Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

To: Administrative File STN: 125641/0

From: Nicole Li, CMC/Facility Reviewer, OCBQ/DMPQ/MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/MRB1

CC: Nicole Trudel, CMC/Facility Reviewer and Inspector, OCBQ/DMPQ
Mikhail Ovanesov, Chair, OTAT/DPPT/HB
Mark Levi, RPM, OTAT/DRPM/RPMBII
Amanda Trayer, DMPQ RPM, OCBQ/DMPQ/RPM
Deborah Trout, Lead Biologist, OCBQ/DMPQ/MRB1

Applicant: Laboratorie Francais du Fractionnement et des Biotechnologies S.A. (License # 2061)

Product: Coagulation Factor VIIa (Recombinant); rhFVIIa LR769; Sevenfact®; Administered by intravenous injection (1 mg/mL)

Indication: For on-demand treatment and control of bleeding in adolescent and adult hemophilia A or B patients with inhibitors to FVIII or FIX

Subject: Review Memo for Biologics License Application (BLA)

Due Date: October 13, 2017

RECOMMENDATION

Based on the deficient CMC and Facilities information provided in the BLA and subsequent amendments and on-going studies and incomplete responses to the FORM FDA 483 issued at the close out of the pre-license inspections, the issuance of a Complete Response Letter is recommended.

The following letter-ready comments shall be communicated to the applicant, in a Complete Response Letter, as written:

Administrative

1. During the May 2017 inspection of LFB USA, Inc. in Charlton, MA, LFB USA informed that the (b) (4) site in (b) (4) had not been used as a FVII (b) (4) source material storage facility for approximately a (b) (4) and was replaced by the storage facility at LFB USA in Charlton, MA. Please confirm and update the application to remove reference to the (b) (4) facility, if applicable.

2. In Les Ulis, France, LFB Biotechnologies and LFB Biomedicaments conduct final release testing. Please separately register the facilities and provide the FEI numbers upon registration.

3. Please provide the FEI number for (b) (4) facility in (b) (4).

CMC

Source Material

4. (b) (4)

(b) (4)

Intermediate

(b) (4)

(b) (4)

Drug Substance

(b) (4)

Diluent

9. For the manufacture of the WFI diluent in PFS, it appears the WFI is filled into syringes and stoppered in Building (b) (4) Please confirm and describe the equipment used to (b) (4) .

10. In Section 3.2.P.3.5.4.9 Deviations, you state there was one recorded deviation (DV1405-125) throughout the process in the 5.2 mL diluent format validation of batch (b) (4) regarding a particle (b) (4) . Please provide the deviation investigation report which should provide the root cause of the (b) (4) and discuss preventative actions taken to prevent the (b) (4) .

11. In Section 3.2.P.3.5.4.8 (b) (4) you state that (b) (4) was evaluated on (b) (4) . It appears that an insufficient number of samples were tested given each diluent format's commercial scale batch is (b) (4) syringes.
    a. Please clarify how many samples were tested for each process validation batch and provide a justification.
    b. Please provide the data for the CCIT for the process validation batches.

12. Please provide a description of the sterilizer load configuration, autoclave loading patterns, and sterilizer hardware (e.g. (b) (4)) used in the (b) (4) autoclave (b) (4) used to (b) (4) .

13. We acknowledge the (b) (4) autoclave (b) (4) heat distribution (empty chamber) and heat penetration tests were described in Amendment 6 with a diagram provided that identified the location of the calibrated thermocouples and biological indicators used in the studies. From the diagram, it does not appear the thermocouples were located at (b) (4) locations of the autoclave for the heat distribution study.
    a. Please clarify the location of the thermocouples used in the heat distribution study and provide a justification for the thermocouples' location that support the identification of the cold spots within the autoclave.
    b. Please provide a justification for the locations of the thermocouples and biological indicators used in the heat penetration study to support the (b) (4) process of the (b) (4).

14. In Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, you describe (b) (4) steps. In each of the steps, equipment has been sterilized before use. During the (b) (4) step, the (b) (4) are sterilized. During the (b) (4) step, the materials used for the filling process, which include the (b) (4) are sterilized.
    a. Please describe the autoclave(s) and sterilization process used to sterilize the equipment used in the (b) (4) steps. The description of the autoclave(s) should include, but is not limited to, information regarding the load configuration, loading patterns, and sterilizing hardware (e.g. carts, shelves, trays).
    b. Please provide the qualification of the autoclave(s) used to sterilize the equipment used in the (b) (4) steps that support the use of all of the sterilized equipment.

15. During the (b) (4) step, the (b) (4) WFI i (b) (4)
    a. Please provide a description of the sterilization cycle.
    b. Please provide the protocol and report that validates the (b) (4) process for the holding (b) (4)

16. We acknowledge you provided protocol PC-003/17-00 and report IV-043/17-00 to support the validation of the (b) (4) method for container closure integrity testing (CCIT) of the diluent PFS. To verify the LOD, you used (b) (4) prepared positive control syringes. Please explain your (b) (4) positive control designs in how they are representative of syringe leaks. The sensitivity of the (b) (4) CCIT method is based on the (b) (4) through positive control defects that are created to be representative of leaks. Typical minimum leak diameters range from (b) (4).

17. In shipping operational qualification protocol No. 16-SCPB-00017-GLL, it is unclear if the internal thermal conditions of the shipping container are monitored. Please clarify if the temperature within the shipping container is monitored and provide the number of temperature probes and location of the probes to specify the shipping enclosure level (e.g. within the (b) (4)).

18. Please provide the protocol Ground-QP-2015-005/01 and reports Ground-QP-2015-005/01-(b) (4) and Ground-QP-2015-005/01-(b) (4) to qualify the vehicles (b) (4) respectively.

19. We acknowledge you provided a progress report of the shipping validation (b) (4) to (b) (4) and noted a deviation (#208486) was open. Please provide the completed shipping validation report, which should include summaries and data of the 3 runs for each diluent format to support the shipping process and provide a description of the deviation(s) and deviation investigation(s) and corrective actions and preventative actions (CAPAs).

