Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Plasma Protein Therapeutics
Hemostasis Branch

M E M O R A N D U M

To:	Administrative file for STN 125641/0
From:	Andrey Sarafanov, PhD; CBER/OTAT/DPPT/HB
Through:	Natalya Ananyeva, PhD; Team Lead; CBER/OTAT/DPPT/HB
	Basil Golding, MD; Division Director; CBER/OTAT/DPPT/HB
Applicant:	Laboratoire Francais du Fractionnement et des Biotechnologies S.A.
Product:	Coagulation Factor VIIa (Recombinant) [Sevenfact]
Indication	Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors
Subject:	Addendum to review of CMC information (Extractables & Leachables, and Diluent)
CC:	Seameen Dehdashti; CBER/OTAT/DRPM/RPMBII

EXECUTIVE SUMMARY

This memorandum represents an addendum to my review of product-related information in the original Biologics License Application (BLA) for Coagulation Factor VIIa (Recombinant) [Sevenfact] submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB). I reviewed the information in Module 3 (Quality) on Extractables & Leachables (E&L) in the Drug Product (DP) and information on the Diluent, sterile Water for Injection (WFI). During the review cycle, I requested additional information, which was included in a Complete Response Letter (CRL) communicated to LFB on October 13, 2017. The company provided their response to the CRL on October 10, 2019 (Amendment 71). Upon review of all the submitted data pertaining to my request, I found them to be sufficient to support the application, and thus, I recommend **approval.**

BACKGROUND

The DP is produced from the milk of transgenic rabbits carrying a recombinant cDNA gene of human Factor VII (rhFVII). The rhFVII is activated during the purification process to rhFVIIa, the active pharmaceutical ingredient. The DP is intended to treat patients with hemophilia A or B with inhibitors. The rhFVIIa is formulated as sterile lyophilized powder in glass vials and reconstituted with WFI prior to administration into patients. During manufacture, at LFB USA Inc. (Charlton MA, USA), the (b) (4) where it is processed to lyophilized powder in vials. Secondary packaging, labeling and quality control testing are performed at (b) (4) located in (b) (4). The DP is released in three dosage forms containing 1 mg, (b) (4) or 5 mg of rhFVIIa supplemented with the diluent in a pre-filled syringe containing 1.1 mL, (b) (4) and 5.2 mL of WFI, respectively. The diluent is manufactured by (b) (4).

During my initial review of the information, I found that all provided information was acceptable, except for deficiencies in assessment of E&L and analytical methods to control the Diluent, as reflected in my memo dated September 28, 2017. My request to resolve these issues was included in the CRL (Questions 5 and 6), which was communicated to LFB on October 13, 2017. The company provided their response to the CRL on October 10, 2019 (Amendment 71). Below, I provide a review of this information.

