CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 12, 2012
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 125349 Resubmission
Applicant	Human Genome Sciences, Inc.
Date of Submission	June 15, 2012 (Resubmission)
PDUFA Goal Date	December 15, 2012
Proprietary Name / Established (USAN) names	Raxibacumab (No Trade Name Proposed)
Dosage forms / Strength	Injection, for Intravenous Solution (1700 mg/34 mL)
Proposed Indication(s)	1. Treatment of Inhalational Anthrax
Recommended:	Approval

1. Introduction

Raxibacumab is a recombinant, human $IgG_1\lambda$ monoclonal antibody that binds the protective antigen (PA) of *Bacillus anthracis*, the causative pathogen of inhalational anthrax. Binding of PA is believed to reduce the toxin-mediated effects of *B. anthracis* infection by interfering with intracellular entry of edema factor and lethal factor.

Biologics License Application (BLA) 125349 for raxibacumab was originally received on May 14, 2009. Because human clinical trials of inhalational anthrax are neither ethical nor feasible, this application was submitted under 21 CFR 601.90-95 Subpart H "Approval of Biological Products when Human Studies are not Ethical or Feasible" also known as the Animal Rule. A complete response letter was sent to the applicant on November 14, 2009, and will be described further in the background section below. The BLA was resubmitted on June 15, 2012.

This memo will focus on the new information submitted in the June 2012 resubmission for raxibacumab, and briefly describe the original BLA data that contribute to the recommendation for approval.

2. Background

The original BLA 125349 for raxibacumab submitted in May 2009 included animal model studies in cynomolgus macaques and New Zealand white (NZW) rabbits to evaluate efficacy of the product for inhalational anthrax. Human efficacy studies could not be conducted, but safety studies of healthy human adults were conducted. The safety studies are described briefly in section 8 of this memo; the human safety evaluation was not directly related to the deficiencies described in the complete response letter of 2009.

Efficacy of raxibacumab was evaluated in two animal models of inhalational anthrax (cynomolgus macaques and NZW rabbits). In these studies, animals were exposed to anthrax spores via inhalation at an exposure level expected to cause death. In macaques, intervention was given when PA was detected in blood. In NZW rabbits, intervention was given when rabbits had sustained fever for 2 hours or when PA was detected. Table 3 in the clinical review by Dr. Yuliya Yasinskaya shows the results of the two placebo-controlled studies submitted in the original BLA. In cynomolgus macaques, 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 NZW rabbits, 40 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, though the survival benefit was not as great as seen with antibacterial treatment in other animal studies, including the combination studies described below.

In the above studies, CNS pathology was noted in a higher proportion of raxibacumab-treated animal that died compared to placebo (see Table 5 in the clinical review). The applicant speculated that longer time to death contributed to more frequent development of CNS pathology in raxibacumab-treated animals, though there was no difference in time to death noted in non-survivors across the two treatment groups. There was no evaluation of CNS pathology in surviving animals. These findings raised questions about the contribution of raxibacumab to CNS pathology, and the potential for adverse CNS effects in survivors.

The original BLA application included two studies comparing raxibacumab with antibacterial treatment to the antibacterial alone. These studies had similar design features to the raxibacumab studies described above, with a primary endpoint of 28-day survival. Both studies included placebo arms demonstrating uniform lethality in the untreated animals. The results are shown in table 4 of the clinical review. In cynomolgus macaques, ciprofloxacin alone resulted in survival in 13/13 (100%) animals, while the combination of ciprofloxacin and raxibacumab resulted in survival in 11/13 (85%) animals. The 95% CI for the treatment difference of raxibacumab plus ciprofloxacin vs. ciprofloxacin alone was (-45.5, 11.4). In NZW rabbits, levofloxacin alone resulted in survival in 19/20 (95%) of rabbits, compared to survival in 16/17 (94%) rabbits treated with levofloxacin plus raxibacumab. The 95% CI for the treatment difference of raxibacumab plus ciprofloxacin vs. ciprofloxacin alone was (-23.9, 19.6). These resulted showed no advantage of combination treatment over use of antibacterial drug alone. In macaques, the results raised concerns about lower survival with the addition of raxibacumab compared to ciprofloxacin alone.