Combination Product

20. We acknowledge you provided a progress report of the shipping validation (b) (4) to US Specialty Distributors) and noted deviations (#208488 and #208744) were open. Please provide a completed shipping validation report, which should include summaries and data to support the shipping process, thermal shipping conditions, and shipping packages/configurations and provide a description of the deviation(s) and deviation investigation(s) and CAPAs.

21. We acknowledge you provided a summary of the procedures for purchasing controls as per CFR 820.50 for the combination product. Please describe the procedures for the purchasing controls to ensure changes to the product, manufacturing process, or services being provided are identified to LFB and to ensure appropriate measures are taken to address the change.

LFB RESPONSE TO FORM FDA 483:

A Pre-License Inspection was conducted at LFB (b) (4) . A Form FDA 483 containing 16 observations was issued at the close-out of the inspection to Roland Beilard, Chariman. LFB submitted several responses to the Form FDA 483. Your responses to the Form FDA 483 Observations were found acceptable and may be followed-up on the next inspection, except for the following issues; furthermore, an amendment should be submitted to provide an update and summary of all commitments made.

22. Regarding FDA Observation 6: In the documents "1.11.1 Quality Information Amendment" submitted on April 14, 2017, on pages 21-22 of 41, and Report No. 000236286 (V 1.0) "Report on validation of the integrity of (b) (4) submitted on July 14, 2017, you describe the study to validate the lowest acceptable (b) (4) required to maintain the container closure integrity of the (b) (4) and present the results and the T_0 results of the qualification of integrity of the container closure.
    a. Please provide justification that the (b) (4) remains stable in the presence of the drug (b) (4) during the qualification of the lowest acceptable (b) (4)
    b. Please note: Your plan to complete the qualification of the integrity of the container closure is acceptable for the (b) (4) .

23. Regarding FDA Observation 7: In the document "1.11.1 Quality Information Amendment" submitted on April 14, 2017, on pages 23-24 of 41, you stated that a shipping validation with the operational qualification to test the effect of (b) (4) will be performed. Receipt of the completed validation and results is pending. Please be advised that additional clarifications may be needed upon review of this validation.

24. Regarding FDA Observation 13: In the document "1.11.1 Quality Information Amendment" submitted on April 14, 2017, on pages 35-36 of 41, you stated that empty chamber mapping studies would be performed for freezers (b) (4) and would use the results to establish equivalency between the freezers. If equivalency is not established, you stated that temperature distribution tests would be performed on all of the freezers. In document 000236024 (V 2.0) *Protocol to study the comparability of the* (b) (4) *freezers*, submitted on July 14, 2017, you provide the protocol to be used to establish freezer equivalency. Receipt of the empty chamber mapping study's results for each freezer is pending as well as possible temperature distribution study results.

25. Regarding FDA Observation 15: In the document "1.11.1 Quality Information Amendment" submitted on April 14, 2017, on pages 39-40 of 41, you stated that a disinfectant effectiveness study will be performed on surfaces representative of the production area. Receipt of the completed study and results is pending. Please be advised that additional clarifications may be needed upon review of this study.

A Pre-License Inspection was conducted at LFB USA, Inc. on May 8-12, 2017. A Form FDA 483 containing 15 observations was issued at the close-out of the inspection to William Gavin, D.V.M., President. LFB submitted several responses to the Form FDA 483. Your responses to the Form FDA 483 Observations were found acceptable (b) (7)(E) , except for the following issues; furthermore, an amendment should be submitted to provide an update and summary of all commitments made.

26. With reference to item # 1 in the Form FDA 483 issued at the end of the Pre-License Inspection of LFB USA, Inc. on 12 May 2017, please provide the following:
    a. Regarding 1a, the final report for process validation that includes data on three (b) (4) batches manufactured using milk sourced from the Charlton Rabbit Facility.
    b. Regarding 1b, the final report for the accelerated stability study
    c. Regarding 1c, the final report on (b) (4) lots manufactured using the Charlton milk, which should include, but not be limited to, trending and comparison of results for (b) (4) .
    d. Regarding 1d, the final report on the study that establishes the acceptance ranges for the storage conditions of the (b) (4)

27. Regarding FDA Observation 4: In the document "1.11.1 Quality Information Amendment" submitted on July 28, 2017, on page 16 of 23, you stated that a (b) (4) study will be performed.
    a. Receipt of the completed (b) (4) study and results is pending.
    b. Your (b) (4) study will evaluate (b) (4)

28. Regarding FDA Observation 5: In the document "1.11.1 Quality Information Amendment" submitted on June 2, 2017, on pages 19-20 of 67, you stated that several studies will be performed.
    a. Receipt of the qualification study and results for (b) (4) to address (b) (4) of milk as part of sampling procedure is pending.
    b. Receipt of the qualification study and results to define and assure (b) (4) prior to sampling the milk is pending.
    c. Receipt of the qualification study and results to evaluate the (b) (4) in milk is pending.
    d. In your response to FDA Observation 5b, you state that (b) (4) will be tested as part of the sampling procedure qualification to evaluate the (b) (4) samples. However, FDA Observation 5b was made related to the ability to recover (b) (4).
        i. Please explain the correlation between (b) (4) (FDA Observation 5b) and (b) (4) (your proposed qualification plan).
        ii. Please provide a (b) (4) study for (b) (4) that supports the (b) (4).

29. Regarding FDA Observation 6: In the document "1.11.1 Quality Information Amendment" submitted on June 2, 2017, on pages 21-22 of 67, you stated that a study will be performed to evaluate the (b) (4). Receipt of the (b) (4) study and results is pending.

30. Regarding FDA Observation 11:
    a. In the document "1.11.1 Quality Information Amendment" submitted on June 2, 2017, on page 59 of 67, you state temperature recovery studies will be performed on empty freezer chamber as they present a worst-case challenge. Please provide the temperature recovery study for Freezer (b) (4)
    b. In the document "1.11.1 Quality Information Amendment" submitted on June 2, 2017, on page 60 of 67, you state a power failure test for Freezer (b) (4) will be performed. Receipt of the test and results are pending.

