CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	(electronic stamp)
From	John Farley, MD, MPH
Subject	Acting Division Director Summary Review
BLA #	125,349
Applicant Name	Human Genome Sciences, Inc.
Date of Submission	June 15, 2012
PDUFA Goal Date	December 15, 2012
Established (USAN) Name	Raxibacumab
Dosage Forms / Strength	Single use vials 1700mg/34mL
Proposed Indication(s)	Treatment of inhalational anthrax
Recommended Action:	Approval with indication as follows: Raxibacumab is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for the prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Yuliya Yasinskaya, MD
Statistical Review	Lan Zeng, MS, Karen Higgins, Sc.D.
Pharmacology Toxicology Review	Terry Miller, Ph.D.
Product Quality Reviews	Chen Sun, MD, Ph.D., Colleen Thomas, Ph.D., David Frucht, MD
Microbiology Review	Lynette Berkeley, Ph.D.
Clinical Pharmacology Review	Ryan Owen, Ph.D., Jerry Yu, Ph.D.
CDTL Review	John Alexander, MD, MPH
Risk Management Review	Mary Dempsey, BS, Cynthia LaCivita, Pharm. D.
Labeling Reviews	Twanda Scales, MSN, Adora Ndu, Pharm. D. Christine Corser, Pharm. D. Aleksander Winiarski, Pharm. D., Kimberly Raines, Pharm. D.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

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1. Introduction

Inhalational anthrax is caused by the exotoxin-producing Gram-positive bacterium, *Bacillus anthracis*. While antibacterial treatment is directed at *B. anthracis* eradication, it has no activity against the toxins produced by *B. anthracis*: lethal toxin (LT) and edema toxin (ET). These toxins are formed when *B. anthracis* elaborates the components needed to form these toxins: protective antigen (PA), lethal factor (LF) and edema factor (EF). The applicant undertook the development of raxibacumab, a recombinant, fully human, IgG1λ monoclonal antibody directed at the PA of *B. anthracis*, as an addition to the available treatment armamentarium for patients with inhalational anthrax.

The development program included studies showing that raxibacumab binds PA with high affinity and inhibits PA binding to anthrax toxin receptor (ATR) on host cells, thereby protecting the cells from anthrax toxin-mediated injury. Proof-of-concept studies with raxibacumab demonstrated a greater proportion of surviving animals in the rat lethal toxin infusion model and in several pre-exposure and post-exposure prophylaxis animal model studies. The raxibacumab development program also included identification and characterization of the natural history of anthrax disease in animal models (New Zealand White rabbits and cynomolgus macaques). These animal models were subsequently used to evaluate the efficacy of raxibacumab in the treatment of inhalational anthrax. Because human clinical trials of inhalational anthrax are neither ethical nor feasible, this application was submitted pursuant to 21CFR§601.90-95 Subpart H "Approval of Biological Products when Human Studies are not Ethical or Feasible".

The Biologics License Application (BLA) 125,349 for raxibacumab was originally received on May 14, 2009 and a Complete Response letter was issued by the Agency on November 14, 2009. The application was resubmitted to the Agency on June 15, 2012 and was deemed a complete response to the deficiencies noted in the November 14, 2009 letter (see Section 2 of this review). The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of raxibacumab. For a detailed discussion of BLA 125,349, the reader is referred to individual discipline specific reviews and the Cross-Discipline Team Leader(CDTL) Review for this review cycle as well as reviews from the original review cycle.

2. Background

Efficacy of raxibacumab compared with placebo was evaluated in two studies of inhalational anthrax (one study a cynomolgus macaque model #724-G005829, and the second study a NZW rabbit model #682-G005758) included in the original BLA. These were reviewed during the first cycle; and salient details including exposure and trigger for treatment are summarized in the review by Dr. Yasinskaya. In the cynomolgus macaque study, a 40 mg/kg dose of raxibacumab resulted in 28-day survival of 9/13 (69%) macaques compared to 0/10 in the placebo group, 95% CI for treatment difference (31.1, 88.9). In the NZW rabbit study, 40

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mg/kg of raxibacumab resulted in 14-day survival of 6/17 (37%) rabbits compared to 0/13 in the placebo group, 95% CI for treatment difference (7.3, 59.6). These studies demonstrated a survival advantage of raxibacumab compared to placebo.

