Summary Basis for Regulatory Action

Date: April 1, 2019

From: Mikhail Ovanesov, PhD, Chair of the Review Committee

STN: BL 125641/0

Applicant Name: Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB)

Date of Submission: Original submission: October 13, 2016
Resubmission: October 11, 2019

Goal Date: April 10, 2020

Proprietary Name / Established Name: SEVENFACT / coagulation factor VIIa (recombinant)-jncw

Indication: Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors

Recommended Action: The Review Committee recommends approval.

Office of Tissues and Advanced Therapies Signatory Authority:

Wilson W. Bryan, MD, Director

- □ I concur with the summary review.
- □ I concur with the summary review and include a separate review to add further analysis.
- □ I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director

- □ I concur with the summary review for the responsibilities assigned to the Office of Compliance and Biologics Quality.
- □ I concur with the summary review and include a separate review to add further analysis.
- □ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name	Memorandum date
<u>CMC Reviews</u>		
• CMC (product office)	Mikhail Ovanesov, PhD, OTAT/DPPT,	September 28, 2017 March 23, 2020
	Alexey Khrenov, PhD, OTAT/DPPT,	September 28, 2017 March 13, 2020
	Wojciech Jankowski, PhD, OTAT/DPPT,	October 2, 2017
	Andrey Sarafanov, PhD, OTAT/DPPT,	September 28, 2017 March 6, 2020
	Yideng Liang, PhD, OTAT/DPPT,	October 6, 2017 March 20, 2020
	Leonid Parunov, PhD, OTAT, DPPT,	March 23, 2020
• Facilities review (OCBQ/DMPQ)	Nicole Li, PhD, OCBQ/DMPQ,	September 26, 2017 March 17, 2020
	Nicole Trudel, OCBQ/DMPQ,	September 27, 2017 March 17, 2020
• QC, Test Methods, Product Quality	Grainne Tobin, PhD, OCBQ/DBSQC,	September 14, 2017 September 29, 2017
	Claire Wernly, PhD, OCBQ/DBSQC,	May 26, 2017
	Charlene Wang, PhD, OCBQ/DBSQC,	September 6, 2017
• QC, Sterility and Endotoxin	Nicole Li, PhD, OCBQ/DMPQ,	September 26, 2017 March 15, 2020
• Establishment Inspection Report (OCBQ/DMPQ)	Nicole Li, PhD, OCBQ/DMPQ,	September 26, 2017 March 17, 2020
	Nicole Trudel, PhD, OCBQ/DMPQ,	September 27, 2017 March 17, 2020
• Testing Plan	Amanda Trayer, PhD, OCBQ/DMPQ	
	Marie Anderson, PhD, OCBQ/DBSQC,	September 19, 2017 March 19, 2020
<u>Clinical Reviews</u>	Poornima Sharma, MD, OTAT/DCEPT,	October 13, 2017 March 26, 2020
• Clinical (product office)	Bindu George, MD, OTAT/DCEPT	
	Tejashri Purohit-Sheth, MD, OTAT/DCEPT	October 13, 2017
• Postmarketing safety Epidemiological review (OBE/DE)	Firoozeh Alvandi, MD, OBE/DE,	September 18, 2017
• BIMO	Colonious King, PhD, OCBQ/BIMO,	September 15, 2017

Document title	Reviewer name	Memorandum date
Statistical Review • Clinical data	Boris Zaslavsky, PhD, Dr. Sc. OBE/DB,	September 11, 2017
Pharmacology/Toxicology Review Toxicology (product office)	Wei Liang, PhD, OTAT/IOD Mercedes Serabian, MS, DABT, OTAT/DCEPT	October 6, 2017
Clinical Pharmacology Review	Xiaofei Wang, PhD, OTAT/DCEPT,	October 11, 2017 March 23, 2020
Labeling Review(s) APLB (OCBQ/APLB)	Kristine Khuc, PharmD, OCBQ/DCM/APLB	August 30, 2017 February 4, 2020
Regulatory Project Management	Jean Dehdashti, MSc, RAC, OTAT/DRPM	March 31, 2020
Advisory Committee summary	Not presented to an advisory committee	

1. INTRODUCTION

Original Biologics License Application (BLA) under STN 125641/0 was submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (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 Factor (F) VII (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 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.

SEVENFACT is indicated for the treatment and control of bleeding episodes in adult and adolescent (12 years to <18 years) hemophilia A and B patients with inhibitors to Factors VIII and IX. SEVENFACT is not indicated for treatment of congenital factor VII deficiency.

To support the proposed indication, the BLA includes results from a pharmacokinetic study and a pivotal Phase 3 safety and efficacy study.

- Study GTC-FVIIA-005-11: A Phase 1b, dose escalation study to assess the safety, pharmacokinetics and pharmacodynamics (PD) of coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B patients.
- RB-FVIIa-006-13 (PERSEPT 1): Phase III study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX.

