M E M O R A N D U M

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 125641/0**)
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Through: Tim Lee, PhD, Chief, HB/DPPT/OTAT

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Subject: Addendum to the memo for the review of the Analytical Methods and Specification sections in LFB's original BLA for Coagulation Factor VIIa (Recombinant) [SEVENFACT]

1. EXECUTIVE SUMMARY

This memorandum is an addendum to the memo for the review of the *Analytical Methods* and *Specification* sections in the original BLA submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB) for Coagulation Factor VIIa (Recombinant) (rhFVIIa). The proposed proprietary name is SEVENFACT, and the proposed indication is for on-demand treatment of bleeding in adolescents and adults with inhibitors against Factor VIII and Factor IX. LFB's internal name for the product is LR769.

A Complete Response Letter (CRL) was issued to the original BLA on October 13, 2017. LFB resubmitted the application, providing a complete response to the CRL on October 11, 2019 in an amendment under STN 125641/0.71.

This addendum to the original review memo summarizes the review of LFB's responses to the issues raised in the original review memo, and conveyed to LFB in the CRL.

LFB adequately addressed the issues, providing sufficient bridging data for the potency assay, modifying procedures for visual inspection, and developing a (b) (4) assay to control the identity of SEVENFACT.

Since the issues raised in the previous review have been resolved, I recommend **APPROVAL** for this BLA.

2. BACKGROUND

The active ingredient in SEVENFACT is a recombinant (r) analogue of activated human Factor VII (FVIIa). The zymogen is expressed in the milk of transgenic rabbits, and converted to its activated form, FVIIa, during the manufacturing process.

FVIIa is an enzyme of the blood coagulation system, which activates Factor (F) X. Under normal conditions, this conversion is performed mostly by the intrinsic Xase complex consisting of FVIIIa and FIXa. As such, FVIIa can bypass the Xase complex, and render a therapeutic effect in the treatment of bleeding episodes in hemophilia A or B individuals who have developed inhibitor antibodies against FVIII or FIX, respectively.

The various steps of the SEVENFACT manufacturing process are performed at multiple locations. The milk is collected on rabbit farms in (b) (4) Charlton, Massachusetts (MA), USA. The first stage of the manufacturing process, including (b) (4), is conducted at the LFB USA facility in (b) (4), resulting in the (b) (4). The (b) (4) stage, including the purification of (b) (4). Final drug product (FDP) manufacture, including filling, lyophilization and primary packaging, is performed at contract facility (b) (4). The FDP is presented at two nominal dosage strengths of 1 and 5 mg of rhFVIIa in single-use glass vials. Initially a (b) (4) dosage strength was also proposed, but was removed from the BLA resubmission. The FDP is reconstituted in sterile Water for Injection (sWFI) provided in a pre-filled syringe (PFS) before intravenous administration to the patient.

Several other facilities, all in (b) (4), are also involved in the testing of the BDS and FDP: LFB (b) (4), LFB Biotechnologies and LFB Biomedicaments in Les Ulis, and (b) (4).

3. REVIEW SUMMARY

The following CRL items were proposed in the original review memo and included in the CRL (the item numbers and language are as listed in the CRL). LFB provided responses which are reviewed below.

a. CRL Item # 2

The design of the combination product and validation of its use are deficient as evidenced by multiple observations of visible particulates found in the reconstituted Final Drug Product (FDP) during release testing and stability studies. The investigations were not successful in identifying the true root cause(s), including the identity and origin of the particulates. Your CAPAs have so far failed to prevent the recurrence of visible particulates in the FDP.

We acknowledge your proposals to (b) (4). However, this proposal does not address the root cause(s) of the problem, and hence are not considered as effective CAPA. For example, the presence of particulates from (b) (4)

acceptable solution to address the deficiencies in the design of the combination product.

Reviewer's Comments (all italicized text in the rest of the memorandum represents this reviewer's comments):
Most of the review regarding investigation of OOS results and CAPAs for visible particles may be found in the review memoranda of reviewers from the Division of Manufacturing and Product Quality (DMPQ). This review is related to the testing procedure and specification acceptance criteria only.

