CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	12/14/2012
From	Edward M. Cox, MD, MPH
Subject	Office Director Decisional Memo
BLA #	125349
Applicant Name	Human Genome Sciences, Inc. (HGS) (a subsidiary of GlaxoSmithKline)
Date of Resubmission (receipt date)	June 15, 2012
PDUFA Goal Date	December 15, 2012
Proposed Proprietary Name / Established (USAN) Name	none raxibacumab
Dosage Forms / Strength	Injection for intravenous use, 1700mg/ 34mL (50 mg/mL)
Proposed Indication	Treatment of patients with inhalational anthrax due to *B. anthracis*
Indication	for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. Raxibacumab is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.
Action:	**Approval**

Raxibacumab is a fully humanized monoclonal antibody that binds to the protective antigen of *B. anthracis*. HGS is developing raxibacumab as a treatment for patients with inhalational anthrax. BLA 125349 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, because human clinical trials of inhalational anthrax are neither ethical nor feasible. Inhalational anthrax is a life-threatening condition with a high mortality rate once disease has developed, even with antibacterial drug treatment. The currently approved drug therapies labeled for the treatment of patients with *B. anthracis* are penicillin G potassium, penicillin G sodium, and penicillin G procaine, and the tetracyclines. For the indication of post-exposure prophylaxis of inhalational anthrax the previously listed antibacterial drugs and also ciprofloxacin and levofloxacin are approved.

During the bioterrorism-related anthrax cases in 2001, there were 11 cases of inhalational anthrax, 5 of which were fatal.[1] *B. anthracis* produces toxins that contribute to much of the pathophysiology of the disease. In inhalational anthrax disease, it is hypothesized that targeting not only the bacteria with antibacterial drugs, but also targeting the toxins produced by *B. anthracis* may be a means to improve survival rates in patients with anthrax disease.

[1] Jernigan DB, Raghunathan PL, Bell BP, et. al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. Emerg Infect Dis. 2002 Oct;8(10):1019-28.

Another potential role for therapies acting via a mechanism different than that of an antibacterial drug is for the treatment or prophylaxis of patients with strains of *B. anthracis* that are resistant to antibacterial drugs. The possibility of antibacterial resistance in *B. anthracis* has been a topic of discussion in presentations and published articles.[2,3]

Protective antigen (PA) of *B. anthracis* binds to the cell surface and forms a heptameric complex that facilitates the entry of lethal and edema toxin into the cell cytosol. Protective antigen also combines with lethal factor and edema factor to form lethal toxin (LT) and edema toxin (ET), respectively. The intended role of an antibody directed against protective antigen is to interrupt the pathophysiologic role of protective antigen in this process.

This is the second review cycle for BLA 125349 for raxibacumab. At the completion of the first cycle of review, BLA 125349 received a complete response action on November 14, 2009 with the following deficiencies:

> *SAFETY AND EFFICACY*
>
> *1. In the animal efficacy studies that evaluated antimicrobial drug alone, antimicrobial drug plus raxibacumab, or placebo, the survival rates were 100% in cynomolgus monkeys and 95% in New Zealand White (NZW) rabbits with antimicrobial drug alone. The high survival rate implies that the timing of intervention was too early to adequately model established anthrax disease in humans. In patients presenting with inhalational anthrax disease in 2001 and treated with antimicrobial therapy, the survival rate was approximately 50%. The animal model should reflect the human disease state for which the product under study is intended. The animal models and the 100% survival rate in cynomolgus monkeys and the 95% survival rates in NZW rabbits with antimicrobial drug alone do not allow for the contribution of the monoclonal antibody to be assessed. In addition, the anticipated use in humans would be using raxibacumab in combination with antimicrobial therapy. The available data do not provide sufficient information to adequately predict response in humans with inhalational anthrax in the manner in which the product is likely to be used.*
>
> *To address this deficiency, we recommend that you 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 alone arm. We recognize that additional animal model developmental work will be*

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[2] HHS Anthrax Medical Countermeasures Program. Presentation to the Anti-Infective Drugs Advisory Committee Meeting, BARDA/ASPR/ HHS. November 2, 2012. available at http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329769.pdf

[3] Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, McDade J, Osterholm MT, Parker G, Perl TM, Russell PK, Tonat K; Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA. 2002 May 1;287(17):2236-52.

needed to perform such a study and recommend that you discuss the proposed study with the division.

