

# MEMORANDUM



Department of Health and Human Services  
Public Health Service  
United States Food and Drug Administration  
Center for Biologics Evaluation and Research



**To:** Administrative File for BLA (STN 125582/0)  
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**Through:** Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR  
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**Subject:** Final review of the *Analytical Methods* and *Specification* sections in CSL's original BLA for Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]

## EXECUTIVE SUMMARY

This memorandum summarizes the review of the *Analytical Methods* and *Specification* sections in CSL's original BLA for Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION] (Applicant – CSL Behring Recombinant Facility AG, Switzerland; proposed proprietary name – IDELVION; company code CSL-654).

All analytical methods used for the characterization of the identity, purity, quality and safety of the (b) (4) drug product have been adequately validated to support their intended use in the manufacture of IDELVION. Specifications for (b) (4) Drug Product (DP) were established appropriately based on the statistical analysis of the manufacturing data. Thus, the information on analytical methods and specifications supports the approval of the BLA.

## BACKGROUND

IDELVION is a recombinant fusion protein based on the sequences of human Factor IX (FIX) and human serum albumin. The FIX moiety in the fusion protein is responsible for the hemostatic therapeutic effect in the treatment of Hemophilia B patients, and the albumin moiety allows for prolonged half-life of the protein in circulation. The protein is expressed in a CHO cell line.

The proposed indications of IDELVION are (1) routine prophylaxis to prevent or reduce the frequency of bleeding episodes, (2) on-demand control and prevention of bleeding episodes, and (3) perioperative management of bleeding in children and adults with hemophilia B (congenital Factor IX deficiency).

IDELVION is manufactured at two locations. The first stage of the manufacturing process, including (b) (4)

formulation, filling and lyophilization of DP is conducted at CSL Behring GmbH, Marburg, Germany. Four nominal dosage strengths at 250, 500, 1000 and 2000 International Units (IU) are manufactured. The DP is presented in single-use glass vials. The IDELVION DP is to be reconstituted in sterile Water for Injection (sWFI) before intravenous administration to the patient.

## **REVIEW SUMMARY**

### **Modules reviewed (including relevant documents supplied in appendices and amendments):**

3.2.S.2.4 Controls of Critical Steps and Intermediates (limited to testing instructions and method validation reports)

3.2.S.4 Control of (b) (4)

3.2.S.5 Reference Standards or Materials

3.2.P.5 Control of Drug Product

3.2.P.6 Reference Standards or Materials

### **Review History**

The application was submitted on 5 December 2014. The BLA was reviewed under the standard schedule of the PDUFA V program.

Review issues were discussed extensively with the company during the pre-license inspection (PLI) of CSL's Marburg facility on 28 May - 5 June 2015. While some concerns were clarified by CSL, an extensive information request (IR) was sent on 12 June 2015 with questions regarding the justification of specifications and validations of analytical procedures. Partial response to the IR was received on 23 June 2015 as amendment 125582/0.19; with subsequent responses received on 15 July 2015 as amendment 125582/0.23; on 31 July 2015 as part of amendment 125582/0.27; on 14 August 2015 as amendment 125582/0.32; on 31 August 2015 as part of amendment 125582/0.34; on 4 September 2015 as amendment 125582/0.37, and on 30 September 2015 as amendment 125582/0.42. A follow-up IR was sent on 20 July 2015. The response to this IR was received on 10 August 2015 as amendment 125582/0.30. Another follow-up IR was sent on 15 October 2015. The response to the IR was received on 5 November 2015 as amendment 125582/0.44. The responses provided adequately resolved the issues which were raised in the IRs. The texts of the IRs are provided in the appendix of this memorandum.

A teleconference to discuss the control of the quality of Polysorbate-80 (PS-80) (see review below) was held on 15 November 2015. (b) (4)

**Narrative:**

This memorandum outlines the issues raised during the review of the BLA and does not contain descriptive information which is found in the BLA. If the section of the BLA is not mentioned in the review, it is because no issues were identified.

(b) (4) **DRUG PRODUCT SPECIFICATIONS**

**1. General Approach to Justification of Specification and setting of acceptance criteria**

The original *Justification of Specification* documents submitted in the BLA did not provide data analysis and clear rationales for the setting of the acceptance criteria for the majority of the specifications for (b) (4) DP. Most of the acceptance criteria were justified as (b) (4)

(b) (4). CSL was requested to review and revise the ranges and limits for all quantitative parameters in the specifications based on statistical analyses of the data acquired from testing of all (b) (4) DS lots manufactured up to date and submit the complete datasets used for the establishment of the revised specification ranges or limits; and the statistical analyses employed.