31. Regarding FDA Observation 12: In the document "1.11.1 Quality Information Amendment" submitted on June 2, 2017, on pages 62-63 of 67, you describe the chart recording at (b) (4) was due to the freezer reverting to (b) (4)
    a. Please clarify if the freezer unit reverted to the default setting after a power failure because of the malfunctioning system battery. If not, please explain the cause for the reversion.
    b. You noted on August 13, 2016 that there was a power outage at the Charlton site. Please explain how you evaluated the performance of all equipment after that power failure and what processes are currently in place to evaluate equipment performance after power failures.

REVIEW MEMO TABLE OF CONTENTS

1. REGULATORY HISTORY 9
2. DESCRIPTION OF PRODUCT 11
3. OVERVIEW OF MANUFACTURING PROCESS 11
    A. Source Material Manufacturing Process 11
    B. Drug Substance Manufacturing Process 12
    C. Drug Product (LR769) Manufacturing Process 12
    D. Drug Product (Diluent) Manufacturing Process 12
    E. Combination Product Labeling and Packaging 13
4. OVERVIEW OF MANUFACTURING AND TESTING FACILITIES 13
5. SOURCE MATERIAL 15
    A. LFB USA Facility 15
    B. (b) (4) Facility 22
    C. Source Material (Milk) Collection Process 26
    D. Comparability of Source Material 27
    E. Container Closure 28
    F. Shipping 28
6. INTERMEDIATE (UPSTREAM) 29
    A. Facility 29
    B. Utilities Systems 33
    C. Manufacturing Process 35
    D. Process Validation 38
    E. Equipment Qualifications 41
    F. Cleaning Validations 49
    G. Container Closure 56
    H. Stability 57
    I. Shipping 57
7. DRUG SUBSTANCE (DOWNSTREAM) 59
    A. Facility 59
    B. Utilities Systems 63
    C. Manufacturing Process 66
    D. Process Validation 70
    E. Equipment Qualifications 73
    F. Cleaning Validations 81

G. Container Closure....81
H. Stability....82
I. Shipping....83
8. DRUG PRODUCT – LR769....84
9. DRUG PRODUCT – DILUENT....84
A. Facility....84
B. Utilities Systems....86
C. Manufacturing Process....87
D. Process Validation....91
E. Equipment Qualifications....94
F. Sterilization Validations....98
G. Container Closure....98
H. Container Closure Integrity Testing....99
I. Stability....100
J. Shipping....102
10. COMBINATION PRODUCT....104
A. Facility....104
B. Manufacturing Process....105
C. Equipment Qualifications....108
D. Shipping....108
E. Device....112
11. ENVIRONMENTAL ASSESSMENT....117
12. INFORMATION REQUEST....118
A. Prior to Filing....118
B. Filing....122
C. Late Cycle....126

1. REGULATORY HISTORY

Laboratorie Francais du Fractionnement et des Biotechnologies S.A. (hereafter referred to as LFB S.A.) submitted a Biologics License Application (BLA) electronically via eCTD format (eCTD sequence # 0000) that was received by DCC on October 13, 2016. The BLA was an application for Sevenfact® (proposed proprietary name for the biological product) whose active ingredient is Coagulation Factor VIIa (Recombinant), also known as rhFVIIa or LR769, a drug product for on-demand treatment and control of bleeding in adolescent and adult hemophilia A or B patients with inhibitors to FVIII or FIX.

Sevenfact® is the second rFVIIa for the US market. It is not approved anywhere in the world. One rFVIIa product, Novoseven RT®, is currently approved in the U.S. for use in the treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets. Novoseven RT®is also approved for use in the treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia. Unlike Novoseven RT®, Sevenfact® will be indicated only for on-demand treatment of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

LFB S.A., is part of LFB group, a multinational French plasma fractionator company. Developed under IND 15183, Sevenfact® was initiated by the U.S. company rEVO Biologics, Inc. (rEVO), formerly known as GTC Biotherapeutics, which was formerly a part of the Genzyme Corporation responsible for development of coagulation factor products produced in the milk of genetically engineered transgenic animals. After rEVO was acquired by LFB Group, it was divided into two companies, rEVO and LFB USA. rEVO currently holds a BLA for the first U.S. biologic produced in the milk of genetically engineered animals, a recombinant human antithrombin, ATRYN, produced in the milk of genetically engineered transgenic goats. LFB USA, which is also part of LFB Group, participates in collection of rabbit transgenic milk and is responsible for purification of Sevenfact® intermediate, and also acts as the U.S. representative for the LFB Group.

In developing the product, LFB had been working with the Center of Veterinary Medicine (CVM) under the Investigational New Animal Drug Application (INAD) and submitted a New Animal Drug Application (NADA) regarding the rabbit transgenic milk collected from the US LFB USA facility. While LFB submitted a Categorical Exclusion (CE) under 21 CFR § 25.31(c), CVM will review the environmental analysis as part of the NADA. To receive approval for the BLA, the NADA must be approved prior to the BLA approval unless the applicant withdraws the LFB USA facility. (It is noted the rabbit transgenic milk is also collected at a (b) (4) facility.)

Prior to submitting the BLA, prior interactions with the applicant included:

- Pre-BLA Type B meeting (Meeting #10181) held on April 14, 2016; and
- IND 15183 related activities.

Two CMC/ facility reviewers were assigned to review the Chemistry, Manufacturing, and Controls (CMC), as they relate to the ability of the establishment, facility, process, and equipment to meet the regulatory requirements for Current Good Manufacturing Practices (CGMPs).

An Inspection Waiver memo was prepared for the following manufacturing sites at:

- (b) (4)
- LFB Biotechnologies in Les Ulis, France (FEI# to be requested); and
- LFB Biomedicaments in Les Ulis, France (FEI # to be requested).