2. In animal studies, non-survivors that received raxibacumab and died of anthrax had a greater rate and severity of central nervous system (CNS) disease than animals that received placebo. The reasons for this greater rate and severity of CNS disease are not clear and the potential relevance to humans is not clear.

To address this deficiency, we recommend that you conduct 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.

CLINICAL PHARMACOLOGY
3. During the inspection of the bioanalytical sites responsible for analysis of serum raxibacumab and plasma ciprofloxacin concentrations in humans, the Division of Scientific Investigations (DSI) noted several deficiencies in the analytical procedures used for each of these products. Therefore, before we can rely on the pharmacokinetic data generated for raxibacumab and ciprofloxacin in humans, you will need to do the following:

a. Revise the analytical procedures for raxibacumab to address these DSI findings, reassay the pharmacokinetic samples obtained from human studies HGS1021-C1063,HGS1021-C1064, and HGS1021-C1069, and re-calculate the pharmacokinetic parameters for raxibacumab from these re-analyses. Depending on the outcome of these re-analyses, additional pharmacokinetic studies may be required.

b. Revise the analytical procedure for ciprof1oxacin to address the DSI findings, re-assay the plasma pharmacokinetic samples obtained from human study HGS1021-C1064, and re-calculate the pharmacokinetic parameters for ciprofloxacin from this reanalysis in humans. Depending on the outcome of this re-analysis, additional pharmacokinetic studies may be required.

4. The DSI findings noted above also bring into question whether we can rely on the pharmacokinetic data generated for raxibacumab from the animal efficacy studies in NZW rabbits and cynomolgus monkeys because these bioanalytical procedures are similar to those used for the human studies. Depending on the outcome of the re-analysis of raxibacumab in humans, re-assay of the pharmacokinetic samples from animal studies 682-G005758 and 724-G005829 and re-calculation of pharmacokinetic parameters for raxibacumab from these re-analyses in rabbits and monkeys may be required.

5. The DSI findings noted above also bring into question whether we can rely on the pharmacokinetic data generated for ciprof1oxacin from the combination animal efficacy study in cynomolgus monkeys because the bioanalytical procedure is similar to

that used for the human studies. Depending on the outcome of the re-analysis of ciprofloxacin in humans, re-assay of the ciprofloxacin pharmacokinetic samples from animal study 789-G923702 in monkeys and re-calculation of pharmacokinetic parameters for ciprofloxacin from this re-analysis may be required.

PHARMACOLOGY /TOXICOLOGY

6. The DSI findings above also raise questions about the reliability of analytic results from the toxicokinetic samples from Study 6962-140 and Study 6962-173. To address this deficiency re-assay plasma toxicokinetic samples for raxibacumab from Study 6962-140 "120-day toxicity study with PA mAb in cynomolgus monkey" and Study 6962-173 "Intravenous study for effect on embryo-fetal development and toxicokinetics with raxibacumab in rabbits" after revising the analytical procedures for raxibacumab to address the DSI findings.

PRODUCT QUALITY

7. The bacterial endotoxin specification for the raxibacumab final product is inadequate. To address this deficiency, re-assess and (b) (4) *the bacterial endotoxin specification for the raxibacumab final product. The re-assessment should consider the endotoxin contribution from the saline solution used to dilute raxibacumab prior to administration. The revised specification should provide a safety factor (e.g., 2-4 fold) when the endotoxin limits from both the saline and the product are considered.*

The applicant submitted a complete response to the above deficiencies on June 15, 2012. The review team has reviewed the issues in detail in their respective disciplines. For a detailed discussion, the reader is referred to the individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Summary Review. This memorandum will focus on selected issues from the application.

