checked="" type="checkbox"/> Environmental Monitoring Program</li> <li><input type="checkbox"/> Lyophilizer validation</li> <li><input checked="" type="checkbox"/> Other needed validation data (hold times)</li> <li><input checked="" type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)</li> <li><input checked="" type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)</li> <li><input checked="" type="checkbox"/> reference standards or materials</li> <li><input checked="" type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> specifications (vial, elastomer, drawings)</li> <li><input checked="" type="checkbox"/> availability of DMF &amp; LOAs</li> <li><input checked="" type="checkbox"/> administration device(s)</li> </ul> </li> <li><input checked="" type="checkbox"/> stability</li> <li><input checked="" type="checkbox"/> summary</li> <li><input checked="" type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul>	<p align="center"><i>N/A</i></p> <p align="center">Y N</p>	
<ul style="list-style-type: none"> <li>Diluent (vials or filled syringes) [3.2.P.7]</li> <li><input type="checkbox"/> description and composition of diluent</li> <li><input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <li><input type="checkbox"/> preservative effectiveness</li> <li><input type="checkbox"/> container-closure integrity</li> </ul> </li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><input type="checkbox"/> description of manufacturing process for production through</li> </ul>	<p align="center"><i>N/A</i></p> <p align="center">Y N</p>	<p align="center"><i>N/A</i></p>



**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A]		
<input checked="" type="checkbox"/> facilities and equipment	<input checked="" type="radio"/> Y    N	
<input type="radio"/> manufacturing flow; adjacent areas		
<input type="radio"/> other products in facility		
<input type="radio"/> equipment dedication, preparation, sterilization and storage		
<input type="radio"/> procedures and design features to prevent contamination and cross-contamination		
<input checked="" type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.:	<input checked="" type="radio"/> Y    N	
<input type="radio"/> avoidance and control procedures		
<input type="radio"/> cell line qualification		
<input type="radio"/> other materials of biological origin		
<input type="radio"/> viral testing of unprocessed bulk		
<input type="radio"/> viral clearance studies		
<input type="radio"/> testing at appropriate stages of production		
<input type="checkbox"/> novel excipients	Y <input checked="" type="radio"/> N	N/A
USA Regional Information [3.2.R]		
<input checked="" type="checkbox"/> executed batch records	<input checked="" type="radio"/> Y    N	
<input checked="" type="checkbox"/> method validation package	<input checked="" type="radio"/> Y    N	
<input checked="" type="checkbox"/> comparability protocols	<input checked="" type="radio"/> Y    N	
Literature references and copies [3.3]	<input checked="" type="radio"/> Y    N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	<input checked="" type="radio"/> Y    N	
Includes data demonstrating consistency of manufacture	<input checked="" type="radio"/> Y    N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="radio"/> Y    N	
Describes changes in the manufacturing process, from material used in clinical	<input checked="" type="radio"/> Y    N	

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
trial to commercial production lots	(Y) N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
Certification that all facilities are ready for inspection	(Y) N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input checked="" type="checkbox"/> LAL instead of rabbit pyrogen <input checked="" type="checkbox"/> mycoplasma <input checked="" type="checkbox"/> sterility	(Y) N (Y) N (Y) N	USP <857 (previously reviewed) per 1993 PTC 3.2.5.4.1...1 used USP <717 (previously reviewed)
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y (N)	N/A
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

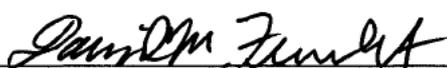
IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes  No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

*N/A*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

	<u>3 July 2012</u>
Product Quality Reviewer(s)	Date
	<u>3 July 2012</u>
Branch Chief/Team Leader/Supervisor	Date
	<u>3 July 2012</u>
Division Director	Date

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHEN SUN  
07/10/2012

DAVID M FRUCHT  
07/10/2012

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

## Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing<sup>1</sup> locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

---

## APPLICATION INFORMATION

PDUFA Action Date: 15-Dec-2012

Applicant Name: Human Genome Sciences

U.S. License #: 1820

STN(s): 125349

Product(s): raxibacumab

Short summary of application: BLA resubmission in response to CR letter dated 14-Nov-2009. Raxibacumab is indicated for the treatment of inhalation anthrax.

