From: Cagungun, Nannette
Sent: Friday, June 20, 2014 5:29 PM
To: Steve McGregor (smcgregor@ebsi.com)
Cc: Valencia, Iliana
Subject: Information Request for Coagulation Factor IX (Recombinant)

Our Reference: BL 125426/0

Dear Mr. McGregor:

We are reviewing your resubmission to your biologics license application (BLA) for Coagulation Factor IX (Recombinant). We are providing the following comments and request for additional information to continue our review:

1. You provided a new Table labeled as Table 44 in the response (Sequence 0019) to clarify the values of Table 3 presented in section 3.2.S.2.5. You have stated that a corrected version of section 3.2.S.2.5 was also provided. However, the new Table 44 now consists of new values and much of the data presented earlier is omitted. Please submit the corrected table corresponding to Table 13 in BLA Sequence 000 4 and highlight/clarify the changes you have made to the original Table which resulted in the new data currently in Table 44.

2. You have provided validation study data demonstrating that the conditions and performance parameters of the small-scale runs are fully representative of the commercial scale process for the (b) (4) . However, the following deficiencies should be addressed and completed in order for the reviewers to finalize the review on this topic:

Please incorporate Tables 45-48 in the response of January 27, 2014, into the current section 3.2.S.2.5.

Please provide a detailed comparison of the lab-scale to the full-scale process, specifically illustrating the differences between lab and the full-scale b) (4) for each (b) (4) step.
The information and data on (b) (4) studies, shown in section 3.2.S.2.5.4.3 (b) (4) Useable Performance over Time in the amendment 4 of the BLA (Table 21-24) has been deleted in the current version of section 3.2.S.2.5. Please include this information and data.

3. You have provided partial data supporting the validation of (b) (4) (b) (4) . However, you have not completed the validation of (b) (4) In addition, you have not completed the validation of (b) (4) Please provide the required data.

4. You have provided clearance studies results for the following process related impurities: (b) (4) CHO HCP, b) (4) . However, you have not provided

the spiking test results for the process-related impurities (including Chinese Hamster Ovary Host Cell Protein (CHO HCP)) at the laboratory-scale. Please provide the required data.

5. In your response to CR items #12 and 14 you described the changes in the data processing procedures. You have reported that the potency test analyzer was changed for the (b) (4), but you have not clarified how the Drug Product is tested. Please provide this information. In addition, data to demonstrate the differences in potency using the (b) (4) should be provided to ensure consistency in product testing.

The description and reports supporting the other changes are complete and satisfactory.

6. In your response to CR items #12 and #14, you have provided the acceptance criteria and limits for the (b) (4) Drug Product:

a. The proposed acceptance criteria for (b) (4) of the Drug Product Release and Stability are too broad and are not representative of the release testing results derived from (b) (4) released lots. Moreover, the limits for the (b) (4) are not aligned with the limits for potency (the acceptance limits for the potency range is (b) (4) of the upper limit, while the acceptance limits for (b) (4) are wider - (b) (4) of the upper limits. Please set a reasonably narrower range of acceptance limits for (b) (4).

b. The proposed acceptance criteria for Drug Product Release and Stability Specifications of the upper limits for the (b) (4) are too broad and are not fully representative of the release testing results derived from the (b) (4) released lots. Based on historical data we recommend that it be lowered to (b) (4) Accordingly, please change the acceptance criteria for Drug Product Release and Stability Specifications of the upper limits for the (b) (4)

7. In your response to CR item # 12c you have noted that no testing or acceptance limits are in place to the (b) (4) process related impurities. However, you have not added these testing and acceptance criteria to the Drug Product specifications (section 3.2.P.5.1). Acceptance criteria should be set for these two process-related impurities in the Final Drug Product specifications.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file

by July 3, 2014
referencing the date of this request. If you anticipate you will not be able to respond by this date,
please contact the Agency immediately so a new response date can be identified.

The action due date for this file is July 29, 2014.

If you have any questions, please contact Ms. Iliana Valencia at 240-402-8444.

Sincerely,
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