FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: File (STN BL 125641/0) & Mark Levi, PhD

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

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Subject: Final CMC Review of LFB's BLA for Coagulation Factor VIIa (Recombinant) [SEVENFACT]

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1. Executive Summary

Introduction

STN 125641/0 is an original biologics license application (BLA) submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB) for Coagulation Factor VIIa (Recombinant), with the proposed proprietary name SEVENFACT. SEVENFACT is a recombinant (r) analogue of human Coagulation Factor VIIa (FVIIa) expressed in and purified from the milk of genetically engineered (GE) rabbits. The product was developed for the U.S. market under Investigational New Drug application (IND) 15183, under LFB's code name LR769. LFB had requested, but did not receive, an orphan designation from FDA for SEVENFACT. This BLA is under the standard 12-month review clock. The PDUFA V goal date is October 13, 2017.

SEVENFACT is a biologics/device combination product[1]. The biologics, rFVIIa, is supplied as a sterile, freeze-dried powder in single-use vials containing 1 mg, (b) (4), or 5 mg of rFVIIa per vial, co-packaged with syringes pre-filled with 1.1 mL, (b) (4), or 5.2 mL of sterile Water for Injection (sWFI) as diluent, respectively. When reconstituted, the concentration of rFVIIa is 1 mg/mL. A 510(k) cleared device, sterile vial adapter (VA) (b) (4), application number (b) (4), is included in the package to transfer sWFI into the drug vial, and the reconstituted product out of the drug vial. The VA contains a 5 µm filter, which allows particulate removal and flow aspiration.

The proposed indication of SEVENFACT is for the on-demand treatment of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors to Factor (F) VIII or FIX. SEVENFACT does not represent a novel product class. Currently, there is one rFVIIa product, NOVOSEVEN RT (Novo Nordisk A/S), licensed in 1999. The proposed indication for SEVENFACT is the same as one of the indications of the licensed rFVIIa product. Both SEVENFACT and NOVOSEVEN RT are dosed by mass. *Potency* and *Specific Activity* of SEVENFACT (b) (4) are controlled by the assays calibrated in units of the WHO 2nd International Standard for FVIIa (NIBSC 07/228)[2]. The clinical development program for SEVENFACT did not include a side-by-side comparison with NOVOSEVEN.

Review summary

The scope of this review covers all CMC product 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 review team from OCBQ/DBSQC and Dr. Alexey Khrenov), extractables and leachables studies and controls of excipients and sWFI (reviewed by Dr. Andrey Sarafanov), characterization of protein integrity (reviewed by Dr. Wojciech Jankowski), facilities and combination product design and controls

[1] 21 CFR Part 3

[2] http://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=07/228

(reviewed by Nicole Li and Nicole Trudel), and rabbit husbandry procedures (reviewed by Dr. John Dennis).

Protein characterization
LFB's rFVIIa is identical in amino acid sequence and structurally similar to human plasma-derived FVIIa and NOVOSEVEN. *In vitro* and *in vivo* biochemical and functional characterization of SEVENFACT demonstrated that its hemostatic activities are comparable, although not identical, to those of human plasma-derived FVIIa and NOVOSEVEN. The results of the protein characterization studies indicate that the FVIIa molecule in SEVENFACT, NOVOSEVEN and plasma-derived FVIIa, are different in their (b) (4) profiles.

Manufacturing process
The **R69 line of GE rabbits** has been established using Specific Pathogen Free (SPF) New Zealand White rabbits in which a transgene containing a (b) (4) human Factor VII gene is stably integrated into the rabbit genome. The genealogy of the R69 lineage is recorded for each animal, and may be used to aid the selection of optimal milk producing rabbits.

Fig. 1: SEVENFACT Manufacturing Process Roadmap

(b) (4)

(b) (4) facilities in (b) (4) countries participate in the manufacture of SEVENFACT and its device components (Fig. 1), and an additional (b) (4) facilities are involved in storage and release testing:

- **Source material (milk)** is collected from GE rabbits at (b) (4)
- **FDP** is manufactured at the (b) (4), filled and lyophilized.
- **sWFI** in prefilled syringes is manufactured by (b) (4)

- **Sterile VA** is purchased from (b) (4) .
- **Product labeling and kit packaging** is done by (b) (4) .
- **Release testing** of milk, (b) (4) FDP are performed at LFB Biotechnologies, LFB Biomedicaments, LFB USA, LFB (b) (4)

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.

Issues identified during review

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 rabbit milk protein (RMP) impurities in the (b) (4), and failures in the performance of (b) (4) purification steps. Many of these deficiencies were not resolved during the BLA review cycle. The following CMC substantive issues were identified during the review of the SEVENFACT BLA:

1. The validation of the manufacturing process for the BDS is deficient. During the pre-license inspection of the manufacturing facility in (b) (4), FDA inspectors noted repeated process failures after the completion of PPQ, some of these failures were related to the (b) (4) steps. As a result, the validated ranges of *Critical Process Parameters* (CPPs) were modified, but these changes were implemented without the support of new process development and validation studies. Additional deficiencies regarding the use of source material from the Massachusetts farm were identified, and documented in Form FDA 483, during the pre-license inspection in May 2017.

2. Some of the assays were not suitable for the control of the (b) (4) manufacturing process, FDP and (b) (4) release and stability testing, and process validation studies. The most significant deficiency is found in the potency assay, which is not suitable for its intended use because LFB has not been using a qualified reference standard for the determination of product potency.

3. The design of the combination product and validation of its use are deficient as evident by the repeated instances of visible particulates found in the reconstituted FDP during release testing and stability studies. The investigations were not successful in identifying the true root cause(s) because the proposed *Corrective and Preventive Actions* (CAPAs) have so far failed to prevent the recurrence of visible particulates in the FDP.

4. The proposed acceptance ranges for the release specifications for *Potency* and *Specific Activity* are not supported by the manufacturing capability, and, are therefore not suitable for the control of product quality and stability.

5. Adverse trends in product *Potency* were observed in the stability studies. Specifically, the stability data for batch (b) (4) do not support the proposed shelf-life for the (b) (4) FDP presentation.

6. The qualification of the analytical methods used for the assessment of extractables and leachables (E&L) is deficient in that it does not include an assessment of the recovery of organic compounds during sample preparation.

7. Information on the validation of the non-USP analytical methods, and verification of the (b) (4) analytical methods used for the release of the Diluent was not provided.

8. Conclusions on the absence of neutralizing anti-drug antibodies (ADA) are not supported by data generated using validated assays.

