



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
December 2, 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. Regarding Q-04-039 *Quantitative determination of albumin in fusion protein rIX-FP on the* (b) (4), the new information provided in Version 2.0 of validation report MVR-04-039 appears acceptable in demonstrating the sensitivity of the method to detect (b) (4) in albumin caused by (b) (4). We agree that this method is suitable for release testing of the (b) (4) Final Drug Product of rIX-FP. However, please provide additional data to demonstrate that this method can also detect (b) (4) in albumin due to (b) (4).
2. With reference to Table 3.2.P.5-1-1: **Drug Product Specification for CSL 654**, please establish supplemental *Identity* test(s) to better define the structural integrity of the rIX-FP molecule, such as those that assess the (b) (4) such as those described in section 3.2.S.3.3.1 **Structural Characterization**, would be appropriate for this purpose. Due to the novelty of this product, it is essential to monitor closely its structural integrity in product batches manufactured even in the later phase of product development through market distribution.
3. Regarding the (b) (4) method used to compare the structure of rIX-FP, please develop a system suitability control and establish quantitative acceptance criteria for rIX-FP batch comparability.
4. Regarding the assays used to assess product immunogenicity in clinical studies,
 - a. You stated that the cut points in screening assays to detect antibodies against albumin, FIX and rIX-FP were set to yield a (b) (4) percent false positive rate, however,

no signs of antibody formation were found in clinical trials. Please develop new cut points to comply with the (b) (4) percent false positive threshold.

- b. Please note that the absence of false positive results may indicate a potential difference between the patient population samples and the healthy volunteer samples used to set the cutoff value. Please compare the cut points determined using healthy volunteer samples and actual patient samples.
- c. Please investigate the interference of anti-albumin antibodies with the detection of inhibitory anti-FIX antibodies.
- d. rIX-FP is co-expressed with (b) (4) . Please determine the ability of your antibody assays to detect antibodies against (b) (4) , including the (b) (4)
 (b) (4)
- e. Please provide an English translation of Standard Operating Procedures (SOP) for the following immunogenicity methods: SOP 020100107 (antibodies against human albumin using (b) (4) SOP 020100114 (antibodies against CHO cell proteins using (b) (4) SOP 020100147 (antibodies against rIX-FP CHO cell proteins using (b) (4) and SOP 020100106 (determination of inhibitory FIX antibodies)

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 December 15, 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 March 5, 2016.

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