A complete response (CR) letter was issued for the original BLA on November 14, 2009. There main deficiencies cited were:

1) Added benefit of raxibacumab for treatment of inhalational anthrax

   The CR letter noted the high survival rates with antibacterial drug treatment alone in the combination studies with raxibacumab, stating: “The high survival rate implies that the timing of intervention was too early to adequately model established anthrax disease in

humans". The available data were considered insufficient to "adequately predict response in humans with inhalational anthrax in the manner in which the product is likely to be used". An additional study in a model of inhalational anthrax to demonstrate the added benefit of raxibacumab used with an antimicrobial was recommended.

2) Evaluation of the contribution of raxibacumab to CNS pathology:

The CR letter noted the "greater rate and severity of central nervous system (CNS) disease" in animals that died after raxibacumab treatment compared to placebo-treated animals. An additional study was recommended 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".

3) Pharmacokinetic assay for raxibacumab and ciprofloxacin:

The CR letter stated: "the Division of Scientific Investigations noted several deficiencies in the analytical procedures used" for measurement of serum raxibacumab and plasma ciprofloxacin concentrations in humans. Because similar procedures were used for pharmacokinetic analysis of raxibacumab in animal model studies, the reliability of raxibacumab and ciprofloxacin measurements in animals was also questioned. The CR letter recommended re-assay of PK samples for raxibacumab and ciprofloxacin from human and some animal studies, after the analytical procedures were revised to address DSI findings.

4) Inadequate bacterial endotoxin specification for the raxibacumab final product

The CR letter recommended re-assessment and (b) (4) the bacterial endotoxin specification for the raxibacumab final product.

The above deficiencies from the CR letter are discussed further in the relevant sections of this memo.

3. CMC/Device

- General product quality considerations

CMC reviews of the BLA resubmission include a product quality review addendum by Dr. Chen Sun, a product quality microbiology review by Dr. Colleen Thomas, and a quality team leader executive summary by Dr. David Frucht. The reviewers recommended approval of the BLA. Dr. Thomas' review specifically addressed the product quality microbiology deficiencies in the CR letter from November 2009. This review notes that the action limits for in process endotoxin and bioburden action limits were (b) (4) for in process materials based on a retrospective analysis of manufacturing data. The reviewers had previously agreed to the

study design. 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.

As noted in the product quality team leader summary, "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 manufacturing process has been shown to produce a consistent product over multiple runs that is free of infectious agents.

The product quality team recommended that the approval letter should indicate that the HGS proposal to extend the expiration date to 60 months is acceptable. The team also cited specific stability protocols for the final product and raxibacumab drug substance to be included in the approval letter.

- Facilities review/inspection

An inspection waiver for the drug product manufacturing facility (b) (4) was recommended based on the compliance history of the facility, its current GMP status, and its approval to manufacture multiple licensed products (b) (4) This recommendation was documented in an inspection waiver memorandum filed to the BLA. The pre-approval inspection of the drug substance manufacturing facility (Human Genome Sciences in Rockville, MD) was conducted in 2009, and a surveillance inspection was performed in 2012. The completed establishment evaluation report stated there are "no pending or ongoing compliance actions that prevent approval of this BLA".

- Other notable issues (resolved or outstanding)

There were two postmarketing commitments recommended by the quality reviewers.

Dr. Frucht's summary notes that HGS has committed to developing and validating 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.

Dr. Thomas' review recommended spiking studies of undiluted formulated bulk drug substance to evaluate whether endotoxin masking occurs over time in undiluted samples. HGS agreed to the proposed commitment.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was conducted by Dr. Terry Miller. The reader is referred to his review for detailed information on his findings. The reviewer concluded that the BLA is approvable from a pharmacology/toxicology perspective. The main body of the review described the two studies provided in the BLA resubmission to address the deficiencies in the complete response letter.