Recommendation:
Many critical elements of the manufacturing process are not fully validated, which include analytical methods, cleaning, process development, and process performance. These deficiencies have been communicated to LFB, and LFB has initiated additional validation studies according to advices provided by FDA reviewers. LFB estimated that many of these studies will be completed in October 2017, which fails to meet the action due date for this BLA. Therefore, I recommend issuing LFB a Complete Response Letter.

2. Background

2.1. Regulatory history

SEVENFACT, if licensed, will be the second rFVIIa product for the U.S. market. SEVENFACT is not approved anywhere in the world. One rFVIIa product, NOVOSEVEN RT, is currently approved in the U.S. for the treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital FVII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets. NOVOSEVEN RT is also approved for the treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia. Unlike NOVOSEVEN RT, the proposed indication of SEVENFACT is only for the on-demand treatment of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors to FVIII or FIX.

The applicant, LFB S.A. is part of the LFB group, a multinational French plasma fractionator company. If approved, SEVENFACT will be the first LFB product on the U.S. market. SEVENFACT was developed under IND 15183 initiated by the U.S. company rEVO Biologics, Inc. (rEVO), formerly known as GTC Biotherapeutics, Inc., formerly a part of Genzyme Corporation. GTC was originally established by Genzyme to develop recombinant coagulation factor products produced in the milk of GE animals. After rEVO was acquired by the LFB Group, it was split into two companies, rEVO and LFB USA, which continue to share facilities and staff. rEVO is currently holding the BLA for ATRYN, a recombinant analogue of human antithrombin, which was the first U.S. licensed biologics produced in the milk of GE animals (goats). LFB USA participates in the collection of GE rabbit milk and is responsible for the purification of SEVENFACT (b) (4), and acts as a U.S. representative for the LFB Group.

The initial rFVIIa process development was performed at LFB with the goal of developing a product with properties similar to (b) (4)

Development of the first and second-generations of rFVIIa product was (b) (4)

(b) (4)

In January 2011, GTC submitted their second Pre-IND meeting package for the same product manufactured from a (b) (4) using a different manufacturing process. In July 2012, GTC submitted a new IND 15183. The following changes were made compared to the first-generation product (previously submitted and reviewed under IND (b) (4)

- (b) (4)
-

2.2. Activated Factor VII: structure and function

2.1.1. Structure of FVIIa

(b) (4)

(b) (4)

2.1.2. Function

FVIIa 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 very little proteolytic activity by itself, and is normally present in the blood stream as a mixture of zymogen and enzyme (at 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, which is not present on any intravascular cells except on extravascular cells, the first event in the initiation of the coagulation cascade is the binding of circulating FVIIa to TF at the site of vascular wall damage. FVIIa in complex with TF on phospholipid membrane activates FIX and FX. More FVII is then activated to FVIIa either by FXa, FIXa or thrombin (feedback activation) or by FVIIa (autoactivation in the presence of TF). Under non-physiological conditions, FVII can be activated by FXIIa as well.

The main inhibitor of FVIIa in plasma is a complex of Tissue Factor Pathway Inhibitor with FXa and TF (TFPI:FXa:TF). FVIIa is also inhibited by Antithrombin III (in the presence of heparin only).

2.1.3. Drug action

The mechanism of SEVENFACT action is similar to that of the licensed rFVIIa product. For the treatment of bleeding in hemophilia A and B patients with inhibitory antibodies, both rFVIIa products are administered at supra-physiological levels of 75-90 µg/kg. rFVIIa has an average recovery of 0.5, which is approximately equivalent to a peak rFVIIa concentration in blood of 25 nM (2.5 µg/mL) which is 2.5 times the concentration of endogenous zymogen FVII (10 nM) and more than 2500 times higher than the endogenous level of the FVIIa enzyme. Despite this high concentration, rFVIIa does not usually cause thrombosis in hemophilia patients as demonstrated by a good safety history comparable to that of other coagulation factor concentrates. Two mechanisms of rFVIIa procoagulant action have been demonstrated. The first mechanism is TF-dependent - it involves the acceleration of the initial stages of coagulation by rFVIIa binding to the sites of vessel wall injury where TF is exposed. This mechanism can be accelerated by the displacement of FVII by rFVIIa from the complex of FVII with TF. The second, procoagulant lipid-dependent, mechanism is mediated by the increased catalytic activity of FVIIa in the presence of the membrane of activated platelets.

3. Source Material: rabbit milk

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

.

4. Manufacturing Process

4.1 Manufacturers

The manufacturing process involves SPF rabbit farming, milk collection, (b) (4) purification, FDP production and labeling as well as release testing and storage activities. Table 3 describes these responsibilities, and the addresses of the (b) (4) facilities involved in SEVENFACT manufacture. In addition, the two device components of the co-packaged combination product, sWFI in prefilled syringes and sterile VA, are manufactured by (b) (4) respectively.

(b) (4)

[3] 3.2.S.2.3 Control of Materials, page 71

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

(b) (4)

4.2 Drug Product

Composition of rFVIIa Drug Product is presented in Table 4.

Table 4: Composition of rFVIIa Drug Product at 1 mg, (b) (4) and 5 mg Dosage Strengths

Component (Quality Standard)	Function	Amount per 1 mg vial[1]	Amount per (b) (4)	Amount per 5 mg vial[3]
(b) (4)	(b) (4)	1 mg	(b) (4)	5 mg
Arginine HCl		(b) (4)		(b) (4)
(b) (4)				
Isoleucine				
(b) (4)				
Trisodium Citrate Dihydrate				
(b) (4)				
Glycine				
(b) (4)				
Lysine HCl				
(b) (4)				
Polysorbate 80				
(b) (4)				
Hydrochloric acid (HCl)				
(b) (4)				
Sterile Water for injection				
(b) (4)				
Nitrogen				
(b) (4)				
(b) (4)			= quantity sufficient	

1 = Does not include target fill volume overfill of (b) (4)
2 = Does not include target fill volume overfill of
3 = Does not include target fill volume overfill of
(b) (4)
5 = amount present before lyophilization

(b) (4)

FDP is manufactured at (b) (4), through a process described in Fig. 8. The batch formula is the same for the 1 mg, (b) (4) and 5 mg package sizes. (b) (4) FDP lot at sizes sufficient to meet commercial production requirements. The following batch sizes were qualified in a PPQ campaign: (b) (4) 1 mg vials, (b) (4), and (b) (4) for 5 mg vial.