---

## FACILITY INFORMATION

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Drug product (DP) manufacturing. Some DP release testing. DP inspecting, labeling, and packaging. Short term DP storage. Preparation of DP for shipment.

(continued next page)

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<sup>1</sup>The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility testing for DP stability studies.

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Container closure integrity testing for DP stability studies.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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COLLEEN THOMAS  
07/09/2012



**BLA # 125349**

**Raxibacumab**

**Human Genome Sciences, Inc.**

**David M. Frucht, M.D** *David M. Frucht*  
**Division of Monoclonal Antibodies** *13 Oct 2009*



# Product Quality Review Data Sheet

1. BLA 125349

2. REVIEW #: 1

3. REVIEW DATE: 13-OCT-2009

4. REVIEWER: David M. Frucht, M.D.

5. COMMUNICATIONS AND PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-BLA meeting	21-OCT-2009
Telecon	16-JUL-2009
Telecon	04-AUG-2009
Telecon	21-SEP-2009
Telecon	28-SEPT-2009
Telecon	06-OCT-2009
Telecon	07-OCT-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
0000 (original submission)	14-MAY-2009
0001 (amendment)	27-MAY-2009
0002 (amendment)	08-JUN-2009
0003 (amendment)	10-JUN-2009
0006 (amendment)	24-JUN-2009
0009 (amendment)	20-JUL-2009
0011 (amendment)	04-SEP-2009
0012 (amendment)	14-SEP-2008
0013 (amendment)	14-SEP-2008
0015 (amendment)	23-SEP-2009



# PRODUCT QUALITY REVIEW TEMPLATE



## Chemistry Assessment Section

### 7. NAME & ADDRESS OF APPLICANT:

Name: Human Genome Sciences, Inc.  
Address: 9910 Belward Campus Drive  
Rockville, MD 20850  
Representative: Sally Bollmer  
Telephone: (301) 309-0311

### 8. DRUG PRODUCT NAME/TYPE:

- a) Proprietary Name: not applicable
- b) Non-Proprietary Name (USAN): Raxibacumab
- c) Other names: HGS1021, PA mAb, Abthrax<sup>TM</sup>
- d) Submission Priority: P

9. PHARMAC. CATEGORY: Anti-anthrax protective antigen IgG<sub>1</sub> monoclonal antibody

10. DOSAGE FORM: provided as a sterile liquid for injection in single-use vials

11. STRENGTH/POTENCY: Raxibacumab is provided at deliverable volume of 34 mL at a concentration of 50 mg/mL (1700 mg deliverable raxibacumab/vial)

Chemistry Assessment Section

**Table 3.2.P.1-1      Composition of commercial raxibacumab FDP**

Component	Concentration (mg/mL)	Amount Per Vial (mg/vial) <sup>1</sup>	Function	Grade
Raxibacumab	50	1700	(b) (4)	HGS Specification
Citric acid	0.13	(b) (4)		Multicompendial <sup>3</sup>
(b) (4)				
Sodium citrate	2.8			Multicompendial <sup>3</sup>
(b) (4)				
Sucrose	10			Multicompendial <sup>4</sup>
Glycine	18			Multicompendial <sup>3</sup>
Polysorbate 80	0.2			Multicompendial <sup>4</sup>
(b) (4)				USP

- <sup>1</sup> Amount listed is deliverable amount.
- <sup>2</sup> API: Active Pharmaceutical Ingredient
- <sup>3</sup> According to supplier's definition, multicompendial grade includes full compendial testing as appropriate to USP or National Formulary (NF), European Pharmacopoeia (EP), British Pharmacopoeia (BP), and Japanese Pharmacopoeia (JP).
- <sup>4</sup> According to supplier's definition, multicompendial grade includes full compendial testing as appropriate to USP/NF, EP, and JP.

