



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Final CMC review

To: File (STN BL 125582/0) & Edward Thompson

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Subject: Final CMC Review of CSLB’s BLA for Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]

Contents

1. Executive Summary	2
2. Background	3
3. Manufacturing Process.....	5
3.1. Manufacturers	5
3.2. Bulk Drug Intermediate and Bulk Drug Substance	7
3.3. Final Drug Product.....	9
3.4. Controls of Critical Steps and Intermediates	11
3.5. Analytical Methods, Release Specifications and Reference Standards	13
3.6. Control of Excipients	14
4. Process Development, Validation and Qualification	14
4.1. Cell Substrate	14
4.2. Process Development.....	15
4.3. Process Validation	17
5. Elucidation of Structure, Function and Impurities.....	17
5.1. Structure and Function Studies	17
5.2. Characterization of Impurities	18
6. Methods Used in Clinical Trials	19
7. Stability	19
8. Issues Resolved During the BLA Review	20
8.1. Review Issues.....	20
8.2. Post Marketing Commitments	24
9. Chemistry, Manufacturing and Controls - Conclusion	24

1. Executive Summary

STN 125582/0 is an original biologics license application (BLA) submitted by CSL Behring Recombinant Facility AG (CSLB) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein with the proprietary name IDELVION (phonetic spelling: *eye del' vee on*). The active ingredient of IDELVION is a recombinant fusion protein linking human coagulation Factor (F) IX with human serum albumin by recombinant DNA technology. The fusion protein is expressed in a Chinese Hamster Ovary (CHO) cell line, and purified using traditional manufacturing processes. The product is supplied as a sterile, freeze-dried concentrate in single-use vials containing nominal potencies of 250 International Units (IU), 500 IU, 1000 IU and 2000 IU of FIX activity. After reconstitution with sterile Water for Injection (sWFI), the product is administered intravenously. Both the nominal and actual FIX potencies are provided on the vial and carton labels.

IDELVION is indicated to treat children and adults with hemophilia B (congenital FIX deficiency) for: (1) on-demand control and prevention of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

STN 125582/0 is reviewed under the standard review schedule of the PDUFA V Program. CSLB submitted the BLA on December 5, 2014. In response to an FDA request for chemistry, manufacturing and controls (CMC) information, CSLB submitted an amendment with new method validation data on August 31, 2015. This submission was designated as a *Major Amendment*, thereby extending the goal date from December 4, 2015 to March 4, 2016. This major amendment was part of a series of 16 CMC amendments submitted by CSLB between June and October of 2015, in which CSLB provided considerable amount of new data to address deficiencies in the (1) validation of analytical methods, (2) establishment of release specifications, and (3) studies to demonstrate comparability of products manufactured using different processes.

The scope of this review covers all CMC product topics except stability studies (reviewed by Dr. Yideng Liang), evaluation of safety regarding adventitious agents (reviewed by Dr. Ze Peng), justification of specifications (reviewed by Dr. Alexey Khrenov), validation of analytical procedures (reviewed by Dr. Alexey Khrenov and an OCBQ/DBSQC review team led by Dr. Lokesh Bhattacharyya), extractables and leachables studies (reviewed by Dr. Andrey Sarafanov), characterization of albumin moiety (b) (4) studies (reviewed by Dr. Wayne Hicks), and (b) (4) studies (reviewed by Drs. Chava Kimchi-Sarfaty and Zuben Sauna).

All substantive CMC issues were resolved during the review of the IDELVION BLA. In addition, CSLB made post-marketing CMC commitments to (b) (4)