4.3 Controls of Critical Steps and Intermediates

The SEVENFACT process control strategy is made by 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 CPPs identified by the Quality Risk Management exercise and confirmed by robustness studies. *Reviewer's comments:*

1. *The SEVENFACT process control strategy was developed using a risk-based and science-based Quality by Design (QbD) approach for process control that assures consistent manufacturing and product quality. However, LFB did not develop a process design space, therefore the SEVENFACT BLA was reviewed as a traditional non-QbD submission.*
2. *However, repeated BDS process failures were experienced after formal PPQ in 2014, including several process failures experienced after the BLA was submitted. LFB initiated additional BDS process evaluation and development studies, which are incomplete. Please refer to Dr. Alexey Khrenov's review memorandum for details.*

The controls performed on the different process steps and intermediates include:

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

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

4.4 Analytical Methods, Release Specifications and Reference Standards

The specifications of (b) (4) FDP are summarized in Tables 7, 8 and 9. The methods and established specifications are based on manufacturing experience and available safety and efficacy data. *Reviewer's comment: Analytical method validations were reviewed by Dr. Alexey Khrenov and a review team from OCBQ/DBSQC. Release specifications were reviewed by Dr. Alexey Khrenov. Multiple deficiencies were found by these reviewers, and addressed during the BLA review cycle. However, issues with the potency assay and visible particles remain unresolved. Please refer to Dr. Alexey Khrenov's review memorandum for details.*

Table 8: BDS Specifications

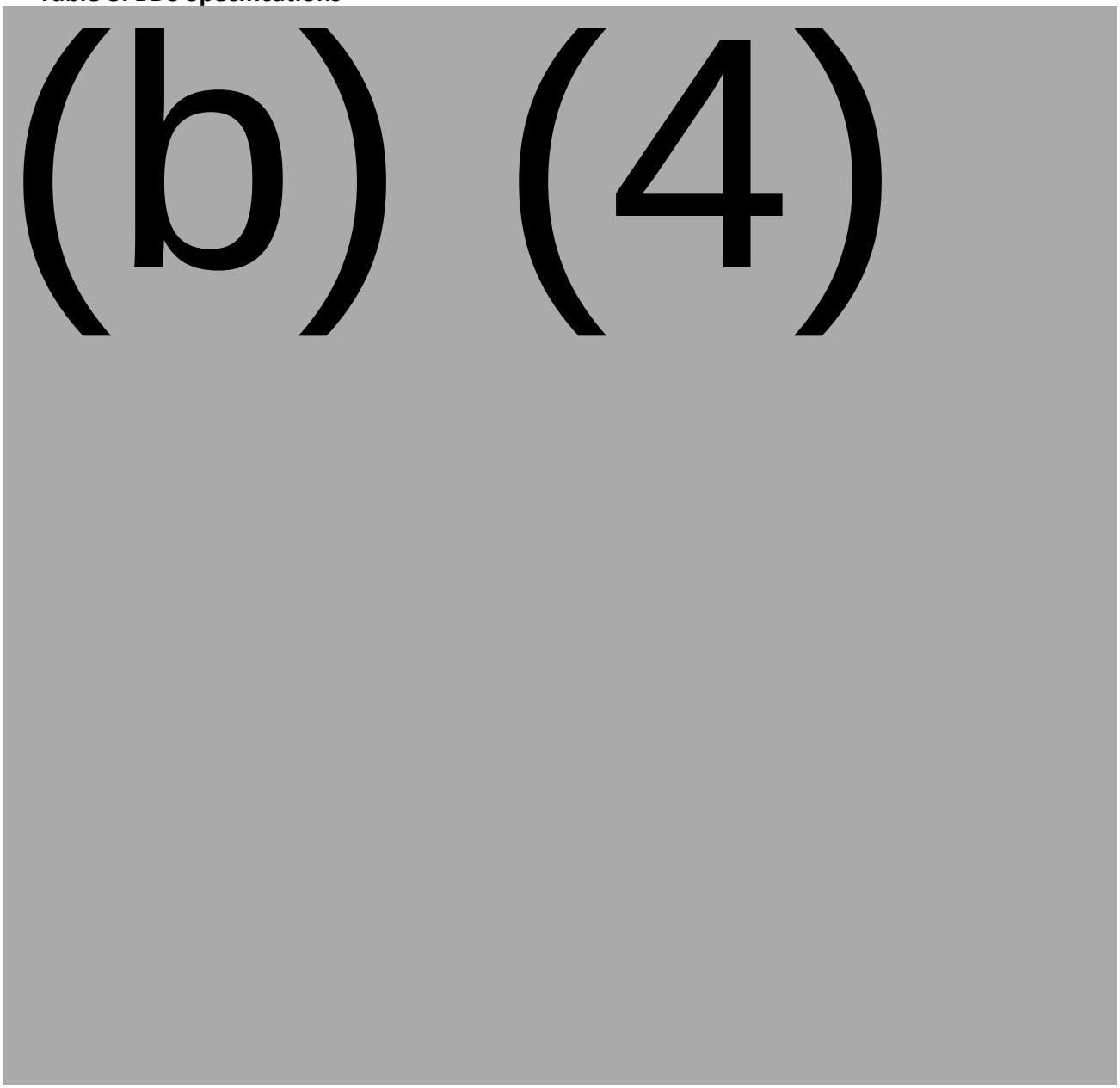


Table 9: FDP Specifications

Attribute	Test Method	Acceptance Criteria
Appearance and description		
Visual appearance of cake	Visual inspection	White to off-white cake or powder
Appearance of reconstituted solution: -Opalescence -Color	(b) (4), visual method (b) (4)	(b) (4)
Visual Appearance of reconstituted solution	(b) (4)	Clear to slightly turbid colorless solution
Visual Appearance of reconstituted solution: visible particulates	(b) (4)	(b) (4)
Identity		
Identity	(b) (4)	(b) (4)
Quality		
pH	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Reconstitution time	Visual determination	(b) (4)
Particulate matter	(b) (4)	(b) (4)
Residual moisture	(b) (4)	(b) (4)
Sterility	(b) (4)	Sterile
Bacterial endotoxins	(b) (4)	(b) (4)
Purity		
(b) (4)	(b) (4)	(b) (4)
Impurities		
(b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Strength, potency		
rFVIIa concentration	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Specific activity	(b) (4)	(b) (4)
Excipients		
Trisodium citrate dihydrate	(b) (4)	(b) (4)
Polysorbate 80	(b) (4)	(b) (4)
Arginine HCl	(b) (4)	(b) (4)
Lysine HCl	(b) (4)	(b) (4)
Isoleucine	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
(b) (4)		

Batch analysis data were provided for each of the (b) (4) lots of SEVENFACT for 1 mg (n=(b) (4) (n(b) (4) and 5 mg (n=(b) (4) vials.