CNS Study (HGS study 1103-G923704)

To address the concerns about central nervous system (CNS) pathology seen at a higher frequency among raxibacumab-treated dead animals compared to placebo, HGS conducted study 1103-G923704: "Evaluation of Raxibacumab as a Therapeutic Treatment Against Inhalation Anthrax in the New Zealand White Rabbit Model". In this blinded, randomized, placebo-controlled, GLP study of NZW rabbits, 48 animals challenged with 200xLD_{50} *B. anthracis* spores via aerosol were randomized to 40 mg/kg of raxibacumab or placebo upon detection of protective antigen (approx. 16-48 hours after challenge). The objectives of the study were to assess terminal pathology in selected organs, particularly the CNS, in both surviving and non-surviving animals, and to evaluate the efficacy (defined by survival to day 28 after challenge) of raxibacumab as monotherapy. Surviving animals were sacrificed after meeting the primary endpoint to allow an assessment of CNS pathology in all treated animals.

The results showed that 11/24 (46%) rabbits in the raxibacumab group survived to day 28; all placebo treated animals died. The pathology results in the CNS of dead animals were consistent with the findings of previous studies, a higher proportion of the 13 dead animals in the raxibacumab group showed evidence of CNS pathology compared to the 24 dead animals in the placebo group (see table 5 of the Pharmacology/Toxicology review for a description of CNS findings in dead animals). In raxibacumab-treated animals that died, the pattern of raxibacumab staining in the CNS was similar to that seen with IgG, suggesting non-specific leakage across a compromised blood brain barrier. None of the surviving animals in the raxibacumab group showed evidence of CNS pathology or raxibacumab staining of neural tissue.

Added Benefit Study (HGS study 1141-CG920871)

To address the deficiency in the CR letter raising concern that prior combination treatment studies of raxibacumab with antibacterial drug initiated treatment too early to be representative of established human anthrax disease, the resubmission included a study described as the added benefit study in most reviews. HGS study 1141-CG920871 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. The planned aerosol exposure (200xLD_{50} of *B. anthracis* spores) for this study was similar to prior studies. In this study, treatment with study drugs was started at 84 hours after spore exposure, at which time animals were randomized to receive levofloxacin alone (50 mg/kg for 3 days) or levofloxacin plus raxibacumab (40 mg/kg single dose). The primary efficacy endpoint of the study was 28-day survival after the last dose of levofloxacin in the ITT study population. The FDA also conducted sensitivity analyses of 28-day survival in the subgroup of bacteremic animals.

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 (n=37) or levofloxacin with raxibacumab (n=39). All except one animal in the raxibacumab/levofloxacin combination group were bacteremic at or before treatment. No differences were seen between study drug groups in baseline characteristics or anthrax exposure. 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 difference in survival rates did not reach statistical significance (p=0.0874). In the subgroup of bacteremic animals, the survival results were similar: 24/37 (65%) NZW rabbits treated with levofloxacin alone, compared to 31/38 (82%) NZW rabbits treated with raxibacumab plus levofloxacin. The one animal that was not bacteremic at baseline was febrile and had a positive assay for protective antigen in plasma.

The safety findings of this study are also notable in that all rabbits surviving to treatment were underwent necropsy. Animals that survived were sacrificed at day 35 of the study (28 days after the last dose of levofloxacin). In this study, there were no brain lesions found in animals receiving raxibacumab plus levofloxacin. There were two animals that received levofloxacin alone with brain lesions consistent with anthrax (meningeal and parenchymal hemorrhage and meningeal vascular necrosis); these two animals died despite levofloxacin treatment.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Ryan Owen. The reader is referred to Dr. Owen's review for details of the clinical pharmacology assessment. The reviewer considered the resubmission acceptable from the clinical pharmacology perspective. The review also included a pharmacometrics analysis by Dr. Jingyu (Jerry) Yu.