12. ROUTE OF ADMINISTRATION: IV

13. ANIMAL- AND HUMAN-DERIVED RAW MATERIALS

Human Genome Sciences states that (b) (4) media are used throughout the process.

14. PRIMARY STRUCTURE, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURES:

Raxibacumab is a fully human IgG<sub>1</sub>λ antibody that binds PA with high affinity and inhibits PA binding to the anthrax toxin receptor. Raxibacumab is expressed in the NS0 mouse myeloma cell line and secreted into cell culture medium. The secreted raxibacumab is recovered from the (b) (4) medium (b) (4) and purified using a series of chromatographic and filtration steps. Raxibacumab has a molecular weight of approximately 146 kD. The expected amino acid sequence from the DNA construct of the heavy chain (b) (4) and the light chain (b) (4) are shown in Figure 3.2.S.3.1-1 below.

133 Page(s) have been withheld in full as b4 (CCI/TS) immediately following this page



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Science  
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123  
29B Lincoln Drive, Bethesda, MD 20892

## The Quality Team Leader's Executive Summary

**From:** Kathleen A. Clouse, Ph.D., Director  
Division of Monoclonal Antibodies (DMA)

**Through:** Patrick Swann, Ph.D., Deputy Director, DMA

**BLA Number:** 125349/0  
**Product:** Raxibacumab  
**Sponsor :** Human Genome Sciences, Inc.

**Date of Review :** October 19, 2009

# Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of raxibacumab is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use (under conditions specified in the package insert).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC-related deficiencies noted in the application which have been requested as post-marketing commitments (PMCs) by the sponsor.

## II. Summary of Quality Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

- Raxibacumab is a recombinant, fully human, IgG<sub>1</sub>λ monoclonal antibody with a molecular weight of ~146 kilodaltons (kDa) that binds the protective antigen (PA) of *Bacillus anthracis* (*B. anthracis*) with high affinity and inhibits PA binding to anthrax toxin receptors. (b) (4)

(b) (4)

- Raxibacumab specifically recognizes the protective antigen (PA) protein produced by *B. anthracis* and its mechanism of action is to inhibit PA binding to its receptors, which prevents PA-mediated cellular cytotoxicity. The biological effects of anthrax toxin have been well characterized and widely reported. The anthrax toxin is a protein complex consisting of the enzymatic moieties, lethal factor (LF) and edema factor (EF), and a binding moiety, PA. The PA protein binds to target cells of the host via the anthrax toxin receptors, anthrax toxin receptor-1 (ATR) and capillary morphogenesis gene-2 (CMG2). The PA-receptor interaction results in a conformational change whereby LF and/or EF

bind and are internalized. The EF and LF proteins are ultimately translocated to the cytosol where they exert toxic effects, including disruption of cellular homeostasis leading to edema (via EF) and specific cleavage and inactivation of key signal transduction molecules, the mitogen activated protein kinase kinases by LT. Inhibition of PA binding to its cellular receptor can abrogate the downstream deleterious effects mediated by anthrax toxin. Thus, the association between PA and its receptor represents a critical molecular junction in the progression of anthrax disease. Nonclinical studies demonstrate that raxibacumab inhibits the anthrax toxin-mediated effects by preventing PA from binding to its receptor.