Exemption from CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot CBER release would not be required for SEVENFACT because it is a well-characterized recombinant product. *Reviewer's comment: If this BLA were approved, exemption of SEVENFACT from CBER Lot Release would be consistent with all of the recently approved coagulation factor products.*

5. Process Development, Validation and Qualification

5.1. Process Development

The development of the SEVENFACT process was based on the experience gained with the first-generation rFVIIa product (b) (4) . The differences between the first and second-generation manufacturing processes are described below:

(b) (4)

(b) (4)

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

(b) (4)

[redacted]

[redacted]

5.2. Process Validation

In accordance with *2011 FDA Guidance on Process Validation*, LFB presented data on (b) (4) stages of process validation, as follows:

(b) (4)

[redacted]

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

- (b) (4)

<u>Reviewer's comment</u>: The viral risk assessment strategy and the design of viral inactivation/removal validation studies and study results are acceptable.

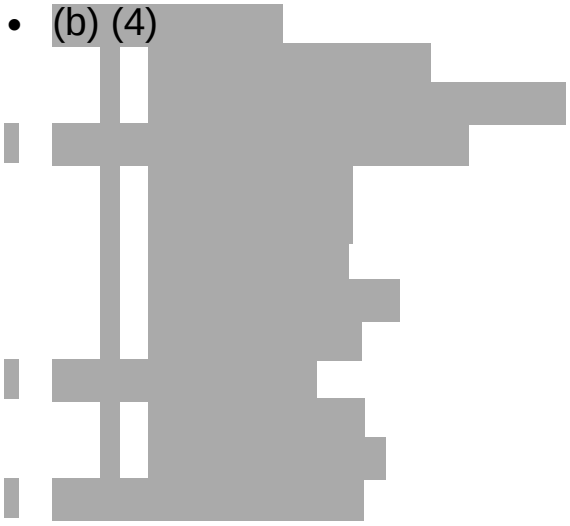
5.3. Elucidation of Structure, Function and Impurities

SEVENFACT characterization program was based on the analysis of (b) (4) Primary Reference Standards (PRS) batches following the development history of the product. When appropriate, rFVIIa characterization data were compared to data generated from commercially available batches of NOVOSEVEN and from human FVIIa purified in-house from human plasma.

5.1.1. Structure

The following studies were performed to elucidate rFVIIa structure:

- (b) (4)



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

(b) (4)

5.4. Stability

LFB claims that BDS can be stored at (b) (4) and FDP can be stored at a temperature of up to 30°C for 36 months. Primary BDS stability data were obtained on batches manufactured from the (b) (4) Primary FDP stability studies were conducted on (b) (4) PPQ batches of including (b) (4) batches of 1 mg, (b) (4) batches of 5 mg, and (b) (4) dosage strength. *Reviewer's comment: The stability data were reviewed by Dr. Yideng Liang. She found deficiencies related to inconsistent potency analyses in FDP stability studies. Please refer to her review memorandum for details. An example of deficient stability data is presented in Fig. 11 below. Please also refer to Appendix 2 for stability data on batch* (b) (4)

(b) (4)

5.5. Biologics/device combination product

SEVENFACT package included rFVIIa FDP vials, prefilled syringe with sWFI (diluent), and VA, therefore SEVENFACT meets the legal definition of a biologics/device combination product (21 CFR Part 3). *Reviewer's comment: In the BLA, LFB did not provide information on the design and controls for the combination product. These sections were requested and reviewed by OCBQ/ DMPQ reviewers Nicole Li and Nicole Trudel. Please refer to their review memoranda for details.*

[5] BLA amendment #53 received on July 24 2017

In their December 2016 amendment[6], LFB reported that several FDP PPQ batches and some other FDP batches had presence of visible particles in at least one reconstituted vial, either at one or several stability time-point or in-process control samples during process validation, for a total of (b) (4) vials with visible particles in (b) (4) batches. Additional examples of visible particulates were reported in May 2017. Presence of visible particles is considered an OOS event for the FDP release and stability assay *Visual Appearance of reconstituted solution: visible particulates* with a specification acceptance criterion of "*absence of visible particle*".

Since the initial investigation did not determine any laboratory error, LFB conducted a series of investigations to determine and control the possible origin of these particles. Particulate matters (b) (4) were identified as (b) (4) . Because a definitive root cause was not identified, LFB proposed to (b) (4) .

Reviewer's comment: *At my advice, the following request was submitted on 12 December 2016:*

5. ***With reference to the CAPAs as a result of the investigations into the presence of visible particles in the reconstituted product as described in Section 3.2.P.8.3,***

- ***a. Please provide the following documents related to the implementation of the short-term action plan for clinical supplies by (b) (4) administration kit:***
  - ***i. All communication with the clinical sites (dated letters and revised Instructions for Use);***
  - ***ii. Factor VIIa lot numbers which were co-packaged with the (b) (4) in the administration kit; and***
  - ***iii. Data to demonstrate that the (b) (4) can remove the visible particles from the product, and is compatible with the product.***
- ***b. Your proposed CAPA for the commercial product, by (b) (4) , does not address the root cause of the visible particles or the user's reaction to their presence in the reconstituted product. In Section 2.4. Administration in the Prescribing Information, the users are instructed to "Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed." Therefore, the user will discard vials containing visible particles rather than withdraw the solution through the 5-µm filter of the vial adapter.***
  Please investigate the root cause of this problem, and propose an effective CAPA to prevent the formation of visible particles, rather than (b) (4) . The presence of foreign particles, i.e., particles not related to the product, indicates incompatibility between the vial adapter and the product. Therefore, please identify the origin of the visible particles by characterizing the chemical make-up of

[6] Report 16-AQ-090 submitted in BLA amendment #6 received on 6 December 2016.

the particles, and compare them to those of the product and its various product-contact components, such as container closure system and vial adapter.

LFB was unable to provide a satisfactory response to question 5.b. For details, please refer to section 7. Summary of Issues Identified During the BLA Review.

6. Analytical Methods Used in Clinical Studies

A list of the analytical assays that were utilized to detect immune response to rFVIIa during the clinical development is provided in Table 11.