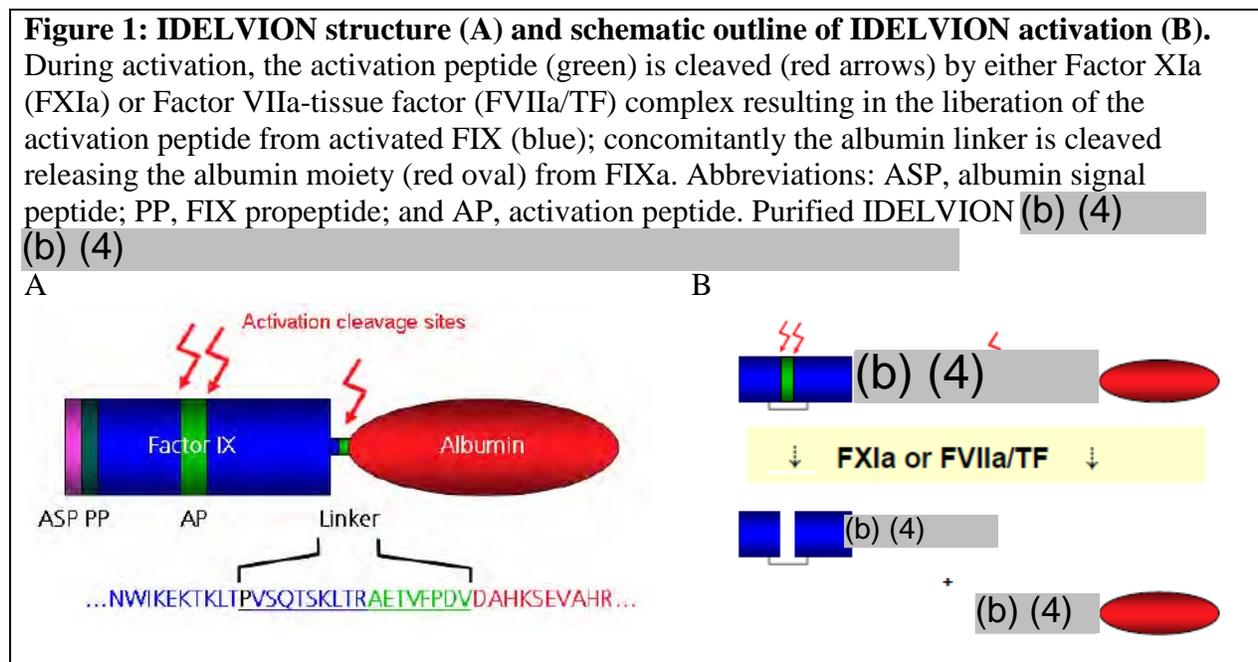
Conclusion

The CMC data support the quality and safety of IDELVION to be used in the treatment of children and adults with hemophilia B. Therefore, approval of the BLA is recommended from a CMC perspective.

2. Background

IDELVION was developed for the U.S. market under IND 14978 for the control and prevention of bleeding episodes, peri-operative management of bleeding, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children and adults with hemophilia B. There are approximately 20,000 people with hemophilia B in the U.S. and several FIX-containing products are licensed in the U.S. for the treatment of patients with hemophilia B. The products include three recombinant FIX products, one recombinant FIX-Fc Fusion Protein product, and several plasma-derived FIX concentrates and complexes.

The IDELVION product is referred to either by its scientific name “*recombinant fusion protein linking coagulation factor IX with albumin*” (rIX-FP), or the company code “CSL654” throughout the application. The FDA proper name is “*Coagulation Factor IX (Recombinant), Albumin Fusion Protein*”. The recommended INN as published in the World Health Organization (WHO)’s List 70 is “*albutrepenonacog alfa*”. IDELVION is a recombinant protein comprised of a human FIX molecule which is genetically linked to a human serum albumin molecule by a short cleavable peptide derived from the activation peptide of native FIX (Figure 1). The structure and function of the recombinant FIX and albumin moieties of IDELVION are shown to be similar to those of the naturally occurring FIX and albumin molecules in human plasma.



Human serum albumin is a carrier protein with a circulatory half-life of 20 days, and genetic fusion of albumin with therapeutic proteins has been shown to improve the half-life and bioavailability of the therapeutic proteins. In clinical trials, IDELVION demonstrated a 3-5 fold prolongation of the half-life of FIX activity in circulation when compared to the typical half-lives reported for licensed unmodified FIX products (Table 1), leading to a less frequent dosing regimen for prophylactic treatment.

Table 1: Comparison of biochemical and pharmacokinetic properties of licensed and investigational FIX replacement products. Data from publicly available sources, including Prescribing Information and publications. Note that *Time-to-1 %* is often used for surrogate assessment of FIX efficacy for prophylaxis indication.

Product	Indications	Molecular weight	Terminal $t_{1/2}$ (hr)	CL (mL/hr/kg)	Time-to-1 % & 3% (days)	Dose in PK study
BeneFIX , rFIX, approved in 1997	indicated for <ul style="list-style-type: none"> control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B, peri-operative management in adult and pediatric patients with hemophilia B 	55 kDa	Study 1: 18.1 ± 5.1 Study 2: 22.4 ± 5.3	Study 1: 8.62 ± 1.7 Study 2: 8.47 ± 2.12	<u>To 1%:</u> 4.5 ¹ <u>To 3%:</u> 2.8 ¹	75 IU/kg
pd FIX	Not provided ¹ (used as BeneFIX study comparator)	(b) (4)	Study 1: 17.7 ± 5.3	Study 1: 6.0 ± 1.4	<u>To 1%:</u> 4.0 ¹ <u>To 3%:</u> 2.7	
Rixubis , rFIX, approved in 2013	indicated in adults and children with hemophilia B for <ul style="list-style-type: none"> control and prevention of bleeding episodes, perioperative management, and routine prophylaxis 	(b) (4)	26.7 ± 9.6	6.4 ± 1.3		75 IU/kg
IXINITY , rFIX, approved in 2015	indicated in adults and children ≥ 12 years of age with hemophilia B for <ul style="list-style-type: none"> control and prevention of bleeding episodes and for perioperative management 	55 kDa	24 ± 7	5.1 ± 1.3		75 IU/kg
ALPROLIX , rFIX-Fc fusion, BLA 125444 approved in 2014	indicated in adults and children with hemophilia B for: <ul style="list-style-type: none"> Control and prevention of bleeding episodes, Perioperative management, Routine prophylaxis to prevent or reduce the frequency of bleeding episodes 	98 kDa	86.53 (CV37.2%)	3.304 (CV28.4%)	<u>To 1%:</u> 11.49 (CV23.8%) <u>To 3%:</u> 6.28 ²	50 IU/kg
IDELVION , rFIX-albumin fusion	<ul style="list-style-type: none"> Routine prophylaxis to prevent or reduce the frequency of bleeding episodes Control and prevention of bleeding episodes Control and prevention of bleeding in the perioperative setting 	123 kDa	104 (CV25%)	0.73 (CV27%)	<u>To 1%:</u> 23.0 <u>To 3%:</u> 17	50 IU/kg