- Raxibacumab is indicated (b) (4). The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. HGS proposes that raxibacumab be administered alone or in combination with antimicrobials. It is intended to be administered as soon as a presumptive diagnosis of inhalation anthrax has been made. A premedication regimen of diphenhydramine administered approximately 1 hour prior to raxibacumab treatment is recommended for the prevention of infusion and hypersensitivity reactions.
- Raxibacumab final drug product (FDP) is supplied as a sterile, preservative-free liquid formulation in vials. Each vial of raxibacumab is intended for single use and is packaged in an individual Unit Dose Carton to provide protection from light. (b) (4)
- Raxibacumab should be stored at 2-8°C, protected from light. It does not contain preservatives; therefore, unused portions of raxibacumab should be discarded.
- Each raxibacumab FDP vial is filled with 35.1 mL of a 50 mg/mL raxibacumab solution (34 mL and 1700 mg deliverable) in a formulation containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5. Each vial contains 34 mL deliverable raxibacumab with a 1.1 mL overfill to ensure that the 34 mL deliverable can be fully recovered from the vial. The container closure for raxibacumab FDP is a 50 mL USP (b) (4) glass vial (b) (4), a 20 mm gray, (b) (4) rubber stopper (b) (4) and a 20 mm flip-off aluminum seal (b) (4).
- The excipients used in the formulation of raxibacumab as noted above are citric acid, sodium citrate, sucrose, glycine, and polysorbate 80. The stability of raxibacumab is affected by pH, as determined by studying thermal transitions of the protein at various pH levels using differential scanning calorimetry (DSC) and fluorescence, but there was no major impact on biological activity. Minimum degradation is observed (b) (4), and FDP is formulated at pH 6.5 with a lot release acceptance criterion of (b) (4) providing adequate stability. The citric acid and sodium citrate (b) (4) Glycine is included (b) (4) and sucrose

is added (b) (4) Polysorbate 80 is added (b) (4)  
(b) (4)

- Studies performed to identify the properties relevant to the performance of FDP revealed that, in addition to pH, protein concentration is an important parameter for protein stability (aggregation) and viscosity. The proposed protein concentration acceptance criterion for commercial FDP is (b) (4) mg/mL. Excipient robustness studies show that protein concentrations ranging from (b) (4) mg/mL do not impact FDP stability; syringe use studies show that FDP at 3 times the target concentration can be delivered in less than 10 seconds using a 26G ½ inch needle. Thus protein concentrations (b) (4) (b) (4) have negligible impact on performance and manufacturability.
- The extinction coefficient for raxibacumab used for calculation of the final protein concentration was determined to be (b) (4) (b) (4), using the Edelhoch method as described by Pace, et. al. (1995). The concentration of raxibacumab is determined by measuring the absorbance wavelength at 280 nm and calculated using the Beer-Lambert law with the extinction coefficient noted previously. To lend confidence that the Edelhoch method for extinction coefficient determination was accurate, the concentration of raxibacumab was determined (b) (4) (b) (4). The reported difference (b) (4) (b) (4) between these two methods is (b) (4) (b) (4) providing confidence in the accuracy of this method.
- The compatibility of raxibacumab with the container closure system was evaluated by performing stability studies of FDP in the upright and inverted position. The stability trajectory was found to be acceptable for long-term storage of the product at intended storage conditions. No differences were observed when raxibacumab was stored in the upright or inverted position, indicating that the product is compatible with both the (b) (4) (b) (4) glass vial and the stopper used in the container closure system.
- Raxibacumab is delivered intravenously and diluted with normal saline prior to administration. The compatibility of raxibacumab with intravenous (IV) bags containing normal saline and administration sets was evaluated by diluting raxibacumab at 20 and 40 mg/kg doses at patient weights bracketing the lowest and highest doses. The effect of using an inline filter during administration was also evaluated. The quality of the samples, analyzed by SEC-HPLC, IE-HPLC, SDS-PAGE and potency showed that the quality of raxibacumab was not affected when infused at normal or very slow rates of infusion. In addition, adsorption of the protein to the IV bag or administration set was not observed. There were no differences in product quality or protein concentration when raxibacumab was delivered with or without an in-line filter. It is recommended that raxibacumab be used immediately after its removal from the protective packaging due to its light sensitivity.
- Stability studies on FDP were performed on commercial development lots with vials maintained in an upright or inverted position at the intended storage condition of 2-8°C. During the course of these studies, it was determined that the product was light-sensitive. Thus, ongoing studies are performed with samples protected from light. Raxibacumab



raxibacumab stability, evaluate the ability of release and characterization methods to monitor degradation products formed under the stress conditions, identify the degradation products formed under these stress conditions, and evaluate the effect of the degradation on raxibacumab bioactivity. The stress conditions evaluated included exposure to oxidants, high temperature and pH, wide pH range, metals, and thermal cycling. Degradation pathways observed in raxibacumab under the different stress conditions and the methods capable of detecting these pathways include (b) (4)

(b) (4)

(b) (4) These studies also documented that raxibacumab is light-sensitive.

