



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our Reference: BL 125582/0

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D White
October 15, 2015
Sent by email

Dear Mr. White:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We are providing the following comments and request for additional information to continue our review:

1. With reference to amendment 128582/0.23 submitted on July 15, 2015, please made changes to the following specifications:

- a. Endotoxin in (b) (4) and Drug Product (DP)

The specification is established based on safety consideration, but does not reflect the manufacturing process capability. Please establish alert and/or action limits which will allow adequate control for the manufacturing process with regard to this parameter.

- b. (b) (4)

[REDACTED]

- c. Mannitol in drug product

The specification limit for the 250 IU presentation is justified based on a limited dataset ((b) (4) batches) and the specification limits for the 500 IU, 1000 IU and 2000 IU presentations are calculated including data from earlier batches and do not reflect the capabilities of the current process. Please commit to revising the specification limits for mannitol for all dosage presentations within 1 year after licensure.

2. With reference to amendment 128582/0.30 submitted on August 10, 2015, please revise section 3.2.P.8.2 Post-Approval Stability Protocol. Please include detailed testing schedule as specified in the stability protocols attached in your response to information request as part of section 3.2.P.8.2.
3. With reference to amendment 128582/0.32 submitted on August 14, 2015, please revise the specification for Host Cell Protein (HCP). The HCP limit is calculated including data from earlier batches and does not reflect the capabilities of the current process. Please commit to re-evaluating the specification limit for HCP within 1 year after licensure.
4. With reference to amendment 128582/0.34 submitted on August 31, 2015, please address the following issue: In method validation report MVR-04-039 "Quantitative determination of albumin in fusion protein rIX-FP on the (b) (4) the specificity of the method is not adequately validated. To adequately control the quality of the albumin moiety, the ability of the method to (b) (4) albumin in a quantitative manner needs to be established. The validation exercise performed did not confirm such ability. You provided the testing of a single sample (b) (4) that resulted in a (b) (4) albumin, and claimed that this result met the acceptance criterion of (b) (4). It is not clear how this acceptance criterion was set and how it is useful for establishing method capabilities. You have not demonstrated any correlation between the (b) (4) and the assay results. Please revalidate the specificity of this method in a way sufficient to establish its suitability to control the quality of the albumin moiety. Otherwise, please explore other analytical procedures to control this quality attribute.
5. With reference to amendment 128582/0.37 submitted on September 4, 2015, please revise the testing instructions and specification for (b) (4). Please modify testing instruction Q-16-405 and DS Specification adding (b) (4) as acceptance criteria. In testing instruction Q-16-405, please clearly define the limits of the regions for different (b) (4) (b) (4) to ensure consistency of the calculations.

6. With reference to amendment 128582/0.41 submitted on September 18, 2015, please address the following issue: The data presented appear to show that impurities in Polysorbate 80 (PS-80) (b) (4)

The exact nature of the impurities is still unknown; however, the experimental data for (b) (4)

Based on the above, we consider the purity of PS-80 to be critical. Please revise the specification for PS-80 to ensure control for the unknown impurities with the ability (b) (4). We recommend you to use (b) (4) of rFIX-FP by (b) (4) in the presence of PS-80 to qualify each batch of PS-80.

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 November 5, 2015 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.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is December 5, 2015.

Please send an acknowledgement for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,
Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/PPMS