In these studies, an exaggerated inflammatory response in the CNS of the raxibacumab treated non-survivors compared to the placebo non-survivors was found on histopathological examination. There was no evaluation in these studies of CNS pathology in surviving animals. These findings raised concern regarding the contribution of raxibacumab to CNS pathology, and these studies did not address the potential for adverse CNS effects in survivors.

The original BLA also included two similarly designed studies (one in macaques #789-G923702 and one in NZW rabbits #781-G923701) comparing raxibacumab with antibacterial treatment to the antibacterial alone. These studies are summarized in Dr. Yasinskaya's review and showed no advantage of combination treatment over the use of antibacterial drug alone. The survival rate was 100% in macaques and 95% in NZW rabbits with antibacterial drug alone. As the survival rate in patients presenting with inhalational anthrax disease in 2001 and treated with antibacterial drugs was approximately 50%, the timing of the intervention in the animal studies may have been too early to adequately model established anthrax disease in humans.

The Complete Response Letter issued on November 14, 2009 recommended, in brief, the following to address major deficiencies:

an additional study in a model of inhalational anthrax to demonstrate the added benefit of raxibacumab when used with an antibacterial drug

a study to evaluate the effect of raxibacumab on the CNS in an animal model of inhalational anthrax and characterize the clinical course and histological appearance of the CNS in animals that survive and animals that die of anthrax

re-assay of PK samples for raxibacumab and ciprofloxacin from human and some animal studies after deficiencies in analytical procedures were addressed

re-assessment and (b) (4) of the bacterial endotoxin specification for the raxibacumab final product

3. Product Quality

Product quality reviewers recommended approval of the BLA and I concur that there are no product quality issues precluding approval. The team leader concluded, "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 endotoxin assay limits for the final product were (b) (4) to (b) (4) EU/mg. The endotoxin specification was considered to provide an adequate safety factor.

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An inspection waiver for the drug product manufacturing facility (b) (4) was recommended.

The reviewers recommended a dating period for raxibacumab 60 months from the date of manufacture when stored at 2-8°C.

Two post-marketing commitments were recommended which are described in section 13 of this review.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology reviewer concluded that there are no Pharmacology Toxicology issues precluding approval, and I concur with this assessment.

In this resubmission, the applicant submitted study #1103-G923704, "Evaluation of Raxibacumab as a Therapeutic Treatment Against Inhalation Anthrax in the New Zealand While Rabbit Model (CNS Toxicity Study). This was a blinded, randomized, placebo-controlled, GLP study of 48 NZW rabbits challenged with 200xLD_{50} ***B. anthracis*** spores via aerosol and randomized to 40 mg/kg of raxibacumab or placebo upon detection of protective antigen (approx. 16-48 hours after challenge). One of the objectives of this study was to assess terminal pathology in selected organs, particularly the CNS, in both surviving and non-surviving animals. Surviving animals were euthanized on day 28 post challenge to allow an assessment of CNS pathology in all treated animals. There were gross and histopathologic lesions in non-survivors and greater CNS lesions in raxibacumab treated animals compared to those non-survivors treated with placebo. In the raxibacumab-treated animals that died, the pattern of raxibacumab staining in the CNS was similar to that seen with IgG. The Pharmacology Toxicology and Clinical reviewers as well as the CDTL noted that this finding was consistent with non-specific leakage across a compromised blood brain barrier. However, at the time of euthanasia at day 28 post-challenge, all surviving animals treated with raxibacumab were negative for bacteremia in the CSF and brain, and had no CNS lesions.