An inspection was conducted at the following three sites:

- LFB (b) (4)
- LFB (b) (4)
- LFB USA, Inc. in Charlton, MA (FEI# 3013501870) on May 8 – 12, 2017.

The sections/items evaluated by DMPQ for the review of the BLA were according to SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements.

During review of the BLA, DMPQ noted several deficiencies and clarifications by LFB were required. Prior to the filing date, correspondence was submitted to LFB to address critical missing information that were potential refuse-to-file (RTF) deficiencies. At filing, a Filing with deficiencies Letter was

submitted to LFB, which identified a deadline for the applicant's response. At the late cycle, significant issues were communicated to the applicant. It is noted that much of the information requested at filing was submitted months after the identified deadline via numerous amendments. Any information or amendment submitted after August 16, 2017 were not reviewed in-depth but may have been used to identify committed deadlines established by LFB. For additional information on the deficiencies and issues submitted to LFB, please refer to Section 12. Information Request.

2. DESCRIPTION OF PRODUCT

Coagulation Factor VIIa (Recombinant) is a recombinant human coagulation Factor VIIa of the vitamin K-dependent family of coagulation factors. In the presence of both calcium and phospholipids, Factor FVII/FVIIa in a complex with tissue factor (TF) can activate Factor X to Factor Xa directly bypassing Factor IX or Factor VIII. Activation of Factor X to Factor Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin and then converts fibrinogen to fibrin.

Coagulation Factor VIIa (Recombinant) is produced in and purified from the milk of transgenic rabbits, whose genome has integrated the human Factor VII transgene. The purification process of Coagulation Factor VIIa (Recombinant) yields a drug product, which is prepared into a lyophilized dosage form.

Coagulation Factor VIIa (Recombinant) will be supplied as a single-use kit, containing:

- a sterile Type (b) (4) single-use glass vial of LR769 (in a sterile lyophilized dosage form) sealed with bromobutyl rubber stopper and an aluminum seal with a plastic flip-off cap;
- a needleless pre-filled syringe of diluent, Sterile Water for Injection (WFI). The prefilled syringe is fitted with a Luer lock, which is compatible with a vial adapter;
- a plunger rod for the syringe; and
- a commercially available FDA cleared vial adapter with a 5 micron filter.

The LR769 drug product is to be reconstituted with Sterile WFI and is intended for administration by the intravenous route. It is noted the diluent syringe is to be used for delivery of the diluent into the drug vial for reconstitution only and is not intended to be used for withdrawal of the reconstituted product from the vial. As such, there is no contact of the diluent syringe with the reconstituted product. Withdrawal, pooling, and/or administration syringes are not supplied as part of the kit.

LR769 is supplied in vials containing 1 mg, (b) (4) or 5 mg of LR769 with each of the vial sizes being packaged with a pre-filled syringe of Sterile WFI, containing 1.1 mL, (b) (4) and 5.2 mL of diluent, respectively. When reconstituted as directed, the concentration of LR769 is 1 mg (1,000 mcg) per mL.

3. OVERVIEW OF MANUFACTURING PROCESS

A. Source Material Manufacturing Process

(b) (4)

- (b) (4)

(b) (4)

B. Drug Substance Manufacturing Process

(b) (4)

C. Drug Product (LR769) Manufacturing Process

At (b) (4) the drug product is produced in (b) (4) dosage strengths (1 mg, (b) (4) and 5mg of lyophilized powder).

(b) (4)

D. Drug Product (Diluent) Manufacturing Process

(b) (4)
.

The diluent is presented as sterile WFI in a single-use prefilled 1.25 mL, (b) (4), or 10 mL capacity Type (b) (4) glass syringe, with fill volumes of 1.1 mL, (b) (4), and 5.2 mL WFI, respectively.

E. Combination Product Labeling and Packaging

(b) (4) the lyophilized drug product in vials and WFI diluent PFS are labelled and packaged as a kit with the remainder of the kit's device and device components.

4. OVERVIEW OF MANUFACTURING AND TESTING FACILITIES

The facilities involved in the manufacture of the Coagulation Factor VIIa (Recombinant) are listed below with a short description of their manufacturing responsibilities and inspectional requirements:

Facility	Manufacturing Process	Inspection
LFB USA, Inc. (b) (4) Charlton, MA 01507, USA FEI: 3013501870	(b) (4)	Not required
	(b) (4))	Inspection
	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
(b) (4)	(b) (4) (b) (4) .	Not required

(b) (4)		
(b) (4)	(b) (4) .	Not required
LFB USA, Inc. 175 Crossing Boulevard Framingham, MA 01702, USA FEI: 3003837678	(b) (4)	Not required
(b) (4)	(b) (4)	Not required
LFB (b) (4)	(b) (4)	Not required
	(b) (4))	Inspection
	(b) (4)	Not required
	(b) (4)	Inspection
LFB Biotechnologies (LFB BTC) 3, avenue des Tropiques ZA de Courtaboeuf 91940 Les Ulis, France (no FEI number yet)	(b) (4)	Not required
	(b) (4)	Waived
LFB (b) (4)	(b) (4)	Not required
	(b) (4)	Not Required
	(b) (4) .	Inspected
LFB Biomedicaments 3, avenue des Tropiques ZA de Courtaboeuf 91940 Les Ulis, France (no FEI number yet)	(b) (4)	Not required
	(b) (4)	Waived
LFB (b) (4))	(b) (4)	Not required
(b) (4)	(b) (4)	Waived
(b) (4)	(b) (4)	Waived
(b) (4)	(b) (4)	Waived
	(b) (4)	Not Required
	(b) (4)	Waived
(b) (4)	(b) (4)	Waived

(b) (4)	(b) (4)	Not required
(b) (4))	(b) (4)	Not required

Review Comments/ Assessment

Please note: In the Filing with deficiencies Letter (#26, Facility), DMPQ requested LFB provide the FEI numbers for all applicable manufacturing sites upon registration In Amendment 12, LFB stated the registration was ongoing and committed to provide the FEI numbers upon availability. It is noted that both LFB Biotechnologies and LFB Biomedicaments, which are located at the same Les Ulis, France address, perform final release testing. LFB S.A., which is also at the same address, was registered and a FEI number was provided for that facility. A request will be made for LFB to register both the LFB Biotechnologies and LFB Biomedicaments facilities in Les Ulis, France and to provide the FEI numbers. A FEI number is also requested for the (b) (4) where final release testing is performed.

