

From: Thompson, Edward
Sent: Friday, December 18, 2015 2:53 PM
To: 'Kevin Darryl (KD) White (Kevin.White@cslbehring.com)'
Cc: Maruna, Thomas
Subject: Information Request - BLA 125591.0 - Please Respond by January 10, 2016

Contacts: Kevin Darryl (KD) White - CSL Behring

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin Darryl White
December 17, 2015
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. Please revise the release specifications, including the "Justification of Specifications," for bulk drug substance (BDS) and final drug product (FDP). Specifically,
 - a. Please review and revise acceptance ranges or limits for all quantitative parameters in the DS and FDP release specifications based on statistical analyses of the data acquired from release results of all FDP and DS lots manufactured, to date. Please submit the complete datasets used for establishment of the revised specification acceptance ranges or limits and the statistical analyses employed.
 - b. The current specification for (b) (4) is not informative and does not allow sufficient control for potential changes in the (b) (4). The Agency considers a (b) (4) to be a critical quality attribute. Please revise the specification to establish quantitative acceptance criteria for (b) (4) analyses to ensure continued product quality and manufacturing consistency.
 - c. The current specification for (b) (4) is not justified. The (b) (4) for identity confirmation are found in all FVIII (b) (4) studied and their presence is not sufficient to confirm identity of rFVIII-Single Chain (see question 3b). Please establish an identity test specific for rFVIII-Single Chain.

- d. Please establish a drug substance release specification for (b) (4), which may be in addition to or *in lieu* of in-process control testing for (b) (4).
2. As we discussed during the pre-license inspection for BLA 125582, the (b) (4) was used inappropriately to set the acceptance criteria in the validation studies. While the use of (b) (4) of the specification range as an assay range may be appropriate in some situations, the use of this value as the standard deviation of the analytical method is not justified. However, the performance characteristics of a number of methods (except for those listed in item 3 below) were established in the validation studies albeit with inappropriately set acceptance criteria. Therefore, please re-evaluate these performance characteristics along with the revised specifications to ensure that the methods are suitable for their intended purpose.
3. The following issues were identified in the validations and/or testing instructions for the specified analytical methods. Please address each item accordingly, and submit the amended documents to the FDA.
 - a. (b) (4)
 - i. Please submit complete Testing Instruction-42-052 including attachments.
 - ii. Method validation used a different procedure from the testing instruction.
(b) (4)
Please re-establish the specification and re-validate the method, accordingly.
 - b. (b) (4) analysis
 - i. Please re-validate the assay for the intended purpose as described under 1(b) above.
 - ii. Please consider qualifying a suitable reference standard for this assay.
 - c. (b) (4)
 - d. CHO Host Cell Protein assay by (b) (4)
 - i. It is not clear from the report 030200111 if the HCP preparation used for the production of (b) (4) was produced with the pilot

or commercial scale process. It is also not clear if the verification of (b) (4) performance was done using commercial scale or pilot scale sample. Please provide this information.

- ii. The quality of (b) (4) (b) (4) used to determine the (b) (4), and does not allow reliable calculation of (b) (4). Please repeat the experiments using commercial scale samples and submit the results.

- e. Protein composition by (b) (4)

The claimed range of the method, (b) (4), is inferred from results of the validation of the linearity and accuracy. However, there is no evidence in the validation report that accuracy was validated over the range of the method. Please provide data establishing the accuracy of the method in the range of (b) (4).

- f. (b) (4)

(b) (4) (b) (4)

- g. Determination of protein content by (b) (4) Assay

Validation of intermediate precision is insufficient. The data demonstrates significant difference (b) (4) analysts who analyzed samples on different days. Due to the limited amount of data and lack of matrix approach in the validation study design, it is impossible to estimate intermediate precision of the method and determine its suitability for intended purpose. Please perform supplemental validation of this parameter.

4. As was discussed during pre-license inspection of (b) (4) facility, please provide in an amendment to the BLA, the specifications for (b) (4)

5. With reference to the post-approval stability studies detailed in the original BLA submission:

- a. Please modify section 3.2.P.8.2 Post-approval Stability Protocol And Stability Commitment, adding detailed stability protocol, including testing schedule
- b. Please submit Stability Protocols for Master Cell Bank and Working Cell Bank, and specify tests to be performed and frequency of testing.



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 January 10, 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 Tom Maruna at (240) 402-8454.

Sincerely,
Edward Thompson
Regulatory Project Manager
FDA/CBER
Office of Blood Research and Review
(240) 402-8443
email: edward.thompson@fda.hhs.gov
10903 New Hampshire Avenue
WO71-4212
Silver Spring, MD 20993-0002

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone and return it to us at the above address by mail. Thank you.