Table 11: Summary of Analytical Methods Used in the Assessment of Pharmacokinetics, Pharmacodynamics, and Immunogenicity in SEVENFACT Clinical Studies

Method type	Analytical method	Principle	Intended use
Pharmacokinetics.	Factor VIIa activity	The rFVIIa activity levels were determined using the (b) (4) in combination with coagulation analyser (b) (4) ssay uses (b) (4) .	To determine the plasma concentration of rFVIIa procoagulant activity after treatment with SEVENFACT
/Pharmacodynamics.	Thrombin generation test (TGT) with addition of platelets	Record of the thrombin generation profile (AUC of the peak and time to peak) using a (b) (4) TGT assay able to show a dose-response with high levels of factor VIIa. (b) (4) .	To assess the coagulation kinetics after rFVIIa administration by the determination of thrombin generation.
	ROTEM analysis	Ability to appreciate the firmness of the fibrin clot and subsequent fibrinolysis phase when the thrombin generation is initiated with FVIIa. Maximal clot firmness, elasticity, time to peak and time to 50% lysis were determined.	To determine the quality of the fibrin clot and the kinetic of the clot lysis
	Activated partial thromboplastin time (aPTT)	The aPTT measures the intrinsic coagulation pathway. aPTT was analyzed with (b) (4) as reagent (b) (4)) using (b) (4) .	To assess the coagulation after rFVIIa administration by a global coagulation test: aPTT which measures the intrinsic coagulation pathway of the coagulation system.
	Prothrombin time (PT)	The PT measures the extrinsic or tissue factor pathway of the coagulation system. PT was analyzed with (b) (4)	To assess the coagulation after rFVIIa administration by a global coagulation test: PT which measures the extrinsic or tissue factor pathway of the coagulation system.
	Diluted prothrombin time (diluted PT)	In contrast to the previously described PT, the diluted PT assay utilizes a (b) (4) reagent that has been previously diluted.	(b) (4) .
	D-dimers	D-dimers are degradation products of cross-linked fibrin (FbDP). FbDP were analyzed using (b) (4)	To assess indirectly the coagulation after rFVIIa administration using a biomarker of

Method type	Analytical method	Principle	Intended use
		(b) (4) .	thrombin generation: D- dimers
	Fragments 1+2 (F1+2)	F1+2, a prothrombin activation fragment, is a marker of activation of the clotting system. F1+2 were analyzed with (b) (4)	To assess the coagulation after rFVIIa administration using a biomarker of thrombin generation: F1+2
	Thrombin antithrombin complexes (TAT)	TAT, a complex formed between thrombin and its cognate serpin antithrombin (AT), is a marker of activation of the clotting system. - TAT were analyzed with (b) (4)	To assess the coagulation after rFVIIa administration using a biomarker of thrombin generation: TAT (prothrombotic biomarkers)
Immunogenicity.	(b) (4) assay (anti-Rabbit Protein)	This assay measures antibodies against rabbit (b) (4) proteins and rabbit (b) (4) potentially present in patients' serum samples. The method is a (b) (4) with rabbit milk proteins in post-treatment serum samples compared to pretreatment.	To detect antibodies to rabbit milk proteins after rFVIIa administration.
	Screening and confirmatory assays (anti-FVIIa)	This assay measures antibodies against recombinant human Factor VIIa potentially present in patients' serum samples using an (b) (4) .	To detect antibodies to rFVIIa after SEVENFACT administration
	Neutralizing assay	Residual activity is tested by utilizing a commercial FVIIa clotting assay (PT- FVII, (b) (4) The neutralization assay determines if antibodies that have been shown to bind to FVIIa also cause the loss of FVII clotting activity while bound to the FVIIa	Determination of the neutralizing potential of antibodies to rFVIIa detected during the immunogenicity screening and confirmatory assay.

<u>Reviewer's comment:</u> All methods were used no earlier than the date of first validation or qualification of the method.

The anti-drug antibody (ADA) assay has been developed, validated and used for the detection of anti-rFVIIa antibodies in human serum using an (b) (4)

<u>Reviewer's comment:</u> During the Late-Cycle Meeting on 17 August 2017, LFB stated that assays for neutralizing ADA were validated for (b) (4) samples, but the neutralizing ADA data were derived from (b) (4) samples. One patient treated with SEVENFACT developed an ADA response as detected by rFVIIa binding antibody assay. LFB used patient (b) (4) to conclude that these ADA do not neutralize rFVIIa. However, these conclusions may be invalid because the neutralizing ADA assay was not validated for (b) (4) samples. This deficiency is serious because neither binding nor inhibitory antibodies to rFVIIa have ever been reported for hemophilia A and B patients treated with another rFVIIa product, NOVOSEVEN, which was approved in 1999.

7. **Summary of Issues Identified During the BLA Review**

CMC review was substantially delayed because LFB did not provide critical process validation reports and data summaries in the BLA.

On 28 November 2016, FDA organized a teleconference to discuss with LFB a path to resolution of the significant deficiencies with the content of the BLA. FDA noted that Refuse-to-File (RTF) action is taken on applications that do not, on their face, contain sufficient information required to conduct a meaningful review. An information request detailing the potential RTF action was sent to LFB on 29 November 16. LFB's response to the RTF deficiencies was received on 5 December 2016, which was incomplete, but the FDA review team decided to file the BLA because LFB made a commitment to address all deficiencies in a timely manner. A new list of 44 deficiencies was communicated to LFB in a 12 December 2016 *Filing Letter with Deficiencies*. LFB then failed to meet the agreed-upon response submission date of 12 January 2017. Most of the requested documents were not provided in full until 17 March 2017; two deficiencies have not been addressed. For subsequent IRs, LFB has repeatedly failed to meet the deadlines for data submission (both the deadlines proposed by the Agency and those offered by LFB). For example, on 15 June 2017, LFB added two weeks to all the previously communicated deadlines because "*documents were originally written in French and have to be translated before submission to the FDA*". Please refer to Appendix 1 for the list of outstanding IRs from CMC and OCBQ/DMPQ reviewers.

The following critical deficiencies remain unresolved:

1. Deficient validation of the BDS manufacturing process is evidenced by repeated process failures:
   i. The (b) (4) manufacture was placed on hold to investigate (b) (4) step in the supplemental PPQ campaign initiated in May-July 2017.
   ii. The validated ranges of CPPs were modified without appropriate process development and validation studies.
   iii. Problems with the performance of (b) (4) steps resulted in rejected BDS batches and failed (b) (4) runs, respectively.