REVIEW SUMMARY

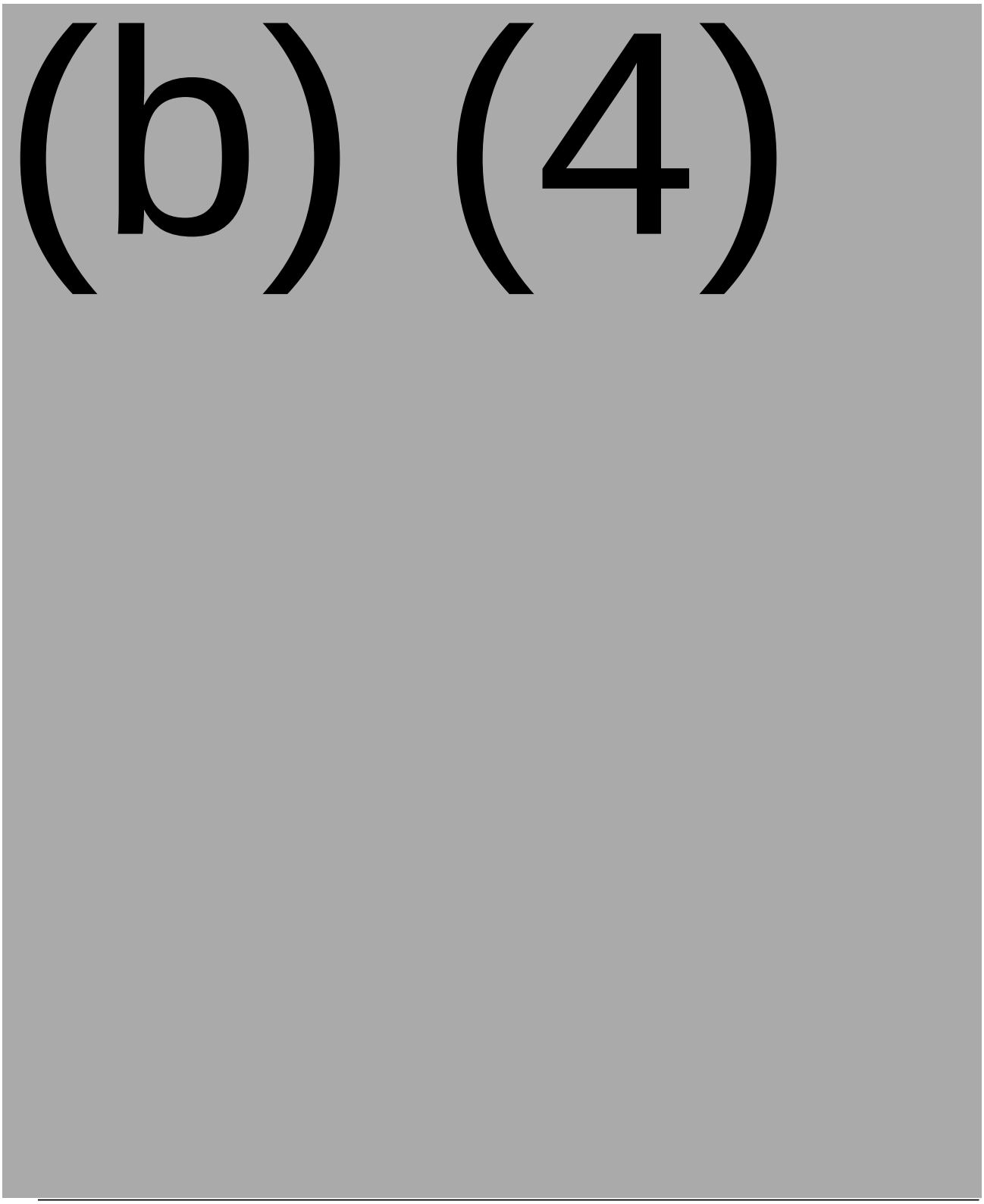
Question 5 (CRL).

In studies to evaluate leachables in the FDP, the recovery values were in the range of (b) (4) *of the amounts of reference compounds spiked in* (b) (4) *-based samples (Amendment #53 dated July 24, 2017). We noticed that the lowest values were mostly associated with the most* (b) (4) *compounds. Please explain the low recoveries for such compounds, and their impacts on analytical quantitation and safety assessment of the respective leachables in the FDP.*

Response

LFB acknowledged that (b) (4)

These developed methods were implemented in the on-going leachable study. The analyzed potential leachables were tested after (b) (4)



The leachables concentrations were below limits of detection and their MACs. It was concluded that these potential leachables do not represent a risk to product safety. The impurity sections 3.2.S.3.2 and 3.2.P.5.5 were updated with this information.

Reviewer's comment. The response is acceptable.

Question 6 (CRL)

Please provide results on the validation of the non-USP analytical methods, and verification of the (b) (4) *analytical methods used for the release of the Diluent (except for Bioburden, Sterility and Bacterial Endotoxin).*

Response

The diluent manufacturer, (b) (4), performed validation of the non-USP and verification of (b) (4) analytical methods used for the analysis of WFI according to (b) (4) The respective methods are to control the following specification parameters: *Clarity, Color,* (b) (4) *, Contamination by Particles,* (b) (4) . The methods were verified or validated using reference standards when available or positive and negative controls. All acceptance criteria were met; thus, the methods were considered validated or verified for testing WFI per (b) (4) compendia methods. This information is provided in updated section 3.2.R.5 (reports MVR-00226, MVR-00693 and MVR-00949).

Reviewer's comment. The response is acceptable.

REVIEWER'S ASSESSMENT

LFB performed all requested studies and adequately addressed all the issues. Overall, the information and study results are acceptable. All other information submitted in the original BLA and relevant to the scope of my review was previously found acceptable as reflected in my review memo dated September 28, 2017.

REVIEW CONCLUSION

From my review perspective, I recommend **approval** of this BLA.