¹ Paul Giangrande. The future is here: long-acting products. On-line Presentation

² Shapiro *et al.* Blood. 2012;119(3):666-672

³ Negrier *et al.* Blood 2011; 118 (10): 2695-2701 & Collins *et al.* J Thromb Haemost 2012; 10: 2305–2312

3. Manufacturing Process

3.1. Manufacturers

The manufacture of IDELVION is divided into ^{(b) (4)} main stages (see Figure 2) conducted at two FDA-licensed manufacturing facilities (Table 2). Production of unprocessed bulk and Bulk Drug Intermediate (BDI) takes place at contract manufacturer (b) (4), (b) (4) and production of Bulk Drug Substance (BDS) and Final Drug Product (FDP) are conducted by CSLB's subsidiary CSL Behring GmbH in Marburg, Germany.



Reviewer's comment: The split BDS manufacturing approach (BDI production by contract manufacturer and further manufacture to the BDS at CSLB in Marburg) is applied for all recombinant coagulation factor products developed by CSLB in recent years, which include a rIX-FP (IDELVION), (b) (4)

(b) (4) Split BDS manufacturing takes advantage of the (b) (4) of specialized contractor companies and the extensive coagulation factor (b) (4) expertise in CSLB's plasma fractionating facility in Marburg, Germany.

Table 2: Manufacturing Facilities for IDELVION

Name/Address	FEI number	DUNS number	Inspection/waiver	Justification / Results
Drug Substance Intermediate Manufacturing and Testing (b) (4)	(b) (4)	(b) (4)	(b) (4)	Team Biologics (b) (4) NAI
Bulk Drug Substance Manufacturing and Testing Final Drug Product Formulation, Fill/Finish, Labeling & Packaging, Testing CSL Behring GmbH (CSLB) Emil-von-Behring-Strasse 76 D-35041 Marburg, Germany	3003098680	326530474	Pre-License Inspection	CBER DMPQ May 28 - June 5, 2015 VAI

Team Biologics performed a surveillance inspection of the (b) (4) drug substance and testing facility from (b) (4). No Form FDA 483 was issued and the inspection was classified as no action indicated (NAI). *Reviewer’s comment: On the advice of LCDR Donald Ertel, DMPQ reviewer, the CMC review team agreed to waive the pre-approval inspection of the (b) (4) manufacturing facility which has good compliance history and is responsible for relatively standard upstream stages of the IDELVION manufacturing process.*

CBER conducted a pre-license inspection (PLI) of CSLB in Marburg from May 28 - June 5, 2015. At the end of the inspection, a Form FDA 483 with 19 observations was issued. Deficiencies were related to the quality and manufacturing systems. The firm responded to the observations on July 1, 2015 and the corrective actions were reviewed and found to be adequate. All inspectional issues were considered to be satisfactorily resolved and the inspection was classified as voluntary action indicated (VAI). *Reviewer’s comment: The inspection team consisted of two DMPQ inspectors, LCDR Donald Ertel and Kevin Foley, and two OBRR product reviewers, Drs. Mikhail Ovanesov and Alexey Khrenov. During the inspection, I evaluated process validation data, interviewed CSLB personnel responsible for IDELVION process development, implementation and control, and observed several key manufacturing unit operations. My overall impression was that the IDELVION process is well controlled, CSLB staff is well trained and the procedures are in place and adequate to handle any process deviations.*

Batch and Scale Definition

(b) (4)

d.

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

(b) (4)

3.3. Final Drug Product

(b) (4) is used to manufacture (b) (4) batches of FDP. The FDP is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 2000 IU of FIX activity (Table 5). *Reviewer's comment: The 250 and 500 IU presentations have a slightly different composition in that the* (b) (4)

All FDP formulations have been used in pivotal clinical trials. The 500 and 1000 IU formulations have remained unchanged since early clinical studies, while the 250 and 2000 IU formulations were introduced during Phase 3 pivotal trials.

