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To STN: #125582/0

Through William M. McCormick, Director, DBSQC/OCBQ

Sponsor CSL Behring

Subject: Review Memo for Biological License Application for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), Idelvion (CSL654)

Summary of Review

The new BLA was submitted for recombinant Coagulation Factor IX Albumin Fusion Protein, rIX-FP, (STN#125582) by CSL Behring. This memo applies to the review of the following analytical methods and their validations, as used for the lot release of the drug product.

1. One-stage Clotting Assay for Factor IX Potency
2. Purity by (b) (4)
3. Purity by (b) (4)
4. Residual Moisture Content by (b) (4)
5. (b) (4)
6. Appearance of Lyophilized Cake
7. Dissolution time
8. Appearance of Reconstituted solution and Dissolution time

An IR was submitted on 7 May 2015. The sponsor provided partial response (Amendments 15 and 19) and committed to provide complete response by 31 July 2015. A second IR was submitted on 15 July 2015.

Background

CSL Behring submitted an original BLA for CSL 654 (IDELVION) drug product, which is a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP). It is indicated in patients with Hemophilia B (congenital factor IX deficiency) for routine prophylaxis to control, prevent or reduce of the frequency of bleeding episodes, and for prevention of bleeding in perioperative setting. The active ingredient is a purified protein derived from Chinese hamster ovary cell line, and is produced by the genetic fusion of recombinant albumin to recombinant factor IX. The final product is provided as a lyophilized powder in single use glass vials containing 250, 500, 1000 or 2000 IU/vial. For application by intravenous injection, the lyophilized drug product is reconstituted using 2.5 mL or 5.0 mL (for 2000 IU) of water for injection.

Submitted Information Reviewed

This is an electronic submission. Information submitted and reviewed includes:

- 125582/0.0 – 3.2.P.5.1 Control of Drug Product – Specification
- 125582/0.0 – 3.2.P.5.2.1 Analytical Procedures Testing Instruction
 - Doc. Q-10-081 Ver. 4: Determination of the Factor IX activity – One stage clotting assay according to (b) (4).
 - Q-16-427: Determination of purity by (b) (4)
 - Q-16-406: (b) (4) distribution of recombinant Factor IX fusion protein (rIX-FP)
 - Q-16-345: Determination of residual water in (b) (4)
 - Q-04-003: Determination of dissolution time and appearance.
 - Q-10-024: Determination of the (b) (4) value
 - Q-04-003) Determination of dissolution time and appearance
- 125582/0.0 – 3.2.P.5.3 Validation of Analytical Procedures
 - MVR-10-081/10-0811 Ver.2: Determination of the Factor IX activity by One stage clotting assay according to (b) (4).
 - MVR-16-427: Validation of the method used for the Determination of Purity by (b) (4)
 - MVR-16-406 (b) (4) distribution of recombinant factor IX-Albumin fusion protein (rIX-FP)
 - MVR-16-345: Determination of residual water in (b) (4)
- 125582/0 – 3.2.P.5.4 Batch Analyses
- 125582/0 – 3.2.P.6.2 Potency Reference Standards
- 125582/0.15 1.11.1 Quality Information Amendment: Response to FDA information request dated 07 May 2015, Received on 22 May 2015

- Doc. RFI21May2015: CSLB Response to FDA's 07 May 2015 Information Request
- 125582/0.19 – 3.2.P.5.2.1 Analytical Procedure Testing Instruction
- Doc. Q-10-081 Ver. 5: Determination of the Factor IX activity – One Stage Clotting Assay according to (b) (4).