In the response, LFB implemented enhanced scheme for the control of visible particles at the FDP stage. The overall control scheme for visible particles (Figure 1) includes the control of individual components (vials, vial adapters (VA) and pre-filled syringes) as well as final control of the combination product (CP). Sampling sizes have been defined taking into account the Acceptable Quality Level (AQL) and batch sizes according to ISO (b) (4). For (b) (4)

(b) (4)

Prior to release testing, FDP vials are inspected for visible particles by their manufacturer. The following controls are performed (b) (4) on the vials:

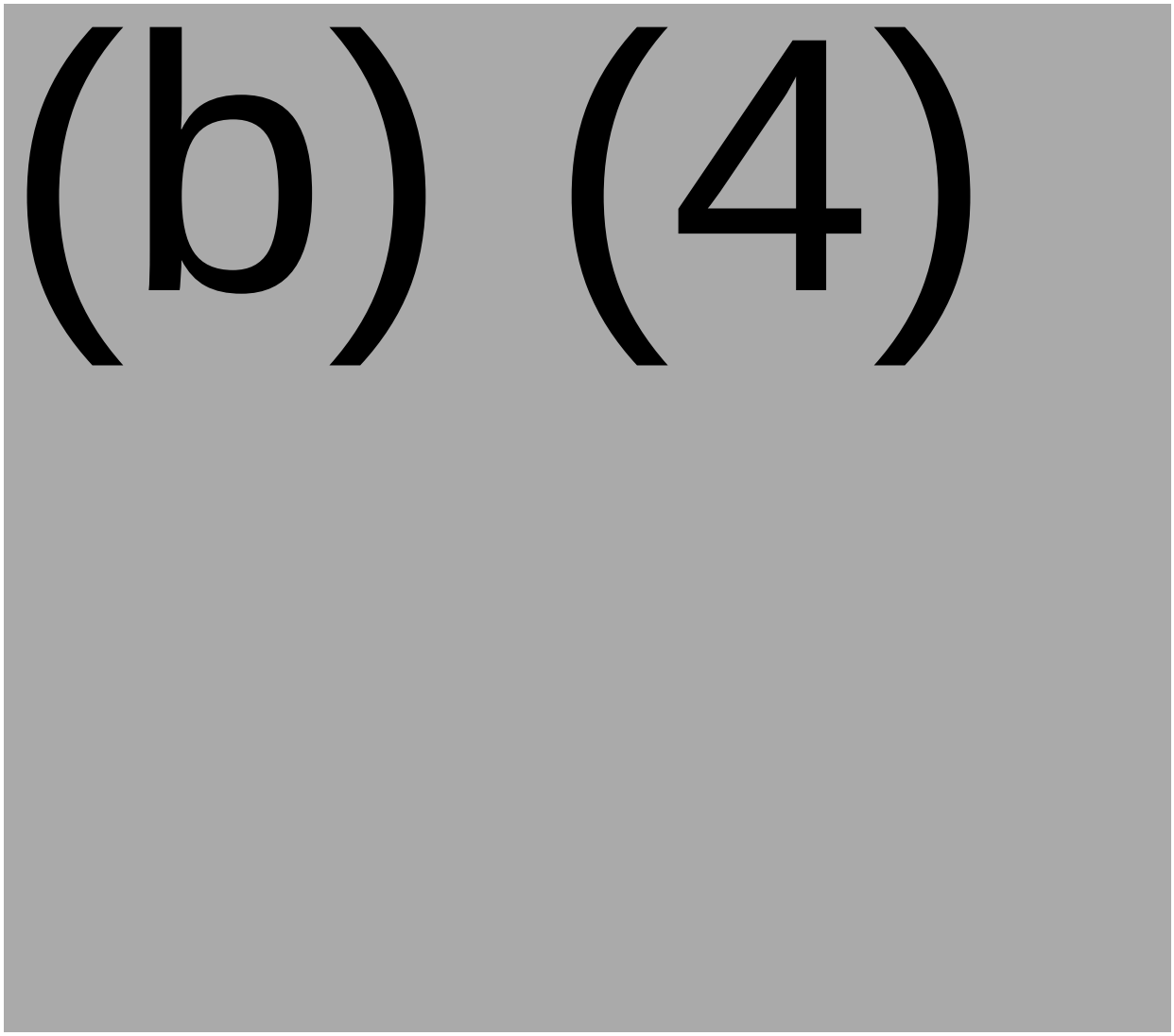
- (b) (4) visual inspection of capped vials (b) (4)
- A subset of (b) (4) vials which passed the (b) (4) visual inspection is subjected to AQL testing for critical defects (AQL (b) (4) that include particles. This test is carried out on (b) (4) vials,
- (b) (4) vials are then subjected to AQL testing for visible particles after reconstitution (b) (4) testing). FDP vials are reconstituted with sWFI using a syringe equipped with a needle. The acceptance criterion for this test is not more than (b) (4) vials out of (b) (4) with visible particles (AQL (b) (4)).