Table 5: Nominal composition of reconstituted IDELVION

Ingredient	Nominal composition after reconstitution with sWFI				Function
	250 IU vial	500 IU vial	1000 IU vial	2000 IU vial	
IDELVION fusion protein	100 IU/mL	200 IU/mL	400 IU/mL	400 IU/mL	Active Substance
Tri-sodium Citrate	(b) (4)				(b) (4)
Polysorbate 80	(b) (4)				(b) (4)
Mannitol	(b) (4)				(b) (4)
Sucrose	(b) (4)				(b) (4)

The FDP is reconstituted with sWFI using a needleless *Mix2vial* device. *Reviewer's comment: Mix2vial is cleared under 510(k) K031861. sWFI is manufactured by CSLB in Marburg. The same sWFI is co-packaged with 5 licensed products manufactured by CSLB, including plasma-derived*

FIX MonoNine ®. CSLB has provided references to DMF (b) (4) under which the sWFI is manufactured. LCDR Donald Ertel (OCBQ) has reviewed DMF (b) (4) in association with STN 125582/0 and found the DMF adequate to support approval of the IDELVION BLA.

There are no overages in the filling of IDELVION per ICH Q8 (R2) definition. However, appropriate (b) (4) are incorporated in the formulations to account for losses after reconstitution with sWFI. FDP specifications are presented in Table 6.

Table 6: FDP Specifications

Test	Parameter Monitored	Specification
(b) (4)	Quantity	(b) (4)
FIX coagulation activity	Potency Identity	
Albumin by (b) (4)	Identity	
(b) (4)	Identity	
(b) (4)	Identity	
(b) (4)	Purity	
(b) (4)	Purity	
Factor IXa Assay	Purity	
(b) (4)	Purity	
(b) (4) Factor IX activity	Purity	
(b) (4)	Purity	
(b) (4)	Purity	

Test	Parameter Monitored	Specification
(b) (4)		
(b) (4)-visible particles by (b) (4)	Purity	(b) (4)
Endotoxin	Purity, Safety	(b) (4)
Sterility	Safety	Pass if no contamination detected
Appearance by visual inspection (Lyophilized cake)	Quality	Pass if pale yellow to white (b) (4) cake
Residual water by (b) (4)	Quality	(b) (4)
(b) (4)	Quality	(b) (4)
Appearance by visual inspection (Dissolution time)	Quality	(b) (4)
Appearance by visual inspection (Appearance after reconstitution)	Quality	Pass if yellow to colorless clear liquid and free of visible particles
(b) (4)	Quality	(b) (4)
(b) (4)	Quality	(b) (4)
Polysorbate 80 by (b) (4)	Quality	(b) (4)
Mannitol by (b) (4)	Quality	(b) (4)
Sucrose by (b) (4)	Quality	(b) (4)
Trisodium Citrate ^g	Quality	(b) (4) (b) (4)

(b) (4)

(b) (4)

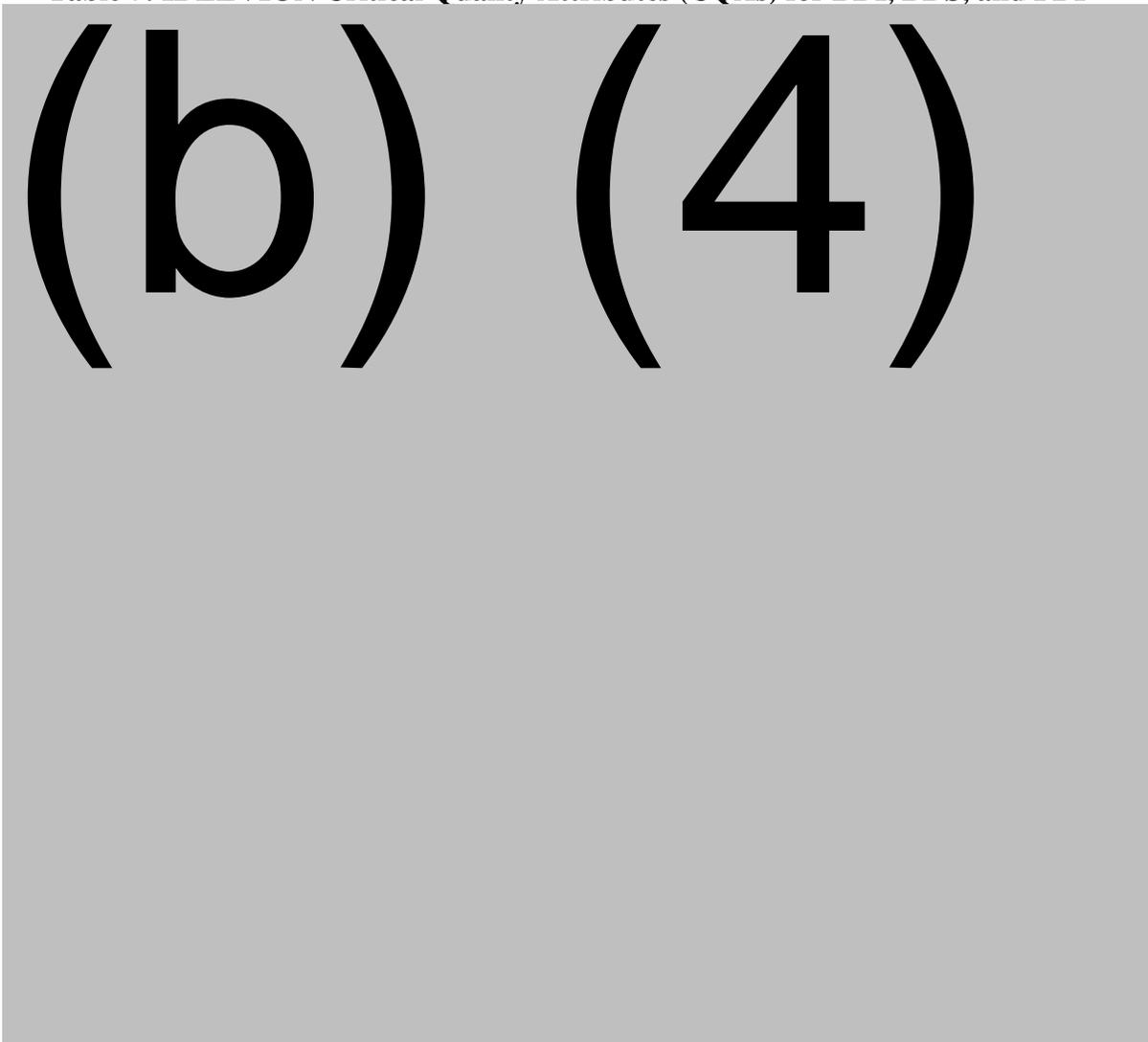
3.4. Controls of Critical Steps and Intermediates