Review Narrative

1. One-stage Clotting Assay for Factor IX Potency

The One-stage clotting assay method is based on the (b) (4) Assay of Human Coagulation Factor IX. The manufacturer provided the Testing Instruction Q-10-081: Determination of the Factor IX activity, Ver.4 and Ver.5 and Method Validation Report, MVR-10-081/10-0811, Ver.2. The proposed specifications are:

For 250 IU: (b) (4)

For 500 IU: (b) (4)

For 1000 IU: (b) (4)

For 2000 IU: (b) (4)

Method

(b) (4)

Method Validation

The method is validated as a quantitative assay and accuracy, repeatability, specificity, linearity, intermediate precision, range and robustness were evaluated.

(b) (4)

(b) (4)

Based on the results from linearity, precision, and accuracy, the range of the assay was defined as (b) (4)

Information Request and Review

The following IR was submitted to the sponsor on 7 May, 2015. The response was received on May 21, 2015 as Amendment 15. The IR questions, the response of the sponsor and review of the response are discussed below.

a. Reference Standard

- i. In section 3.2.P.6.2 Potency Reference Standards, you indicated a product specific Primary Reference Standard (PRS1) or a Working Reference Standard (WRS1) is to be used for this assay. However, in Section 3.2 of your Testing Instruction (Doc # Q-10-081), you indicated that you will use either the International Standard or (b) (4) (in-house standard) as the standard. It appears that you have done all of your method validation using (b) (4) as the only standard. Please clarify your intention – which standard you will use under what circumstances.

Review of Response: The sponsor clarified that they used a qualified lot of rFIX-FP as the standard more recently and submitted the qualification report. The Testing Instruction (Doc # Q-10-081) document is confusing because it is used for different products, not specifically for the current product (Idelvion) only. The reference standards are listed in SOP # 555200, however, the document is in German language. The sponsor did not provide English translation of this document. However, it is clear from that document that rFIX-FP is used as the standard for potency assay for Idelvion.

- ii. Please clarify what reference standard you used for method validation for FIX-FP.

Review of Response: The sponsor clarified that with the exception of specificity, all other validation characteristics were evaluated using the qualified lot of rFIX-FP as the standard. (b) (4) DP is used as the standard for specificity evaluation. Although not ideal, this is acceptable in this case because Idelvion (b) (4) , both FIX product, showed positive response by the assay method, however, other products and the (b) (4) , which did not contain FIX, did not show any response. In addition, accuracy, linearity and precision of the method were demonstrated adequately.

- iii. Please provide data for qualification/calibration of reference standard used in method validation, if it is anything other than the International Standard.

Review of Response: The data related to qualification/calibration is submitted as part of Amendment 15. The CSL654 lot (b) (4) was standardized against the WHO IS (b) (4) in November 2009. (b) (4) of this lot were assayed by (b) (4) analysts on (b) (4) separate days using WHO IS as the standard. The parallelism between CSL654 lot# (b) (4) and the WHO IS was demonstrated for each day of analysis by (b) (4). The overall CV was found to be (b) (4) and mean was (b) (4). This standard was, thus, assigned a potency of (b) (4). The IR has been answered adequately.

- b. Please revise and update your Testing Instruction, Q-10-081 to include the following information and submit for review.
 - i. In section 4.3.1.1 of your Testing Instruction, Q-10-081, it is stated, "Starting from this (b) (4) (b) (4) " Please revise the Testing Instruction to include specific dilutions for the FIX-FP drug product.

(b) (4)

- ii. In section 5.1, it seems that the results may be obtained from one replicate measurement or two independent measurements. It is not clear when one replicate measurement is acceptable and when two independent measurements are necessary. Please revise the Testing Instruction to include circumstances under which one replicate measurement is acceptable and when two independent measurements are necessary. For the FIX-FP drug product, will you perform one replicate measurement or two independent measurements?

Review of Response: The sponsor clarified that for release and stability tests, the reportable result would be generated from (b) (4) results. For identity tests, (b) (4) (b) (4) would be tested. For special samples the reportable results is generated from (b) (4)

(b) (4) results. The Testing Instruction, Q-10-081, was revised (ver. 5) accordingly and submitted as Amendment 19.

c. For your Method Validation Report (MVR-10-081/10-081I)

i. (b) (4)

Review of Response: The (b) (4) composition has been provided via Amendment 15. Both (b) (4) have the same composition.

ii. How does the (b) (4) used in the specificity study (Table 19) differ from the actual (b) (4) used to (b) (4) the drug product?