In this resubmission, the applicant also submitted study #1141-CG920871, "Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-Exposure Treatment in the New Zealand White Rabbit Inhalation Model" (Added Benefit Study) which is described further in section 7 of this review. Animals that survived were euthanized on day 35 of the study (28 days after the last dose of levofloxacin). Surviving rabbits that were euthanized on day 35 who had been treated with raxibacumab were negative for bacteremia and toxemia, and had no gross or microscopic CNS findings.

With respect to the need for additional CNS pathology studies raised in the first cycle Complete Response letter, the reviewer concluded that, "In the absence of any significant CNS pathology or clinical symptoms in survivors, no positive staining of raxibacumab with neural tissues in survivors, and in consideration of both the seriousness of the indication and the recommendation that this drug be co-administered with CNS penetrating antibacterial drugs,

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…it is likely these findings will pose minimal risk to patients in the clinic". I concur with this assessment.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer concluded that the BLA is acceptable from the Clinical Pharmacology perspective. I concur that there are no Clinical Pharmacology issues precluding approval.

Submissions were made by the applicant prior to the BLA resubmission which addressed the first cycle inspection findings regarding the adequacy of the assay methodology for raxibacumab and ciprofloxacin. The analytical sites also underwent re-inspection to assess the methodology for raxibacumab measurements; no concerns were raised on re-inspection regarding the modified assay. Thus, Clinical Pharmacology and Pharmacology Toxicology deficiencies cited in the Complete Response letter were addressed. The PK results for raxibacumab obtained by both the original and modified assays were considered reliable, and sufficient to support comparability of raxibacumab exposures in humans and animals. Based on these submissions and a review of the data, it was concluded that the data was sufficient for the purposes of extrapolating animal efficacy findings to humans by bridging pharmacokinetic data between animals and humans.

Pharmacokinetic modeling described in the review by Dr. Jerry Yu served as the basis for pediatric dosing recommendations which will be included in the product label. The modeling used to generate pediatric dosing recommendations was based on the exposure data available for adults and models of the PK/clearance of other monoclonal antibodies in adult and pediatric patients. Simulations were used to derive dose regimens for pediatric patients in different weight ranges, with the objective of matching exposures in adults receiving 40 mg/kg of raxibacumab.

6. Clinical Microbiology

The Clinical Microbiology reviewer raised no issues which would preclude approval. She concluded based on her review of the animal studies in the resubmission, "that the presence of raxibacumab offered slightly greater protection than without it". I concur that there are no clinical microbiology issues precluding approval.

7. Clinical/Statistical-Efficacy

Both the Clinical and Statistical reviewers and the CDTL recommended approval. I concur that the standards for evidence of effectiveness from studies in animals at 21CFR§601.91 have been met.

Studies #724-G005829 (macaque model) and #682-G005758 (NZW rabbit model) submitted in the original BLA submission (described in Section 2 of this review) demonstrated a survival advantage of raxibacumab compared to placebo. In study #724-G005829, intervention was

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given when PA was detected in blood. In study #682-G005758, intervention was given when rabbits had sustained fever or when PA was detected in blood.

Study 1141-CG920871 (Added Benefit Study) was conducted by the applicant to address the deficiency cited in the Complete Response letter and the recommendation to, "conduct a study in an animal model of inhalational anthrax to demonstrate the added benefit of raxibacumab when used with an antimicrobial drug, for example, by showing that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial arm alone". This was a parallel-group, blinded, randomized, placebo-controlled GLP study in NZW rabbits to evaluate the added benefit of therapeutic treatment of raxibacumab combined with levofloxacin compared to levofloxacin alone. Animals were exposed by aerosol to 200xLD_{50} of *B. anthracis* spores similar to prior studies. A total of 180 NZW rabbits were exposed to *B. anthracis* spores by aerosol, but 104 (58%) died before the 84-hour timepoint of randomization. The 76 (42%) NZW rabbits that survived to 84 hours were randomized to treatment with levofloxacin alone (50 mg/kg for 3 days) (n=37) or levofloxacin with raxibacumab (40 mg/kg single dose) (n=39). All except one animal in the raxibacumab/levofloxacin combination group were bacteremic at or before treatment. The results of the primary analysis showed survival in 24/37 (65%) NZW rabbits treated with levofloxacin alone, compared to 32/39 (82%) NZW rabbits treated with raxibacumab plus levofloxacin. The 17% difference in survival rates did not reach statistical significance (p=0.0874).

