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To STN: #125582/0

Through William M. McCormick, Director, DBSQC/OCBQ

Sponsor CSL Behring

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

Summary of Review

A 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. Residual Moisture Content (b) (4)

The validations of these three methods had outstanding issues at the time of writing the PDR memo for STN# 125582 (Levi et al., 22 July 2015). The issues have been resolved and the methods are found to be approvable for quality control lot-release. The methods and method validations of all other quality control lot-release tests were found to be approvable for their intended purposes (PDR memo for STN# 125582).

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 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.

In the PDR memo for STN# 125582 (Levi et al., 22 July 2015), we indicated that the following tests used for quality control lot-release of the drug product and their validations are adequate for their intended purpose.

1. Purity (b) (4)
2. (b) (4)
3. Appearance of Lyophilized Cake
4. Dissolution time
5. Appearance of Reconstituted solution and Dissolution time

However, there were some outstanding issues for three of the tests,

1. One-stage Clotting Assay for Factor IX Potency
2. Purity (b) (4)
3. Residual Moisture Content (b) (4)

The review of the outstanding issues has been presented in the current Addendum (Final) memo.

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
- 125582/0.25 1.11.1 Quality Information Amendment: Response to FDA information request dated 15 July 2015, Received on 29 July 2015
 - Q-16-427 vs 2.0: Determination of purity by (b) (4)
- 125582/0.27 1.11.1 Quality Information Amendment: Response to FDA information request dated 15 July 2015, Received on 31 July 2015
 - MVR-16-345 Addendum 01: Updated report for the Validation of the method used for the Determination of residual water (b) (4)
 - MVR-10-081/10-081I Version 3.0: Method Validation Report – One Stage Clotting Assay for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)
- 125582/0.34 1.11.1 Quality Information Amendment: Response to FDA information request dated 15 July 2015, Received on 31 August 2015
- MVR-16-427: Updated report for the Validation of the method used for the Determination of Purity by (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.


Information Request and Review

The following IR was submitted to the sponsor on 7 May, 2015.

The IR questions, the response of the sponsor and review of the response are discussed below.

- i. Robustness of the assay was demonstrated using reconstituted (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.


(b) (4)



Conclusion: One Stage Clotting Assay for FIX method is clearly described and adequately validated. Approval is recommended.

2. **Purity** (b) (4)

The purity of rIX-FP protein is determined by (b) (4) following the procedure described (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. The responses from CSL Behring are discussed below.

- a. Please submit a copy of your revised SOP Q-16-427 which includes the system suitability criteria for (b) (4) performance for review.

Review of response: As requested, the sponsor submitted the revised copy of analytical testing procedure, Q-16-427 (Amendment 25).

- 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 relative percent area. 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.

Review of response: In Amendment 25, the sponsor committed to perform additional validation experiments to demonstrate accuracy over the proposed assay range, and submit the amended report as Amendment 34 on 31 August 2015. In the additional validation study, (b) (4)

The sponsor's response is acceptable.

Conclusion: The method is clearly described and adequately validated. Approval is recommended.

3. Residual Moisture Content (b) (4)

The analytical procedures were described in details in Document#Q-16-345 version 6.0. The proposed specification for residual water content determined by (b) (4) method is (b) (4) for all of the 4 dose formulations.





Second Information request: After the review of response in Amendment 15, a new IR was submitted to the sponsor on 15 July 2015. The response was received as Amendment 27.

- 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 (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.

Review of response: The sponsor provided additional data on the validation of the following assay characteristics: intermediate precision, accuracy, linearity and range.

(b) (4)

(b) (4)



Based on the data from Amendment 27, the accuracy, intermediate precision, linearity, and range of (b) (4) method with (b) (4) technique were validated. In combination with the data provided in the original submission, this method has been validated for its intended use: the lot release of rIX-FP drug product.

In Amendment 0.27, data on the validation of (b) (4) method with (b) (4) technique were also included; however, no detailed description on the method was provided and its validation was not carried out by applying the rIX-FP drug product matrix, therefore, (b) (4) method with (b) (4) technique was not validated.

Conclusion: (b) (4) method with (b) (4) technique is clearly described and adequately validated. Approval is recommended.