Review of Response: The (b) (4) is same as in i above.

iii. In section 10.4, you have presented linearity data by plotting (b) (4). Linearity should be presented by plotting (b) (4) (after mathematical transformations, if necessary). Please provide linearity data by plotting (b) (4) (after mathematical transformations, if necessary) for the standard and the drug product, including slope and R^2 values from regression analyses for both to show that they are parallel.

(b) (4)

iv. In Tables 28-34, you demonstrated accuracy of your method by comparing your measured values against expected values. How did you obtain expected values? If you measured the expected value using the same method as being validated, it is circular and not acceptable. If you used an orthogonal method to obtain expected values, the results are acceptable. Please explain how you obtained expected values.

(b) (4)

v. Robustness of the assay was demonstrated using (b) (4) (section 7.7). However, (b) (4) is not the product for which you are validating the method in the current BLA. The results obtained with (b) (4) may not be valid for FIX-FP

product because they are different proteins. Please provide robustness data obtained using FIX-FP product.

Review of Response: The sponsor agreed to provide robustness data as requested by 31 July 2015.

2. Purity by (b) (4)

The purity of rIX-FP protein is determined by (b) (4) following the procedure described in document Q16-427. The proposed specification is (b) (4) for the main rIX-FP (b) (4).

Method

(b) (4)




(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)




First Information request: The following IR was submitted to the sponsor on 07 May 2015. The response from CSL Behring received as Amendment 15 on 21 May 2015, is discussed below.

- a. Your Testing Instruction (Document Q-16-427) does not include the system suitability criteria for the (b) (4) system. Please revise the Testing Instruction to include appropriate acceptance criteria for (b) (4) performance/efficiency as measured by the (b) (4), etc. based on your historical data and submit for review.

Review of response: To assure (b) (4) efficiency/performance, the sponsor included a system suitability criterion for theoretical (b) (4) in the testing instruction. The acceptable minimum theoretical (b) (4) was determined on the (b) (4) sample and justified by the data obtained from (b) (4). However, the sponsor did not submit the modified SOP, and informed that the revised SOP would be submitted later in the Annual Report.

- b. We have the following questions/comments regarding the Method validation report, Document MVR-16-427.

- i. (b) (4)



(b) (4)

- ii. Please re-evaluate your range based on the revised accuracy (as explained above), and existing linearity and precision data obtained from your drug product, and update your validation report accordingly.

Review of response: In response, the sponsor explained that since the (b) (4) of rIX-FP (b) (4) was independent of the (b) (4) (as demonstrated in the linearity (b) (4)

Second Information request: After the review of response to the first IR, a second IR was submitted to the sponsor on 15 July 2015.

- a. Please submit a copy of your revised SOP Q-16-427 which includes the system suitability criteria for (b) (4) performance for review.
- b. You have not evaluated accuracy of your method in the required range, and have provided an explanation to support the data obtained in validation report MVR-16-427, as sufficient for demonstrating accuracy of (b) (4) methods where the response is reported as (b) (4). This explanation is not sufficient to facilitate the complete review of your method validation. Please provide data to demonstrate accuracy of the method over the proposed assay range.

Conclusion: The method is clearly described. However, there are outstanding issues with the method validation as discussed in the second IR, which need to be addressed.




3. Purity by (b) (4)

The relative percentages of (b) (4) in the drug product are determined using (b) (4). The Testing Instruction (Q-16-406) for the method was included in the submission. Specifications for purity are (b) (4)

Method

(b) (4)




(b) (4)



Information Request and Review

The following information requests were submitted on 7 May 2015. The response was received from the sponsor on 21 May 2015 as Amendment 15.