The Statistical reviewer noted that this study was not powered to demonstrate a statistically significant result with an absolute difference in survival rate of 17%. A study powered at 80% with the survival difference and pre-randomization mortality observed in Study 1141-CG920871 would require over 550 animals to be spore-challenged. A study of this size may not be feasible and raises animal use concerns.

I concur with the CDTL that the results of this study establish that raxibacumab when used with an antibacterial drug to treat anthrax disease is reasonably likely to produce clinical benefit in patients.

Several members of the Advisory Committee (see section 9 of this review) opined that raxibacumab may also be of benefit for post-exposure prophylaxis in the event of release of a strain of *B. anthracis* which is resistant to available antibacterial drugs. As described previously, studies #724-G005829 (macaque model) and #682-G005758 (NZW rabbit model) demonstrated a survival advantage of raxibacumab compared to placebo in animals when administered early in the course of anthrax disease.

Study #358-N005999, "Post-Exposure Therapeutic Intervention in Rabbits", was performed earlier in product development using a different manufacturing process than the process proposed for the to be marketed product. One of the objectives of this study was to examine the efficacy of raxibacumab administered as a therapeutic treatment at varying time intervals (0 hours, 12 hours, 24 hours, and 36 hours) post-spore challenge. The number of survivors was: vehicle treated 1/12, raxibacumab treated at 0 hours 12/12, raxibacumab treated at 12 hours 12/12, raxibacumab treated at 24 hours 6/12, and raxibacumab treated at 36 hours 5/12.

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This study provides supportive evidence for the benefit of raxibacumab in a post-exposure setting.

Thus, it is reasonable to conclude that raxibacumab used as post-exposure prophylaxis when alternative therapies are not available or are not appropriate would be reasonably likely to produce clinical benefit in exposed persons, and I recommend broadening the labeled indication accordingly.

8. Safety

The Clinical reviewer and CDTL both summarize safety findings from raxibacumab studies in 326 healthy volunteers. Both conclude that there are no safety issues precluding approval and I concur.

The main safety findings associated with raxibacumab was the occurrence of infusion reactions manifested by rash, urticaria, or pruritus. Following modification of the protocol to include pretreatment with diphenhydramine within 1 hour before raxibacumab infusion, the incidence of rash was 8/88 (9%) among those pretreated with diphenhydramine, whereas rash occurred in 6/27 (22%) of subjects who were not pretreated with diphenhydramine.

9. Advisory Committee Meeting

A meeting of the Anti-Infective Drugs Advisory Committee was held on November 2, 2012 to discuss the BLA for raxibacumab. The committee was asked two voting questions:

VOTE: Do the results from the therapeutic studies of raxibacumab with and without antimicrobials in two animal models of inhalational anthrax provide substantial evidence that raxibacumab (40 mg/kg IV single dose in adults) is reasonably likely to produce clinical benefit for the treatment of humans with inhalational anthrax?

There were 16 committee members who voted yes, 1 voted no, and 1 abstention. Most committee members opined that Study 1141-CG920871 (Added Benefit Study) was sufficient to show a lack of antagonistic effect between raxibacumab and antibacterial treatment, and demonstrated that raxibacumab was likely to be of added benefit when administered with antibacterial drug treatment.

VOTE: Do the results from raxibacumab safety trials in healthy volunteers and studies in animals support an acceptable risk benefit profile given the benefits of the therapy discussed in Question 1?

