



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: BLA STN 125582/0 & Edward Thompson, IOD/RPMB
From: Andrey Sarafanov, PhD, DHRR/LH
Through: Mark Weinstein, PhD, IOD
Basil Golding, MD, Director, DHRR
Applicant: CSL Behring Recombinant Facility AG
Product: Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]
Indication: To treat patients with congenital Factor IX deficiency (Hemophilia B)
Subject: Chemistry, Manufacturing and Controls Review
CC: Timothy Lee, PhD; Mikhail Ovanesov, PhD

EXECUTIVE SUMMARY

This memorandum summarizes a review of product-related information in an original Biologics License Application (BLA) under STN 1255825/0 submitted by CSL Behring Recombinant Facility AG (CSLB) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. The proposed proprietary name of the product is IDELVION. In the submission, I reviewed evaluation of Leachables and (b) (4) (process-related impurities), presented in relevant sections of the Module 3 (Quality). During the review, the Applicant provided additional information. Upon completion of the review of all data, I recommend approval of the BLA.

BACKGROUND

CSL Behring (CSLB) developed a recombinant human coagulation factor IX (FIX) with a prolonged half-life in the circulation. This product is referred to either as “recombinant fusion protein linking coagulation factor IX with albumin” (rFIX-FP) or according to the company’s code “CSL654”, and is indicated for treatment of patients with congenital Factor IX deficiency (Hemophilia B). The active ingredient, rFIX-FP, is derived from a Chinese Hamster Ovary (CHO) cell line using a recombinant DNA technology. Using this technology, the rFIX-FP was generated by genetic fusion of albumin to FIX. The cleavable linker between FIX and albumin is derived from an “activation peptide” of the native FIX. Upon rFIX-FP activation in the circulation, the albumin moiety is cleaved off and the remaining FIX moiety is equivalent to that of the activated form of native FIX.

The Drug Substance (DS) manufacturing process involves (b) (4)

(b) (4) The drug product (DP) manufacturing process involves the formulation of DS (b) (4) filling and lyophilization. The lyophilized powder is supplied in glass vials with nominal dosages of 250, 500, 1000 or 2000 international units (IU) of rFIX-FP. The potency is determined using a one-stage clotting assay calibrated against the World Health Organization (WHO) International Standard (IS) for Factor IX concentrate. For infusion, the lyophilized powder is reconstituted with sterile water for injection (WFI) using a needleless device.

REVIEW SUMMARY

The following sections of the Module 3 were reviewed.

- 3.2.S.3.2.2.1 (b) (4).
- 3.2.S.3.2-3 Leachables from Scale-Up Manufacture (Report 16108WD).
- 3.2.S.3.2-7 Identification and Quantification of a (b) (4) in rFIX-FP (Report REP-14434).
- 3.2.S.3.2-8 Analytical Screening of (b) (4) Impurities (Report REP 1402/24251).
- 3.2.S.3.2-9 Leachables in (b) (4) (Report REP-15852WD).
- 3.2.S.6.2.1 Extractables in (b) (4) (Report ES-071-02).
- 3.2.S.6.2.2 Extractables & Leachables in (b) (4) (Report EL-071-03).
- 3.2.P.5.5.3 Extractables and Leachables in Drug Product.
- 3.2.P.5.5-1 Leachables Profiling in Drug Product (Report 2709218-04).
- 3.2.P.5.5-2 Medical assessment of (b) (4) in CSL654.

(b) (4)



(b) (4)

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3.2.P.5.5.3 Extractables and Leachables in the Drug Product

The study was performed by (b) (4) as described under section 3.2.P.5.5-1, Leachables Profiling Report (2709218-04). The evaluation of leachables was performed for DP (250 IU, lot (b) (4) and 2000 IU, lot (b) (4) and the DP (b) (4). The samples were (b) (4)

as described under review of section 3.2.S.3.2-3 and 3.2.S.3.2-8 above. Though the

methods used were non-validated, their suitability for the intended use was confirmed in control experiments to determine recovery of reference compounds (b) (4) in the respective samples. These compounds (standards) were representative of the common types of leachables found in plastic materials and are relevant to the type of assay used (b) (4)

For these standards, the recovery values varied from (b) (4) depending on chemical nature of each compound.

(b) (4)

Reviewer's Comments

This study is relevant to the analysis of leachables, but not to extractables, as no "accelerated" conditions of the extraction were used.

COMMUNICATION WITH THE APPLICANT

An information request (IR) was sent to the company on July 17, 2015, which responded on July 31, 2015 (Amendment 28) as the following.

Question 1

In your studies to evaluate Leachables in various batches of the (b) (4) (Sections 3.2.S.3.2-3, 3.2.S.3.2-8 and 3.2.S.3.2-9), you found relatively high amounts of the following impurities:

(b) (4)

(b) (4)

(b) (4)

Response

Question 1

The company provided a toxicological analysis of the above mentioned impurities based on the maximum clinical dose of CSL654, i.e. 75 IU/kg per week and assuming a 70 kg person, and the lowest concentration presentation of 100 IU/mL. In regard to the (b) (4), they also considered the FDA database for substances, Generally Recognized as Safe substances (GRAS), <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm>. For elemental impurities assessment, the company used ICH Q3D guideline (2014), Elemental Impurities. Upon the assessment, the exposures to the (b) (4) were considered not to present a safety concern. The most abundant elemental impurities with relatively low toxicity, (b) (4), were considered to not cause toxicological concerns. The estimated daily exposure of (b) (4) was approximately ^{(b) (4)} times lower than its maximal amount (b) (4) in an individual dose established by (b) (4). For (b) (4), the estimated daily exposures were significantly lower (up to (b) (4)) than the respective permissible daily exposures.

Question 2

a) The company explained that the differences in the quantifications were due to using different conditions of measurement. The studies were performed by ^{(b) (4)} different laboratories, which used methodologies that varied in the conditions. At the same time, for the toxicology assessment, they used the highest concentrations values of the respective compounds.

b-c) The company explained that the unitages used in the elemental analysis were actually in the ppb scale, and the relatively high (b) (4) content of (b) (4) was observed in a batch of ^{(b) (4)} manufactured in a pilot scale process (typically, in the commercial scale process it is less in (b) (4)). Nevertheless,

according to the risk assessment, the highest (b) (4) in the maximal dose of (b) (4) of the DP is (b) (4) times below the dose limit of (b) (4)

d) The company explained that the failure with quantification of the elements was due to an interfering effect of the (b) (4). Upon optimization of the sample preparation, this issue was overcome and data for elements, as required by (b) (4), were obtained. In particular, these elements were (b) (4). These concentrations were far below the concentrations limited by (b) (4) and thus, were considered not to present a risk to the patients.

Reviewer's Comment

The response is acceptable.

CONCLUSION

The assessments of (b) (4) and leachables in the drug product are acceptable. The data indicate that the amounts of these impurities do not pose a concern for the product's safety and efficacy. From this perspective, I recommend approval of the BLA.