U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: File (STN BL 125641/0) & Seameen Dehdashti, PhD, RPM, RPMB/DRPM/OTAT

From: Mikhail Ovanesov, PhD, Research Biologist, Hemostasis Branch (HB), Division of Plasma Protein Therapeutics (DPPT), OTAT

Leonid Parunov, PhD, Visiting Fellow, HB/DPPT/OTAT/CBER

Through: Tim Lee, PhD, Chief, HB/DPPT/OTAT/CBER

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Subject: Addendum to the Final CMC Review of LFB's BLA for Coagulation Factor VIIa (Recombinant)-jncw [SEVENFACT] - Review of LFB's Response to the Complete Response Letter

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1. Executive Summary

This memorandum is an addendum to the memo for the review of the *Chemistry, Manufacturing and Controls (CMC)* sections in the original BLA submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB) for Coagulation Factor VIIa (Recombinant)-jncw (FVIIa). 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 has adequately responded to the CRL items, providing sufficient data to address the issues within the CMC section in the previous BLA submission.

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

2. Regulatory background and product overview

Original BLA under STN 125641/0 was submitted by LFB for coagulation factor VIIa (recombinant)-jncw, with the proposed proprietary name SEVENFACT. The active ingredient of SEVENFACT is a recombinant analogue of activated human coagulation FVIIa expressed in and purified from the milk of genetically engineered (GE) rabbits. LFB also submitted a New Animal Drug Application (NADA) under # 141-511, entitled "Bc2371 rDNA construct in R69 New Zealand white rabbits. Heritable Construct. Domesticated Rabbits" to support the commercial housing and milking of the GE rabbits in their Massachusetts farm facility. The NADA was approved by the Center for Veterinary Medicine (CVM) on December 27, 2018.

SEVENFACT is indicated for the on-demand treatment and control of bleeding episodes in adult and adolescent (12 years to < 18 years) hemophilia A and B patients with inhibitors to Factor (F) VIII and FIX. It is recommended for treatment at home or in a hospital under the supervision of a healthcare provider.

To support the proposed indication, the BLA includes results from one Phase 3 study for efficacy and safety. The two doses evaluated in the Phase 3 study were selected based on the pharmacokinetic (PK) assessments from a single-arm Phase 1 study investigating three doses. The Phase 1 study provides limited data supporting the safety of SEVENFACT based on limited doses of SEVENFACT as compared to the Phase 3 study that permitted treatment of many bleeding episodes with two of the initial dosing regimens over a period of three months each.

SEVENFACT is a biologics/device combination product. The biological product, coagulation factor VIIa (recombinant)-jncw, is supplied as a sterile, freeze-dried powder in single-use vials containing 1 mg or 5 mg of recombinant FVIIa per vial, co-packaged with a syringe pre-filled with the diluent, sterile Water for Injection (sWFI), in a volume of 1.1 mL or 5.2 mL, respectively. A 510(k)-cleared device, sterile vial adapter (VA) (b) (4) , application number (b) (4) , is included in the package for the transfer of sWFI into the drug vial, and the withdrawal of the reconstituted product out of the drug vial for intravenous infusion into the patient. The VA contains a 5-µm filter, which allows particulate removal and flow aspiration. The combination product package also contains one plunger rod and one backstop.

Disease Background

Hemophilia A and B are inherited deficiencies of FVIII and FIX, respectively, that manifest as lifelong bleeding disorders. Hemophilia A is the most common X chromosome-linked disease with an estimated incidence of 1 in 5,000 male births. Hemophilia B is about 4 times less common than hemophilia A. There are about 20,000 people with hemophilia in the U.S.

Bleeding in individuals with hemophilia is controlled with prophylactic and on-demand therapies with plasma-derived and recombinant FVIII or FIX concentrates that replace the respective factor deficiency. The development of inhibitors to FVIII or FIX is the most significant complication in hemophilia treatment, and occurs in up to 33% of patients with severe hemophilia A, and in 3% of patients with severe hemophilia B. Patients with low levels of inhibitors can continue to be treated with factor replacement therapy at the same or higher dose. For patients with high inhibitor titers, administration of FVIII or FIX concentrates is ineffective, and bypassing agents are needed to control the bleed.

Hemophilia patients with inhibitors experience severe morbidity with recurrent episodes of bleeding in joints, muscle and deep tissues, which can be limb and life threatening. Recurrent joint bleeding events result in synovial inflammation, hypertrophy leading to more bleeding episodes and progressive damage to cartilage and subchondral bone. This leads to progressive severe arthropathy that can adversely impact health, and significantly reduce health status and quality of life in patients.

Several patient and treatment related factors can predict the development of inhibitors. Specific mutations associated with inhibitors include nonsense mutations, Intron 22 inversion and large deletions. The type of FVIII mutation may also influence the inhibitor titer as evidenced by the fact that 68.8% of patients with large deletions have high-titer inhibitors when compared to 21% with missense mutations, and 30-40% with all other mutation types. Severity of disease that requires early intervention carries an increased risk of inhibitor formation. People of African or Hispanic heritage, and those or with a family history of inhibitors are also at a higher risk of inhibitor development.

Available Therapies

Hemophilia patients with inhibitors at high titers require bypassing agents to control bleeding episodes or in the perioperative setting. The two currently available therapies for on-demand treatment of bleeding episodes are FEIBA® (Takeda), a human plasma-derived activated Prothrombin Complex Concentrate (PCC), and NOVOSEVEN RT® (Novo Nordisk A/S), a recombinant FVIIa product.