5. SOURCE MATERIAL

At (b) (4) LFB USA, transgenic rabbits are maintained and milked.

A. LFB USA Facility

In Charlton, MA, the LFB USA facility contains the Charlton Rabbit Facility (CRF), which is comprised of 212 acres dedicated to the production and use of transgenic rabbits and milk collection. (The remaining animal facility area of LFB USA is dedicated to goats.)

Activities specific to the transgenic rhFVIIa rabbits include:

- General rabbit health, welfare, and maintenance, which includes housing, feeding, breeding, rearing, and animal husbandry;
- Expansion and maintenance of the transgenic rabbit line through natural breeding and/or artificial insemination;
- Milk Collection and storage from transgenic rhFVIIa rabbits; and
- General Quality Assurance (QA) oversight.

Animal Welfare Assurances

A Rabbit Oversight Committee (ROC), which includes a veterinarian and non-LFB employees, oversees the rabbit operations and evaluates and maintains the policies for animal health, welfare, and care. The ROC reviews and inspects the animal care and use program, establishes and reviews policies for animal care and use, and makes recommendations as appropriate.

The New Zealand White (NZW) rabbit was chosen as the non-transgenic/background wild-type breed because of its (b) (4)

(b) (4)

(b) (4)

Animal Health and Husbandry

The primary goal of the animal care and husbandry program at LFB USA is to maintain the health of the rabbit population to ensure the source material produced is of the highest quality and appropriate for use. Accordingly, measures are implemented at LFB USA to protect the rabbit colony by preventing the introduction of diseases. The program includes a facility barrier, biosecurity program, preventative health practices, disease monitoring and continuous monitoring to ensure the SPF colony status, animal husbandry practices, and QA oversight:

- **External Biosecurity:** The external biosecurity practices include screening personnel and visitors for potential threat and an integrated pest management (IPM) program to vertebrate and invertebrate pests.

    - *Personnel and Visitors*: The biosecurity policy includes a provision for pet ownership, which limits personally owned species of pets that pose risk to the colony. The CRF staff are dedicated personnel who are limited on cross-tracking to other areas of LFB USA. Upon entry to the CRF SPF Core, individuals change into dedicated clothing, shoes, and personal protective equipment (PPE). After donning the appropriate attire, personnel enter an air shower.

      All LFB USA Charlton staff complete pre-employment exams and may be screened for specific diseases. A third party medical provider conducts physicals biannually for staff. There is a policy at LFB USA in which employees, who are sick or have a medical condition that can impact animal health, self-report to a supervisor/manager and are excluded from certain animal-specific tasks.

      All personnel and visitors are required to complete a biosecurity questionnaire in advance or upon entry to the site to establish if an individual poses a threat to the animal colony or has clothing or possessions that act as a potential fomite for disease transmission. The Rabbit Operations (ROP) oversees and evaluates the questionnaires. When granted access, visitors are directly supervised and provided with appropriate barrier clothing.

- *Activists*: The LFB USA Charlton site is equipped with an electronically controlled gated fence around the CRF building, with limited access. The site is staffed seven days a week with a security force that patrols during the day through the weekends and off-hours. A video surveillance system is in place to monitor key entry points and remote sections of the perimeter. Twenty-four video recording is also performed in specific areas.

- *Vertebrate and Invertebrate Pests*: The IPM program was developed to prevent and remedy potential pest problems, which include rodents, birds, and insects. The main aspects of the IPM program includes restricting the access of the pest species into the facilities, monitoring, identifying, and quantitating pest levels, and continually and quickly removing pests if and when found.

  The rabbit colony is maintained in a controlled building without expose to livestock or other species and is surrounded by a perimeter fence. A site veterinarian regularly monitors electronic public health bulletin boards and potential networks to evaluate potential threats due to potential international/national/regional disease outbreaks.

  Rodents are discouraged from the animal facility by a (b) (4) concrete foundation and paving around the building perimeter. Rodent traps, which are located in external feed storage areas, and bait stations, which are place around the building perimeter, are monitored by a contracted service provider per schedule and a log is maintained. ROP regularly reviews the logs.

  Birds are discouraged from the CRF as there are no open doors or windows that lead directly into the animal housing or use areas. Trees on the property are located away from the perimeter fence. A pest contractor regularly monitors for evidence of bird activity around the building. Any nesting activity is removed and modifications are made to prevent future nesting in those sites.

  The key elements of insect control are rabbit fecal elimination and documented facility sanitation management practices to discourage and/or disrupt insect lifecycles, and monitor adult insect numbers using traps. Where appropriate, electronic insect light traps were installed, which are monitored on an established schedule by a contracted service provider and/or ROP staff (for areas within the SPF core) and logs are maintained. Paving around the building perimeter further discourages plant growth and subsequent insect populations. Pesticide use is governed by established procedures and must be approved prior to use by QA and the site veterinarian.

- **Internal Biosecurity:** Internal biosecurity are practices that contain or limit spread of disease between animals in the colony. At LFB USA, this internal biosecurity is achieved by health screening, routine veterinary care, husbandry practices, analyses of data and record-keeping, controlled animal movement, animal traceability, and regular review of colony health monitoring (necropsies, morbidity, and mortality).

- *Colony Closure*: All animals on site originated from the SPF colony that was transferred to the US from (b) (4) in 2015. The LFB USA colony is a closed rabbit colony and since start-up in 2015, all additions to the colony have been through births derived from within the colony itself. Animal transfers are limited within the CRF.

- *Feed and Water*: (b) (4)
  .

