

From: Thompson, Edward
Sent: Friday, May 22, 2015 11:29 AM
To: 'Kevin Darryl (KD) White (Kevin.White@cslbehring.com)'
Cc: Monica.Richardson@cslbehring.com
Subject: Information Request for BL 125582/0

Contacts: Kevin Darryl (KD) White - CSL Behring

Dear Mr. White:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We determined that the following information is necessary to continue our review:

1. Scientific Report GT-SR-CS_016-01 (b) (4) Analysis of Factor IX-FP (CSL-654) should contain the following information that is not present:
 - a. Please provide the (b) (4) of the individual peptide identifications.
 - b. Please provide the (b) (4) parameters used during the database search for identification of peptides and proteins.
 - c. Please provide the acceptance criteria used for positive identification of peptides.
2. Scientific report GT-SR-CS_016-01 (b) (4) Analysis of Factor IX-FP (CLS-654) should contain information on system suitability, specifically:
 - a. Please provide the (b) (4) immediately prior to the testing reported in GT-SR-CS_016-01.
3. Please provide information on the method used to calibrate the (b) (4) and the (b) (4) system including:
 - a. The composition of the (b) (4) standard obtained from (b) (4) used for calibration.
 - b. The range of the calibration, and the number of (b) (4) identified from the standard vs. the number of (b) (4) that can be expected.
 - c. The detection limit for the (b) (4) at the manufacturers proscribed (b) (4)
4. The data provided in 3.2.S.3.1.1 is in summary table format. The sponsor should provide raw data in the form of (b) (4) obtained during the analytical runs for data file MAX-00528; MAX-00531-00532; MAX-00536;

MAX00540; MAX-00672 - MAX-00673. As part of this data package please specify which (b) (4) analysis.

5. On page 4 of REP-15891 you state that (b) (4) Please express these quantities in terms of molar concentration to facilitate comparison.
6. Report 15891 states that the (b) (4) data analysis, (b) (4) software program were used to evaluate the data. Please provide more complete description of how these tools were used for the data evaluation process.
7. In the results section of REP-15891 you state that (b) (4) was not consistently achieved for the (b) (4) of rFIX-FP. Please provide an explanation for the lack of (b) (4) data for those peptides that did not yield (b) (4) data of sufficient quality for identification.
8. In the discussion section of REP-15891 you state that the majority of (b) (4) in the fusion protein were the same as the (b) (4) in the native proteins. The three manufacturing lots of rFIX-FP were shown to have essentially the (b) (4) Please clarify the terms “majority” and “essentially”.
9. Were the XIC’s that were generated from the (b) (4) data for the PPQ lots studied in REP-15891 used for a quantitative comparison of (b) (4) peptides between PPQ lots, and PPQ lots against the (b) (4) standard?
10. The results section of REP-15892 states, (b) (4)
 - a. What parameter used during (b) (4) was used to trigger an (b) (4)
 - b. Was the failure to obtain adequate (b) (4) for all of the expected (b) (4) peptides due to (b) (4) parameters, or another cause?
11. Report GT-SR -CS_015-02 describes (b) (4) analysis, Sections 4.2 -4.10 describes the preparation of the samples listed in section 4.1. Please clarify which samples underwent which treatments, and what quantities of sample were used for each individual treatment?
12. Report GT-SR -CS_015-02 describes (b) (4) analysis, Sections 4.2 -4.10 describes the preparation of the samples listed in section 4.1. Section 4.6 and 4.7 indicate that (b) (4)

(b) (4) . Please clarify which samples were analyzed using which (b) (4) and why there is a discrepancy in the amount of sample (b) (4)

13. Section 3.2.1.3.1-4 REP 10016 provides comparisons of the (b) (4) Marburg CSL654 drug substance as well as the (b) (4) standard using (b) (4).
 - a. How many replicates were done for each sample when using this test?
 - b. Was this method validated for precision?
 - c. Was this method validated for robustness?
 - d. Was this method validated for intermediate precision?
14. Section 3.2.1.3.1-4 REP 10016, Table 5 indicates that (b) (4) is similar for the (b) (4) Marburg reference proteins, however there is a considerable difference for (b) (4) which is (b) (4) for the Marburg. How does this difference in the (b) (4) reflect on the difference in structure of the (b) (4) CSL 654 drug substance and the Marburg 654 DS?
15. Section 3.2.1.3.1-4 REP 10016, Table 5 shows that the (b) (4) Marburg drug substance respectively is similar; although both differ from the (b) (4) standard. The (b) (4) is considerably different. You reported a value of (b) (4) for the Marburg DS. How does this difference in the (b) (4) reflect on the difference in structure of the (b) (4) CSL 654 drug substance and the Marburg 654 DS?
16. Section 3.2.S.3.1.1-6 REP 15244 Please explain why the (b) (4) was lowered from (b) (4) and how this may affect the resulting (b) (4)



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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 June 12, 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

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Our Reference: BL 125582/0

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