(b) (4)



Conclusion: The method is clearly described and adequately validated. There is no outstanding information request.

4. Residual Moisture Content (b) (4)

The proposed specification for residual water content determined by a (b) (4) method is (b) (4) for all of the 4 dose formulations.

Method:

The analytical procedures were described in details in Document#Q-16-345 version 6.0, in which information such as sample preparation, equipment setting, and assay execution, was provided; however, no description was provided on assay validity criteria, assay range, and the procedures to generate reportable results. An IR question was submitted to seek further clarification.

Method Validation

(b) (4)

(b) (4)

(b) (4)

Information Request and Review:

IR questions concerning this method were sent on 7 May 2015, and the sponsor responded in Amendment 15 on 21 May 2015.

- a. The Testing Instruction (Document Q-16-345) did not include assay validity criteria. Please update the document to include adequate assay validity criteria (based on your historical data) and resubmit.

Review of the response: In Amendment 15, the sponsor provided the assay validity criteria as: “The water content of the control material must be determined within the range of (b) (4) of the value specified in the respective CoA” and indicated that the document Q-16-345 will be revised to include the validity criteria in a separate section during the next routine revision cycle of this document and will be provided in the first annual report of CSL654. The response is adequate.

- b. We have the following questions/comments regarding the Method validation report, Document MVR-16-345.
 - i. You have evaluated the intermediate precision, linearity, and range of the method using (b) (4) standard. These validation characteristics should be evaluated using the drug product for which the method is intended to be used, i.e., FIX-FP. Please provide the results of intermediate precision, linearity, and range based on analyses of the drug product.
 - ii. You evaluated accuracy of your method by (b) (4). This is significantly above the range of your assay and your proposed specification of (b) (4). Please

provide data to demonstrate accuracy of your method within your proposed validated range of (b) (4).

Review of the response: The sponsor explained in the Amendment 15, that it is difficult and impossible to (b) (4) standard into the drug product matrix so that the accuracy and linearity of the method can be validated within its specified range. This argument didn't address our concern, because the accuracy and linearity of the assay should be established across the specified range of the analytical method. A second round IR question was submitted to seek further clarification. As for the intermediate precision validation, the sponsor indicated in the Amendment that it will provide the requested data by July 31, 2015.

Second Information request: After the review of response in Amendment 15, a new IR was submitted to the sponsor on 15 July 2015.

- a. In your response (Amendment 15), you stated that it was technically impossible to "develop an experiment set up of the method Q-16-345 to cover linearity and accuracy by (b) (4). We do not agree. The accuracy and linearity of the assay should be established across the specified range of the analytical method. It is our experience that it is possible. For example, (b) (4). Please provide the required data by validating the accuracy and linearity of the analytical method covering the assay's range.

Conclusion

For the (b) (4) method to determine the water content in the final drug product and its validation, the selection of validation characteristics was appropriate. However, the validation of linearity, intermediate precision, and range of the method were not performed with the use of drug product; and the accuracy was not validated in the range covered by the method. IR was submitted to seek appropriate data.

5. (b) (4)

(b) (4)

Method

(b) (4)

6. Appearance by Visual inspection (Lyophilized Cake)

The specification for appearance of Cake is pale yellow to white (b) (4) plug.

Method

The lyophilized material is visually examined for appearance and color, as described in (b) (4). The volume of the cake is compared with the in-house lyophilized control. Visual inspection is appropriate to verify appearance of the lyophilized cake, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for Idelvion drug product. No additional information is required.

7. Appearance of Reconstituted solution and Dissolution time

The specification for appearance of Reconstituted solution is colorless clear liquid and free from visible particles in accordance with (b) (4). The dissolution time must be less than or equal to (b) (4).

Method

(b) (4)

Conclusion:

The assay is approvable as a release test for Idelvion drug product. No additional information is required.