

From: Maruna, Thomas
Sent: Wednesday, February 17, 2016 1:22 PM
To: 'Angela.Azzara@cslbehring.com'; KevinDarryl.White@cslbehring.com
Cc: Khrenov, Alexey (CBER)
Subject: February 17, 2016 Information Request - BLA 125591.0 - Please Respond By March 8, 2016

Importance: High

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin Darryl White
February 17, 2016
Sent by email

Dear Mr. White:

We are reviewing your May 29, 2015 biologics license application (BLA) for the following:

STN	Name of Biological Products
125591/0	Antihemophilic Factor (Recombinant), Single Chain

We determined that the following information is necessary to continue our review:

1. With reference to amendment STN 125591/0.15 dated 8 January 2016 (your responses to our Information Request (IR) dated 18 December 2015), please address the following:
 - a. In your responses, you committed to revise the acceptance criteria of the (b) (4) specification after the analysis of the results of (b) (4) (b) (4). Please provide a draft text of the Post-Marketing Commitment, which should include the date of the submission of the final study report.
 - b. In the modified (b) (4) test, the system suitability criterion of (b) (4) . Please clarify how this acceptance criterion was established. Please provide the data for (b) (4) for the samples which were analyzed by date.
 - c. Regarding the determination of *Protein Content* by the (b) (4) Assay, please address the following:
 - i. You claim that the suitability of the assay for its intended purpose is demonstrated in the **Justification of Specification** section for the parameter (b) (4) . Therefore, please provide the results of protein concentration measurements used to calculate the (b) (4)

for each of the (b) (4) batches referenced in the **Justification of Specification** section. Please provide the sample dilution scheme used in the analysis of each dosage strengths of the rFVIII-SC Drug Product (DP). Please also provide the dates when the measurements were performed.

- ii. The validated range of the (b) (4) .
With the working range of the assay after (b) (4) . However, the validated range was based on the much lower (b) (4) than that of rFVIII-SC. The batch analysis data show that the protein concentrations (b) (4) , which will require a (b) (4) . Please perform supplemental validation to establish the assay capability for the analysis of samples with protein concentration (b) (4) i.e., in the concentration range typically found in the rFVIII-SC DP.

- d. The stability program for Master and Working Cell Banks (MCB and WCB) described in the amendment was incomplete in that it is limited to the assessment of cell growth and viability during (b) (4) . Please include genetic characterization as recommended in ICH Guideline Q5(b), i.e., assessment of the integrity of the coding region, integration status and copy number for the rFVIII-Single Chain construct; and identify the testing intervals. Also, please explain in detail if your stability program includes testing for adventitious viruses and what tests are to be performed. Please submit an updated SOP for cell banks storage stability investigation.

2. With reference to amendment 125591/0.18 dated 29 January 2016 (your responses to our IR dated 18 December 2015), please provide the updated Section 3.2.S.4.1 **Specification** for the Drug Substance including the updated acceptance criteria for (b) (4) .
3. With reference to amendment 125591/0.21 dated 3 February 2016 (your responses to our IR dated 20 January 2016), please provide the following information.
 - a. The original report of the investigation, referenced in your response, performed in 2013 by CSLB.
 - b. The (b) (4) presented in Figures 1 and 2 appear different. The (b) (4) in Figure 1 is (b) (4) in Figure 2 does not have these features. Please explain the discrepancy.
 - c. As inferred from the data in Figure 1, the (b) (4) .
Please provide an explanation for this phenomenon. Since only samples at (b) (4) were analyzed, please analyze several intermediate concentrations.

- d. Please analyze (b) (4)
- e. You claim that the (b) (4)

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 responses as an amendment to this file by March 8, 2016 referencing the date of this request.

The action due date for this file is May 28, 2016.

If you have any questions, please contact me.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH

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