

From: Thompson, Edward
Sent: Friday, June 12, 2015 2:57 PM
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 are providing the following comments and request for additional information to continue our review:

1. Please amend the deficiencies in the Justifications of Specifications for bulk drug substance (BDS) and final drug product (FDP). Specifically,
 - a. Please review and revise the ranges and limits for all quantitative parameters in the FDP specifications based on statistical analyses of the data acquired from testing of all FDP and DS lots manufactured up to date. Please submit the complete datasets used for the establishment of the revised specification ranges or limits; and the statistical analyses employed.
 - b. The current specification for (b) (4) is not informative and does not allow for control or monitoring of changes in the (b) (4). We consider this parameter a critical quality attribute. Please revise the specification and acceptance criteria for (b) (4) analysis to allow this parameter to be used to control the quality of the product and consistency of the manufacturing process.
 - c. The current specification does not include adequate controls for the albumin moiety of the fusion protein. The current test by (b) (4) is for (b) (4) only and acceptance criterion for albumin (b) (4) is qualitative and insufficient to assess the quality of the protein. Please establish a test(s) and acceptance criterion to allow for quantitative control of the albumin moiety.
2. As we discussed during the pre-license inspection, the (b) (4) were 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. Albumin by (b) (4)

(b) (4)

b. Activity of Factor IXa by (b) (4) assay

- i. The range of the assay was not properly validated. Due to calculation errors, the validated range was (b) (4) whereas the working range of the assay is (b) (4). Please validate the appropriate range as well as other assay parameters within this range.
- ii. Please establish a qualification procedure and acceptance criteria for (b) (4) lots.
- iii. Please revise the test instructions and calculation sheet to improve clarity. The documents must mention the actual dilution steps performed in the assay and clearly delineate the steps performed by the technician and by the instrument.

c. (b) (4) analysis

- i. Please re-validate the assay for its intended use as described under 1(b) above.
- ii. Please validate Specificity of the assay using proteins with different (b) (4)
[REDACTED]
- iii. Please establish and include reference standard for this assay.

d. Factor IX activity by one-stage clotting assay

- i. The range of the assay was not properly validated. Due to calculation errors, the validated range was (b) (4) [REDACTED] whereas the working range of the assay is (b) (4) [REDACTED]. Please revise the working range of the assay so it is validated.
- ii. Please revise the test instruction and calculation sheet to improve clarity. The documents must mention the actual dilution steps performed in the assay and clearly delineate the steps performed by the technician and by the instrument.
- iii. Please submit the amended test instructions, which allow the testing of rFIX-FP using the (b) (4) instrument only.

e. (b) (4)

f. Mannitol by (b) (4)

Specificity of the method is not sufficiently validated. Please perform supplemental validation to demonstrate that the method is specific for mannitol, and not other sugars.

g. (b) (4)

[REDACTED]

h. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

ii. Please submit the test instruction in English.

j. CHO Host Cell Protein assay by (b) (4)

i. The performance of the assay is not verified using (b) (4) derived from the commercial manufacturing process. Please verify the performance of the (b) (4) using samples from the commercial process at (b) (4). The samples should be from the same process stage as the material used in the verification studies presented in the BLA.

ii. Accuracy is not sufficiently validated. Please ensure that Accuracy is validated over the entire range of the assay. You may recalculate existing data factoring in the dilutions used for different samples. However, additional validation studies may be required if the range of the assay is not covered by the existing data.



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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 23, 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



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
June 12, 2015
Sent by email

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 - b. The current specification for (b) (4) is not informative and does not allow for control or monitoring of changes in the (b) (4). We consider this parameter a critical quality attribute. Please revise the specification and acceptance criteria for (b) (4) analysis to allow this parameter to be used to control the quality of the product and consistency of the manufacturing process.
 - c. The current specification does not include adequate controls for the albumin moiety of the fusion protein. The current test by (b) (4) is for (b) (4) only and acceptance criterion for albumin (b) (4) is qualitative and insufficient to assess the quality of the protein. Please establish a test(s) and acceptance criterion to allow for quantitative control of the albumin moiety.
2. As we discussed during the pre-license inspection, the (b) (4) were 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.

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- c. (b) (4) analysis
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 - ii. Please revise the test instruction and calculation sheet to improve clarity. The documents must mention the actual dilution steps performed in the assay and clearly delineate the steps performed by the technician and by the instrument.
 - iii. Please submit the amended test instructions, which allow the testing of rFIX-FP using the (b) (4) instrument only.
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(b) (4)

h. (b) (4)

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Thank you

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