- The *in vitro* potency assay is based on the ability of raxibacumab to bind to *B. anthracis* PA, thereby preventing PA from shuttling another anthrax toxin component, EF (a bacterial adenylate cyclase), into targeted CHO cells. (b) (4)

(b) (4)

- Raxibacumab is expressed in NS0 murine myeloma cells stably transfected with expression constructs for the antibody heavy and light chains. The cell bank system consists of a Master Cell Bank (b) (4) and a Working Cell Bank (b) (4)

(b) (4)

- Raxibacumab is manufactured (b) (4)  
(b) (4)

- The (b) (4) impurities validated to be effectively cleared during manufacturing include (b) (4)  
(b) (4)

- Major modifications to the raxibacumab drug substance and drug product manufacturing processes occurred only once during clinical development (b) (4)  
(b) (4)

**B. Description of How the Drug Product is Intended to be Used**

- Raxibacumab is indicated (b) (4)  
(b) (4)
- Raxibacumab drug product is provided as a sterile, preservative-free liquid formulation in vials. Each vial contains 35.1 mL of a 50 mg/mL raxibacumab solution in a formulation containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5. Each vial contains a 1.1 mL overfill to ensure that the 34 mL deliverable drug product can be fully recovered from the vial. Each vial of raxibacumab is intended for single use and is packaged in an individual carton to provide protection from light.
- Recommended storage of raxibacumab is at 2-8°C, protected from light. Raxibacumab is packaged as a single use presentation. Formulation does not include preservatives, so any unused portion remaining in the vial must be discarded immediately.

- The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. HGS proposes that raxibacumab be administered alone or in combination with antimicrobials, but it is intended to be administered as soon as a presumptive diagnosis of inhalation anthrax has been made. A premedication regimen of diphenhydramine administered approximately 1 hour prior to raxibacumab treatment is recommended for the prevention of infusion and hypersensitivity reactions.

**C. Basis for Approvability**

- Raxibacumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Raxibacumab is manufactured consistently, leading to a safe and effective product for the intended indication; sufficient product quality data support its licensure.
- The approval letter should indicate drug substance and drug product storage conditions and expiry dating (b)(4). In addition, the approval letter should note approval of the HGS proposal (b)(4) the expiration date for the final drug product (b)(4) based on data from two full-scale GMP lots and two (b)(4) developmental lots. The protocols to be approved for (b)(4) the expiration date of the commercial final drug product (FDP) to (b)(4) are as follows: M2106014, M2107012, M2109001, Study #17, and Study #19 . Protocols M2106014, M2107012, and M2109001 should also be approved to enable the extension of the FDP expiry to 60 months. Protocols M210611 and M2109002 should be approved as the stability protocol for (b)(4) the expiry of commercial BDS.

**Quality Unit Assessment**

**I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA**

The review of module 3.2 is attached as a separate document that also includes review of the human anti-human antibody immunogenicity assay.

**II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**

**A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION**

HGS contends that raxibacumab qualifies for a categorical exclusion under 21 CFR 25.31(c), and to our knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). There is minimal impact expected of Raxibacumab manufacturing on the environment.

**III. LIST OF DEFICIENCIES TO BE COMMUNICATED**

Not applicable.