Mechanism of SEVENFACT Action

Activated FVII is an enzyme involved in the activation of the blood coagulation cascade via the tissue factor (TF)-dependent pathway. Unlike all other blood coagulation enzymes, FVIIa has little proteolytic activity by itself, and is normally present in the blood (zymogen FVII and enzyme FVIIa circulate in a ratio of ~1000:1). Binding to the cofactor TF is required for FVIIa to exert its proteolytic activity towards FIX and FX. Since TF is a transmembrane protein present

on extravascular cells, but absent from any intravascular cell, the first event in the initiation of the coagulation cascade is the binding of circulating FVIIa to TF at the site of vascular damage. FVIIa in complex with TF on a phospholipid membrane activates FIX and FX. More FVII is then activated to FVIIa by FXa, FIXa or thrombin (feedback activation) and by FVIIa (autoactivation in the presence of TF). The main inhibitors of FVIIa in plasma are a complex of Tissue Factor Pathway Inhibitor with FXa and TF (TFPI:FXa:TF) and Antithrombin III.

The mechanism of action of SEVENFACT and NOVOSEVEN RT for the treatment of bleeding in hemophilia A and B patients with inhibitory antibodies appears to be different from that of endogenous FVIIa. Both recombinant FVIIa products are administered at doses that result in supra-physiological level of FVIIa in blood that is approximately equivalent to about 2.5 times the concentration of the endogenous zymogen FVII, and more than 2,500 times higher than the level of the endogenous enzyme FVIIa. Despite this high concentration, recombinant FVIIa does not usually cause thrombosis in hemophilia patients as demonstrated by comparable safety record to that of other coagulation factor concentrates. Two mechanisms of the procoagulant action of recombinant FVIIa have been demonstrated. The first mechanism is TF-dependent, i.e., it involves the acceleration of the initial stages of coagulation by the binding of recombinant FVIIa to the sites of vessel wall injury where TF is exposed. This mechanism can also include a displacement of FVII (which acts as a competitive inhibitor of the TF-FVIIa complex) by recombinant FVIIa from TF. The second mechanism is procoagulant lipid-dependent, and mediated by the increased catalytic activity of FVIIa when it is bound to the membrane of activated platelets.

Regulatory History

Key regulatory milestones in the development of SEVENFACT are summarized in Table 1. An early version of GE rabbit milk-derived FVIIa product was developed by GTC Biotherapeutics Inc. and studied under Investigational New Drug application (IND) (b) (4). SEVENFACT, an improved version of this product, was developed for the U.S. market under IND 15183, under the product code name LR769.

Table 1. Regulatory Milestones

Date	Milestone
January 26, 2010	Pre-IND meeting
April 30, 2010	IND (b) (4) submission
December 13, 2011	Pre-IND meeting
July 16, 2011	IND 15183 submission
April 25, 2016	Pre-BLA meeting with LFB
October 13, 2016	BLA 125641/0 submission
December 12, 2016	BLA filed
October 13, 2017	Complete Response Letter (CRL) issued
October 11, 2019	CRL response submission
April 10, 2020	PDUFA* Action Due Date

*PDUFA=Prescription Drug User Fee Act

In 2013, GTC Biotherapeutics Inc. changed its name to rEVO Biologics Inc; and in 2015, changed its name again to LFB USA. LFB USA and LFB (the applicant of this BLA) are separate entities owned by the LFB Group.

FDA rejected LFB's request for orphan designation for SEVENFACT. SEVENFACT is not licensed outside the U.S.

During the first review cycle, CBER reviewers found significant deficiencies in CMC, which resulted in the issuance of a CRL to LFB on October 13, 2017.

3. Overview of Chemistry, Manufacturing and Controls

Reviewer's comment: The CMC overview in the section was updated with the information presented in LFB's Responses to the CRL and manufacturing amendments received and reviewed in the second review cycle.

Product Quality

The active ingredient in SEVENFACT, coagulation factor VIIa (recombinant)-jncw, is a glycoprotein of 406 amino acids (AA) with a molecular weight of approximately 50 kilodaltons. The amino acid sequence of coagulation factor VIIa (recombinant)-jncw is identical to that of human plasma-derived FVIIa. It is > 99% pure with a nominal specific activity of about 45,000 IU/mg of protein when tested against the World Health Organization (WHO) international standard for human FVIIa activity.

SEVENFACT® is produced by recombinant DNA technology using genetically engineered rabbits into which the (b) (4) DNA coding sequence for human FVII has been introduced along with a promotor DNA sequence, which directs the expression of the rFVII protein in the mammary gland, and secretion of which into the milk. During purification and processing, FVII is enzymatically converted to FVIIa.

Zymogen FVII contains four distinct structural domains: N-terminal γ-carboxyglutamic acid (Gla) domain, two epidermal growth factor (EGF) like domains, and one serine protease domain. Activation of FVII into FVIIa results in the cleavage of the peptide bond Arg 152-Ile 153. FVIIa is composed of an N-terminal Light Chain (LC) of 152 AA, and a C-terminal Heavy Chain (HC) of 254 AA, held together by a single disulfide bridge (Cys 135-Cys 262).

Structure, Function and Impurities

Coagulation factor VIIa (recombinant)-jncw was found to be fully activated, the N-terminal sequence of the light chain indicates (b) (4) . The experimentally determined sequence of coagulation factor VIIa (recombinant)-jncw is consistent with the theoretical one, with (b) (4) sequence coverage. Post-translational modification analysis revealed that the (b) (4) differ between SEVENFACT (exclusively (b) (4), NOVOSEVEN (exclusively (b) (4) and plasma-derived FVIIa (b) (4) The results of the *in*

vitro functional characterization studies demonstrated similarity between SEVENFACT, NOVOSEVEN and plasma-derived FVIIa.

The orthogonal methods employed to characterize SEVENFACT demonstrated a high level of purity as shown by (b) (4) analyses. Low levels of product-related substances are detected, which are identified mainly as (b) (4).