The IDELVION process control strategy (PCS) was developed using a risk-based and science-based Quality by Design (QbD) approach for process control that assures consistent manufacturing and

product quality. However, CSLB did not develop a process design space, therefore the IDELVION BLA was reviewed as a traditional non-QbD submission. *Reviewer's comment: During the inspection of the Marburg facility in May of 2015, I had extensive discussions of CSLB's approach to control the IDELVION process. CSLB explained that pursuing a QbD-only BLA requirement was not intended, however QbD elements were extensively applied during process development to ensure predictable yield and operation. This approach is acceptable.*

Critical Quality Attributes (CQAs) were defined based on the IDELVION Quality Target Product Profile (QTPP) and risk assessment of quality attributes, see Table 7. *Reviewer's comment: I found these CQAs adequate and complete. The QTPP for IDELVION was consistent with typical development targets for coagulation factor products developed for hemophilia treatment .*

Table 7: IDELVION Critical Quality Attributes (CQAs) for BDI, BDS, and FDP



(b) (4)

CSLB defined critical process steps as those containing either a CPP, an In-Process Control (IPC), or In-Process Acceptance Criterion (IPAC) or both. Critical process steps were derived from

extensive risk assessments, process characterization studies, manufacturing experience, and scientific rationale. In-process testing is performed at each process parameter by process step.

BDS and FDP process parameters were assessed via a Failure Mode and Effect Analysis (FMEA). The purpose of this assessment was to evaluate all process parameters with regard to risk of failure (i.e., operating outside of the defined operating ranges) and to consequently identify a list of High Risk Process Parameters (further sub-categorized into Critical, Less Critical, Key, and Non-Critical based on a defined scoring system) according to a pre-determined set of FMEA scoring criteria.

A binary classification system was used for facilitation of post-approval change management, but a further sub-tiered classification system was deemed appropriate for process development and process validation, as each category represents a slightly different type of process and/or product risk. *Reviewer's comment: I found that the controls of critical steps and intermediates are acceptable. The tiered classification system allows for better process understanding and facilitates risk management. During the CSLB facility inspection, I evaluated CSLB's implementation of continued process control and evaluation. I was able to review the interim and annual reports that demonstrated the active use and analysis of trends in the IDELVION process.*

3.5. Analytical Methods, Release Specifications and Reference Standards

The specifications of BDI, BDS and FDP are summarized above in Tables 3, 4 and 6. The methods and established specifications are based on manufacturing experience and available safety and efficacy data. *Reviewer's comment: Analytical method validations were reviewed by Dr. Alexey Khrenov and a review team from OCBQ/DBSQC. Release specifications were reviewed by Dr. Alexey Khrenov. Multiple deficiencies were found by these reviewers. CSLB provided additional method validation data and justification for release specifications, all of which were found acceptable. Please refer to their review memoranda for details.*

Reference Standards and Materials

Key standards are the product-specific working reference standard 1 (WRS1) and the host cell protein (HCP) (b) (4) standard. *Reviewer's comment: In agreement with regulatory expectations, the HCP standard has been prepared from the a (b) (4) . It was used to (b) (4) used in the assay.*