The Phase 1 study was a single-arm study that assessed the pharmacokinetic parameters of three doses of SEVENFACT, and provides limited data supporting the safety of SEVENFACT. The two doses evaluated in the Phase 3 study were selected based on the pharmacokinetic (PK) assessments from the Phase 1 study. The Phase 3 study, PERSEPT 1, supports the safety and efficacy of SEVENFACT for on-demand treatment and control of bleeding episodes in adult and adolescent hemophilia A and B patients with inhibitors to FVIII and IX.

SEVENFACT has a favorable benefit-risk profile, and the review team recommends approval of SEVENFACT for the indication of treatment and control of bleeding episodes in adult and adolescent (12 to <18 years) hemophilia A and B patients with inhibitors. SEVENFACT is not indicated for treatment of congenital factor VII deficiency.

2. BACKGROUND

Disease Background

The development of inhibitors to Factor VIII or Factor IX is the most significant complication of 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 responding inhibitor titers [<5 Bethesda Unit (BU)/ml] continue treatment with factor replacement at the same or higher dose. For patients with high responding inhibitor titers (≥ 5 BU/ml) to Factor VIII (hemophilia A) or Factor IX (hemophilia B), replacement is ineffective and bypassing agents are needed. Bypassing agents, such as Factor VIIa, generate thrombin by bypassing Factor VIII and Factor IX.

Patients with hemophilia and inhibitors experience severe morbidity with recurrent episodes of joint, muscle, and deep tissue bleeding events which can be limb- and life-threatening. Recurrent joint bleeding events lead to synovial inflammation and hypertrophy, leading to more bleeding episodes and progressive damage to cartilage and subchondral bone. The result is progressive severe arthropathy that can significantly reduce the health status and quality of life in patients. Available bypassing agents include plasma-derived Activated Prothrombin Complex Concentrate (aPCC, FEIBA, Takeda) and recombinant Factor VIIa (NOVOSEVEN RT, Novo Nordisk).

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, like the other current availably recombinant FVIIa NOVSEVEN RT, appears to be different from that of endogenous FVIIa. Recombinant FVIIa product for treatment of bleeding in hemophilia A and B patients with inhibitory antibodies is administered at doses that result in a supra-physiological level of FVIIa in blood that is 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, FVIIa does not usually cause thrombosis in hemophilia patients, as demonstrated by a safety record comparable 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, a revised version of this product, was developed for the U.S. market under IND 15183, under the product code name LR769. 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 (Laboratoire Francais du Fractionnement et des Biotechnologies S.A., the applicant of this BLA) are separate entities owned by the LFB Group.

SEVENFACT is not licensed outside the U.S.

During the first review cycle, CBER reviewers found significant deficiencies in Chemistry, Manufacturing and Controls (CMC), which resulted in the issuance of a *Complete Response Letter* (CRL) to LFB on October 13, 2017.

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

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

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.

a) 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 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 promoter DNA sequence, which directs the expression of the FVII protein in the mammary gland, and secretion of the FVII protein 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 to 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 amino acids (AA), and a C-terminal Heavy Chain (HC) of 254 AA, held together by a single disulfide bridge (Cys 135-Cys 262).

<u>SEVENFACT - Structure, Function, and Impurities</u>
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 RT (exclusively (b) (4) and plasma-derived FVIIa (b) (4) The results of the *in vitro* functional characterization studies demonstrated similarity between SEVENFACT, NOVOSEVEN RT, 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. (b) (4) 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)

(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).

(b) (4)
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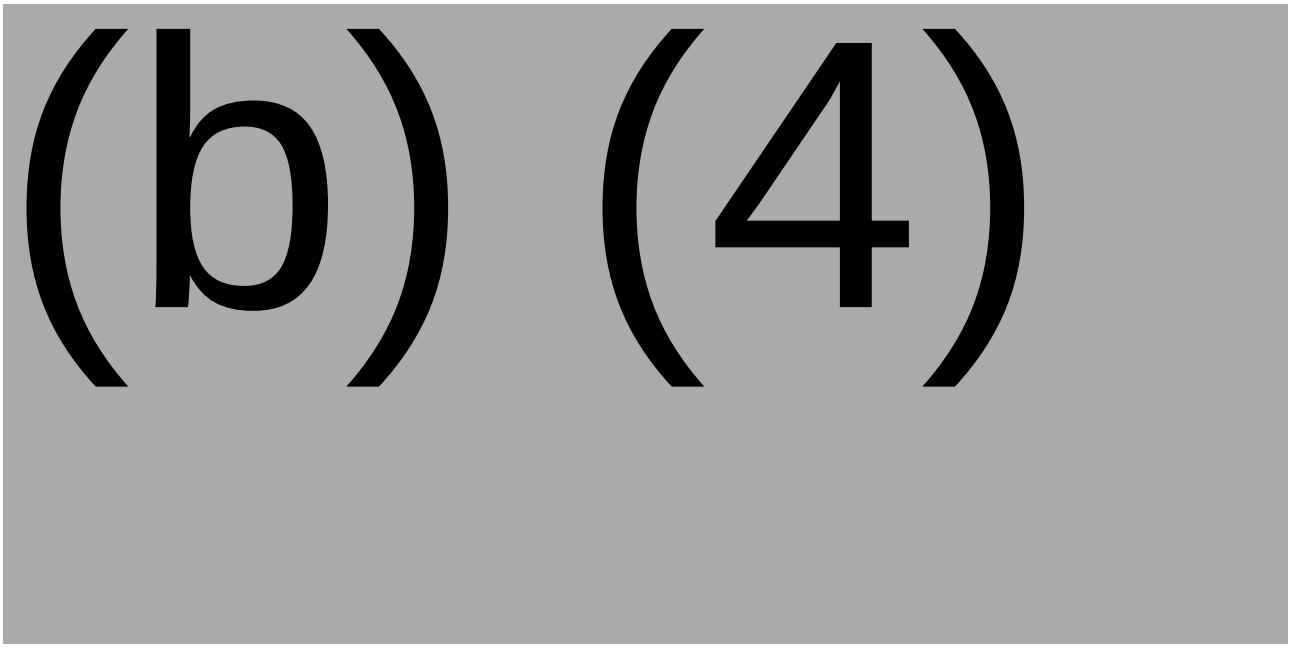
R69 line of GE rabbits