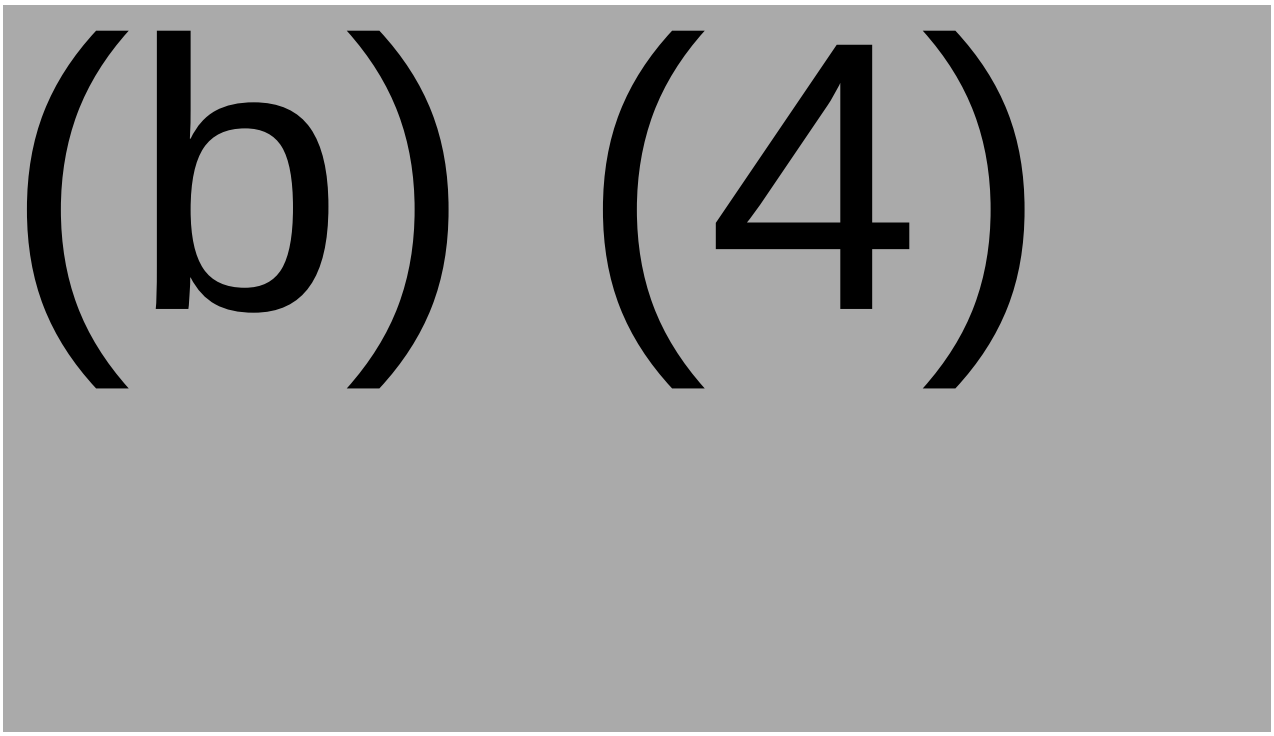
LFB conducted extensive evaluation of the potential impurities from the source material, rabbit milk. Milk is a non-sterile colloidal suspension of soluble whey proteins and insoluble casein micelles and fat globules. Non-activated recombinant FVII is synthesized and secreted by the mammary epithelial cells and found in the soluble whey fraction. The following impurities may originate from the rabbit milk: (b) (4)

The manufacturing process for SEVENFACT was designed to reduce rabbit-derived impurities. Residual rabbit (b) (4) is the only RMP impurity detectable by (b) (4) process. (b) (4) was demonstrated as the major residual RMP in the (b) (4) at a level of about (b) (4) depending on the test method) in the (b) (4) of RMP identified in 1 mg of SEVENFACT (b) (4)

R69 line of GE rabbits

The original colony of production rabbits was established using Specific Pathogen Free (SPF) wild-type New Zealand White rabbits and fresh rabbit semen from the first generation R69 male. The genealogy of the R69 lineage is recorded for each animal and may be used to aid the selection of optimal milk producing rabbits.

A health monitoring program (also performed on wild-type rabbits) for the milk production facilities is based in part on the health monitoring recommendations from the Federation of European Laboratory Animal Science Associations (FELASA), in part on a European Note for Guidance on the production and quality control of animal immunoglobulin and immunosera for human use (CPMP/BWP/3354/99), as well as upon advice from internationally recognized rabbit virus experts and in-depth knowledge of the relevant rabbit diseases of concern. LFB implemented controls for the diseases considered to pose the greatest concern to rabbits, their milk, or with potential zoonotic concerns for humans.



Manufacturing process

(b) (4) facilities in (b) (4) countries participate in the manufacture of SEVENFACT and its device components, and an additional (b) (4) facilities are involved in its storage and release testing:

- *Source material (milk)* is collected from GE rabbits at (b) (4) SEVENFACT-(b) (4)
- (b) (4) .
- (b) (4) .

- The *Final Drug Product (FDP)* is manufactured by (b) (4) filled and lyophilized.