  On-site wells provide water to the CRF that is chlorinated and regularly monitored for the presence of coliforms, heavy metals, pesticides, chemicals, and trace minerals.

- *Colony Health*: All rabbits are monitored for disease status and maintained under conditions that favor optimum health. An animal health (b) (4) testing)
  (b) (4)

- *Waste Management*: Waste is collected, documented, and disposed in accordance with local, state, and federal regulations. Hazardous waste is managed by the Environmental Health and Safety Department and/or ROP and archived. ROP maintains applicable records.

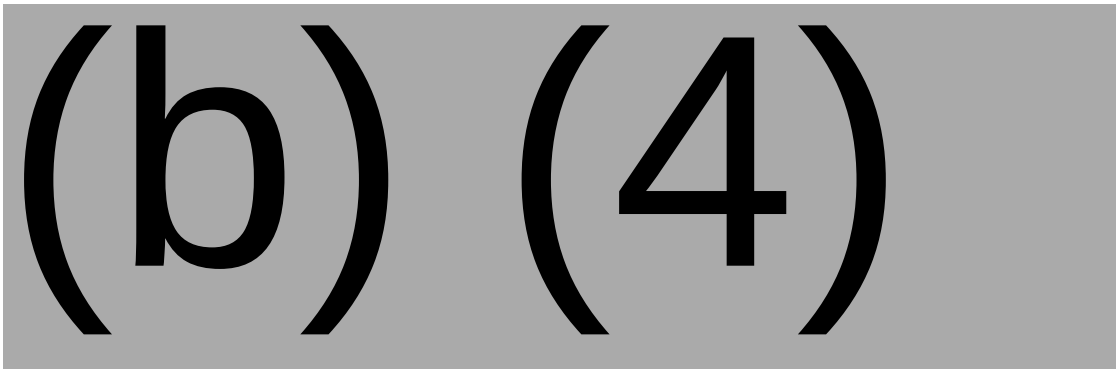
  Liquid waste, which is comprised of animal excrement, surface wash water, and milk-equipment cleaning solutions, is directed to an external tank and collected by a licensed waste removal service for transport and processing at a water treatment facility.

  Solid waste which includes sharps (sharps, needles, etc.) are collected in dedicated containers and disposed per regulations and incinerated by a contractor. Other waste which may include milk production waste (bottles, tubes), soiled bedding, and general non-hazardous waste, are collected and disposed by a contracted waste disposal company.

  Rabbit carcasses are disposed in accordance with the applicable laws and removed by a contractor and taken for complete incineration off-site.

- *Facilities and Equipment Cleaning Management*: Standard equipment, which may include pressure washers, chemical proportioners, etc., are used to remove excrement

(b) (4)



III. **Maintenance of Rabbits**

The rabbits are housed in a facility that is designed and constructed to maintain animals in an SPF status and be able to withstand cleaning with detergents and disinfectants. The rabbit health program was developed to maintain the health and well-being of the rabbit colony.

- **Veterinary Care and Oversight Veterinary Care:** Veterinary and on-call coverage is provided (b) (4) 7 days a week.
- **Animal Husbandry:** The ROP staff performs all routine animal husbandry activities, which may include (b) (4)
- **Rabbit Identification and Segregation:** Animals are segregated within (b) (4) which can confirm transgenic status.

IV. **Colony Health Maintenance**

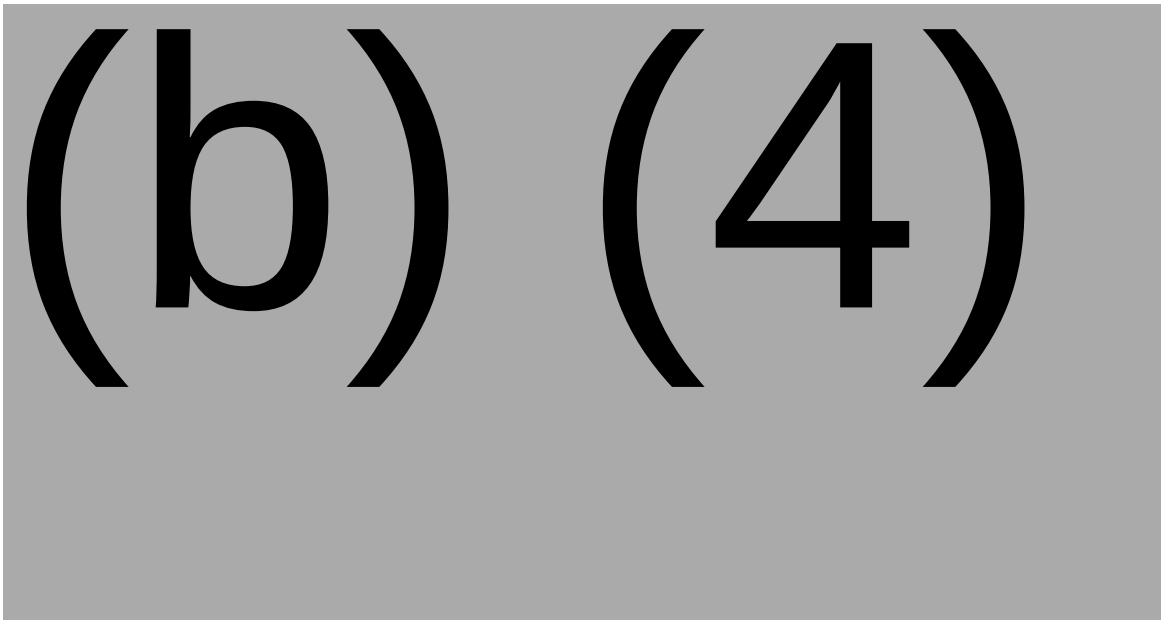
A preventative health and monitoring program is in place to monitor specific diseases that are considered to pose greatest concern to the rabbits, their milk, or with potential zoonotic concerns for humans.