In-support testing

CBER has performed in-support testing of commercial scale IDELVION product lots of the lowest and highest nominal potencies (i.e., 250 IU and 2000 IU, a bracketing approach). Test results were deemed consistent with the proposed commercial release specifications. *Reviewer's comment: A total of 8 batches were tested by DBSQC. On my advice, the requested batches were selected to represent the validation and stability studies as well as the end-of-shelf-life and recently manufactured batches (see Table 8).*

Table 8: IDELVION batches tested by DBSQC

Batch # (Vial size)	Justification for requesting CBER in-support testing
02580911 (250 IU) 02780911 (2000 IU)	These two batches were used to qualify the process. The shelf-life is 24 months for 250 IU and 36 months for 2000 IU. Since the process validation was completed in 2013, these two batches represented the end-of-shelf life product.
02880941 (250 IU) 01680911 (2000 IU)	These two batches were used in stability studies and were manufactured in April of 2013 or September of 2012, respectively, providing the end-of-shelf-life estimate.
04580911 (250 IU) 04880921 (250 IU) 04580921 (2000 IU) 04780921 (2000 IU)	Recently manufactured product, two batches each for 250 IU and 2000 IU

Exemption from CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot CBER release is not required for IDELVION because it is a well-characterized recombinant product. *Reviewer’s comment: Exemption of IDELVION from CBER Lot Release is consistent with all of the recently approved coagulation factor products.*

3.6. Control of Excipients

All excipients used in the preparation of IDELVION meet defined specifications. Prior to release, all raw materials used in the manufacturing process are tested according to CSLB’s in-house specifications and comply with the USP and international Pharmacopeial standards. All excipient test procedures are performed according to methods described in the current international compendia monographs. *Reviewer’s comment: CSLB has qualified all analytical procedures described in the USP as well as validated all non-USP procedures. During the facility inspection, FDA reviewed CSLB procedures for maintaining the list of approved suppliers as well as the plans for supplier audits, all of which were found acceptable.*

4. Process Development, Validation and Qualification

4.1. Cell Substrate

(b) (4)



(b) (4)

4.2. Process Development

The BDS manufacturing process was developed in ^{(b) (4)} key stages described in Table 9. Various process changes were implemented throughout the process development history in response to increased process knowledge and scale-up activities. No significant manufacturing changes were made from the initiation of pivotal Phase 3 study #3001 onward.

(b) (4)

Development of the FDP manufacturing process occurred in two stages, pilot scale and commercial scale (see Table 9). In order to establish that the early nonclinical and clinical data generated using material from the pilot scale process was supportive of conducting further clinical studies using material manufactured by the commercial scale process, an extensive comparability exercise was undertaken. This comparability exercise included both *nonclinical animal studies* and *analytical comparability studies*.

The nonclinical component involved repeating a high dose toxicology and PK study in rats to compare materials from the pilot and commercial scale processes. The analytical comparability study included comparison of the results of release tests and characterization assays, including structural and functional assays, conducted at the production stages of BDI, BDS and FDP, as relevant. Stability data were also compared and found to be comparable.

Reviewer's comment: CSLB's data demonstrate that the current and previous IDELVION BDS and FDP manufacturing processes are comparable with regard to consistency of manufacture, quality and stability of IDELVION BDS. However, the original (b) (4)

As discussed below, the extensive investigations into the (b) (4) have revealed the root cause and confirmed the comparability of the remaining product characteristics.

(b) (4)

(b) (4)

Reviewer's comment: In conclusion, comparison of IDELVION batches manufactured at the commercial scale with the lots produced at the pilot scale (used in preclinical studies and Phase 1/2

clinical trials) revealed differences in process-related impurities (b) (4) The presence of (b) (4) Polysorbate 80 impurities did not affect any other parameters tested regarding the structure and function of IDELVION. These impurities are now controlled to acceptable levels by dedicated assays at the release of the (b) (4) FDP.

4.3. Process Validation

Process Performance Qualification (PPQ) was accomplished in three separate parts, corresponding to the three major stages of production, BDI (b) (4) PPQ batches), BDS (b) (4) PPQ batches) and FDP (b) (4) PPQ batches). PPQ for FDP consisted of the manufacture of (b) (4) consecutive batches covering each of the filling sizes. The PPQ data demonstrated that the manufacturing processes for IDELVION BDI, BDS and FDP were successfully qualified.

In addition to the PPQ studies, several ancillary validation studies were performed to support the consistency of the manufacture of IDELVION BDI and BDS. The studies included *Impurity Clearance Validation, In-Process Hold Time Validation, (b) (4) Validation, Mixing Validation, (b) (4) and Shipping Qualification.*

CSLB developed Continued Process Verification (CPV) plans at both (b) (4) and CSL Behring GmbH to ensure the validated state of the IDELVION manufacturing process throughout the product lifecycle. The CPV program is designed to collect process data and perform statistical evaluation of the dataset in order to routinely confirm the validated state and to identify and evaluate planned and unplanned changes in the manufacturing process.