**PRODUCT QUALITY (Biotechnology)**  
**FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: *125349*      Applicant: *Human Genome Sciences, Inc.*      Stamp Date: *14 May 2009*

Established/Proper Name: *Toxibacumab*      BLA/NDA Type: *BLA*

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="radio"/> Y <input type="radio"/> N	
Form 356h completed	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y <input type="radio"/> N	
Comprehensive Table of Contents	<input checked="" type="radio"/> Y <input type="radio"/> N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Labeling:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> PI –non-annotated <i>1.14.1.3</i>	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> PI –annotated <i>1.14.1.2</i>	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> PI (electronic)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> Medication Guide	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> Patient Insert	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> package and container	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> diluent	Y <input checked="" type="radio"/> N	<i>N/A</i>
<input type="checkbox"/> other components	Y <input checked="" type="radio"/> N	<i>N/A</i>
<input checked="" type="checkbox"/> established name (e.g. USAN)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> proprietary name (for review)	Y <input checked="" type="radio"/> N	<i>N/A; us &amp; n name to be used solely</i>

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input checked="" type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Companion application received if a shared or divided manufacturing arrangement	Y <input checked="" type="radio"/> N	<i>N/A</i>

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 2 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Overall CTD Table of Contents [2.1]	Y <del>N</del>	<i>Present for each major subsection</i>
Introduction to the summary documents (1 page) [2.2]	<del>Y</del> N	
Quality overall summary [2.3]	<del>Y</del> N	
<input checked="" type="checkbox"/> Drug Substance	<del>Y</del> N	
<input checked="" type="checkbox"/> Drug Product	<del>Y</del> N	
<input checked="" type="checkbox"/> Facilities and Equipment	<del>Y</del> N	2.3.A
<input checked="" type="checkbox"/> Adventitious Agents Safety Evaluation	<del>Y</del> N	3.2.A.2
<input type="checkbox"/> Novel Excipients	Y <del>N</del>	<i>N/A. All excipients compendial</i>
<input checked="" type="checkbox"/> Executed Batch Records	<del>Y</del> N	3.2.R
<input checked="" type="checkbox"/> Method Validation Package	<del>Y</del> N	3.2.S.4.3 & 3.2.P.S.3
<input checked="" type="checkbox"/> Comparability Protocols	<del>Y</del> N	3.2.S.2.6

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Module Table of Contents [3.1]	<del>Y</del> N	
Drug Substance [3.2.S]		
<input checked="" type="checkbox"/> general info	<del>Y</del> N	
<input checked="" type="checkbox"/> nomenclature		
<input checked="" type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input checked="" type="checkbox"/> properties		
<input checked="" type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<del>Y</del> N	
<input checked="" type="checkbox"/> description of manufacturing process and process control	<del>Y</del> N	
<input checked="" type="checkbox"/> batch numbering and pooling scheme		
<input checked="" type="checkbox"/> cell culture and harvest		
<input checked="" type="checkbox"/> purification		
<input checked="" type="checkbox"/> filling, storage and shipping		
<input checked="" type="checkbox"/> control of materials	<del>Y</del> N	
<input checked="" type="checkbox"/> raw materials and reagents		
<input checked="" type="checkbox"/> biological source and starting materials		
<input checked="" type="checkbox"/> cell substrate: source, history, and generation		
<input checked="" type="checkbox"/> cell banking system, characterization, and testing		
<input checked="" type="checkbox"/> control of critical steps and intermediates	<del>Y</del> N	
<input checked="" type="checkbox"/> justification of specifications		
<input checked="" type="checkbox"/> stability		









**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
Certification that all facilities are ready for inspection	Y N	<i>Defer to BMT</i>
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	<i>3.2.P.8</i>
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input checked="" type="checkbox"/> LAL instead of rabbit pyrogen <input checked="" type="checkbox"/> mycoplasma <input checked="" type="checkbox"/> sterility	(Y) N (Y) N (Y) N	<i>→ Some rabbit pyrogen data shown for DS. → States consistent with "Points to Consider..."</i>
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y (N)	<i>N/A not requested</i>
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	

**PRODUCT QUALITY (Biotechnology)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes  No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