At release, the CP is tested by LFB for visible particles. The reconstitution method for CP testing is aligned with the user instructions and uses the same components as those included in the CP (VA and sWFI PFS). Visual examination is performed in the vial after reconstitution using (b) (4) operating conditions.

This test uses (b) (4)

This method was recently implemented by LFB and tested on (b) (4)

The proposed specification and testing scheme are acceptable. They satisfy the DMPQ requirements to control total visible particulates in the CP, using reconstitution procedure involving the supplied CP components. Additional controls implemented allow the manufacturer to control and discriminate particles coming from the different components of the CP.



b. CRL Item # 3a

The potency assay is not suitable for its intended use because LFB has not been using a qualified reference standard for the determination of product potency. Specifically, LFB should evaluate

- **i. The impact of assay variability and lack of results traceability, due to lack of common internal standard, on the determination of product potency at the various stages of process development, product characterization, and in stability studies. So far, the additional provided data are insufficient in addressing the deficiencies, for example,**
  1. **LFB confirmed relative comparability of the results obtained using international standard and standard provided with the kit, but this study was performed using only (b) (4) lots of kit and did not fully eliminate concerns regarding assays prior performance.**

- **ii. The stability of the proposed product-specific reference standard. Please establish stability program for product-specific standard.**

LFB provided additional data to support the validity of the results generated prior to the introduction of the internal reference standard, and potency assay revalidation. At that time, the assay used (b) (4)

(b) (4)

For all tested kits, QC sample results complied with the (b) (4) acceptance limits, and are within (b) (4) standard deviations. (b) (4)

After revalidation of the potency assay, all available lots (including stability) were retested and the data were within acceptable ranges. All data moving forward after revalidation will include a common product-specific standard according to the updated procedure.

I agree with LFB's assessment that the data demonstrated that results, generated prior to the introduction of the potency assay using product-specific standard, are likely reliable and can be used to for the assessment of SEVENFACT. There were no unexpected deviations from nominal values for the QC samples, which indirectly confirmed that the calibrators used in the assay kits were likely correctly calibrated and assigned the correct potency.

CRL item 3.a.i (paragraphs 2 and 3) also included requests for additional potency assay data related to stability and process comparability. These requests were mad by other HB CMC reviewers, and LFB's responses are reviewed and provided in their respective memoranda. I consider the deficiencies I identified in this CRL item to be resolved.

A stability program was implemented for batch (b) (4), which serves as a product-specific reference material, and will be used for a new reference standard batch. The stability protocol

(b) (4)

(b) (4)

(b) (4)

(b) (4)

c. CRL Item #3b

The current (b) (4) method is not sensitive enough to detect minor (b) (4) changes and is not sufficient to control the Identity of recombinant proteins. Please develop a (b) (4) method for Identity testing.

LFB has implemented the (b) (4) method originally used for characterization for identity testing of the (b) (4) FDP.

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

(b) (4)

(b) (4)

(b) (4)

4. CONCLUSION & RECOMMENDATION

The CRL issues related to analytical analytical methods and specifications used for the characterization of identity, purity, quality and safety of SEVENFACT bulk drug substance and final drug product are successfully resolved. I recommend approval of the BLA for SEVENFACT from the perspective of analytical methodology and control of Bulk Drug Substance and Final Drug Product.