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 the Quality Risk Management exercise and confirmed by robustness studies. The controls performed on the different process steps and intermediates include the (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.

Viral safety of SEVENFACT relies on complementary measures as follows:

- *The SPF status of rabbit colony:* To ensure the SPF status, health 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 whether the rabbit milk (source material) contains adventitious agents that can be detected by (b) (4) The source material was examined for (b) (4). Based on this assay, only source material which is free of detectable viruses may be used in the manufacture of 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).

Issues identified during review

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: (i) presence of particulate materials noted in the testing and stability studies on reconstituted SEVENFACT, (ii) poor robustness of the BDS manufacturing process, (iii) product-related stability issues that impact the shelf-life, (iv) deficient analytical methods for assessment of extractables and leachables, (v) absence of proper validation or verification of analytical methods to control Diluent according to its release specifications, (vi) deficient shipping validation studies, (vii) deficient combination product design and validation, (viii) incomplete facilities information, and (ix) 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.

One remaining CMC deficiency will be addressed as a Post-Marketing Commitment: LFB committed to completing a series of post-marketing performance qualification (b) (4) studies to support (b) (4) of the drug product, (b) (4)

b) 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.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of coagulation factor VIIa (recombinant)-jncw [SEVENFACT] are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 2. Manufacturing facilities for coagulation factor VIIa (recombinant)-jncw [SEVENFACT]

Name/Address (*Activities*)	**FEI Number**	**DUNS number**	**Inspection/ Waiver**	**Justification/Results**
Source Material Processing, Drug Substance Intermediate Manufacturing LFB USA, Inc. (b) (4) Charlton, MA 01507	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ May 8 – 12, 2017 VAI
Drug Substance Manufacturing, Drug Product Release Testing LFB (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
Drug Product Manufacturing, Primary Packaging, Final Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI
Drug Product Manufacturing, Primary Packaging, Final Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI
Drug Product Labeling	(b) (4)	(b) (4)	Waived	ANSM (b) (4) Complies

Name/Address (*Activities*)	FEI Number	DUNS number	Inspection/ Waiver	Justification/Results
(b) (4)				
Drug Product Release Testing LFB Biotechnologies Zone Artisanale de Courtaboeuf 3 avenue des Tropiques Courtaboeuf Cedex Les Ulis, Essonne, 91958, France	3003539722	395918936	Waived	ANSM November 2018 Complies
Drug Product Release Testing LFB Biomedicaments Zone Artisanale de Courtaboeuf 3 avenue des Tropiques Courtaboeuf Cedex Les Ulis, Essonne, 91958, France	3003539722	395918936	Waived	ANSM June 2019 Complies
Drug Product Release Testing LFB (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
Drug Product Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

CBER conducted a pre-license inspection (PLI) of LFB USA, Inc. from May 8 – 12, 2017. At the end of this inspection, a Form FDA 483 was issued. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be resolved and the inspection was classified as voluntary action indicated (VAI).

CBER conducted a PLI of LFB (b) (4) . At the end of this inspection, a Form FDA 483 was issued. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be resolved and the inspection was classified as VAI.

The Office of Regulatory Affairs (ORA) conducted a surveillance inspection of (b) (4) . All the 483 issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) . The inspection was classified as No Action Indicated (NAI).

The Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), otherwise known as the French National Agency for Medicines and Health Products Safety, conducted an inspection of (b) (4) . A certificate of Good Manufacturing Practice (GMP) compliance was issued.

ANSM conducted an inspection of LFB Biotechnologies in November 2018. A certificate of Good Manufacturing Practice (GMP) compliance was issued.

ANSM conducted an inspection of LFB Biomedicaments (Les Ulis) in June 2019. A certificate of Good Manufacturing Practice (GMP) compliance was issued.

CBER conducted a PLI of LFB (b) (4) . At the end of this inspection, a Form FDA 483 was issued. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be resolved and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) The inspection was classified as NAI.

d) Container Closure System

The lyophilized drug product is contained in a Type (b) (4) borosilicate glass vial with a siliconized bromobutyl rubber stopper closure, not made with natural rubber latex. The primary container closure system is capped with an aluminum flip-off seal (b) (4) the caps are colored yellow and purple for the 1 mg dosage, and 5 mg dosage, respectively.