One deficiency of the original BLA application was related to the pharmacokinetic assays for raxibacumab and ciprofloxacin. The background section of the clinical pharmacology review addresses this deficiency, since there were submissions to the BB-IND for raxibacumab that addressed this deficiency. The clinical pharmacology reviewer cites the BB-IND reviews by Dr. Kimberly Bergman, the clinical pharmacology team leader, in the background section. Submissions made to the BB-IND before the BLA resubmission addressed the inspection findings regarding the adequacy of the assay methodology for raxibacumab and ciprofloxacin. The analytical sites also underwent re-inspection by DSI to assess the methodology for raxibacumab measurements; no concerns were raised on re-inspection regarding the modified assay. The sponsor and review division came to an agreement on equivalence criteria for comparing raxibacumab concentrations measured by a modified assay with the original results. After conducting the study, the results were provided in an April 2010 submission to the BB-IND. The reviewer of this submission found that the data adequately addressed the deficiency in the CR letter. 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.

The clinical pharmacology review also evaluated PK data obtained in the studies provided in the resubmission. For the added benefit study, the reviewer concluded that the PK results in this study were consistent with the PK results of previous rabbit studies. For the CNS study, excluding the results for one animal with high CSF concentrations (likely contaminated with blood), penetration of raxibacumab into the CNS is low (less than 2%). The clinical pharmacology review also assessed the ciprofloxacin concentrations in one of the human volunteer studies after samples were re-assayed. There were inconsistencies comparing results

from the original and the modified assay for ciprofloxacin, but overall these inconsistencies were considered minor. The reviewer agreed with the sponsor's assertion that the differences in ciprofloxacin concentrations between assay methods were not clinically relevant.

The pharmacometric review in the appendix of the clinical pharmacology review provided the basis for dose recommendations in the pediatric age group. Raxibacumab has not been administered to pediatric age subjects. Despite this lack of PK data, dosing recommendations for the pediatric age group were generated, 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. This modeling is the basis for the dosing recommendations included in the product label.

6. Clinical Microbiology

A clinical microbiology review of the BLA resubmission was conducted by Dr. Lynnette Berkeley. The reader is referred to her review for detailed information about the clinical microbiology findings. There were no approvability issues in the complete response letter from the clinical microbiology review of the original BLA. Dr. Berkeley reviewed the animal studies in the resubmission. Dr. Berkeley concluded that these studies show that the presence of raxibacumab offered slightly greater protection than without it. Dr. Berkeley provided labeling recommendations for the microbiology section (12.4) to describe the mechanism of action of raxibacumab.

7. Clinical/Statistical- Efficacy

The clinical review of the resubmission was conducted by Dr. Yuliya Yasinskaya. The statistical review was conducted by Dr. Lan Zeng. Both reviewers evaluated the two animal studies submitted to address deficiencies cited in the complete response letter. The clinical reviewer recommended approval of the BLA. The statistical review stated that the two animal studies included in the BLA resubmission adequately addressed the added benefit of raxibacumab and the CNS effects in survivors that received raxibacumab.

[CDTL Comment: The efficacy findings for the added benefit study were described in section 4 of this memo. Taken together with the findings from animal studies in the original BLA (described in section 2 of this memo), the results of the animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans.]

8. Safety

The clinical review by Dr. Yuliya Yasinskaya summarizes the safety findings from raxibacumab studies in healthy volunteers. There were no new human studies of raxibacumab

in the BLA resubmission. This safety information was reviewed in the original BLA submission in 2009.

Briefly, a total of 326 healthy adult volunteers have received raxibacumab in three phase 1 clinical studies to evaluate the safety and PK of the biological product. A single 40 mg/kg dose of raxibacumab was given to 303 healthy volunteers in two studies, and 23 subjects received a second dose of raxibacumab two weeks after the first dose. There were 20 subjects who received a second dose of raxibacumab more than 4 months after the first dose.