The evaluation from the Product Quality standpoint for raxibacumab finds that the manufacturing is well controlled and leads to a product that is pure and potent. During the first review cycle, there was a Product Quality microbiology deficiency noted during the first review cycle that the endotoxin for the product needed to be re-assessed and (b) (4). As noted in the Product Quality Microbiology Review for this second cycle, this deficiency has been adequately addressed; the endotoxin specification for drug substance was (b) (4) to ≤ (b) (4) EU/mg (corresponds to (b) (4) EU/mL) which matches the endotoxin specification for the final drug product. The manufacturing process is found to be acceptable.

There is a Product Quality postmarketing commitment that will be included in the approval letter to evaluate whether endotoxin detection can be masked in some protein solutions due to protein or excipients.

The pharmacology/toxicology review notes no significant adverse nonclinical findings and also notes the finding of binding of raxibacumab to thyroid in human and non-human primate ex-vivo tissue. The limitations of the assay to evaluate immunogenicity in the animal studies

are also noted and raise questions about conclusions that can be drawn from animal studies to evaluate immunogenicity. The recommendation from Pharmacology/Toxicology regarding Pregnancy Category is, Category B. The findings from the study conducted to further evaluate the previously noted CNS findings (deficiency #2 in the November 14, 2009 complete response letter) are discussed in the animal safety section.

The Microbiology reviews describe the in vitro and animal model studies done with raxibacumab. Of note from the studies evaluating the binding of raxibacumab to free PA or PA bound on the cell surface, it appears that raxibacumab binds to free PA, but not to PA bound to cellular receptors suggesting the binding site for raxibacumab may not be available after PA has bound to its cellular receptor. The rabbit anti-PA polyclonal anti-sera used in these experiments bound to PA after it was bound to the cell surface receptor.

The applicant's proposed dose in humans is a single dose of 40 mg/kg administered intravenously over 2 hours and 15 minutes after diphenhydramine pre-medication. During the first review cycle, the findings from the inspections of the analytic methods and procedures for the human pharmacokinetic studies raised important concerns about the quality and reliability of human pharmacokinetic data in this application. These issues have now been adequately addressed. As noted in the Clinical Pharmacology Review, equivalence criteria were agreed upon between the applicant and the Agency. The assays for serum raxibacumab levels were re-validated and a subsequent OSI inspection did not identify concerns with the modified assay for raxibacumab serum levels. The result of these analyses is that the results obtained by the original and modified bioanalytical methods are both considered reliable and provide adequate data for determining the dose for humans. The finding that the original bioanalytic methods were in fact reliable also addresses the deficiency noted in the November 2009 CR letter related to determinations of drug levels for the toxicokinetic studies from two toxicology studies.

Pediatric dosing instructions were developed using a population PK approach to derive dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving raxibacumab at 40 mg/kg. This approach was taken because exposure of healthy children to raxibacumab is not ethical. A weight based dosing regimen for pediatric patients is provided in the product labeling.

Raxibacumab is administered as an intravenous infusion over 2 hours and 15 minutes. Premedication with diphenhydramine is also recommended to reduce the risk of infusion reactions.

Animal Studies Evaluating Activity and Effectiveness

For a complete discussion of the animal studies evaluating activity and effectiveness, the reader is referred to the Microbiology, Statistical, and Medical Officer Reviews from the first and second cycles. The sections that follow provide an overview of the findings from these studies.

The activity of raxibacumab was evaluated in rat toxin models. The studies evaluated the effect of raxibacumab (produced by an earlier manufacturing process) on survival of rats administered LT. The studies showed that intravenous administration of raxibacumab administered prior to, or for a limited time after an infusion of lethal toxin, was able to improve survival compared to placebo. The studies provide proof of concept for the role of raxibacumab in interrupting the lethality of LT in the rat models that were studied.

In a rabbit study (Experiment #1 in the table below) of 12 rabbits in each of 5 groups, rabbits received either placebo or 40 mg/kg of raxibacumab at 0, 12, 24, 36 hours post exposure/ challenge with aerosolized *B. anthracis* 100 LD_{50}. Administration of raxibacumab at 0 or 12 hours post exposure resulted in 12 of 12 animals surviving; survival rates declined at later time points. This study was conducted using material produced using the M10 processes. I have discussed the quality of the material with the product quality reviewer and clinical pharmacology reviewer and the material is sufficiently similar to provide supportive information on the efficacy of raxibacumab at the time points studied in this animal model.