CSL acknowledged the deficiency, performed the requested analysis and provided FDA with the data. They chose to establish the acceptance criteria based on the tolerance limits. Statistical tolerance limits were calculated assuming a normal distribution of the data. Tolerance intervals reflect the combined variability of the process and assay. They can thus be used to define the limits within which the data of a stable process should lie. Specifically, for two-sided specifications, two-sided tolerance intervals were calculated that contain 99.5% of the future values with 95% confidence. For one-sided specifications, one-sided tolerance intervals were calculated that contain 99.75% of the future values with 95% confidence.

The tolerance limits are given by

(b) (4)

The use of 99.5% of the population for two-sided specifications and 99.75% for one-sided specification is analogous to the use of (b) (4) limits for both one-sided and two-sided specification: the tolerance factors for one-sided and two-sided specifications are similar.

As a result, a number of (b) (4) DP specifications were changed (mostly tightened) as presented in Tables 1 and 2 at the end of this section (revised specifications are listed in bold). In this reviewer's opinion, the current specifications are adequate to control the quality of IDELVION DP (b) (4).

Additionally, as it was found that the commercial process is more consistent than the pilot scale process, CSL committed to revise the acceptance criteria when sufficient data are available from commercial process manufacturing.

## 2. Specifications found to be inadequate and non-informative

### a. Albumin by (b) (4)

CSL initially proposed the specifications for (b) (4) DP for albumin by (b) (4) with the acceptance criteria listed as (b) (4) respectively.

Considering that (b) (4) was the only test specific to the albumin moiety of the fusion protein, the specifications were considered grossly inadequate. As proposed, the test is used for (b) (4) albumin moiety in the product. However, complying with these acceptance criteria did not allow for adequate control of the albumin moiety and would not prevent the release of (b) (4) DP in which the albumin moiety is (b) (4).

The (b) (4) test method itself was validated for quantitative analysis, but its suitability for use was not adequately established, since the *Specificity* of the method was not adequately validated. In particular, the ability of the method to (b) (4) albumin was not demonstrated.

CSL was requested to perform supplemental validation of the method, establishing the specificity and suitability for quantitative analysis of the albumin moiety. Alternatively, if the suitability of the (b) (4) method could not be confirmed, other test(s) should be developed for the control of the albumin moiety. Based on the test method used, CSL was requested to establish acceptance criteria to allow for the quantitative control of the albumin moiety in the IDELVION (b) (4) DP.

CSL's initial attempt to re-validate the method was found inadequate, but subsequent exercise performed per FDA's follow-up request accompanied by studies that established the correlation between the quality of the albumin moiety and method response was found acceptable. The current method is suitable for use and the acceptance criteria ((b) (4)) are considered adequate to control the integrity of the albumin moiety.

### b. (b) (4)

(b) (4)

2 Pages determined to be not releasable: (b)(4)

**Table 2 Initial and revised Specification for IDELVION DP**

Test	Initial Acceptance Criteria	Revised Acceptance Criteria
(b) (4)	Report value for calculation	(b) (4)
FIX coagulation Assay	(b) (4)	
Quantitative Albumin by (b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	

(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
FIXa Assay	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4) <b>FIX activity</b>	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)-visible particles by (b) (4)	(b) (4)	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Sterility	Pass if no contamination detected	Pass if no contamination detected
Appearance by visual inspection (Lyophilized cake)	Pass if pale yellow to white (b) (4) (b) (4) cake	(b) (4)
Residual water by (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Appearance by visual inspection (Dissolution time)	(b) (4)	(b) (4)
Appearance by visual inspection (Appearance after reconstitution)	Pass if yellow to colorless clear liquid and free of visible particles	Pass if yellow to colorless clear liquid and free of visible particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Polysorbate 80 by (b) (4)	(b) (4)	(b) (4)
Mannitol by (b) (4)	(b) (4)	(b) (4)
Sucrose by (b) (4)	(b) (4)	(b) (4)
Determinat Citrate by (b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)