*N/A*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- 1. Please provide data that demonstrates that your current endotoxin assay is an equivalent alternative to the rabbit pyrogen test.*
- 2. Please provide information regarding the derivation of the extinction coefficient used to determine protein concentration.*
- 3. Please provide a comprehensive list of each of the product classes for those products manufactured at (b)(4). All monoclonal antibodies should be listed with isotype and subclass.*

*Judith M. Fink*  
Product Quality Reviewer(s)

*9 June 2009*  
Date

*Kathleen A. Clouse*  
Branch Chief/Team Leader/Supervisor

*06/09/2009*  
Date

*Kathleen A. Clouse*  
Division Director

*06/09/2009*  
Date

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

**BLA/NDA Number:** 125349    **Applicant:** Human Genome Sciences, Inc.    **Stamp Date:** 15-May-2009

**Established/Proper Name:**    **BLA/NDA Type:** Priority requested  
Raxibacumab (ABthrax™)

On **initial** overview of the BLA/NDA application for filing:

<b>CTD Module 1 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Cover Letter	<u>Y</u>	
Form 356h completed <input type="checkbox"/> including list of all establishment sites and their registration numbers	<u>Y</u> <u>N</u>	Not all facilities have the registration number listed, DS facility registration pending
Comprehensive Table of Contents	<u>Y</u>	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	<u>Y</u>	Very brief
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y    N Y    N	Labeling states that product is sterile. Defer to OBP for rest.

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<u>Y</u>  <u>Y</u> <u>Y</u> <u>Y</u> <u>Y</u> <u>Y</u>  <u>Y</u>	
Companion application received if a shared or divided manufacturing	Y    N	N/A

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
arrangement		

<b>CTD Module 2 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>	
Overall CTD Table of Contents [2.1]	<u>Y</u>		
Introduction to the summary documents (1 page) [2.2]	<u>Y</u>		
Quality overall summary [2.3]	<u>Y</u>	Bioburden and endotoxins only	
<input type="checkbox"/> Drug Substance	<u>Y</u>		
<input type="checkbox"/> Drug Product	<u>Y</u>		
<input type="checkbox"/> Facilities and Equipment	<u>Y</u>		
<input type="checkbox"/> Adventitious Agents Safety Evaluation	<u>Y</u>		
<input type="checkbox"/> Novel Excipients	Y N		Defer to OBP
<input type="checkbox"/> Executed Batch Records	Y N		Defer to OBP
<input type="checkbox"/> Method Validation Package	<u>Y</u>		
<input type="checkbox"/> Comparability Protocols	Y N		N/A

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Module Table of Contents [3.1]	<u>Y</u>	
Drug Substance [3.2.S]		DS site registration pending
<input type="checkbox"/> general info	<u>Y</u>	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<u>Y</u>	
<input type="checkbox"/> description of manufacturing process and process control	<u>Y</u>	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	<u>Y</u>	OBP Lead
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> <li>○ justification of specifications</li> <li>○ stability</li> </ul>	<u>Y</u>	Bioburden and endotoxin controls only
<input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)	<u>Y</u>	
<input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	<u>Y</u>	OBP Lead
<input type="checkbox"/> characterization of drug substance	Y    N	Defer to OBP
<input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <li>○ specifications <ul style="list-style-type: none"> <li>○ justification of specs.</li> </ul> </li> <li>○ analytical procedures</li> <li>○ analytical method validation</li> <li>○ batch analyses</li> </ul>	<u>Y</u>	Bioburden and endotoxin only
<input type="checkbox"/> reference standards	Y    N	Defer to OBP
<input type="checkbox"/> container closure system	<u>Y</u>	
<input type="checkbox"/> stability <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> <li>○ method validation</li> </ul> </li> </ul>	<u>Y</u>	Bioburden only, not tested for endotoxin
<b>Drug Product [3.2.P] [Dosage Form]</b>		
<input type="checkbox"/> description and composition	<u>Y</u>	
<input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <li>○ preservative effectiveness</li> <li>○ container-closure integrity</li> </ul>	<u>Y</u> N	Not applicable
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<u>Y</u>	
<input type="checkbox"/> batch formula	Y    N	Defer to OBP
<input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	<u>Y</u>	OBP lead

