From: Pracht, Leigh
Sent: Tuesday, June 04, 2013 3:23 PM
To: 'Steve McGregor'
Subject: FDA follow-up responses and additional request for information STN 125426/0 and IND 13551

Cangene Corporation
Attention: Mr. Steve McGregor
June 4, 2013
Sent by email

Dear Mr. McGregor:

We are reviewing both your May 14, 2013 biologics license application (BLA) submission for Coagulation Factor IX (Recombinant) and your May 16, 2013 IND submission for Coagulation Factor IX (Recombinant) rFIX, IB1001. We are providing the following comments and request for additional information to continue our review:

Applicant requests for clarification #1-3

1) It is well established that subcutaneous administration can influence the rapid production of antibody response to immunogenic proteins compared to intravenous route of administration. However, Cangene is proposing to use repeat IV route of administration to mimic the clinical scenario. Does the Agency agree with this approach?

   Yes, we agree that intravenous administration of IB 1001 produced by the former and modified commercial processes to rabbits is appropriate to use in your proposed study.

2) Is the current proposed study design with intravenous administration of 0.5 mg/kg dose at 2x/wk for 12 weeks with IB1001 (estimated concurrent dose of HCP at 22-44,000 and 21-30 ng/mg with former commercial and modified commercial process, respectively) adequate to address the effective removal of immunogenic components in the HCP from the Chinese hamster ovary cells used to produce IB1001?

   Your proposal to administer the former and modified versions of IB 1001 by twice weekly dosing of 0.5 mg/kg/dose for 12 weeks is a reasonable study design to assess the potential immunogenicity of residual amounts of Chinese hamster ovary HCP that may remain in the drug product after (b)(4) .

3) Although rabbits are a highly immunoreactive species, extremely low levels of HCP present in the drug product produced from the modified commercial process may not be sufficient to induce an immune response even after repeat administration. If there is a rapid antibody response with high incidence in the rabbits given drug product produced from the former process by 4 weeks and no response in the rabbits given product from the modified process indicating insufficient immunogenic components in the IB1001 dose to produce an immune response, the study will be stopped at 8 weeks. Does the Agency agree with this approach?

Yes, we agree that your study can be terminated at 8 weeks provided that the rabbits administered IB 1001 produced by the former commercial process develop a positive antibody response at 4 weeks.

Additional request

1. Please provide a more complete description of the (b)(4) procedure that will be used to evaluate rabbit plasma for the presence of anti-HCP antibodies. Specifically, please include a description of the (b)(4) for the antibodies against the CHO HCP, and identify any positive controls that will be used.

The review of these submissions is on-going and issues may be added, expanded upon, or modified as we continue our review.

Please submit your responses to this information request as amendments both files referencing the date of this request.

If you have any questions, please contact me at (301) 827-6116.

Sincerely,

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