Reviewer's comment: *Please also refer to Dr. Alexey Khrenov's review memorandum for details.*

2. The design of the combination product and validation of its use are deficient as evident by repeated instances of visible particulates found in the reconstituted product during release testing and stability studies:
   i. The visible particulates do not appear to come from the biological product, and are most likely come from the environment but the contribution of the device components of the combination product could not be excluded. The material and

composition of visible particulates were not properly investigated to establish their relationship to the rubber stopper, VA, or syringe with diluent.

ii. We do not agree with LFB's proposal to address the visible particulate issue by only (b) (4) Our concerns:

1. The investigations were not successful in identifying the true root cause(s) because the proposed CAPAs have so far failed to prevent the recurrence of visible particulates in the reconstituted FDP.
2. This approach contradicts the *Section 2.4 Administration* in the *Prescribing Information* which instructs users to "*Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed*". LFB noted that the user will not notice these particles[7]. This response is not acceptable.

Reviewer's comment: Please also refer to the review memoranda by Alexey Khrenov, Nicole Li and Nicole Trudel for additional details.

3. Poor robustness of the improperly validated potency assay does not support the conclusions of process validation and stability studies, and PK evaluations of Process A (small scale) and Process B (commercial scale) materials in humans. The impact on the control of the (b) (4) manufacturing process, FDP (b) (4) release testing, stability studies, and process validation studies is still under investigation.

Reviewer's comment: Please also refer to Dr. Alexey Khrenov's review memorandum for additional details.

4. Adverse trends in product *Potency* were observed in stability studies. These trends cannot be investigated because the *Potency* assay re-validation was not available until 7 July 2017, and the retesting of retained samples and development of new specifications for *Potency* are not yet completed.

Reviewer's comment: Please also refer to Drs. Alexey Khrenov's and Yideng Liang's review memoranda for additional details.

5. The acceptance ranges for (b) (4) FDP release specifications were not supported by manufacturing experience, process capability, and are not suitable for the control of

[7] LFB provided the following statement in amendment STN 125641/0.12: *In Section 2.4 Administration in the Prescribing Information, the users are instructed to "Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed." This is a mitigation against unforeseen appearance of the reconstituted product and not specifically related to potential visible particles. Of note, visible particles of the aforementioned investigation* ***cannot easily be detected by untrained human eye*** *in a labelled vial and without appropriate light. So there is a low probability that the user could detect visible particles of "Environment cause" and discard the vial.*

product quality and stability. Specifically, insufficient data are provided using re-validated *Potency* and *Specific Activity* assays.

Reviewer's comment: Please also refer to Dr. Alexey Khrenov's review memorandum for additional details. In addition, I noted that the proposed specifications for Specific Activity and Potency are much wider than those of the licensed product, NOVOSEVEN.

In addition, deficiencies in the *New Animal Drug Application* (NADA) for the Genetically Engineered Rabbits will likely result in a delay in NADA approval by CVM. Approval of NADA is required for the use of rabbit milk from the LFB USA facility in this BLA.

8. Chemistry, Manufacturing and Controls - Conclusion

At this time, from a basic assessment of the CMC information provided thus far, the manufacturing process of SEVENFACT is not considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the release specifications.

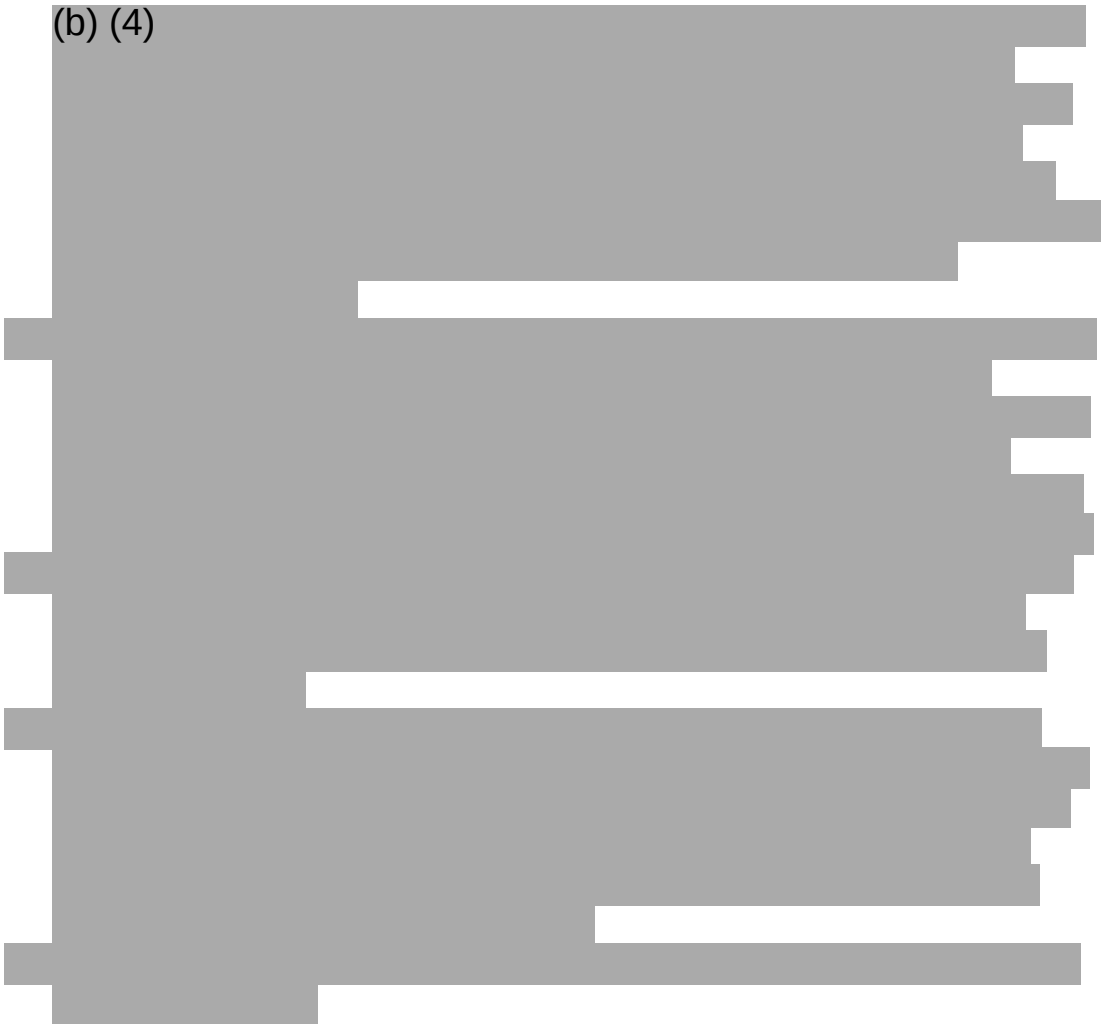
In summary, I found the CMC information inadequate to support the quality, identity, purity, potency and safety of SEVENFACT, and recommend issuing a *Complete Response* (CR) *Letter* in which all CMC deficiency items will be listed.

