CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA 125349

COMPLETE RESPONSE

November 14, 2009

Human Genome Sciences, Inc.
Attn: Sally Bolmer, Ph.D.
Senior Vice President, Regulatory Affairs
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Bolmer:

Please refer to your biologics license application (BLA), dated May 13, 2009, received May 14, 2009, and submitted under section 351 of the Public Health Service Act for raxibacumab injection for intravenous infusion.

We acknowledge receipt of your amendments dated:

May 27, 2009	June 8, 2009
June 10, 2009	June 16, 2009
June 18, 2009	June 24, 2009
July 10, 2009	July 15, 2009
July 20, 2009	August 7, 2009
September 4, 2009	September 14, 2009 (2)
September 18, 2009	September 23, 2009
October 2, 2009	October 29, 2009
November 4, 2009	November 10, 2009

Please note that your amendment dated November 10, 2009 was not reviewed for this action. You may incorporate this amendment, or applicable sections, by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

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 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, re-assay 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 ciprofloxacin 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 re-analysis 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 ciprofloxacin 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 (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.

LABELING

We reserve comment on the proposed labeling until the information requested above is provided and the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

ADDITIONAL REQUESTS

Although not deficiencies, we have the following additional requests:

Clinical

1. Submit the clinical protocol for a field study that would be conducted in the event of an anthrax exposure and raxibacumab would be administered to humans.

2. Given that survival rates of raxibacumab at 40 mg/kg were 35% in rabbits and 69% in monkeys, design and conduct a study to further evaluate the efficacy, safety/tolerability, pharmacokinetics, and dose-response of raxibacumab doses higher than 40 mg/kg (e.g., 60 mg/kg and 80 mg/kg) in an animal treatment model of inhalational anthrax.

Product Quality

3. Update the stability testing protocol to include endotoxin testing at expiry.

4. Develop and validate a container closure integrity test to be used *in lieu* of sterility testing for samples on stability. The dye ingress method described in the BLA is not validated and therefore not suitable for use *in lieu* of sterility testing. Conduct sterility testing instead of container closure integrity testing for samples on stability until a validated ingress test method is developed and implemented.

5. Implement in-process bioburden testing of the bulk drug product (b) (4) (b) (4) Alternatively, perform full-scale validation of the time limit from (b) (4) (b) (4)

6. Conduct a validation of the hold time of (b) (4) for microbial control at-scale. The validation study should demonstrate that bioburden and endotoxin measurements at the end of the proposed hold meet the acceptance criteria described in the BLA.

7. Conduct a validation study that supports the proposed hold-times of in-process materials for bioburden and endotoxin control. The study should support manufacturing holding practices and capabilities for microbial control. You may consider conducting a

retrospective analysis of at-scale production runs but the analysis should include verifiable information such as batch run numbers and hold conditions.

8. Re-assess (b) (4) endotoxin and bioburden action limits for in-process materials. These limits should reflect the current manufacturing process capabilities. Provide a final report with summary data and information justifying any re-assessed limits for the in-process materials.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

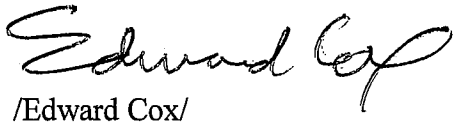
Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Rebecca D. McKinnon, Pharm.D., Regulatory Project Manager, at 301-796-1600.

Sincerely,



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