The container closure integrity testing was performed by the contract manufacturer, (b) (4) test methods; all acceptance criteria were met.

The diluent is filled into a 1.25 mL or 10 mL Type (b) (4) borosilicate glass syringe that is (b) (4) with a bromobutyl plunger stopper and a plastic rigid tip cap. The plastic rigid tip cap consists of a rigid plastic cap, not made with natural rubber latex (b) (4) tip cap for the 1.25 mL syringe and (b) (4) tip cap for the 10 mL syringe and Luer-Lok adapter. The syringe, plunger stopper, and tip cap are supplied by (b) (4) The container closure integrity testing was conducted at the (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

e) Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of SEVENFACT will not result in any significant environmental impact. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

f) Product Comparability

First-Generation and Licensed Manufacturing Processes

The development of the SEVENFACT manufacturing process was based on the experience (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 Phase 3 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 subjects 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 showed higher Cmax and AUC than Process A. 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 variability in subject responses in the Process A and Process B arms of the study.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The pharmacology/toxicology program for SEVENFACT consisted of multiple *in vitro* and *in vivo* studies. The activity of SEVENFACT in plasma samples collected from hemophilia A and B patients was confirmed with determination of thrombin generation time (TGT), activated partial thromboplastin time (aPTT), and prothrombin time (PT) coagulation parameters. Single intravenous (IV) administration of SEVENFACT (1-6 mg/kg) in hemophilia A mice resulted in reduced bleeding time and blood loss following tail vein resection. Single IV administration (0.1 mg/kg) in hemophilia A dogs resulted in reduced PT values. Single IV injection 0.1-1 mg/kg) in rats using the Wessler's venous stasis method showed thrombogenic activity at levels similar to that for the NOVOSEVEN RT reference control.

Single-dose and repeat-dose (daily for up to 28 days or for 13 weeks) toxicity studies with SEVENFACT were conducted in healthy rats at dose levels of 0.1-11 mg/kg/day and in cynomolgus monkeys (NHPs) at dose levels of 0.1-3 mg/kg/day. The resulting data showed dose-related decreased platelet counts and reduced PT values, which are expected pharmacological effects. Additional findings attributed to SEVENFACT included thickening or mass formation at the injection site, which correlated with thrombosis and perivascular inflammation observed microscopically. The injection site findings were noted only in rats. Microscopically, thrombosis of the right heart ventricle was noted in two NHPs at 3 mg/kg/day, which was related to the pharmacological action of the product. Thrombosis was more extensive in animals dosed at levels equal to, or greater than, 3 mg/kg/day. Anti-drug antibodies (ADAs) were detected in almost all rats and NHPs following repeat administration of SEVENFACT. The presence of ADAs was not associated with any adverse effects in the animals.

Pharmacokinetic (PK) and toxicokinetic (TK) assessments were performed following single and repeat dosing in healthy rats, hemophilia A dogs, and healthy NHPs. A general dose/exposure relationship was observed in all species. The no-observed-adverse-effect-level (NOAEL) was 1 mg/kg/day (28-day rat study), 1 mg/kg/day (28-day NHP study), and 1 mg/kg/day (13-week NHP study). This dose level is 4-fold higher than the highest recommended human dose level of 0.225 mg/kg.

A fertility and reproductive performance study was conducted in healthy rats. Males were administered SEVENFACT at dose levels of 0.1 to 3 mg/kg/day, daily for approximately one month prior to mating. The females were sacrificed and examined at 13 days post-coitum. Resulting data did not show any detrimental effects on fertility (sperm morphology, concentration, motility) or reproductive performance (e.g., corpora lutea, implantation sites, resorptions, etc.).

Genotoxicity and carcinogenicity/tumorigenicity studies were not warranted and therefore not conducted for SEVENFACT.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology program of SEVENFACT consisted of two clinical studies: a Phase 1b, dose-escalation study (Study GTC-FVIIa-005-11) and a Phase 3, multicenter, open-label, randomized, crossover study (Study RB-FVIIa-006-13, PERSEPT 1).

Study GTC-FVIIa-005-11 assessed the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of SEVENFACT across three dose levels (25, 75, and 225 mcg/kg). Pharmacokinetics of a single dose of SEVENFACT were evaluated in 15 adult male subjects (age range: 20-61 years, body weight range: 60.5 – 102.7 kg) with congenital Hemophilia A or B with or without inhibitors. Each subject received two of the three dose levels of SEVENFACT, and 10 subjects were treated at each dose level. Blood samples were collected for PK and PD analysis with an intensive sampling schedule. FVIIa activity was measured for PK assessments. Non-compartmental analysis showed that the maximum concentration (Cmax) and area under the concentration vs. time curve (AUC0-t) increased in a dose-dependent manner. The half-life of SEVENFACT was around 2 hours for all three dose levels.