9. Proposed CMC Deficiency Items to be included in the Complete Response Letter

I recommend that the following summary of deficiencies identified by the CMC review team (Drs. Alexey Khrenov, Yideng Liang, Andrey Sarafanov and myself) be included in the CR Letter:

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated August 15, August 23, August 31, September 8, September 15, and September 22, 2017. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below:

1. *The data you provided do not adequately address the deficiencies in the validation of the manufacturing process for Coagulation Factor VIIa (Recombinant) [rFVIIa] that were identified during the Pre-license Inspections of your facilities. Please provide data to demonstrate the following:*
   a. (b) (4)



2. *The design of the combination product and validation of its use are deficient as evident by the repeated instances 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 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 introduce new kit components to remove the particulates, and a (b) (4) *-tiered testing scheme for Visible Particulates for the release of the FDP. However, these proposals do not address the root cause(s) of the problem, and hence are not considered as effective CAPAs.*

   Please provide the final investigation report that include, but not be limited to, identification of the root cause(s) and data to demonstrate that the proposed CAPAs are effective.

3. *The following assays are not suitable for the control of the* (b) (4) *and FDP release, stability studies, and process validation studies:*
    a. *The potency assay is not suitable for its intended use because you have not been using 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, all 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. But, 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.*
            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.*
            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.*
        ii. *The stability of the proposed product-specific reference standard. Please establish a stability program for this standard.*
    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.*

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*
    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*
    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.

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.*
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).*
7. *Your conclusions on the absence of neutralizing anti-drug antibodies (ADA) are not supported by data generated using validated assays. Specifically, during the Late-Cycle Meeting, you stated that assays for neutralizing ADA were validated for (b) (4) samples, but the neutralizing ADA data were derived from (b) (4) samples. In addition, please demonstrate that the lowest ADA levels that can inhibit the rFVIIa activity PK assay are also detected by the re-validated neutralizing ADA assay.*

Appendix 1: Outstanding Information Requests

List of outstanding information requests for the CMC discipline (all reviewers) as of August 7, 2017:

- FDA IR REGARDING POSSIBLE REFUSE TO FILE (RTF) ISSUES DATED 29 NOVEMBER 2016
  - Request #2f (also repeated as Request #36 in the BLA *Filing Letter with Deficiencies* dated 12 December 2016, see below) regarding the design control overview and data to support design verification requirements as per CFR 820.30(f): shipment validation studies of commercial product (study results are expected to be available **in July 2017**). Two new in-use stability studies after reconstitution needed to be repeated with the new vial adapter equipped with the 5-µm filter. LFB informed us that the study would start in **May 2017** but no update has been submitted to date.

- BLA FILING LETTER WITH DEFICIENCIES DATED 12 DECEMBER 2016
  - Response to Request #6 regarding the validation of the non-USP and verification of the (b) (4) analytical methods used for the FDP diluent, Water for Injection (WFI), was **not** provided by the deadline. LFB promised to submit these reports by the **end of June 2017,** but did not do so. This request was repeated in an IR dated 24 April 2017.

- Request #13 regarding equipment performance qualification data for the labeling and packaging equipment used in the manufacture of rFVIIa FDP. The qualification exercise for this equipment was scheduled for **May 2017.** Performance qualification protocol will be available by **August 2017** and performance qualification **will be performed for the launching batches** of SEVENFACT (using real GTIN and serial number), the exact date is linked to the BLA review timelines.
- Request #16 regarding test method validation protocol and results for the (b) (4) container closure integrity test method for the diluent pre-filled syringe and the lyophilized powder vial: validation study report was expected by the **end of March 2016** but not received.
- Request #19 "Please submit the shipping validation for the (b) (4) diluent pre-filled syringe from (b) (4) . Studies are currently being performed and reports for these OQ protocols will be available by **July 2017**. Due to product availability, report for 1 mg DP will be available in **October 2017**.

- FDA IR DATED 05 APRIL 2017 regarding (b) (4) method validation deficiencies
  - New method validation report is to be approved by **mid-July**.

- FDA IR DATED 24 APRIL 2017 regarding Extractables and Leachables (E&L) studies
  - Response to a request to revise analytical methodology to consider degree of extraction of organic E&L into organic phase, and re-evaluate final results and risk assessment for the leachables in the FDP was expected to be available in **July 2017**.
  - The results of FDP Container Closure System Leachables studies were expected to be available in **July 2017**.

- FDA IR DATED 04 MAY 2017 regarding release specifications
  - LFB committed to implement alert and action limits for bacterial endotoxin levels. The alert and action limits for bacterial endotoxin levels will be communicated to the Agency **once available**.
  - LFB explained that (b) (4) *Accuracy* could not be validated since no reference standard material was available for non-activated FVII. LFB reported that this standard was qualified in early July 2017.
  - LFB committed to revise the acceptance criteria for Specific Activity in (b) (4) FDP once the potency assay is revalidated. The target date for this revision was **mid-July**.
  - LFB commits to revise the acceptance criteria for (b) (4) Assay in FDP once the potency assay is revalidated. The target date for this revision was **mid-July**.

- FDA IR DATED 31 MAY 2017

- Regarding the deficiencies in the potency assay (also noted in Observation #1 in Form FDA 483 for the (b) (4) inspection, see below), a total of (b) (4) FDP batches will be re-tested with the re-validated potency method by the **end of July**.

- INSPECTIONAL OBSERVATIONS (FORM FDA 483) DATED (b) (4) TO LFB (b) (4)
  - OBSERVATION 1: The (b) (4) assay as a final release test is not suitable for its intended purpose. Response to a follow-up response regarding (b) (4) Assay specifications and retests will be available by the **end of July**.
  - OBSERVATION 2: The deviations investigation is deficient in failing to identify the root cause and in implementing a corrective action. LFB has submitted results of the efficacy of the proposed reconstitution method; responses appear deficient.
  - OBSERVATION 3: The sample for the Visual Appearance of Reconstituted Solution: Visible Particulates test method is not prepared in accordance with end-user (patient) instructions. Responses were submitted in June 2017; responses appear deficient.