The *Product kit* is packaged by (b) (4) using sWFI-prefilled syringes manufactured by (b) (4) and sterile Vial Adapter (VA) from (b) (4)

Controls and validation of manufacturing process
The SEVENFACT *process control strategy* is composed of a combination of process and product controls on the different process steps and intermediates. Specifications for the control of the manufacturing process parameters have been established for Critical Process Parameters (CPPs) identified by a Quality Risk Management exercise and confirmed by robustness studies. The controls performed on the different process steps and intermediates include the control of (b) (4)

The control strategy includes *lot release testing of* (b) (4) *FDP* for microbial contaminants, identity, purity and strength. SEVENFACT activity (strength) is assessed as potency and specific activity using FVIIa-specific assays calibrated in units of the WHO 2nd International Standard for FVIIa (NIBSC 07/228). The BDS is tested for (b) (4) The FDP is tested for visual appearance of cake and reconstituted solution and visible particulates, identity by (b) (4), pH, (b) (4), sterility, bacterial endotoxins, reconstitution time, particulate matter, residual moisture, excipients (trisodium citrate dihydrate, polysorbate 80, arginine HCl, lysine HCl, isoleucine, and glycine), purity (b) (4) impurities (b) (4), and strength.

The *release analytical methods* and their validations or qualifications for (b) (4), SEVENFACT BDS and FDP were reviewed and found to be adequate for their intended use.

The *process validation* program consisted of a *Process Design* stage (i.e., studies at reduced scale to evaluate robustness, and process evaluation studies at full scale) and a *Process Performance Qualification (PPQ)* stage at commercial scale. LFB conducted separate PPQ studies for the (b) (4), BDS and FDP manufacturing processes, each consisting of 3 PPQ batches of (b) (4), BDS and FDP (1 mg, (b) (4) and 5 mg), respectively. Due to issues with the stability of the (b) (4) dosage batches, LFB decided not to seek approval of the (b) (4) FDP.

Reviewer's comment: In their response to CRL Item 26j, LFB stated that "the (b) (4) dose has been removed from the BLA (b) (4) *However, the* (b) (4) *dosage form continues to be referenced along with the 1-mg and 5-mg dosage forms in various sections of the BLA file. Therefore, on March 4, 2020, I*

requested that LFB updates these sections of the BLA file to clarify that the (b) (4) *dosage form is currently excluded from the BLA. On March 12, 2020, LFB updated the CTD Module 2 and Module 3 sections to include the following disclaimer:*

> *Disclaimer:* ***LR769*** (b) (4) ***dosage strength information described in this BLA section is for reference only.*** *LR769* (b) (4) *dosage strength is currently excluded from BLA 125641 and has not been evaluated under the BLA review and licensure process.*

The disclaimer above was added on the first page of Section 2.3.P.1 and Section 3.2.P.1 and at the end of each subsequent Module 2 and Module 3 Sections, in which information relating to the (b) (4) *dosage strength is used for reference.*

Viral safety of SEVENFACT relies on complementary measures as follows:

- *The SPF status of rabbit colony:* To ensure the SPF status, heath monitoring has been incorporated into the assessments of the GE rabbits and specific controls have been implemented to ensure the health of the rabbit colony.
- *An in vitro assay for detection of adventitious viruses:* An *in vitro* assay for the detection of adventitious viruses has been implemented to evaluate (b) (4) material which is free of detectable viruses may be used in the manufacture of the product.
- *The capacity of the purification process to inactivate and/or remove a panel of model viruses:* The manufacturing process includes (b) (4) Viral clearance was validated by (b) (4) experiments performed according to ICH and EMA guidelines, ICH Q5A (R1) and CPMP/BWP/268/95 (revised).

CBER Lot Release

Under the provision described in the Federal Register (FR) 60:63048-63049 publication (December 8, 1995), routine lot-by-lot release by CBER is not required for SEVENFACT because it is a well-characterized therapeutic recombinant product. Thus, exemption of SEVENFACT from CBER Lot Release is justified.

Product Comparability

First-Generation and Licensed Manufacturing Processes

The development of the SEVENFACT manufacturing process was based on the experience gained with the first-generation product (b) (4)

(b) (4)

Manufacturing Process A and Process B

The development of the SEVENFACT manufacturing process has been conducted in two (b) (4) phases, denoted as Process A and Process B. Process B is an optimized, (b) (4) fold scaled-up version of Process A. Products from both processes were used in the pivotal clinical trial, the results of which support the safety and efficacy of this product.

An analytical comparability exercise was conducted following a Quality Risk Management approach, demonstrating acceptable biochemical and functional comparability between the materials from Processes A and B. An extensive characterization study was also performed on the previous and current batches of Primary Reference Standard, manufactured from Processes A and B, respectively, demonstrating consistency between both materials.

In addition to analytical comparability, a pharmacokinetic (PK) assessment was performed within the PERSEPT 1 clinical trial on patients treated with SEVENFACT batches from Processes A and B. PK profiles showed differences between the two process materials: at a dose of 225 mcg/kg, Process B material showed higher Cmax and AUC than Process A material. The PK differences at the dose of 75 mcg/kg were smaller. Root-cause investigations found no underlying problems with the manufacturing process or bioanalytical methods. Therefore, the failure of PK comparability could be attributed to the differences between patient populations used in the Process A and Process B arms of the study. *Reviewer's comment: The investigation of analytical root-causes for the observed PK differences between the Process A and B materials is discussed below in the LFB response to CRL Item 3.a.i.2*

4. Review of CRL Responses

Reviewer's comment: In the first review cycle, the review of CMC information was delayed because incomplete or incorrect information was provided on the investigations into the out-of-specification (OOS) results for Visible Particulates in the reconstituted FDP, OOS results for RMP impurities in the (b) (4), and failures in the performance of (b) (4) purification steps. Many of these deficiencies remained unresolved during the first review cycle.

The following substantive CMC issues were included in the CRL issued on October 13, 2017:

1. *presence of particulate materials noted in the testing and stability studies on reconstituted SEVENFACT,*
2. *poor robustness of the BDS manufacturing process,*
3. *product-related stability issues that impact the shelf-life,*
4. *deficient analytical methods for assessment of extractables and leachables,*
5. *absence of proper validation or verification of analytical methods to control diluent according to its release specifications ,*
6. *deficient shipping validation studies,*

7. *deficient combination product design and validation,*
8. *incomplete facilities information, and*
9. *unresolved pre-license inspection issues.*

These deficiencies were resolved with the new data provided in LFB's response to the CRL submitted on October 11, 2019 (reviewed below).