To aid in the selection of doses with maximum pharmacodynamic effects, the applicant assessed multiple pharmacodynamic parameters of the coagulation cascade, including thrombin generation test (TGT), thrombin generation test with added platelets (TGTp, also

referred to as TGA platelets), activated partial thromboplastin time (aPTT), prothrombin time (PT), rotational thromboelastometry (MCF-FibTEM), prothrombin fragments 1+2 (F1+2), D-dimers, and thrombin antithrombin complexes (TAT). SEVENFACT demonstrated a dose and concentration-dependent pharmacodynamic effect on the coagulation system, including shortening of activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin generation time with platelets (TGT), and increasing maximum clot firmness (ROTEM-FIBTEM test). A two-compartment model with allometric scaling relating clearance and volume of distribution to subject's body weight was used in population PK modeling. Population PK/PD analysis showed a correlation between SEVENFACT plasma activity levels and coagulation PD markers with a saturable relationship. It should be noted that there is no standardized and validated assay currently available to predict the clinical response of bypassing agents such as FVIIa. Laboratory pharmacodynamic assessments of coagulation do not necessarily correlate with or predict the hemostatic effectiveness of LR769. Therefore, the PK/PD analysis results should be interpreted with caution. Per clinical review, efficacy was demonstrated with the dosing regimens that were used in the Phase 3 study (RB-FVIIa-006-13).

Based on PK and PD data from Study GTC-FVIIa-005-11, doses of 75 and 225 mcg/kg were selected for the Phase 3 study.

Study RB-FVIIa-006-13 (PERSEPT 1) evaluated the safety, pharmacokinetics, and efficacy of SEVENFACT in congenital hemophilia A or B subjects with inhibitors to FVIII or IX. In this study, a subset of 14 subjects participated in the PK evaluation to compare the PK profiles of SEVENFACT from a small-scale process (Process A) and SEVENFACT from a larger scale process (Process B, commercial process). There were 7 subjects each at 75 mcg/kg and 225 mcg/kg. Eleven subjects (6 for 75 mcg/kg and 5 for 225 mcg/kg) completed the PK evaluation. PK profiles of SEVENFACT were comparable between Process A and B for the dose of 75 mcg/kg. However, the Cmax and AUCinf of SEVENFACT from Process B were 75% and 40% higher than Cmax and AUC0-t of Process A SEVENFACT. Manufacturing process changes, small sample size, intra-subject variability, and inter-subject variability may have contributed to above observed differences. There were no safety issues noted following SEVENFACT administration from Process B noted during this study.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

To support the clinical indication of on-demand treatment of bleeding episodes in adolescent and adult patients with hemophilia A or B with inhibitors, the clinical development program included the following studies to evaluate the safety and efficacy of SEVENFACT:

- Study RB-FVIIa-006-13 (PERSEPT 1): Phase III study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX.

- Study GTC-FVIIA-005-11: A Phase 1b, dose escalation study to assess the safety, pharmacokinetics and pharmacodynamics of coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B patients.

<u>PERSEPT 1:</u>
The safety and efficacy of SEVENFACT were evaluated in 27 subjects with 465 mild or moderate bleeding episodes in a prospective, open-label, randomized, crossover study. Mean

age of the study population was 31 years (range: 12-54 years) and 93% of the population was Caucasian. Majority of the subjects had hemophilia A (93%) and 52% had a high titer of inhibitors. Overall, the characteristics of the study subjects is representative of the real-world hemophilia population, which lends external validity to the study.

Study subjects were randomized to one of the following two study drug regimens: 75 mcg/kg or 225 mcg/kg. The study had two phases, Phases A and B.

In Phase A, subjects received a single infusion of either 75 mcg/kg or 225 mcg/kg to assess safety. A subset of subjects in Phase A underwent PK (pharmacokinetic) analysis. Twenty-four hours after study drug administration in Phase A, subjects then entered into Phase B.

In Phase B, subjects were treated for bleeding episodes at the dose regimen they were initially randomized to, followed by cross over to the alternate dose regimen. Subjects continued to alternate between the two regimens every 3 months until the end of the study. Thus, subjects received treatment with one of two dose regimens for a total of six months. Mild or moderate bleeding events were treated at home by subjects or caregivers. Subjects with severe bleeding could receive the first dose at home but required hospitalization for subsequent management of the bleeding episode. After completion of Phase B, a repeat of the PK sampling was performed with SEVENFACT obtained from a scaled-up manufacturing process. All subjects were followed for at least 6 months after initial SEVENFACT administration.

Treatment regimen for mild or moderate bleeding events:
A 75 mcg/kg dose was administered initially, repeated, if needed, every 3 hours until the bleeding episode was successfully treated. A maximum of eight administrations were allowed. A 225 mcg/kg dose was followed 9 hours later with a 75 mcg/kg dose if the hemostatic response to treatment was unsatisfactory. The 75 mcg/kg dose could be repeated, if needed, every 3 hours. A maximum of six administrations was allowed. If bleeding was not successfully treated at 24 hours after initial administration, SEVENFACT was not continued and alternative treatment would be considered.

