U.S. FOOD & DRUG ADMINISTRATION

To:	STN 125641/0 & Mark Levi, PhD, RPM, RPMB/DRPM/OTAT
From:	Wojciech Jankowski, CMC Reviewer, Hemostasis Branch (HB)/DPPT/OTAT
Through:	Tim Lee, Acting Chief, HB/DPPT/OTAT Basil Golding, Director, DPPT/OTAT
Subject:	Final review of information related to structural characterization of Coagulation Factor VIIa (Recombinant) [SEVENFACT]
CC:	Zuben Sauna, HB/DPPT/OTAT

EXECUTIVE SUMMARY

This memorandum summarizes the review of the information related to the structural characterization of Coagulation Factor VIIa (Recombinant) [SEVENFACT] submitted in an original BLA by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB). The proposed indication of SEVENFACT is for on-demand treatment and control of bleeding in adolescent and adult patients with hemophilia A or B with inhibitors to Factors VIII and IX. Within the areas of review assigned to me, no substantive issues that could prevent approval or impact the review timeline were identified. Several release specifications that are crucial for product quality assessment but were not properly established, were re-established. The new release specifications were found to be adequate. However, I defer the decision on regulatory action for this BLA to the chairperson of the review committee.

BACKGROUND

The active ingredient in SEVENFACT (also referred to in this BLA as LR769) is a recombinant analogue of activated human Factor VIIa (rFVIIa). The zymogen of rFVIIa is expressed in the milk of genetically engineered (GE) rabbits, which is activated during the purification process to rFVIIa. The rFVIIa protein is formulated as a sterile lyophilized powder and reconstituted with sterile Water for Injection (SWFI) before intravenous administration to the patients. The manufacturing process of rFVIIa is performed at several manufacturing locations. The milk is collected on the rabbit farms in Charlton, MA, USA(b) (4) The (b) (4) milk (b) (4) (for milk collected at (b) (4) rabbit farms) is conducted at the LFB USA facility in Charlton, MA. The (b) (4)

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(b) (4) where the final drug product (FDP) is manufactured. The FDP is presented in (b) (4) dosage strengths of 1, (b) (4) 5 mg of rFVIIa, and co-packaged with a single-use pre-filled syringe (PFS) containing SWFI used to reconstitute the lyophilized FDP.

REVIEW SUMMARY

Sections reviewed:

3.2.S.3 Characterization
3.2.S.4 Control of Drug Substance
3.2.P.5 Control of Drug Product

During the pre-license inspection at LFB USA, Inc. Charlton, MA, USA (May 8 – 12, 2017), several issues with analytical techniques and procedures related to the characterization and control of rFVIIa were discussed. This memorandum does not contain the discussions during the inspection. For details on the specific topics discussed, please refer to the Establishment Inspectional Report (EIR BLA125641 LFBUSA MAY2017).

As several aspects related to the analytical procedures are also discussed in detail in Dr. Alexey Khrenov's final review memo, only the sections that were found insufficient or required further clarification are described in this memorandum. An information request (IR) related to the justification of specifications for the BBDS and FDP was sent on May 01, 2017. The response was received on May 15 (SN0036). The details of this IR and LFB's responses are discussed below.

The IR

Your proposed acceptance ranges for the methods related to structural integrity of rFVIIa molecule in the *Release Specifications* of the Drug Product (DP) (b) (4) are not supported by the capability of the manufacturing process, and are not suitable for the control of product quality and stability. Specifically, please address the following deficiencies in *Justification of Specifications:*

a. In *Justification of Specification for* (b) (4), the acceptance criterion for rFVIIa (b) (4)

3 pages determined to be not releasable: (b)(4)

(b) (4)

Table 2. Initial and revised Specification for rFVIIa FDP

Attribute	Test Method	Initial Acceptance Criteria	Revised Acceptance Criteria
Appearance and description			
Visual appearance of cake	Visual inspection	White to off-white cake or powder	NO CHANGE
Appearance of reconstituted solution: • Opalescence • Color	(b) (4)	(b) (4) (b) (4)	NO CHANGE NO CHANGE
Visual Appearance of reconstituted solution	(b) (4)	Clear to slightly turbid colorless solution	NO CHANGE
Visual Appearance of reconstituted solution: visible particulates	(b) (4)	(b) (4)	(b) (4)
Identity			
Identity	(b) (4)	(b) (4)	(b) (4)
Quality			
pH	(b) (4)	(b) (4)	NO CHANGE
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Reconstitution time	Visual determination	(b) (4)	NO CHANGE
Particulate matter	(b) (4) (b) (4)	(b) (4)	NO CHANGE

(b) (4)	(b) (4)	(b) (4)	**Release** **1 mg vials:** (b) (4) (b) (4) **5 mg vials:** (b) (4) **Shelf Life** **1 mg vials:** (b) (4) (b) (4) **5 mg vials:** (b) (4)
Sterility	(b) (4)	Sterile	NO CHANGE
Bacterial endotoxins	(b) (4)	(b) (4)	NO CHANGE
Purity			
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Impurities			
(b) (4)	(b) (4)	(b) (4)	NO CHANGE
(b) (4)	(b) (4)	(b) (4)	NO CHANGE
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Strength, potency			
rFVIIa concentration	(b) (4))	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Specific activity	(b) (4)	(b) (4)	NO CHANGE
Excipients			
Trisodium citrate dihydrate	(b) (4)	(b) (4)	(b) (4)

Polysorbate 80	(b) (4)		(b) (4)	(b) (4)
Arginine HCl				
Lysine HCl				
Isoleucine				
Glycine				

CONCLUSION

There are no significant issues related to rFVIIa structural integrity characteristics reviewed by me. I shared review responsibilities for analytical methods and specifications used for characterization of rFVIIa with Dr. Khrenov. Please refer to his memo for additional details.

I defer the decision on regulatory action for this BLA to the chairperson of the review committee.