The scope of this review of LFB's CRL response covers all CMC topics except stability studies (reviewed by Dr. Yideng Liang), Bulk Drug Substance (BDS) and Final Drug Product (FDP) release specifications (reviewed by Dr. Alexey Khrenov), FDP release methods (reviewed by a team from OCBQ/DBSQC and Dr. Alexey Khrenov), extractables and leachables studies and controls of excipients and sWFI (reviewed by Dr. Andrey Sarafanov), and facilities and combination product design and controls (reviewed by Mrs. Nicole Li, Mrs. Nicole Trudel, and Dr. Alexey Khrenov.)

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). For ease of review, the Agency's deficiencies are provided in bolded italics, and our review of LFB's responses are provided in plain text.

Item 1

The data you provided do not adequately address the deficiencies in the validation of the manufacturing process for Coagulation Factor VIIa (Recombinant) that were identified during the Pre-license Inspections of your facilities. Please provide data to demonstrate the following:

(b) (4)

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

(b) (4)

(b) (4)

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Item 2

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

We acknowledge your proposal to (b) (4) ***. However, this proposal does not address the root cause(s) of the problem, and hence is not considered an effective CAPA. For example,*** (b) (4)

not an acceptable solution to address the deficiencies in the design of the combination product.

Please provide the final investigation report that includes but is not limited to, identification of the root cause{s) and data to demonstrate that the proposed CAPAs are effective in addressing the design and validation issues of the combination product.

Summary of LFB Response:

OOS results were reported during stability studies for visible particles in 2015 and 2016, and visible particulates in the reconstituted FDP were investigated. The investigation determined (b) (4)

Reviewer's comment: Repeated OOS results for particulates and inadequate root-cause investigations presented to the Agency during the first review cycle were troubling, and raised concerns about potential problems with the container closure system chosen for this product. In response to the CRL, LFB conducted extensive investigations to address the concerns regarding the container closure, including the (b) (4) *. Several root causes were identified including* (b) (4) *Most important CAPAs were the revision of* (b) (4) *system). These CAPAs appeared effective. The potential deficiency in either the primary components of the container closure or the diluent delivery devices can be excluded. The response is acceptable.*

Please also refer to Dr. Alexey Khrenov's review memorandum for additional assessment of LFB's responses to CRL Item # 3. Dr. Khrenov found these responses acceptable.

Item 3

The following assays are not suitable for the control of the (b) (4) ***FDP release stability studies, and process validation studies:***

- ***a. The potency assay is not suitable for its intended use because you have not used a qualified reference standard for the determination of product potency. Specifically, please evaluate the following:***
  - ***i. Lack of a common internal standard and its impact on the determination of rFVIIa potency at the various stages of process development, product characterization***

and in stability studies. So far, the data provided are insufficient in addressing the deficiencies. For example;

1. ***You showed comparability of the results obtained using an international standard and the standard provided with the rFVIIa assay kit. However, this study was performed using only (b) (4) lots of the kit, and did not fully address our concerns regarding the assay's prior performance.***

Summary of LFB Response:

During the early LR769 development phase and prior to the introduction of the internal reference standard for rFVIIa in 2017 (method revalidation), the potency data had been generated using the (b) (4) kit supplied by (b) (4). Throughout this period of time, LFB relied on reference standards supplied with the (b) (4) kit because the kit manufacturer calibrates each standard in in house. Additionally, each assay run was evaluated using internal controls supplied with the kit as a method suitability test (MST).

To confirm the adequate performance of the assay prior to the implementation of product-specific standard, LFB provided trending data for internal control samples (several lots) tested in each of the assay performed by the QC lab. Additionally, LFB presented data obtained from (b) (4) calibration exercises.

This response was reviewed by Dr. Leonid Parunov.
Reviewer's comment: The assay suitability has been demonstrated throughout product development by using both the internal standard calibrated by (b) (4) against the WHO International Standard 07/228, and the quality control samples, also supplied by (b) (4) as part of the kit.

A total of (b) (4) runs generated by LFB from QC samples from 2013 to 2017 prior to method revalidation demonstrate adequate quality of potency data (only (b) (4) runs did not meet the acceptance criteria for quality control samples) and good lot-to-lot consistency of the (b) (4) standards and controls. Therefore, the potency data generated over that period of time were acceptable, i.e., all data from Process B batches (clinical and process validation batches) including stability data. The response is acceptable.

The revalidated potency assay was introduced to analyze Process Performance Qualification (PPQ) batches starting at their 36-month stability time-point (24 months for batch (b) (4). The updated stability data were provided in response to FDA CRL Item 4a. All potency and specific activity results generated from these batches meet the acceptance criteria after 36 months of storage under long-term conditions (5°C, 25°C/(b) (4) RH and 30°C/(b) (4) RH). The (b) (4)-month results available for one batch (b) (4) also meet the acceptance criteria under long-term conditions. This real-time data supports the proposed shelf life of 36 months at a temperature not exceeding 30°C.

The revalidated potency assay has also been used for additional process validation studies carried out to respond to FDA CRL Item 1 (b) (4) and FDA CRL Item 26 (FDP).

Reviewer's comment: The provided evidence confirms that the stability study conclusions were not affected by the prior deficiencies in potency method calibration. The response is acceptable.

Please also refer to Dr. Alexey Khrenov's review memorandum for additional assessment of this LFB response. Dr. Khrenov found it acceptable.