Treatment regimen for severe bleeding events:
Severe bleeding required an initial dose of 225 mcg/kg, which was followed by subsequent treatments at 75 mcg/kg every 2 hours in a medical facility, and the dosing interval was adjusted based on the bleeding assessments. If response to treatment after the first or any subsequent administrations of study drug was satisfactory (i.e., efficacy assessment was rated as “good” or “excellent”), subsequent doses of 75 mg/kg were administered at 3-hour intervals for 1 to 2 days, after which the interval could be increased to 4 to 12 hours, depending on the type of bleeding episode, for as long as needed.

Primary efficacy endpoint and analysis:
The primary efficacy endpoint was successful treatment of mild or moderate bleeding events at 12 hours after the first administration of SEVENFACT. Efficacy assessments included a combination of response assessments based on a 4-point hemostatic efficacy scale, need for other hemostatic or blood products, need for ongoing treatment with study drug, and pain status 12 hours after study drug administration. Primary efficacy analysis was the comparison of the proportion of successfully treated mild or moderate bleeding episodes in each of the two dosing regimens, based on a pre-specified objective performance criterion (OPC) of 55%. The OPC was determined from hemostatic efficacy of bypassing agents noted in literature. The study was powered to detect a 15% improvement over OPC for each of the two dosing regimens with 80% power at 0.125 type 1 error. An important secondary efficacy endpoint of the study was the

proportion of mild or moderate bleeding episodes with subject-reported outcomes of good or excellent response 12 hours after initial treatment. Time to assessment of good or excellent response by subjects, number of administrations, and total amount of drug administered per bleeding episode were additional secondary efficacy endpoints.

Key Review Issues:
The FDA clinical reviewer identified clinical issues that were related to the efficacy assessment methods. The overall hemostatic efficacy outcome was based on a four-point hemostatic efficacy scale, which included assessment of pain, swelling, tenderness and decreased range of motion. The hemostatic efficacy outcome was reported as excellent, good, moderate, or poor taking into account all four components; however, the raw data for the individual components of swelling, tenderness, or range of motion were not provided. The Applicant confirmed that the efficacy outcome was reported by subjects using the four-point scale, but only visual analog scores (VAS) for pain were reported by subjects during the study. Other components of the 4-point scale: swelling, tenderness or range of motion were not individually captured by the subjects, but were taken into account in the assessment of overall hemostatic efficacy. The reviewer used the VAS scores for pain to verify correlation with the reported hemostatic efficacy outcomes, and the reviewer identified discrepancies between the hemostatic outcomes reported by the Applicant and the assessment by the reviewer based on assessing the raw pain scores and correlation to overall hemostatic efficacy. In addition, pain assessments were also confounded by concomitant analgesic use, which in turn affected the assessment of hemostatic efficacy. Thus, both the adjudication of efficacy using VAS pain scores and the confounding of the pain assessment from concomitant analgesic use resulted in discordances in the assessments of hemostatic outcomes between the Applicant and reviewer. In total, discordance in efficacy outcomes were observed for 15 mild or moderate bleeding events. The Applicant and the FDA clinical team reached an agreement on these efficacy outcome assessments and the primary efficacy analyses were then performed on data sets that were based on the agreement. The results of the primary efficacy analyses (see below-Table 2) are adequate to support an efficacy claim for both doses: 75 mcg/kg and 225 mcg/kg.

Table 3: Primary Efficacy Analysis Results for 465 mild or moderate bleeding events

Dose administered	**Success**	**Success proportion**	**95% CI (p value)**	**Failures**	**Missing**	**Total**
75 mcg/kg	197	81.7%	72.3; 91.2 (p<0.001)	44	11	252
225 mcg/kg	188	90.8%	83.7; 98 (p<0.001)	19	6	213
Total	385	85.9%	78.4; 93.5 (p<0.001)	63	17	465

Severe Bleeding Events:
Three severe bleeding events occurred during the study and all three were treated on the 225 mcg/kg arm. The severe bleeding events occurred in the right hip, soft tissue / muscle and kidney. Two episodes occurred spontaneously, and one episode was traumatic. All three episodes required hospitalization as specified in the protocol.

One subject was treated with three 225 mcg/kg doses of SEVENFACT, which constituted a major protocol violation. The remaining two subjects were treated with 1 and 5 doses of SEVENFACT, respectively. All 3 severe bleeding events were treated successfully, and this was accompanied by an improvement in the pain score. The low incidence (0.6%) of severe

bleeding events in this study is consistent with observed frequency of severe bleeding events in hemophilia patients with inhibitors.

Dose Response:
The study was not powered to compare the efficacy of the two dose regimens; however, the proportion of successfully treated mild or moderate bleeding episodes for the 225 mcg/kg regimen was higher than that for the 75 mcg/kg regimen (See Table 2). The rate of treatment failure at 12 hours was higher in the treatment arm with 75 mcg/kg dosing (18%) than in the treatment arm with 225 mcg/kg dosing (9%); however, a statistical comparison of both arms was not planned. The median time to hemostatic efficacy for an excellent or good outcome was shorter with 225 mcg/kg dose at 3 hours versus 5.9 hours with the 75 mcg/kg dose. The median and mean infusions administered in the higher-dose arm were less than in the lower-dose arm. These findings support a dose-response relationship. The risk of thrombosis and the severity of the bleed may need to be considered and deferred to the prescriber, when making a choice as to the dose.