Reviewer's comment: I found no deficiencies in the process validation studies. The company used a QbD approach as a process development tool. The process validation exercises, release specifications and in-process controls are as extensive as those found in traditional BLAs. This approach is acceptable and no issues with process validation studies were found during the review. The PPQ data demonstrate that the IDELVION BDI, BDS and FDP manufacturing processes were successfully qualified confirming the suitability of the Process Control Strategy.

5. Elucidation of Structure, Function and Impurities

5.1. Structure and Function Studies

The structure and function of the FIX and albumin moieties in IDELVION were characterized in a series of studies, which also examined the comparability of IDELVION batches manufactured at different sites and scales of the manufacturing process during product development.

Materials used for these studies included

- (b) (4)

assessed for (b) (4)

(b) (4). *Reviewer's comments: I found that CSLB's impurity investigations were complete and their findings were acceptable. IDELVION does not contain unexpected impurities that may have a negative impact on the safety and efficacy of IDELVION. The levels of product and process-related impurities were similar or below those found in licensed recombinant FIX products. For example, the level of potentially thrombogenic impurity (b) (4) was lower than in the older licensed recombinant FIX product.*

6. Methods Used in Clinical Trials

FIX activity in pharmacokinetic samples were determined using a validated APTT-based assay performed in a central laboratory in Marburg, Germany. *Reviewer's comments: Two field studies were performed to compare the central laboratory results with those from the local clinical laboratories at participating clinical sites. These studies confirmed an up to two-fold discrepancy in FIX activity levels by laboratories using certain combinations of APTT reagents.*

The testing for the presence of antibodies against IDELVION uses a tiered approach. An initial screening assay, purposely designed to have a (b) (4) false positive rate, is carried out to detect antibodies against IDELVION. Antibodies against human albumin in human plasma are detected using an (b) (4). (b) (4) with a sample of the subject's plasma, and albumin antibodies are detected by a (b) (4) (b) (4). The assay was validated with commercially available anti-albumin antibody ((b) (4)

An (b) (4) method was developed and validated to monitor the development of antibodies against CHO host cell proteins from the IDELVION cell line in plasma samples. An initial screening assay, purposely designed to have a (b) (4) false positive rate, is carried out to detect antibodies against CHO host cell proteins (IDELVION).

Reviewer's comments: Review of pharmacokinetics and immunogenicity assays did not identify significant issues. CSLB developed and used four assays to measure antibodies that can bind FIX, albumin, IDELVION and host cell proteins. In addition, anti-FIX inhibitory antibody activity was measured by a traditional Bethesda clotting assay.

7. Stability

The stability data were reviewed by Dr. Yideng Liang. I concur with her assessment that BDS can be stored at (b) (4). The FDP can be stored at +5°C to +25°C for 24 months for the 250 IU and 500 IU dosage strengths and for 36 months for the 1000 IU and 2000 IU dosage strengths. *Reviewer's comment: At my request, CSLB provided previously collected data to support stability of sWFI under the proposed FDP storage conditions.*

8. Issues Resolved During the BLA Review

8.1. Review Issues

The following substantive issues were resolved during the review of the IDELVION BLA:

a. Deficiencies in method validations

Review of method validation found multiple deficiencies, including incomplete validation of some parameters, validation of incorrect assay ranges, and acceptance criteria inappropriate for assessing method performance. Some of these deficiencies could be traced back to deficiencies in the standard operating procedures (SOPs) identified during the facility inspection. CSLB satisfactorily addressed these review concerns by conducting additional validation studies, and preparing new SOPs and test instructions. These newly developed validation data were used to confirm the validity of the data associated with process development, qualification and verification, and comparability studies.

b. Deficiencies in specifications

Multiple deficiencies were found in the specifications of the BDS and FDP. The acceptance criteria in the original application were established arbitrarily. The justifications of specifications were not supported by statistical analysis of manufacturing data, so the specifications did not allow for adequate control of the manufacturing process. Additionally, as verified during the pre-license inspection, CSLB did not have in place a procedure to establish BDS and FDP specifications. CSLB successfully addressed these concerns by re-assessing the manufacturing data, revising, and justifying the specifications. CSLB also committed to re-assess the acceptance criteria for some parameters when more data are available from the commercial manufacturing process for statistical analysis. Procedures are now established to ensure that specifications will be set based on scientifically sound principles in the future.

c. Insufficient control of the albumin moiety

The IDELVION product belongs to a new class of albumin-fusion products, e.g., IDELVION will be the second such product in the USA. The first albumin-fusion product was approved by CDER in 2014 under STN BLA 125431/0: Tanzeum (albiglutide) subcutaneous injection is indicated to improve glycemic control. Tanzeum is made up of two copies of recombinant modified human Glucagon like peptide-1 (GLP-1, a 4.1 kDa protein) fused in tandem to recombinant human albumin⁴. Other albumin fusion proteins have been evaluated in clinical trials (Table 11).