2. ***In the Process A and Process B bridging PK Study No. RB-FVIIa-06-013, higher recovery was observed in patients treated with Process B materials. Your investigation did not include retesting of retained samples of all the lots used in the clinical studies by the validated assays for Specific Activity and Potency.***

Summary of LFB Response:

All clinical batches used in the clinical phase 3 program were retested in December 2017 using the validated potency assay. Results were generated from retained samples stored at (b) (4) to avoid any bias due to product degradation.

Statistical analysis shows that both sets of data have homogeneous variances at 5% risk and no significant difference in potency at 95% confidence.

Reviewer's comment: I agree with LFB's conclusion that LR769 clinical batches manufactured either from Process A or B have comparable potency and specific activity. The response is acceptable.

3. ***You claimed that the potency of the product is not impacted by storage temperature, therefore, results from retests of all in-date lots can be used to support the new release specifications for Potency and Specific Activity. However, the data in Tables 24 and 26 of Amendment #53 dated July 24, 2017, show potency loss for lot (b) (4) over time is affected by storage temperature.***

Summary of LFB response:

LFB agreed that the data presented in the first review cycle indicated that the Specific Activity of batch (b) (4) was steadily decreasing showing a negative trend even if it was within the specification. Extrapolation of the previous data predicted that specific activity can fall below the specification limit of (b) (4) before 30 months of storage at room temperature. In the resubmission, the adverse trend was broken by the 36- and (b) (4) -months data-points, which remain well within the specific limit and away from the previous negative trend.

Similarly, the previously observed increase in potency loss for lot (b) (4) at elevated storage temperatures was not reproduced at subsequent time-points obtained with the revalidated potency assay.

Reviewer's comment: The results indicate that the negative trend was due to variability in the existing method. In addition, analysis of stability study data indicated no negative impact on product quality as measured by various analytical methods. Overall, the full set of long-term stability data generated throughout 36 months at (b) (4) *temperatures of storage on batch* (b) (4) *as well as on* (b) (4) *PPQ batches indicate a satisfactory stability profile in a temperature range from 5°C to 30°C. This long-term real-time data support the proposed shelf life of 36 months at a temperature not exceeding 30°C. The answer is acceptable.*

Please also refer to Dr. Yideng Liang's review memorandum for additional assessment of this LFB response. Dr. Liang found it acceptable.

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

Summary of LFB response:

The current LR769 Reference Standard batch is (b) (4)

(b) (4)

b. The current (b) (4) ***method is not sensitive enough to detect minor*** (b) (4) ***changes; and therefore, not suitable for control of the Identity of rFVIIa. Please develop a*** (b) (4) ***method for Identity testing.***

Summary of LFB Response:

A (b) (4) method was developed as part of a battery of methods used for the extensive characterization of recombinant FVIIa. LFB has implemented a (b) (4) method for identity testing of the (b) (4) FDP.

LR769 test sample (b) (4)

(b) (4)

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Reviewer's comment: The response is acceptable. For additional details, please also refer to Dr. Alexey Khrenov's review memorandum.

Item 4

The proposed shelf-life for the FDP is not supported by stability data. Please provide the following:

a. ***The potency results of all stability samples, determined using a fully validated Potency assay.***

Summary of LFB Response:

LFB provided all potency data from stability studies with PPQ and engineering FDP batches, obtained with the old and new revalidated potency methods. The revalidated potency assay with the implementation of a potency working standard and a (b) (4) sample was introduced in July 2017. At that time, the PPQ batches (except (b) (4) batch (b) (4) had already been analyzed at their 24-month time-point and the stability program of development batches (pilot and engineering batches) was completed. The revalidated potency assay was therefore used to analyze PPQ batches starting at the 36-month time-point (24 months for batch (b) (4)

additional engineering batches manufactured after PPQ batches were placed on stability and potency data generated with the revalidated method are available from these batches.

Reviewer's comment: All potency and specific activity results met the acceptance criteria for all storage conditions, dosage format or potency method up to 36 months under long-term conditions (5°C to 30°C) and (b) (4) months under accelerated conditions (b) (4). The (b) (4)-month results available for one batch (b) (4) also meet the acceptance criteria under long-term conditions. These data support the proposed shelf life of 36 months at a temperature not exceeding 30°C.

b. ***The investigation reports for all the out-of-specification (OOS) results in Potency and Specific Activity for FDP release and stability evaluation against the proposed acceptance limits.***

Summary of LFB Response:

There was no OOS potency or specific activity result as shown in response to Item 4a, including for batch (b) (4) for which an apparent loss of potency was detected at the 23-month time-point (refer to CRL Item 3.a.i.3 response above). Because of the variability of the method, fluctuating results were sometimes generated, although no investigation was triggered as they remained within specification limits. For commercial batches, a trending analysis has been implemented with an alert limit set at (b) (4) standard deviations to detect out-of-trend results.

Reviewer's comment: The response and the implementation of the out-of-trend alert limits are acceptable.

c. ***The investigation report for the declining trends in Potency as shown in the stability studies for the (b) (4) FDP presentation. Specifically, the updated stability data presented in Table 26 of Amendment #53 dated July 24, 2017, demonstrate that after storage for 23 months under the recommended conditions, Potency of batch (b) (4) is decreased by (b) (4), and its Specific Activity by (b) (4). At this rate, the Potency is projected to be OOS at 30 months of storage, 6 months before the proposed shelf-life.***

Summary of LFB Response:

LFB has addressed this comment in the response to FDA CRL Item 3.a.i.3. Long-term stability data up to (b) (4) months is now available for batch (b) (4) does not show a loss in potency. Overall, the full set of long-term stability data generated throughout (b) (4) months at three temperatures of storage (5, 25 and 30°C) on batch (b) (4) as well as on (b) (4) other PPQ batches indicates a satisfactory stability profile in a temperature range from 5°C to 30°C.