Study GTC-FVIIA-005-11**:**
This was a single-arm, open-label, dose-escalation trial that enrolled subjects to 3 dose cohorts of 25 mcg/kg, 75 mcg/kg and 225 mcg/kg. The study permitted subjects to be exposed to two doses in an escalating manner (for example, subjects who received 75 mcg/kg received 225 mcg/kg dose subsequently). Fifteen subjects were treated and evaluable for pharmacokinetic and safety assessments.

The PK studies confirmed a relationship between dose and PK parameters (AUC and Cmax), and the study results confirmed that 75 mcg/kg dosing every 2-3 hours provided a pharmacodynamic effect that was adequate for hemostasis. The 225 mcg/kg dosing allowed for longer interval before the need for repeat dosing. Based on the results, the 75 mcg/kg dose and the 225 mcg/kg dose were evaluated in the Phase 3 trial, as previously discussed.

Summary of Efficacy:
The indication for the on-demand treatment and control of bleeding episodes in adolescent and adult subjects is supported by the efficacy results provided in Table 2. This study met the success criteria for the primary efficacy analysis with and without the re-adjudicated outcomes. Both dose regimens: 75 mcg/kg and 225 mcg/kg achieved statistically significant results as compared to the pre-specified objective performance criteria. The clinical reviewer recommends approval of both dose regimens. The recommendation to include the higher dose (225 mcg/kg) in the label is based on the shorter time to hemostatic response and fewer (mean and median) administrations with the higher dose of 225 mcg/kg. The efficacy data noted in a limited number of subjects with severe bleeding and the favorable safety data also support approval of the 225 mcg/kg dose.

Summary of Safety:
Overall, SEVENFACT was well tolerated. There were no deaths, thromboembolic events, or neutralizing inhibitors to factor VII reported in both clinical studies with SEVENFACT; however, the clinical studies of SEVENFACT were conducted in a population that excluded risk factors for thrombotic risks. To address this issue, the Prescribing Information will include a boxed warning for the risk of serious arterial and venous thrombotic events, to inform prescribers about this potential toxicity, given its mechanism of action and known thrombotic risk with NOVOSEVEN RT, an approved product in the same class. The Warnings and Precautions (W&P) section of the label will reference the potential for development of neutralizing antibody, based on the information for the class of products. No subject developed anti-rabbit milk protein antibodies

during treatment with SEVENFACT. The Safety database for SEVENFACT included 42 subjects. Data from the two studies were not analyzed in a pooled manner due to differences in the study population and dosing. Safety findings from the two studies are summarized separately.

- PERSEPT-1:
  Adverse events that were associated with the administration of SEVENFACT included one episode of fever in a single subject (3.7%). Four episodes of infusion-site discomfort and two episodes of infusion-site hematoma occurred in 1 study subject (3.7%).

- Study GTC-FVIIA-005-11**:**
  A single episode of infusion-related reaction occurred with the 75 mcg/kg dose. Symptoms resolved without any intervention and did not recur with rechallenge with a higher dose of 225 mcg/kg. Other adverse reactions include two episodes of dizziness in 1 subject (6.6%) and 5 episodes of headache in 3 subjects (20%).

  The W&P section of the label will include information regarding risks of thrombosis related to the class of products.

Discussion of Post-Marketing Requirements (PMR) and Post-Marketing Commitments (PMC)
Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a post-marketing commitment (PMC), or a post-marketing required (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

SEVENFACT is not marketed anywhere worldwide and thus there is no post marketing information available for this product.

Statistical Summary:
Statistical review of the Phase 3 study concurs with the clinical review. Additionally, the statistical reviewer re-analyzed the primary efficacy endpoint based on the clinical reviewer's assessment of bleed outcomes with re-adjudication of 15 bleed outcomes. Despite the re-adjudication, the primary efficacy endpoint met its success threshold. The secondary endpoint analyses provided by the Applicant were verified by the statistical reviewer. The results of the efficacy analysis based on the re-adjudicated outcomes are included in Section 14 of the label.

Bioresearch Monitoring
Bioresearch Monitoring (BIMO) inspections were issued for one foreign and two domestic clinical study sites participating in the conduct of Study RB-FVIIa-006-13 in support of BLA 125641/0. The inspections did not reveal problems that impact the data submitted in this Biologics License Application (BLA).

b) Pediatrics
Five out of 27 (18.5%) subjects enrolled in PERSEPT 1 were adolescents (age 12-18 years) and contributed 79 bleeding events to the study. For these subjects, the proportion of successfully treated bleeding events was higher for both treatment regimens compared to the overall results of the primary efficacy analysis including adults and adolescents. For the 75 mcg/kg arm, the success rate was 93.2% (95% CI; 81.3%-98.5%) and 91.4% % (95% CI;76.9%-98.2%) for 225 mcg/kg arm. The review team concludes that the efficacy in the adult population was similar to the efficacy in the adolescent population, as limited sample size

precludes conclusion that efficacy in the adolescent population is superior to efficacy in adults. No safety concerns were identified in the adolescent age group.

