



Our Reference: BL 125582/0

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D White
July 20, 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 your 23 June 2015 amendment in which you responded to our information request dated 12 June 2015, please address the following issues:
 - a. Regarding testing instruction Q-10-081 in item 2.4.4 (response for FDA Request #3d),
 - i. In sections 5, please describe in clear, prescriptive language and with sufficient details to instruct the analyst on how to prepare the samples and perform the assay. Please use active voice to specify the preparer (the analyst or instrument), the volumes of the sample and buffer used for each dilution, and the number of tubes required for each assay. Please reference the (b) (4) SOP for potency testing, Testing Instruction QCA-474, submitted in section 3.2.S.2.4 of the BLA, for the level of details needed for meaningful technical instructions.
 - ii. In section 6.2, please amend the system validity criteria to add “Only results that are within the assay range are considered valid”. You may use either the range of concentrations of the sample after it is (b) (4) in the instrument (b) (4) , or that of concentrations of the samples prepared by the analyst for the assay (b) (4) . As all (b) (4) of the sample are used to calculate the its potency, and the (b) (4) are performed as part of set protocol the use of “working range” as defined in the validation report (b) (4) is confusing and not justified.
 - b. Regarding item 2.4.9 (response for FDA Request #3i),
 - i. Your proposal to increase the acceptance limit of in-process control for (b) (4) is not justified by your manufacturing experience, and therefore

unacceptable. If you cannot improve the performance of the method, please retain the previously established acceptance criterion of (b) (4)

- ii. Please reinstate (b) (4) specification with an acceptance criterion of (b) (4), either along with or in lieu of in-process control testing for (b) (4).

2. With reference to the original BLA submission, section 3.2.P.8.2 Post-approval Stability Protocol And Stability Commitment:

Please modify this section adding detailed stability protocol, indicating the tests performed at each stability time point.

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 August 10, 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/RPMS