- **Rabbit Health Records**
    - *Individual Health Incidents*: An animal observation/treatment records is opened and maintained for any rabbit that presents with a potential clinical/health abnormality
    - *Health Monitoring Results*: The results from the (b) (4) health monitoring activities ((b) (4) ,

(b) (4) of the SPF (b) (4) animal testing program are reviewed internally and signed by the site veterinarian.

- *Mortality and Morbidity (M&M)*: Records of individual breeding performance and animal disposition are maintained as M&M reports, which are reviewed by Veterinary Services and the ROC, for potential significant trends.
- Veterinary/Animal Health Statement: The veterinarian produces and signs a veterinary health statement certifying the colony is exempt of health issues that could negatively impact the source material for each source material batch. The statement is derived from reproductive performance, M&M trends, SPF health monitoring results, and other events that may negatively impact the source material.

- **Health Screening and Diagnostic Testing:** Rabbit Disease testing is contracted to various local/regional veterinary diagnostic laboratories. The SPF Health Monitoring Profile and Additional Health Monitoring agents are identified on the following table:



- (b) (4)

(b) (4)

.

V. **Veterinary Pharmaceutical Use**

When trained personnel administer pharmaceutical to the rabbits, the treatments are documented in the health treatment records. The pharmaceuticals administered are evaluated for potential residues in the milk. Animals receiving medical intervention are removed from the active milking campaign to prevent treated rabbits from contributing to the source material collection.

- (b) (4)

Review Comments/ Assessment

There is agreement that LFB USA appears to have the appropriate measures and practices in place to protect the transgenic rabbit colony to ensure the quality and safety of its source material. Specifically, the biosecurity program has a pest management program, physical barriers, and procedures to limit access to the CRF to only authorized visitors and its dedicated staff to prevent or reduce the risk of introducing diseases to the transgenic rabbit colony. The transgenic rabbits, which are each clearly identified, are maintained in a controlled manner by a trained veterinary staff in which routine animal husbandry activities are performed and health monitoring plans are established to prevent product contamination

with adventitious agents, pesticides, and animal medications. Health records practices include documenting the complete history from birth to death, including any administration of drugs or supplements. Disease episodes are to be diagnosed to the fullest extent possible with sick animals removed from production. Animal and by-product removal and disposable procedures are established. Feed and water consumption are monitored, regularly tested, and documented to provide records for review if there is any early indication of disease. The housing facilities and product recovery equipment, which includes the milking parlor and manifold assembly, are cleaned and sanitized after every milking.

The CRF was inspected during the May 2017 PLI of LFB USA. For an assessment, please refer to the CBER verterinarian's review and narrative in Section 12. Control and Care of Transgenic Rabbits in the LFB USA, Inc. EIR. FORM FDA 483 Observation #14 was made regarding the absence of studies that demonstrate the effective sanitization of the rabbit enclosures and ancillary equipment.

Please note: In the Filing with deficiencies Letter (#32, Facility), DMPQ requested details of the rabbit husbandry and animal facility biosecurity and information about the submission of the NADA to CVM. In Amendment 9, LFB provided the requested information, which was in the BLA, and stated the NADA would be submitted in the first quarter of 2017. No further action is required.

B. (b) (4) **Facility**

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

C. Source Material (Milk) Collection Process

(b) (4)

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

(b) (4)

.

8. DRUG PRODUCT – LR769

The lyophilized drug product manufactured at the (b) (4) facility was reviewed by DMPQ CMC/ facilities reviewer, Nicole Trudel.

9. DRUG PRODUCT – DILUENT

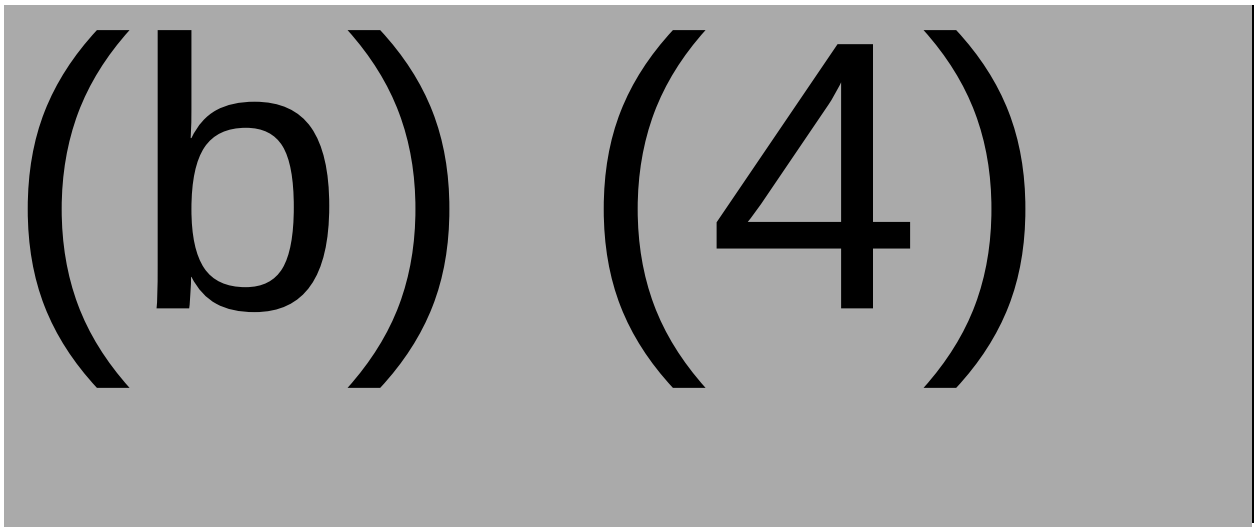
At (b) (4), water for injection (WFI) in pre-filled syringes (PFS) are manufactured.