The main safety finding associated with raxibacumab was the occurrence of infusion reactions. The infusion reactions were manifested by rash, urticaria, or pruritus. In the first 25 subjects, five developed dermatologic reactions. Three responded to diphenhydramine treatment, and two subjects discontinued infusion of raxibacumab. Therefore, the protocol was modified to include pretreatment with diphenhydramine within 1 hour before raxibacumab infusion. A total of 8/88 (9%) subjects in this study reported rash, whereas rash occurred in 6/27 (22%) subjects who did not receive diphenhydramine premedication.

One death was reported in a placebo subject, 39 days after the first of two doses of study drug. This subject died in a motor vehicle accident; the death was not considered related to raxibacumab.

Two non-fatal serious adverse events were reported. One 52-year-old woman developed cholecystitis 24 days after receiving the first of two doses of raxibacumab. She was hospitalized, underwent surgery, and recovered. She had multiple risk factors for cholecystitis. A 48-year-old male reported auditory hallucinations, was diagnosed with schizophrenia and started treatment. However, this subject disclosed a history of schizophrenia dating back to his 20's. No other serious adverse reactions were reported. It should be noted that the safety database is limited by the small number of subjects, and there is no evaluation of the potential drug-disease interactions, since studies of anthrax patients are not feasible.

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 meeting included presentations from the applicant and FDA reviewers (clinical, pharmacology/toxicology, and pharmacometrics) to discuss various aspects of the resubmission. The committee was asked two voting questions.

1. **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 advisors who voted yes, 1 voted no, and 1 abstention. Most committee members agreed that the results of the animal studies provided evidence of the likely clinical benefit in humans with anthrax. Most committee members agreed that the raxibacumab-

levofloxacin combination study (described in the efficacy section of this memo) was sufficient to show a lack of antagonistic effect between raxibacumab and antibacterial treatment, and was likely to be of added benefit. The one committee member voting no cited the failure to achieve statistical significance in this study as reason to vote no. This committee member was concerned that providers would think the product had been proven to provide added benefit, despite lack of statistical significance for the treatment difference, but still proposed to make the product available through an emergency use authorization or treatment IND.

2. **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 advisors voted yes for this question. The committee agreed that there was adequate information to support an acceptable risk-benefit profile for the product. The committee agreed that the deficiencies identified for the original BLA submission had been adequately addressed.

10. Pediatrics

No pediatric studies of raxibacumab have been conducted. Raxibacumab has received orphan designation for treatment of anthrax. Therefore, the Pediatric Research Equity Act (PREA) does not apply.

Anthrax is an extremely rare disease, so pediatric studies of this condition would not be feasible in any case. In addition, raxibacumab presents more than a minor increase over minimal risk to pediatric patients. Absent a medical need for the product, studies in children would not offer a prospect of direct benefit as required under 21 CFR 50.52. There is also currently no other therapeutic indication for raxibacumab in the pediatric population from which PK and safety could be obtained. Even for adults, clinical trials to evaluate efficacy are not feasible, which is why animal models were needed to demonstrate likely clinical benefit for humans. Based on what is known about anthrax disease, it is reasonable to expect that animal model data supporting efficacy of raxibacumab would predict likely clinical benefit for pediatric patients as well as adults. Similar pathogenesis from inhalation of anthrax spores and exposure to anthrax toxin is expected for pediatric patients as for adults.

As noted in the clinical pharmacology section of this memo, pediatric dose recommendations were generated for raxibacumab on the basis of the pharmacokinetics of the product in adults, and simulations of PK changes for pediatric age groups. PK data for other monoclonal antibodies were used to estimate the expected changes in exposure to raxibacumab with decreasing age in the pediatric population.