A second rabbit study (experiment #2) evaluated different doses of raxibacumab administered either 24 or 36 hours post exposure. Survival rates for doses of raxibacumab administered 24 hours after challenge were between 3/12 animals and 5/12 animals for the doses between 5 mg/kg and 40 mg/kg. At 36 hours, at a dose of 20 mg/kg, 0/12 animals survived. Bacteremia status was not assessed in this study.

Table. Summary of Survival Data in NZW Rabbits Treated with Raxibacumab at Various Times After Aerosol Exposure to Spores from the Ames Strain of *B. anthracis*

Treatment Group (Raxibacumab dose)	Time of Treatment (hours PI)	Survivors at 14 Days PI*	Median Time to Death Days PI (range)	Bacteremic at Time of Treatment
Experiment 1:				
1 (Placebo)	0	1/12 (8 %)	(2 – 3)	0/12 (0 %)
2 (40 mg/kg)	0	12/12 (100 %)	NA	0/12 (0 %)
3 (40 mg/kg)	12	12/12 (100 %)	NA	0/12 (0 %)
4 (40 mg/kg)	24	6/12 (50 %)	(1 – 3)	1/12 (8 %)
5 (40 mg/kg)	36	5/12 (42 %)	(2 – 4)	9/12 (75 %)
Experiment 2:				
1 (Placebo)	0	0/12 (0 %)	3 (1-4)	Not measured
2 (5 mg/kg)	24	3/12 (25 %)	3.5 (1-4)	Not measured
3 (10 mg/kg)	24	4/12 (33 %)	2.5 (1- 3)	Not measured
4 (20 mg/kg)	24	5/12 (42 %) *	6.0 (2 - 8)#	Not measured
5 (40 mg/kg)	24	4/12 (33 %)	2.5 (2 -8)	Not measured
6 (20 mg/kg)	36	0/12 (0 %)	3.0 (1- 9)	Not measured

Note: No rabbits died during the additional 28 day observation period in experiment 1
*Statistically different from placebo; p = 0.0373
#Statistically different from placebo; p = 0.0020

Studies evaluating raxibacumab administered subcutaneously as pre-exposure prophylaxis (two days prior to aerosol challenge) in cynomolgus monkeys found 0/10 animals surviving in the placebo group and 9/10 surviving in the raxibacumab 40 mg/kg dose group.

Table. Survival Results in Cynomolgus Monkeys at Day 28 PI following SC Prophylactic Treatment of Inhalational Anthrax with Raxibacumab*				
Treatment	**Dose (mg/kg)**	**LD_{50} Dose (mean ± SD)**	**Survivors / Total Infected**	**Time to Death for Animals That Died (Days)**
Placebo	0	180 ± 72	0/10	2-5
Raxibacumab	10	187 ± 52	6/10	4-6
Raxibacumab	20	177 ± 61	7/10	4-6
Raxibacumab	40	194 ± 79	9/10	3
All treatments administered by the SC route two days prior to aerosol challenge with *B. anthracis* spores. *Survivors were observed for an additional 60 days. There were no additional deaths during this 60-day observation period.				

These studies show activity of raxibacumab, based upon differences in survival rates in animal models when given prior to or soon after exposure to aerosol challenge with *B. anthracis* spores.

Studies in cynomolgus monkeys and New Zealand white (NZW) rabbits were performed evaluating the effect of raxibacumab monotherapy at 20 mg/kg and 40 mg/kg following aerosol exposure to *B. anthracis* spores. Animals were exposed to aerosolized *B. anthracis* spores and followed for development of PA in serum (monkeys) or PA in serum along with elevated temperature (rabbits) at which time raxibacumab was administered intravenously. The dose groups were placebo, raxibacumab 20 mg/kg, and raxibacumab 40 mg/kg. Survival rates at the 40 mg/kg dose in cynomolgus monkeys was 9/13 (69%) compared to 0/10 (0%) for placebo recipients. For NZW rabbits the survival rate in the 40 mg/kg group was 6/17 (35%) compared to 0/13 (0%) for the placebo group. The survival rates for the raxibacumab 40 mg/kg dose groups were significantly better than placebo with p-values less than 0.05. The studies show an effect of raxibacumab in increasing survival in cynomolgus monkeys and rabbits with inhalational anthrax in these animal studies.