## ANALYTICAL PROCEDURES

### 1. Approach to setting acceptance criteria in the validation of analytical procedures.

During the review of the validation reports for the majority of the analytical procedures, I found the approach CSL used to set the acceptance criteria for validation parameters to be statistically unsound. In particular, CSL would define a single acceptance criterion for relative standard deviation (RSD) to be <sup>(b) (4)</sup> of the specification range while validating the precision or accuracy of the analytical methods. This approach is clearly incorrect, as specification ranges should be established based on the analysis of results from a number of product lots taking into consideration the variations both in the manufacturing process and analytical methods. As  $\pm 3$  RSD around the true value of the sample establishes the range where measurement result will fall with a probability of 99.73%, setting the acceptance criteria at <sup>(b) (4)</sup> of specification range allows only the samples with the true value in the center of specification range to reliably pass the specification. Such method is not suitable (too inaccurate or imprecise) to be used for release testing, making the acceptance criteria set in such a way meaningless. As a result of this approach, the results obtained during validation not only met acceptance criteria but were also very significantly better than the set limits (e.g., acceptance criterion for the determination of purity by (b) (4) report MVR-16-427) was RSD (b) (4) whereas the actual RSD values were between (b) (4). Also, this single acceptance criterion was used for other parameters, including Accuracy, Repeatability, and Intermediate precision, which is not acceptable due to the different nature of these parameters.

The cause of the issue was traced back to CSL SOP 505042 "Validation of analytical methods" which included incorrect and/or misleading information in regards to setting acceptance criteria. As a result, the acceptance criteria in most of the validation reports were set not in accordance with the intended purpose. As a result of discussions during the PLI, CSL acknowledged the mistake and agreed to correct the SOP and would not use this algorithm for setting acceptance criteria during subsequent validation studies.

As the performance characteristics of a number of methods were established in the validation studies albeit with inappropriately set acceptance criteria, we decided not to request revalidations of these methods, but rather to request CSL to re-evaluate these performance characteristics along with the revised specifications to ensure that the methods are still suitable for their intended purpose, which was done. We consider this issue to be resolved.

## 2. Deficiencies in Validation of Analytical procedures

### a. Host Cell Protein (HCP) (b) (4)

The performance of the assay was not verified using intermediates derived from the commercial manufacturing process. Considering that change of the process scale or transfer (b) (4) may potentially affect HCP (b) (4) we requested CSL to 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.

Additionally, since Accuracy was not sufficiently validated over the entire range of the assay, we asked CSL to ensure that Accuracy is validated over the entire range of the assay.

CSL adequately addressed these issues in subsequent submissions. In particular, additional studies were performed and (b) (4) were provided. They confirmed that there are no significant differences between the HCP (b) (4) between the pilot- and commercial-scale processes, and supported the continued use of the (b) (4) with the pilot-scale material.

(b) (4)

[Redacted]

[Redacted]

### c. Other issues

Multiple issues (incorrect Range validated, incorrect matrices used, insufficient Specificity validation, etc.) were identified in the validation reports for several analytical procedures, and

were conveyed to the company through IRs, which are provided in the appendix. All the issues were successfully addressed by the company.

## **CONTROL OF QUALITY OF POLYSORBATE-80 (PS-80)**

During the review of the comparability section of the BLA, other members of the review team observed significant differences in the (b) (4) between the materials manufactured at the pilot and commercial scale (see review memoranda by Dr. Ovanosov and Dr. Hicks). CSL attributed the differences to the variability in the impurity (b) (4) in PS-80 from different suppliers used in the pilot and commercial scale manufacture. The data presented appear to show that impurities in PS-80 (b) (4)

The exact nature of the impurities is still unknown; however, the experimental data for (b) (4)

Considering the potential risk of PS-80 impurities (b) (4) control of the purity of PS-80 is critical. CSL was requested to revise the specification for PS-80 raw material to ensure control for the unknown impurities (b) (4). In the absence of a validated analytical method for PS-80 (b) (4), we recommended CSL to use (b) (4) in the presence of PS-80 to qualify each batch of PS-80.

CSL explained the technical difficulties in using of (b) (4) to control PS-80 quality, and suggested the development of a method for PS-80 analysis (b) (4). We found the proposal acceptable. However, while the (b) (4) FDA requested CSL to analyze each IDELVION batch by (b) (4) to ensure that the (b) (4) is consistent. This interim control strategy for PS-80 quality was found acceptable, (b) (4).

## **CONCLUSION & RECOMMENDATION**

*All the analytical methods used for the characterization of identity, purity, quality and safety of IDELVION (b) (4) and final drug product have been adequately validated to support the control of the quality of the product and establishment of its specifications. I recommend approval of the BLA for IDELVION from the perspective of analytical methodology and control of (b) (4) Drug Product.*

## APPENDIX

### Information requests sent to the company.

#### IR sent on 12 June 2015.

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 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)

[Redacted text block]

- 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).

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) whereas the working range of the assay is (b) (4). 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)

[Redacted]

f. Mannitol (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]

[Redacted]

(b) (4)

j. CHO Host Cell Protein assay (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.