A pediatric ethics consultation was written by Dr. Michelle Roth-Cline, and Jeanine Best wrote a consult memo for the pediatric and maternal health staff. The documents addressed the question from the review division about including dose information for pediatric patients in labeling, despite the lack of pediatric PK or safety data. Both consult reviews suggested

inclusion of dose recommendations in the pediatric use section, while acknowledging that no pediatric data were available to support safety or PK. However, these proposals still considered the available data inadequate to support approval of pediatric use of raxibacumab.

The office and division management went one step further and recommended approval of raxibacumab for pediatric use despite the lack of pediatric safety and PK data. The reasoning is as follows:

- The data from animal studies support the likely clinical benefit of raxibacumab, in addition to antibacterial drug, for both adult and pediatric patients.
- The pharmacometrics review has provided pediatric dose recommendations expected to provide similar exposures for pediatric patients as for adults. Because raxibacumab is a human monoclonal antibody, the information on exposures in pediatric patients (relative to adults) receiving other monoclonal antibodies provide a strong basis for prediction of raxibacumab dose-exposure for pediatric patients.
- As a monoclonal antibody, it is unlikely that raxibacumab would result in adverse reactions for pediatric patients that differ for those identified for adults (mainly rash, extremity pain, and pruritus). Even in the event that raxibacumab causes other adverse reactions in pediatric patients, the benefits of treatment with raxibacumab to reduce anthrax mortality are likely to outweigh potential risks of treatment.

This recommendation for approval of raxibacumab for pediatric patients is reasonable when weighing the benefits and risks of the proposed treatment. Clearly, the approval of pediatric use in the absence of pediatric safety and PK data should be an exception to the usual circumstances for decisions about pediatric use of a new drug or biological product.

11. Other Relevant Regulatory Issues

The BLA is being considered for approval under the "animal rule", 21 CFR 601 – Subpart H "Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible". As such, the sponsor has submitted a synopsis for a proposed field study. The clinical review by Dr. Yasinskaya includes a description of the proposed study and some comments about the trial for the applicant. The applicant has agreed to conduct the field study as a postmarketing requirement. HGS committed to final protocol submission in June 2013, though dates for study completion and final report submission are dependent on the occurrence of an event.

The review division did not consider it necessary to have a REMS (risk evaluation and management strategy) program for raxibacumab. A risk management review by Mary Dempsey concurred that "the risks associated with raxibacumab could be managed through labeling".

12. Labeling

The labeling of raxibacumab was relatively non-controversial. There was no proprietary name proposed for the product. The product labeling and patient information sheet adequately

address the requirement of the animal rule regarding information to be provided to patients [21 CFR 601.91 (b)(3)]. Labeling reviews by Twanda Scales (Patient Labeling Review), Adora Ndu (Division of Consumer Drug Promotion), Christine Corser (Division of Professional Drug Promotion), Aleksander Winiarski (Division of Medication Error Prevention and Analysis), and Kimberly Rains (Office of Biotechnology Products) provided recommendations for the physician labeling, patient information, and carton/container labeling. Their recommendations were followed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of raxibacumab for treatment of inhalational anthrax and prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate.

- Risk Benefit Assessment

The identified risks of raxibacumab, mainly infusion reactions that are reduced by pretreatment with diphenhydramine, are clearly outweighed by the potential to reduce mortality from anthrax. None of the review team expressed any dissent from this assessment of the risks and benefits.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not Applicable – REMS were not considered necessary for the product

- Recommendation for other Postmarketing Requirements and Commitments

A post marketing requirement for the applicant to conduct a field study is a condition of the animal rule. The applicant has agreed to submission of a final protocol for this field study by June 2013.

The applicant has also agreed to the following postmarketing commitments recommended by the review team:

- 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.
- 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.
- Conduct a study to determine whether raxibacumab administration interferes with immunogenicity of anthrax vaccine.

- Recommended Comments to Applicant

The approval letter should include the statements from the product quality team regarding the (b) (4) expiry for the product and the specific stability protocols for the final product and raxibacumab drug substance.

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/s/

JOHN J ALEXANDER
12/12/2012