Treatment Group	**Cynomolgus Monkeys at 28 days**			**NZW Rabbits at 28 days**		
	Number (%) of survivors	**P value vs. placebo[1]**	**95% CI of raxibacumab – placebo[2]**	**Number (%) of survivors**	**P value vs. placebo[1]**	**95% CI of raxibacumab – placebo[2]**
Placebo	0/10 (0%)			0/13 (0%)		
20 mg/kg raxibacumab	5/12 (41.7%)	0.0396	(7.2, 68.7)	4/16 (25.0%)	0.1067	(-2.2, 50.9)
40 mg/kg raxibacumab	9/13 (69.2%)	0.016	(31.1, 88.9)	6/17 (35.3%)	0.0237	(7.3, 59.6)

[1] P value based on 2-sided Fisher's exact test fro the comparison vs. the placebo control group
[2] 95% CIs are exact confidence intervals

Studies in cynomolgus monkeys and NZW rabbits evaluated the effect of an antibacterial drug (either ciprofloxacin or levofloxacin), an antibacterial drug plus raxibacumab, and placebo in animals exposed to aerosolized *B. anthracis* spores. Treatment was initiated at the time of a positive PA serum assay (monkeys) or PA in serum along with elevated temperature (rabbits). The FDA analysis population is comprised of animals that were bacteremic at the time that therapy was started. In cynomolgus monkeys 13/13 (100%) animals that received antibacterial

drug alone survived compared to 11/13 (85%) that received antibacterial agent and raxibacumab. The survival rate in the placebo group was 0/10 (0%). In NZW rabbits 19/20 (95.0%) survived that received antibacterial drug alone and 16/17 (94.1%) survived that received antibacterial agent plus raxibacumab. In the placebo group 0/10 (0%) survived.

Treatment group	**Cynomolgus Monkeys at 28 days**		**NZW Rabbits at 28 days**	
	Number (%) of Survivors	95% CI of Cipro/raxibacumab-Cipro[2]	**Number (%) of Survivors**	95% CI of Levo/raxibacumab-Levo[2]
Placebo	**0/10 (0%)**	-	**0/10 (0%)**	-
Antibacterial Alone[1]	**13/13 (100%)**	-	**19/20 (95.0%)**	-
Antibacterial[1] + raxibacumab 40 mg/kg	**11/13 (84.6%)**	(-45.5, 11.4)	**16/17 (94.1%)**	(-23.9, 19.6)

[1] NHP study antibacterial was 75 mg ciprofloxacin twice daily x 3 days
NZW rabbit study antibacterial was 50 mg/kg levofloxacin daily x 3 days
[2] 95% CIs are exact confidence intervals

In the antibacterial drug alone group, survival was 13/13 in monkeys and 19/20 in rabbits. The very high survival rates for antibacterial drug therapy alone in these studies do not allow for any additional benefit of raxibacumab to be shown above what the antibacterial drug alone provides. During the bioterrorism event of 2001 in humans presenting with established anthrax disease antibacterial drug therapy alone achieved an approximately 50% survival rate. Given the high survival rate in the animal studies with antibacterial drug alone, it appears that the time of intervention may be too early, and that the animal models do not adequately model the human disease state where use is anticipated. These studies lack capacity to determine if raxibacumab will provide benefit beyond what antibacterial drug therapy alone can provide.

An additional study was conducted to evaluate whether raxibacumab provides benefit beyond antibacterial drug alone when used with an antibacterial drug. This study also allowed for the evaluation for interference of raxibacumab with the therapeutic effect and PK of levofloxacin and raxibacumab. The study also evaluated raxibacumab use at a later stage of disease in animals; a scenario that reflects when humans might present with disease and receive raxibacumab treatment in combination with antibacterial drug treatment.