All 18 committee members voted yes for this question. Committee members opined that there was adequate information to support an acceptable risk-benefit profile for the product.

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Committee members were also asked to discuss any recommendations regarding the pediatric dosing based on body weight. While one committee member noted limitations in the model of pediatric dosing, the committee was generally favorable regarding inclusion of pediatric dosing recommendations in labeling.

As noted above, several committee members opined that the product could be used for post-exposure prophylaxis if antibacterial drugs could not be used, but there were significant logistical limitations due to the requirement for intravenous dosing. Committee members raised concern regarding whether concurrent use of raxibacumab and anthrax vaccination may impact vaccination efficacy.

10. Pediatrics

While studies in children have not been performed, I recommend in this unusual circumstance stating in labeling that raxibacumab is indicated for the treatment of children with inhalational anthrax. Studies in children outside of the setting of an anthrax bioterrorism event are not ethically acceptable. The data from the animal studies support the likely benefit of raxibacumab for both adults and children. The pediatric dose recommendations would be expected to provide similar exposures for children as for adults, and the raxibacumab pediatric dosing recommendations were based in part on information on exposures in pediatric patients relative to adults for other human monoclonal antibody products. While it is not likely that adverse reactions would be different in children, the benefits of treatment of children with inhalational anthrax with raxibacumab to reduce anthrax mortality are likely to outweigh known and unknown risks.

11. Other Relevant Regulatory Issues

The applicant has submitted a synopsis for a future field study required for a BLA submitted pursuant to 21CFR§601.90-95. This study synopsis is described in the Clinical Review.

12. Labeling

I concur with the recommendations of the review team with respect to the following:
The indication should be broadened to include prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate.
The indication should state that raxibacumab is indicated for the treatment of inhalational anthrax and post-exposure prophylaxis of children.
Pediatric dosing recommendations should be included in Section 2 of the Prescribing Information, “Dosage and Administration”.

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13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend approval and concur with the review team that the standards for evidence of effectiveness at 21CFR§601.91 have been met.

- Risk Benefit Assessment

In animal models in two species, raxibacumab demonstrated a statistically robust survival advantage compared to placebo. A study in rabbits with an overall mortality rate similar to that seen in humans with inhalational anthrax, while not statistically significant, provided evidence that raxibacumab when used with an antibacterial drug to treat anthrax disease is reasonably likely to produce clinical benefit in patients. The major risk of raxibacumab in healthy volunteer studies was hypersensitivity usually manifesting as rash, and the incidence of rash was decreased to <10% with diphenhydramine pre-treatment. Thus, the risk benefit of raxibacumab for the treatment of inhalational anthrax disease in combination with appropriate antibacterial drug therapy is positive.

A situation may arise when antibacterial drug therapy as post-exposure prophylaxis would not be expected to be effective, such as release of an engineered strain of *B. anthracis* resistant to available antibacterial therapy. In this situation, there would be no alternatives to prevent a disease which would be expected to have a very high mortality rate. There is evidence of a positive risk benefit for the use of raxibacumab in this situation from the placebo controlled animal studies demonstrating a robust survival advantage in PA positive but often asymptomatic animals as well as supportive evidence from Study #358-N005999, "Post-Exposure Therapeutic Intervention in Rabbits" suggesting a treatment effect of dosing closer to the time of exposure.

The risk benefit in children would be expected to be the same as that in adults. Although studies in children are not acceptable outside the context of a bioterrorism event and have not been performed, a pediatric indication is appropriate for raxibacumab and pediatric dosing information should be provided in the Dosage and Administration section of the Prescribing Information.

- Recommendations for Postmarketing Requirements

The applicant is required by 21CFR§601.91 to conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

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- Recommendations for Postmarketing Commitments (treatment indication)

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

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

- Recommendations for Postmarketing Commitments (prophylaxis indication)

Conduct a Phase 4 study to evaluate the effect of raxibacumab on immunogenicity of anthrax vaccine.

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/s/

JOHN J FARLEY
12/14/2012