Please respond by 23 June 2015 by providing FDA with a written plan to addressing the aforementioned issues and submitting the requested documents.

**IR sent on 20 July 2015.**

1. With reference to your 23 June 2015 amendment in which you responded to our information request dated 12 June 2015, please address the following issues:
  - a. Regarding testing instruction Q-10-081 in item 2.4.4 (response for FDA Request #3d),
    - i. In sections 5, please describe in clear, prescriptive language and with sufficient details to instruct the analyst on how to prepare the samples and perform the assay. Please use active voice to specify the preparer (the analyst or instrument), the volumes of the sample and buffer used for each dilution, and the number of tubes required for each assay. Please

reference the (b) (4) SOP for potency testing, Testing Instruction QCA-474, submitted in section 3.2.S.2.4 of the BLA, for the level of details needed for meaningful technical instructions.

- ii. In section 6.2, please amend the system validity criteria to add “Only results that are within the assay range are considered valid”. You may use either the range of concentrations of the sample after it is (b) (4) in the instrument (b) (4), or that of concentrations of the samples prepared by the analyst for the assay (b) (4). As all (b) (4) of the sample are used to calculate the its potency, and the (b) (4) are performed as part of set protocol the use of “working range” as defined in the validation report (b) (4) is confusing and not justified.

b. Regarding item 2.4.9 (response for FDA Request #3i),

- i. Your proposal to increase the acceptance limit of in-process control for (b) (4) is not justified by your manufacturing experience, and therefore unacceptable. If you cannot improve the performance of the method, please retain the previously established acceptance criterion of (b) (4).
- ii. Please reinstate (b) (4) specification with an acceptance criterion of (b) (4) either along with or in lieu of in-process control testing for (b) (4).

2. With reference to the original BLA submission, section 3.2.P.8.2 Post-approval Stability Protocol And Stability Commitment:

Please modify this section adding detailed stability protocol, indicating the tests performed at each stability time point.

**IR sent on 15 October 2015.**

1. With reference to amendment 128582/0.23 submitted on July 15, 2015, please made changes to the following specifications:

- a. Endotoxin in (b) (4) Drug Product (DP)

The specification is established based on safety consideration, but does not reflect the manufacturing process capability. Please establish alert and/or action limits which will allow adequate control for the manufacturing process with regard to this parameter.

- b. (b) (4)

(b) (4)

c. Mannitol in drug product

The specification limit for the 250 IU presentation is justified based on a limited dataset ((b) (4) batches) and the specification limits for the 500 IU, 1000 IU and 2000 IU presentations are calculated including data from earlier batches and do not reflect the capabilities of the current process. Please commit to revising the specification limits for mannitol for all dosage presentations within 1 year after licensure.

2. With reference to amendment 128582/0.30 submitted on August 10, 2015, please revise section 3.2.P.8.2 Post-Approval Stability Protocol. Please include detailed testing schedule as specified in the stability protocols attached in your response to request for information as part of section 3.2.P.8.2.
3. With reference to amendment 128582/0.32 submitted on August 14, 2015, please revise the specification for Host Cell Protein (HCP). The HCP limit is calculated including data from earlier batches and does not reflect the capabilities of the current process. Please commit to re-evaluating the specification limit for HCP within 1 year after licensure.
4. With reference to amendment 128582/0.34 submitted on August 31, 2015, please address the following issue: In method validation report MVR-04-039 “Quantitative determination of albumin in fusion protein rIX-FP on the (b) (4) the specificity of the method is not adequately validated. To adequately control the quality of the albumin moiety, the ability of the method to (b) (4) in a quantitative manner needs to be established. The validation exercise performed did not confirm such ability. You provided the testing of a (b) (4) (b) (4) that resulted in a (b) (4) albumin, and claimed that this result met the acceptance criterion of (b) (4). It is not clear how this acceptance criterion was set and how it is useful for establishing method capabilities. You have not demonstrated any correlation between the (b) (4) and the assay results. Please revalidate the specificity of this method in a way sufficient to establish its suitability to control the quality of the albumin moiety. Otherwise, please explore other analytical procedures to control this quality attribute.
5. With reference to amendment 128582/0.37 submitted on September 4, 2015, please revise the testing instructions and specification for (b) (4). Please modify testing instruction Q-16-405 and (b) (4) Specification adding (b) (4) as acceptance criteria. In testing instruction Q-16-405, please clearly define the limits of the regions for different (b) (4) to ensure consistency of the calculations.
6. With reference to amendment 128582/0.41 submitted on September 18, 2015, please address the following issue: The data presented appear to show that impurities in

1 Page determined to be not releasable: (b)(4)