The results from this additional study are provided in this resubmission. The study was conducted in New Zealand White rabbits where the time to initiation of treatment was later than the previous trials (mean of 84 hours between spore challenge and initiation of treatment). The two treatment groups were antibacterial drug alone (levofloxacin), and antibacterial drug + raxibacumab at 40 mg/kg IV as a single dose. The dose of levofloxacin was chosen to yield a comparable exposure to that achieved by the recommended doses in humans. Forty-two percent of challenged animals survived to treatment. Treatment with antibacterial drug plus raxibacumab resulted in 82% survival compared to 65% survival in rabbits treated with antibacterial drug alone, $p=0.0874$. While the results did not achieve $p\leq 0.05$, the higher point estimate for the antibacterial drug + raxibacumab group, considered in the context of the results from other studies, and taking into consideration the limits of practical feasibility of the

conduct of animal studies, the results support an increased likelihood that raxibacumab can provide benefit beyond what antibacterial drug therapy alone can achieve. In addition, the Levofloxacin and raxibacumab pharmacokinetics in this study were unaffected by product co-administration.

Survival Rates in NZW Rabbits in Combination Therapy Study, All Treated Animals

	NZW Rabbits (35 days)[1] Study 1		
	Number (%) Survivors	**P value[2]**	**95% CI[3] Levo vs Levo + Raxibacumab**
Antibacterial drug alone	24/37 (65%)	-	-
Antibacterial drug + Raxibacumab 40 mg/kg IV single dose	32/39 (82%)	0.0874	(-2.4, 36.7)

[1] Survival assessed 28 days after last dose of levofloxacin.
[2] P value based on a two-sided likelihood ratio chi-square test.
[3] 95% confidence interval based on normal approximation.

Studies Evaluating Safety

Animals

In animal toxicology studies, there was no evidence of CNS toxicity in monkeys dosed with 120 mg/kg raxibacumab. In the animal models of infection a greater rate and severity of CNS disease was found in non-surviving animals that received raxibacumab compared to non-surviving animals that received placebo. In the rabbit combination study where animals received antibacterial drug alone or antibacterial drug + raxibacumab, animals were sacrificed and examined for CNS lesions. There were no brain lesions seen in the surviving animals that received raxibacumab plus levofloxacin, or that received levofloxacin alone.

An additional study was conducted and provided in the resubmission to further evaluate the CNS findings. The study was a randomized study of placebo vs. raxibacumab 40 mg/kg with 24 animals in each treatment arm performed in New Zealand White rabbits. Animals were challenged with 200xLD_{50} spores of *B. anthracis* via an inhalational route. Study treatment was initiated at the time of qualitative positive PA by electrochemiluminescence assay. The 28-day survival rates for the ITT analysis population was 11/24 (46%) of raxibacumab treated animals survived to day 28 compared to 0/24 (0%) placebo animals. Detailed gross and microscopic evaluation of the brain in surviving and non-surviving animals showed that brain lesions occurred predominantly in non-surviving animals in the raxibacumab and placebo treatment groups; however, surviving animals (raxibacumab arm) showed no brain lesions, raxibacumab staining of neural tissue, or clinical signs of CNS toxicity. Information on the CNS lesion findings in animals are described in the Animal Toxicology section of the product labeling.

Humans

The safety of raxibacumab 40 mg/kg IV was evaluated in 326 normal volunteers, and compared to adverse events reported in 80 normal volunteers who received placebo. Rash was seen initially in 6/25 (24%) of volunteers. Then diphenhydramine pre-treatment was initiated

for all and the observed rash rate decreased to 2/61 (3%). Diphenhydramine pretreatment will be recommended, and was used in the monkey efficacy study. Four subjects (1.2%) had their infusion of raxibacumab discontinued for adverse reactions. Two subjects (neither of whom received diphenhydramine premedication) discontinued due to urticaria (mild), one subject discontinued due to clonus (mild), and one subject discontinued due to dyspnea (moderate). The most frequently reported adverse reactions were rash, pain in extremity, pruritus, and somnolence. Other adverse effects include infusion site pain and headache.