Reviewer's comment: The apparent decline in potency as described in the CRL was likely related to assay variability and incomplete bridging of the old and new calibrated potency methods

introduced around that time. Collectively, the stability data support the proposed shelf life of (b) (4) *months at a temperature not exceeding 30°C. The response is acceptable.*

Item 5

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.***

Summary of LFB Response:

Among (b) (4) potential organic leachables that were evaluated, (b) (4) displayed low recoveries below (b) (4). These low recoveries could impact the accuracy of their quantitation and therefore their safety assessment. LFB concluded (b) (4) . LFB concluded that the tested leachables do not represent a risk for the patient safety.

Reviewer's comment: The response is acceptable. For additional details, please also refer to Dr. Andrey Sarafanov's review memorandum.

Item 6

Please provide validation results for 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).***

Summary of LFB Response:

The diluent manufacturer (b) (4) performed validation of non-USP and verification of (b) (4) analytical methods used for the analysis of water for injections according to (b) (4) Methods were verified or validated using reference standards when available or positive and negative controls. Overall, all acceptance criteria have been met and all data used for verification and validation purposes are valid.

Reviewer's comment: The response is acceptable. The "Water for Injection" methods are considered validated or verified for testing of water for injection per (b) (4) compendial methods. For additional details, please also refer to Dr. Andrey Sarafanov's and Dr. Alexey Khrenov's review memorandums.

Item 7

You have reported the status of neutralizing anti-drug antibodies (ADAs) in (b) (4) samples, using an assay that has been validated for the detection of ADA in (b) (4) rather than (b) (4) Therefore, your conclusion that ADAs were absent in a (b) (4) sample should be confirmed using a validated (b) (4) specific way. In addition, please use this (b) (4) specific ADA assay to determine the lowest ADA levels that can inhibit the rFVIIa activity as shown in the PK assay.

Summary of LFB Response:

The neutralizing ADA assay was revalidated using (b) (4) samples. According to the validation report (VAL-0272-RPT), all validation results met all acceptance criteria. The assay is validated for detecting neutralizing FVIIa antibodies in human (b) (4) samples.

The neutralizing ADA assay was validated for the following parameters:

- **Cut Point:** (b) (4)
- **Sensitivity:** The assay sensitivity was evaluated by (b) (4)
- **Specificity:** Assay specificity was evaluated by analyzing positive and negative control samples. All results were satisfactory.
- **Precision:** Both repeatability and intermediate precision were evaluated on positive and negative control samples. All results met the acceptance criteria.
- **Robustness:** (b) (4)

Reviewer's comment: The response is acceptable. The revalidated assay was also used to retest retained samples collected in clinical trials, please see review section 5 below.

5. Validation of bioanalytical procedures

Reviewer's comment: During labeling negotiations, I conducted additional review of the bioanalytical method validation reports to confirm that the methods were adequately calibrated to support the data in the immunogenicity and clinical pharmacology sections of the Prescribing Information, i.e., sections 5.3 Immunogenicity and Antibody Formation, 6.2 Immunogenicity, 12.1 Mechanism of Action, 12.2 Pharmacodynamics and 12.4 Pharmacokinetics.

5.1. Pharmacodynamics and Pharmacokinetics assays

Several *in vitro* activity assays were used to characterize the activity of SEVENFACT compared to either plasma-derived FVIIa and NovoSeven®. Comparisons were done with an assay for binding to tissue factor (TF), with two assays that measured the ability to generate FXa (amidolytic and FVIIa activity), a clotting assay for FVIIa activity, and a thrombin generation test (TGT) assay. The results of the functional characterization showed that SEVENFACT is functional, i.e., it is able to generate FXa and thrombin in the presence of procoagulant lipid vesicles and/or TF. In addition, SEVENFACT binds TF with a similar affinity and avidity as that seen with other FVIIa-containing products.

Reviewer's comment: The choice of in vitro activity assays is appropriate and scientifically sound. However, the information about in vitro effects of SEVENFACT adds no additional value to the extensive human in vivo PK and PD data discussed below.

In the clinical study GTC-FVIIa-005-11, 15 adult Hemophilia A or B patients with or without inhibitors were treated in 3 dosing cohorts. Serial assessments of pharmacokinetics (PK) and pharmacodynamics (PD) were performed at baseline (pre-infusion), up to 12 hours after administration, and at the 24- to 36-hour safety assessment time-point.

PD assays: TGT output (once with low TF and once with activated platelets); aPTT; PT; F1+2; D-dimers; TAT; and rotational thromboelastography (maximum clot firmness [MCF] parameter of the ROTEM's FibTEM variant).

Reviewer's comment: The PD assays were adequate for the study of by-passing coagulation FVIIa therapy. As expected, SEVENFACT administration was associated with elevation of markers of coagulation activation F1+2, D-dimers and TAT, shortening of clotting tests PT and aPTT, elevation of thrombin generation assay, and improvement of thromboelastography. TF-activated TGT demonstrated large variability and poor dose-response, and this method was not useful in the evaluation of dose-response effect of SEVENFACT in clinical trials, which was

predictable and observed before[1]. Therefore, LFB chose to analyze and present the data with platelet-activated TGT assay only. I agree with this approach.

It should be noted that effect of FVIIa on either of the PD methods may not correlate with the clinical efficacy of the product. The presented results should be viewed as a confirmation that SEVENFACT has the expected effect on the tests which are known to be affected by NovoSeven. However, SEVENFACT and NovoSeven were not compared side-by-side in the clinical trials, therefore, it is not possible to compare the PD effects of these two products.

PK assay: Plasma FVIIa concentration (by modified (b) (4) assay) was measured at the same time-points for PK evaluation.