- INSPECTIONAL OBSERVATIONS (FORM FDA 483) DATED (b) (4) TO LFB (b) (4)
  - OBSERVATION 1: Deficient BDS process validation. (b) (4) . An investigation was initiated to identify the root cause(s) for this contamination. The manufacture of BDS will resume when the root cause(s) for the (b) (4) failure is identified and appropriate corrective and preventive actions are implemented. LFB has committed that upon completion of the (b) (4) deviation investigations, the investigation report and CAPA will be provided to CBER.
  - OBSERVATION 4: Specifications for critical incoming materials and components are not established. LFB will implement the proposed action plan by **15 August 2017**.
  - OBSERVATION 6: The integrity of the BDS container closure system (b) (4) and closure assembly was not tested. LFB committed to send FDA the T_0 results for Study 2: Qualification of integrity of the container closure and **to complete the study with the proposed duration (3 years).**
  - OBSERVATION 7: Shipping validation studies of the BDS with the (b) (4) are incomplete. The study report will be available by the **end of September 2017**.
  - OBSERVATION 13: Equipment qualifications for the freezers used to (b) (4) are not complete.

        - Freezers Qualification reports will be submitted by **14 August 2017** and **15 September 2017.**
        - Report to assess freezers' equivalence will be done by **15 August 2017.**
    - OBSERVATION 14: The procedures for cleaning production equipment are not validated. LFB (b) (4) will reassess the adequacy between the intended use and the Supplier Qualification level by **15 August 2017**.
    - OBSERVATION 15: No disinfectant effectiveness studies are performed to support the facility cleaning method.
        - LFB will finalize the evaluation of the supplier's technical data regarding the effectiveness of the disinfectants by the **end of June 2017**. Report was not received.
        - LFB will build and perform a study consisting of assessing the effectiveness of disinfectants on surfaces representative of the production areas. A validation report will be completed by the **end of 2017**.
    - OBSERVATION 16: The (b) (4) will be re-qualified by **15 August 2017**.

- INSPECTIONAL OBSERVATIONS (FORM FDA 483) DATED 12 MAY 2017 TO LFB USA IN CHARLTON, MA
    - OBSERVATION 1: Process validation is deficient. Specifically,
        - (b) (4)

- OBSERVATION 2: (b) (4) was released on September 7, 2016 and shipped to the (b) (4) for further processing, even though (b) (4) producing (b) (4)) was isolated from the (b) (4) sample post cleaning. LFB committed to perform a "holistic comprehensive evaluation" on all (b) (4) results within the (b) (4) process by **31 December 2017.**
- OBSERVATION 3: Storage, sanitization and cleaning efficacy have not been demonstrated for the (b) (4).
  - A short-term storage study will be completed by **31 December 2017**.
  - Additionally, LFB committed to perform a "holistic comprehensive evaluation" on all (b) (4) results within the (b) (4) process by **31 December 2017.**
- OBSERVATION 4: The firm has no data to demonstrate they can recover (b) (4) LFB committed to provide the data **by 14 July 2017**.
- OBSERVATION 5: The current process for preparing samples for bacterial endotoxin testing is inadequate. LFB committed that (b) (4) storage studies will be finalized by **December 2017**.
- OBSERVATION 6: A study was not performed to evaluate the (b) (4) The study report will be provided to the FDA by **15 September 2017**.
- OBSERVATION 7: The specifications for the incoming critical materials and components are not established. Regarding the (b) (4), LFB is currently revising SOP-0108-QA to be specific for Raw Materials and Consumables. LFB proposed a due date of **31 July 2017**. A related IR was submitted on 20 June 2017.
- OBSERVATION 8: The container closure integrity of the (b) (4) and closure assembly was not tested. The study report for the Qualification of the lowest acceptable (b) (4) was to be provided by **14 July 2017**. LFB committed to send to the FDA the T_0 results for the validation of the container closure integrity by **14 July 2017** and to complete the study within the proposed duration (b) (4)
- OBSERVATION 9: Shipping validation studies of the (b) (4) with the (b) (4) are incomplete. The study report will be provided by **29 December 2017**.
- OBSERVATION 10: There is inadequate review of batch records by the Quality Unit. The batch records were to be amended and approved by **15 June 2017** (not received). Batch record MPR-B0019, product (b) (4) and formulation of FVII, was to be updated to include having the Quality Assurance unit present at the time of (b) (4) to reconcile product and labels by **30 June 2017**.

- OBSERVATION 11: The following deficiencies were noted during the review of various equipment qualifications.
  - a. A power failure test on an empty chamber for (b) (4) was not performed. LFB stated that this improvement will be aligned with any determined gaps and will be completed by **31 December 2017.**
  - b. Equipment used in the laboratories is not always qualified before use. LFB stated that the risk assessment will be amended by **30 June 2017** and any determined gaps in the original qualification, ranked medium or above, will be remediated by **31 July 2017**. The documents have not yet been received.
- OBSERVATION 12: Inadequate change control was noted. LFB stated that: (1) (b) (4) (b) (4) will be added to the preventive maintenance SOP-0001-FC for the freezer and applicable units by **30 June 2017**; (2) an assessment of all the GMP utilities and equipment in Building (b) (4) will be completed to determine the requirements for verification following a power outage by **31 July 2017;** (3) SOP-0038-FC, (b) (4) Power Outage Restoration, will be updated to include the results of assessment by **31 August 2017**. The documents have not yet been received.
- OBSERVATION 13: Equipment swabbing and percent recovery studies demonstrating cleaning efficacy were not performed during cleaning validation. LFB proposed the due date of the memo to the CAPA file be **31 July 2017**. Various other activities will be completed between **30 August 2017** and **31 May 2018**.
- OBSERVATION 14: Studies have not been performed to verify that the current methods are adequate to ensure effective sanitation of the rabbit enclosures and ancillary equipment. LFB protocol will be executed **over the next** (b) (4) **months** to evaluate the cleaning procedures that result in acceptable post-cleaning residual levels as measured by the (b) (4)

Appendix 2: Stability data for batch (b) (4)

During the Late Cycle Meeting with the FDA on 17 August 2017, LFB claimed that "*Downward trend in the potency for batch* (b) (4) *stored at 30°C* (b) (4) *RH, over 23 months of stability* (b) (4) *loss in potency).*"[8] This statement contradicts the data presented to the FDA in amendment #53[9] which indicated a (b) (4) reduction of *Potency* and (b) (4) reduction of *Specific Activity* in batch (b) (4) stored for 24 months at 30°C (b) (4). The tables are reproduced from the amendment #53.

[8] Slide 9 of LFB's Late Cycle Meeting presentation
[9] BLA amendment #53 received on 24 July 2017.

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