Office/Division of Scientific Investigations (DSI) Inspections
During the first cycle, inspections of the bioanalytical assay methods and conduct of the clinical trials found deficiencies in the testing done (bioanalytic methods) to measure levels of raxibacumab and ciprofloxacin in the human pharmacokinetic studies. Additional information about the testing methods, the assay, use of the appropriate number of QC samples to calibrate the concentration curve and re-analysis of samples was requested from HGS to address the noted deficiencies. As noted in the section discussing clinical pharmacology, this deficiency has been addressed and the results obtained by the original and modified bioanalytical methods are both considered reliable.

Anti-Infective Drugs Advisory Committee Meetings
The application for raxibacumab was first presented to the Anti-Infective Drugs Advisory Committee on October 27th, 2009. The Committee was made aware of the questions on the reliability of the human PK data based upon inspectional findings, that the data should be disregarded, and that no question on approval/licensure would be asked of the Committee. The concerns regarding the human pharmacokinetic data were also posted publicly in advance of the meeting in an addendum to the FDA briefing material.

The Committee was asked if the animal studies predict efficacy in humans. The vote on this question was Yes 16; No 7; Abstain 1. During the discussion of this question, a reason cited among those that voted "No" was that the time of intervention for the animal models appeared to be early in disease, noting the 95-100% survival rates with antimicrobial drug alone. On the question of whether raxibacumab will not interfere with antibacterial drug, the Committee voted, Yes 10; No 11; Abstain 3. Some expressed concerns that the ciprofloxacin dose was too high and therefore the study was not a sensitive test to detect interference with antibacterial drugs. On the question of whether a study should be done to look for added benefit of raxibacumab plus antibacterial over antibacterial alone, the Committee voted Yes 17; No 5; Abstain 1. During the discussion of this question some Committee members commented that the study could be done post-approval and some noted the study could be done in rabbits only. The Committee also expressed interest in additional work to understand the CNS findings seen with raxibacumab in animal effectiveness studies and additional safety data in the very young (the idea of doing juvenile animal studies was briefly mentioned) and elderly.

The application was presented during this second cycle of review to the Anti-Infective Drugs Advisory Committee on November 2, 2012. On the question of whether 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, the committee voted Yes 16; No 1; Abstain 1. The committee also mentioned the use of raxibacumab not just for treatment, but also for prophylaxis. On the question of whether the safety trials in healthy volunteers and studies in animals support an acceptable risk benefit profile given the benefits of the therapy discussed in first question, the Committee voted Yes 18; No 0; Abstain 0. The third question asked about the proposed pediatric dosing regimen. There was some discussion about dosing based upon weight bands compared to dosing based upon body surface area. Some Committee members also mentioned the practicality of a 2 hour IV infusion.

Discussion
I concur with the recommendation from the review team, the Cross Discipline Team Leader, and the Acting Division Director that the evidence supports the approval of raxibacumab for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and that raxibacumab is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The limited safety database provides adequate information to support a satisfactory risk benefit ratio for the treatment of anthrax disease. In addition, in the setting where antibacterial therapy is not appropriate or available (e.g., in the setting of resistance to multiple antibacterial drugs) the risk benefit supports use of raxibacumab for prophylaxis.

Inhalational anthrax is a disease for which it is not ethical or feasible to conduct controlled clinical trials. Therefore the assessment of the effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax. The criteria of the animal rule are satisfied in that there is a reasonably well understood pathophysiological mechanism of the toxicity of *B. anthracis* and the effects of raxibacumab on the mechanisms of toxicity of *B. anthracis*, the etiologic agent of inhalational anthrax; the effect has been shown in multiple animals studies and multiple animal species where the time of intervention has ranged from early to late in the course of disease; the endpoint of mortality in the animal studies is clearly related to the desired effect of improving survival in humans with inhalational anthrax; the pharmacokinetic data allow for a dose to be selected in humans. In addition, as described in the section addressing human safety, safety data from human subjects has been provide that demonstrate an acceptable safety profile for raxibacumab for the proposed indication of use. Hence, the product will be approved under 21 CFR 601.90-95 Subpart H “Approval of Biological Products when Human Studies are not Ethical or Feasible”.