Since SEVENFACT is not designated as an orphan product, PREA (Pediatric Research Equity Act) is triggered. During the initial BLA review cycle, the Applicant had requested deferral for the pediatric population <12 years of age. The application was presented to the pediatric review committee (PeRC). PeRC recommended that a pediatric deferral for patients <12 years could be granted if marketing approval is planned. A clinical study evaluating efficacy and safety of SEVENFACT in subjects <12 years of age (PERSEPT 2) has since been completed on June 30, 2017; however, the final study report has not been submitted to the agency for review. Hence, the requirement under PREA is not fulfilled. The Applicant noted that the final study report will be submitted to the Agency on July 10, 2020.

c) Other Special Populations

None of the subjects treated with SEVENFACT were 65 years of age or older. No information is available in specific populations such as pregnant or nursing females, or patients with a history of arterial or venous thromboembolic disease.

7. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not convened per FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE] because the product is not the first in its class; the design of the clinical studies is similar to studies conducted to support other approved products of this class; the review of the application did not raise significant safety concerns that could not be addressed through information in the label; consultative expertise was not required; and no public health concerns arose upon review of this file.

8. OTHER RELEVANT REGULATORY ISSUES

No major regulatory issues were identified. Review of financial disclosure forms did not raise any concerns regarding study conduct.

9. LABELING

The proposed proprietary name, SEVENFACT, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on December 8, 2016 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on January 13, 2017.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and package and container labeling, and found them acceptable from a promotional and comprehension perspective. The product labeling (i.e., Prescribing Information, Patient Package Insert, and Instructions for Use) were reviewed, commented on, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. APLB recommendations included formatting, organization of subsections, use of active voice in the label, and removal of promotional tone.

<u>Key Changes made to the label are outlined below:</u>

- Section 14:

    1. Clinical studies: Efficacy data in Table 5 was updated to reflect analysis of FDA review team (Table 2).

2. The dosing information will include two choices of dose regimens for treatment of mild or moderate bleeding and a single regimen for treatment of severe bleeding.

3. Information about patient reported pain relief at 12 hours was removed from the label as this endpoint represents an exploratory endpoint per the study protocol.

- Section 6: was updated to include only adverse reactions that are possibly related to SEVENFACT. Due to differences in the study population and dosing regimen, the safety data from PERSEPT 1 and Phase 1 study GTC-FVIIA-005-11 were not pooled. Hence, the safety data from both studies are presented separately. Infusion-related reaction is added under adverse reactions that have occurred in the Phase 1 study GTC-FVIIA-005-11.

- Section 4: Contraindications: SEVENFACT is derived from the milk of transgenic rabbits and may contain traces of rabbit proteins, including rabbit coagulation factor VII. Patients with allergy to rabbits were excluded from clinical studies with SEVENFACT. Based on these considerations, a contraindication to the use in patients with known hypersensitivity to rabbits is added under Section 4.

- Under Section 1, the review team has added a Limitation of Use (LOU) statement for congenital Factor VII deficiency patients as the safety and efficacy of SEVENFACT in patients with congenital factor VII deficiency has not been evaluated. Within the same class of recombinant factor VII, note that NOVOSEVEN RT is approved for treatment of congenital Factor VII deficiency.

- A Boxed warning is added to the label to inform prescribers about the potential risk of serious arterial and venous thrombotic events with SEVENFACT. Prescribers are advised to discuss the risks of thromboembolic disease and to monitor patients for signs and symptoms of thrombosis.

10. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends approval of SEVENFACT for the treatment and control of bleeding in adults and adolescent patients with congenital hemophilia with inhibitors.

b) Benefit/Risk Assessment

Potential Benefit:

The Phase 3 study met the success criteria for hemostatic efficacy. The data indicate that SEVENFACT is effective in the control and treatment of bleeding. The benefit of the higher dose (225 mcg/kg) include a shorter time to hemostatic response and fewer administrations. Hence, it is reasonable to approve the higher dose (225 mcg/kg) and include it in the dosage section of the label.

Potential Risks

The risks from treatment include risks of thrombosis, hypersensitivity reactions, and potential for development of neutralizing antibodies to factor VIIa. However, considering the benefit in the treatment of life-threatening or joint-damaging bleeding events in the indicated population, the risks are acceptable.

The benefit-risk profile of SEVENFACT for the treatment and control of bleeding in adults and adolescents with congenital hemophilia is favorable.

c) Recommendation for Post-marketing Activities

Clinical data raised no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a post-marketing commitment (PMC) or a post-marketing required (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

Routine pharmacovigilance is recommended. Post-marketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80. Routine surveillance includes 15-day expedited reports for serious, unlabeled/ unexpected adverse events, and quarterly periodic safety reports for 3 years, and annually thereafter. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.

The review committee agrees with the pharmacovigilance activities in the applicant's proposed pharmacovigilance plan. The pharmacovigilance plan includes routine pharmacovigilance for adverse event reporting.

The deferred pediatric study will be a PREA post-marketing required (PMR) study. This study has been completed, and the final report will be submitted to the Agency by July 10, 2020.