The initially proposed release assays and specifications were not sufficient to control the quality of the albumin moiety. An *Inter-center Request for Consultative Review* was submitted to CDER/CTP to seek an opinion of analytical requirements for albumin-fusion products. CDER CMC expert Dr. João A. Pedras-Vasconcelos provided critical comments on the adequacy of the analytical methods and release specifications for control of albumin moiety in (b) (4) FDP of the IDELVION. CSLB conducted additional method qualification studies to demonstrate that the analysis of the albumin moiety by the proposed release method (b) (4)

⁴ <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm393289.htm>

(b) (4)

Table 11: Albumin fusion proteins in clinical and preclinical development. Adapted from ⁵.

Fusion Target	Fusion mechanism(s)	Clinical Indication	Clinical Trial Status
Glucagon like peptide-1 (GLP-1)	(b) (4) of GLP-1 fused to (b) (4) of Albumin (b) (4)	Type 2 diabetes	FDA/CDER approved in 2014, Tanzeum® (albiglutide)

(b) (4)

d. Deficiencies in comparability studies

Results from the studies by (b) (4) indicated qualitative differences between product lots manufactured at the pilot vs. commercial scales. CSLB found the probable cause to be due to different impurities in the Polysorbate 80 used in the manufacture of the product batches. The Polysorbate 80 used for the pilot scale batches contained impurities which, (b) (4) (b) (4). Based on the results of *in vitro* characterization studies and nonclinical animal studies, the Polysorbate 80 impurities did not appear to affect the structural and functional properties of IDELVION. Furthermore, to ensure consistent quality of IDELVION, a (b) (4) method was added as a temporary release assay for the FDP. CSLB is in the process of (b) (4)

⁵ Curr Pharm Des. 2015;21(14):1899-907 <http://www.ncbi.nlm.nih.gov/pubmed/25732550>

(b) (4)

e. Reagent-dependent potency discrepancies

IDELVION is labeled with the actual FIX potency as measured by a one-stage clotting assay in units traceable to the ^{(b) (4)} WHO International Standard for FIX concentrate, which is a plasma-derived preparation. Variations in the biochemistry and instrumentation in FIX activity assay systems (e.g., composition of phospholipids, coagulation activators, reagent concentrations or instrument settings) may lead to differences of up to 50% in the potency assignment of IDELVION against plasma-derived reference standards. As a result, under- or over-estimation of FIX activity in post-infusion patient plasma samples is expected in different clinical laboratories because plasma reference standards of FIX activity are customarily used to calibrate assays in clinical laboratories. The effect of assay differences on product manufacturing is mitigated because CSLB has established a product-specific reference standard, which ensures consistent potency assignment and dosage throughout the product life-cycle of IDELVION. (b) (4)

(b) (4)

(b) (4)

(b) (4)

- (b) (4)

(b) (4)

Reviewer's comments:

1. CSLB reported an up to 50 % discrepancy in measured FIX activity levels in clinical pharmacology assays calibrated using plasma-derived FIX activity standards. This discrepancy is consistent with the results from the WHO Collaborative Study to Investigate the Comparability of Recombinant and New Generation Factor IX products with WHO International Standard for FIX Concentrate⁶, in which my laboratory has participated.
2. The discrepancy is caused by the known biochemical differences between IDELVION molecule and the naturally occurring FIX molecules. From a biochemical perspective, IDELVION is not FIX as it is defined by the plasma-derived International Standard.
3. I agree that the CMC aspect of this issue is essentially mitigated by a product-specific potency standard. This standard is on stability program and its integrity is monitored against the international standard for FIX activity. Introduction of a product-specific standard fulfills the "like vs like" analytical principle and eliminates most if not all discrepancy issues. Interestingly, CSLB is no longer maintaining the potency assay which was used to assign IU activity of the product specific standard. This means that IDELVION's unitage is no longer connected to the IU from the current International Standard for FIX activity (although the unit of IDELVION is properly traceable to a previous International standard). I conclude that CSLB is using a product specific unit of FIX-like activity. I agree with this approach because the product-specific standard is properly implemented and ensures consistent labeling (e.g. mass of the protein in the vial) at all stages of clinical development and post-licensure.
4. Clinical laboratories do not have access to IDELVION product-specific standard, therefore clinical testing may over- or under-estimate the FIX activity in plasma samples from IDELVION-treated patients. The issue probably affects determination of low (e.g., trough) FIX levels.

⁶ Helen Wilmot, Thomas Dougall, Peter Rigsby and Elaine Gray Collaborative Study to Investigate the Comparability of Recombinant and New Generation Factor IX products with WHO International Standard for FIX Concentrate. Report to the Participants. NIBSC, Potters Bar. October 2013

specifications. The CMC data support the quality and safety of IDELVION to be used in the treatment of children and adults with hemophilia B.

I found the CMC information to be supportive of the quality, identity, purity, potency and safety of IDELVION, and recommend approval of this BLA.