The indication includes prophylaxis when alternative therapies are not available or are not appropriate because of the evidence from the studies performed which studied a range of times for initiation of intervention that support use for prophylaxis. In the setting of when alternative therapies are not available or are not appropriate there is a positive risk-benefit balance for use of raxibacumab for prophylaxis (e.g., *B. anthracis* with engineered antibacterial resistance). Even with the limited safety database, the positive risk-benefit balance becomes apparent if one considers a person exposed to a multi-drug resistant strain of *B. anthracis* where antibacterial drugs cannot be relied upon for adequate prophylaxis of patients. The evidence on safety and efficacy supports that using raxibacumab is an appropriate choice for prophylaxis in this scenario.

For pediatric use, even in the absence of pediatric safety and pharmacokinetic data with raxibacumab, there is a reasonable basis for determining pediatric dosing based on a pharmacometric analysis. A population pharmacokinetic approach was used to derive dosing regimens that are predicted to provide pediatric patients with raxibacumab exposures comparable to the observed exposure in adults. The dosing of raxibacumab for pediatrics is based upon the pharmacokinetics of the product in adults and simulations of pharmacokinetc changes for pediatric age groups generated from pharmacokinetic data for other monoclonal antibodies. No pediatric studies of raxibacumab have been conducted. Anthrax is an extremely rare and highly fatal disease, so pediatric studies of this condition would not be feasible. The risk-benefit balance for the raxibacumab indication supports including pediatric patients given the high fatality rate for inhalational anthrax or risk of life-threatening disease with inadequate prophylaxis. Clearly, the approval of pediatric use in the absence of pediatric safety and pharmacokinetc data should be an exception to the usual circumstances for decisions about pediatric use of a new drug or biological product; inhalational anthrax, a highly fatal condition where drugs are evaluated using the animal rule, is not a usual circumstance. Inhalational anthrax is also an extremely rare disease and pediatric studies would not be ethical or feasible.

In summary, raxibacumab should be approved for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The product labeling and accompanying patient information sheet adequately described the risk, benefits, and use of the product.

Subpart H Approval Requirements, Postmarketing Requirements, and Postmarketing Commitments

SUBPART H APPROVAL REQUIREMENTS

The approval under 21CFR Part 601, Subpart H (Approval of Biological Product When Human Efficacy Studies Are Not Ethical or Feasible) is subject to three requirements

1. Approval with restrictions to ensure safe use. This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that raxibacumab can be safely used without restrictions on distribution or use.

2. Information to be provided to patient recipients. This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Patient Labeling for raxibacumab meets the requirements of this subsection. The Applicant is reminded that the Patient Labeling must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. Postmarketing Studies. This subsection requires the Applicant 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. We refer to the Applicant's letter dated December 7, 2012, stating agreement to conduct a field study to evaluate the efficacy and safety of raxibacumab use for *Bacillus anthracis* in the United States and to submit a protocol on or before June 13, 2013.

POSTMARKETING REQUIREMENTS

In accordance with the Subpart H 21CFR 601 requirement 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, the Applicant has committed to the following postmarketing requirement (see the Applicant's submission dated December 7, 2012.

1. Conduct a field study to evaluate the efficacy, pharmacokinetics, and safety of raxibacumab use for *Bacillus anthracis* in the United States.

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

The Applicant will submit their clinical protocol to IND 011069. Submit final reports to the BLA as supplemental applications. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "Subpart H Postmarketing Requirements."

The Applicant has also committed to the following postmarketing commitments specified in the Applicant's submission of December 17, 2012. These requirements, along with any agreed upon completion dates, are listed below.

POSTMARKETING COMMITMENT FOR THE PROPHYLAXIS INDICATION (SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B)

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

Final Protocol Submission:	November 1, 2014
Study/Trial Completion:	October 1, 2016
Final Report Submission:	October 1, 2017

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

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

Final Protocol Submission:	August 29, 2013

Study/Trial Completion: November 30, 2013
Final Report Submission: December 15, 2013

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

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

Edward Cox, M.D., MPH
Director
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

EDWARD M COX
12/14/2012