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> controls of critical steps and intermediates	<u>Y</u>	Microbial controls only
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	<u>Y</u>	
<input type="checkbox"/> Filter validation	<u>Y</u>	
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	<u>Y</u>	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	<u>Y</u>	
<input type="checkbox"/> Environmental Monitoring Program	<u>Y</u>	
<input type="checkbox"/> Lyophilizer validation	Y	N Not applicable
<input type="checkbox"/> Other needed validation data (hold times)	<u>Y</u>	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N Defer to OBP
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	<u>Y</u>	Sterility and endotoxin only
<input type="checkbox"/> reference standards or materials	Y	N Defer to OBP
<input type="checkbox"/> container closure system [3.2.P.7]	Y	N Defer to OBP
<input type="checkbox"/> specifications (vial, elastomer, drawings)		
<input type="checkbox"/> availability of DMF & LOAs		
<input type="checkbox"/> administration device(s)		
<input type="checkbox"/> stability	<u>Y</u>	Sterility only; not tested for endotoxin
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment		
<input type="checkbox"/> pre-approval		
<input type="checkbox"/> protocol		
<input type="checkbox"/> results		
<input type="checkbox"/> method validation		
Diluent (vials or filled syringes) [3.2.P']	Y	N N/A
<input type="checkbox"/> description and composition of diluent	Y	N
<input type="checkbox"/> pharmaceutical development	Y	N

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
○ preservative effectiveness	Y    N	
○ container-closure integrity	Y    N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y    N	
❑ batch formula	Y    N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y    N	
❑ controls of critical steps and intermediates	Y    N	
❑ process validation including aseptic processing & sterility assurance:	Y    N	
○ Filter validation	Y    N	
○ Component, container, closure depyrogenation and sterilization validation	Y    N	
○ Validation of aseptic processing (media simulations)	Y    N	
○ Environmental Monitoring Program	Y    N	
○ Lyophilizer sterilization validation	Y    N	
○ Other needed validation data (hold times)	Y    N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y    N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y    N	
❑ reference standards	Y    N	
❑ container closure system	Y    N	
○ specifications (vial, elastomer, drawings)	Y    N	



**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	<u>Y</u>	
Includes data demonstrating consistency of manufacture	<u>Y</u>	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y    N	Defer to OBP
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y    N	Defer to OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y    N	Defer to OBP
Certification that all facilities are ready for inspection	<u>N</u>	It is stated that facilities are ready for inspection. A production schedule for DS has not been submitted. DS facility not registered.
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y    N	Defer to OBP
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y    N  Y    N <u>N</u>	Defer to OBP   N/A for DS, No for DP
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y    N	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<u>Y</u>	
Description of precautions taken to	<u>Y</u>	

**PRODUCT QUALITY (BIOTECHNOLOGY)  
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment		

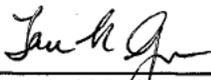
**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? \_\_\_ Y \_\_\_**

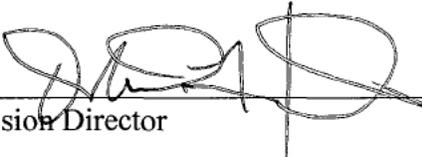
If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

HGS has indicated in a phone communication (05-Jun-2009) that they intend to be manufacturing DS during the whole review cycle. A production schedule will be submitted as an amendment to the BLA soon.

   
 Anastasia Lolos for Mary Farbman, Colleen Thomas 9 Jun 09  
6/9/09  
 \_\_\_\_\_  
 Product Quality Reviewer(s) Date

 for CC (acting)  
 Branch Chief/Team Leader/Supervisor 6/9/09  
 \_\_\_\_\_  
 Date

  
 Division Director 6/9/09  
 \_\_\_\_\_  
 Date