Reviewer's comment: The PK assay is appropriate because it is based on the commercial kit which allows measurement of FVIIa in the presence of (b) (4) FVII in patient plasma. The same commercial kit forms the basis of the potency assay used for (b) (4) FDP release. Therefore, the PK assay can also be viewed as a PD assay. However, the results of these two assays cannot be compared directly. The PK assay is calibrated in (b) (4) of FVIIa (b) (4), and potency assay is calibrated in activity units traceable to the WHO international unit for FVIIa activity (IU/mL). In addition, the PK assay has been modified to improve the assay range to allow testing of high FVIIa concentrations in patients treated with the high dose of SEVENFACT. The modification, i.e., (b) (4), was well justified and properly validated, but precludes it from a proper comparison of the PK and potency data.

Reviewer's conclusion on PK and PD assay data:

Since the introduction of recombinant factor VIIa to clinical practice, a substantial body of work was dedicated to the evaluation of NovoSeven dosing by PK and PD assays. Unfortunately, clinical laboratory assays were found to be of low predictive value on the need for FVIIa redosing or FVIIa dose efficacy. Substantial variability from patient-to-patient and from bleed-to-bleed in PD responses was also noted. Therefore, unlike the practice in replacement therapies for FVIII- and FIX-deficient patients, where both the dose and dosing intervals can be optimized through measurements of FVIII and FIX activity in post-infusion samples, dosing of SEVENFACT and NovoSeven cannot and should not be based on results of PK or PD testing.

I, therefore, recommended to shorten and simplify the PD and PK sections of the PI to avoid the appearance that the PK and PD information in the PI can be used for dosing optimization. Instead, the PK and PD sections only inform the patients and physicians that SEVENFACT has an impact on the presented PK and PD assay.

[1] Predicting dosing advantages of factor VIIa variants with altered tissue factor-dependent and lipid-dependent activities. Shibeko AM, Woodle SA, Mahmood I, Jain N, Ovanesov MV. J Thromb Haemost. 2014 Aug;12(8):1302-12

In addition, simplification of the PK and PD sections of the PI were justified by the following statement proposed by LFB in their draft PI: "Laboratory assessment of coagulation does not necessarily correlate with or predict the hemostatic effectiveness of SEVENFACT"

To better understand LFB's rationale for this statement, I recommended the following information request (submitted on January 15, 2020):

Regarding your statement "Laboratory assessment of coagulation does not necessarily correlate with or predict the hemostatic effectiveness of SEVENFACT" in section 12.2 Pharmacodynamics, please provide a justification for including this statement in the product labeling along with supporting information from your studies or published studies. Please also consider providing a reference next to this statement in the labeling text.

Summary of LFB Response

On January 23, 2020, LFB responded by clarifying that the above statement has been based on the well understood limitations of coagulation studies in predicting the clinical effect of a given dose of FVIIa. Inclusion of the statement is predicated on the objective to supply a package insert that supports and promotes the practitioners' standards of practice for clinical and safety monitoring of those patients receiving rFVIIa administration.

Specifically, LFB noted that the ability to monitor FVIII and FIX levels is integral to the clinical management of Hemophilia A and B patients, respectively. Factor activity levels are checked during regular follow-up, post-infusion of factor concentrates, during pre- and post-operative assessments, and when the presence of an inhibitor is suspected. However, the ability to accurately and reproducibly measure factor activity levels with standard coagulation assays has been challenging with bypassing agents which can show wide variability in potency when measured using factor assays of different methodologies and/or reagents. Per LFB, bypass agents do not restore the common pathways of hemostasis in hemophilia, but rather increase thrombin generation by binding to the surface of platelets and by binding to TF present at the site of vascular disruption. As a result, common clinical laboratory coagulation assays may not reflect the clinically relevant hemostatic activity of bypassing agents, and no validated assay is available with which to measure the *in vivo* efficacy of these agents or predict individual patient responses to treatment.

The limitations of coagulation studies in predicting clinical effect is also described in the SEVENFACT variant label, NOVOSEVEN which states: "*Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents*[2]." Based on the fact that the monitoring and predicting the response of patients to bypassing agents remains a significant challenge, as no standardized and validated assay is currently available for that

[2] NOVOSEVEN RT package insert, revised 1/2019

purpose, LFB considers it prudent to provide the above-mentioned statement in the SEVENFACT package insert that support the practitioners' standards of practice for monitoring those patients receiving rFVIIa administration. Per FDA request, three (3) references are formally submitted in Section 5.4 Literature References.

Reviewer's comment: The response is acceptable and consistent with my expectations.

5.2. Immunogenicity assays

The following methods were used to evaluate immunogenicity of SEVENFACT and its components:

1. Detection of anti-rhFVIIa antibodies in human serum by an (b) (4)
2. Assay to detect neutralizing FVIIa antibodies in human serum: (b) (4) assay in FVII-deficient plasma:
3. IgE seroreactivity to LFB-rhFVIIa and NovoSeven® in patients allergic to rabbit epithelium and cow's milk casein

Reviewer's comment: Development of neutralizing antibodies against FVIIa is an unwanted immune response to a therapeutic protein product as defined in the FDA 2014 Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products. To ensure protection of clinical study participants from exposure to a product with a non-redundant endogenous counterpart, LFB was requested to have a means of testing for neutralizing antibodies against endogenous FVIIa. LFB has developed a robust immunogenicity program for evaluation of both binding and inhibitory ADAs. Additionally, LFB evaluated potential risk of allergic reactions to rabbit proteins that may be present in rabbit milk-derived SEVENFACT product. Method validation reports are appropriate.

6. Conclusion and recommendation

The CRL issues related to 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.

The CMC review team concludes that the manufacturing process for SEVENFACT is capable of yielding a product with consistent quality characteristics, and recommends approval of the BLA.