A. Facility

Facility Description

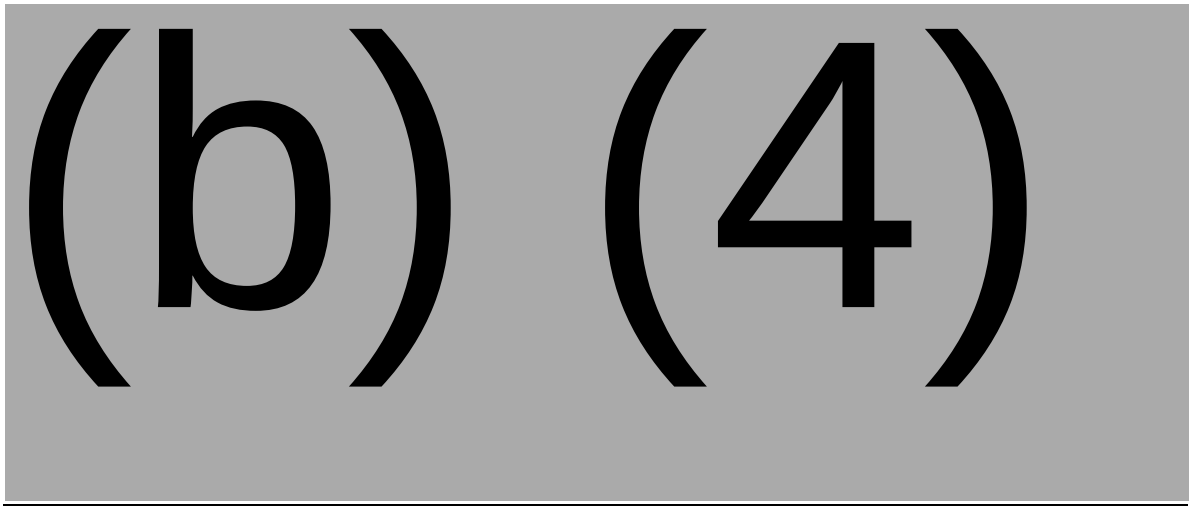
At the (b) (4) facility, there are manufacturing, research and development, marketing operations for small molecules and biological medical specialities. The (b) (4) facility also includes a specific WFI production plant where, the diluent, sterile WFI in 1.25 mL, (b) (4) and 10 mL prefilled syringes, is manufactured. The following table identifies the main buildings that constitute the (b) (4) manufacturing complex:

(b) (4)



Other Products

(b) (4) is a multi-product facility, where (b) (4) , both in prefilled syringes and vials, are manufactured in a dedicated facility or on a campaign basis:



(b) (4) .

III. **Contamination Control**

Preparation and filtration steps for the WFI in PFS are conducted in a (b) (4) area in Building (b) (4) .

Most of the equipment, tanks, processing lines, filling machines and other small equipment used in the manufacture of the diluent are made of (b) (4)

Materials, utensils and equipment used during the production in the facility are of pharmaceutical grade, (b) (4)

A cleaning validation master plan program for the process validations, equipment, critical areas in direct contact with product in all manufacturing steps and clean areas ensures the successful cleaning procedures and the effectiveness of the cleaning agents.

Review Comments/ Assessment

(b) (4) is a multi-product facility in which production occurs on a campaign basis or in dedicated facilities. Appropriate contamination controls specific to the WFI manufacture in PFS appear to be in place.

Please note: The (b) (4) facility is used to manufacture sterile WFI in PFS, which first received FDA approval in (b) (4). A comparison of the approved WFI in PFS and the (b) (4) can be found on a table in Section 9. Drug Product – Diluent, Section D. Process Validation.

Please note: An inspection of the (b) (4) facility was waived as a surveillance inspection was conducted in (b) (4). It is noted an inspected product was the sterile WFI. Coverage of the inspection was given to Quality, Facilities and Equipment, Materials, Production, Laboratory, and Packaging and Labeling systems. A FORM FDA 483 was issued with three observations and the inspection was classified as VAI.

B. Utilities Systems

- **HVAC System**

The HVAC systems consist of (b) (4) systems (b) (4) .

HVAC system is periodically requalified and covers all classified areas. Filters are periodically replaced depending on the type of filter and application.

Production and laboratory areas are supplied by independent HVAC units. The HVAC system is designed to prevent potential contamination caused by the circulation of materials and contaminants into the critical areas.

The HVAC system is comprised of several Air Handling Units (AHUs), which supply fresh and clean High Efficiency Particle Air-filtered (HEPA) air to the different areas. The air coming from the HEPA filters is distributed to the production areas through individual air ducts. The efficiency of the HEPA filters is monitored by calibrated magnehelic gauges located in critical areas. Each area is classified according to differentials pressure.

A (b) (4) generator provides water at (b) (4) to the different air units located on the (b) (4) floor of Building (b) (4) The temperature at the filling area is maintained at (b) (4)

The relative humidity (RH) in the filling areas is adjusted with (b) (4) generator. The HVAC system provides at least (b) (4) per hour for Building (b) (4) in the aseptic filling rooms: (b) (4) and vials area. In the aseptic filling room (b) (4) the system provides at least (b) (4) renewals per hour.

- **Water System**

Input water is received from the domestic water supply, which is treated in (b) (4)

(b) (4)

C. Manufacturing Process

At present, (b) (4) manufactures sterile WFI in PFS (data related to the PFS were submitted as part of the DMFs (b) (4) developed the 1.1 mL, (b) (4), and 5.2 mL sterile WFI in PFS in the same (b) (4) syringes by adjusting filling volumes. The following table compares the WFI in PFS that has already been commercialized by (b) (4) and what is proposed for LFB:

(b) (4)

- **Preparation of Purified Water**

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

E. Equipment Qualifications

- **Autoclave Qualification –** (b) (4)

(b) (4)

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

(b) (4)

Autoclave Qualification - Equipment

(b) (4)

(b) (4)

F. Sterilization Validations

During the (b) (4) step, the (b) (4) WFI is (b) (4)

Review Comments/ Assessment

A sterilization cycle description and validation was not provided. A request will be made for LFB to provide the sterilization description and validation. This deficiency was communicated to LFB during the late cycle meeting.

G. Container Closure

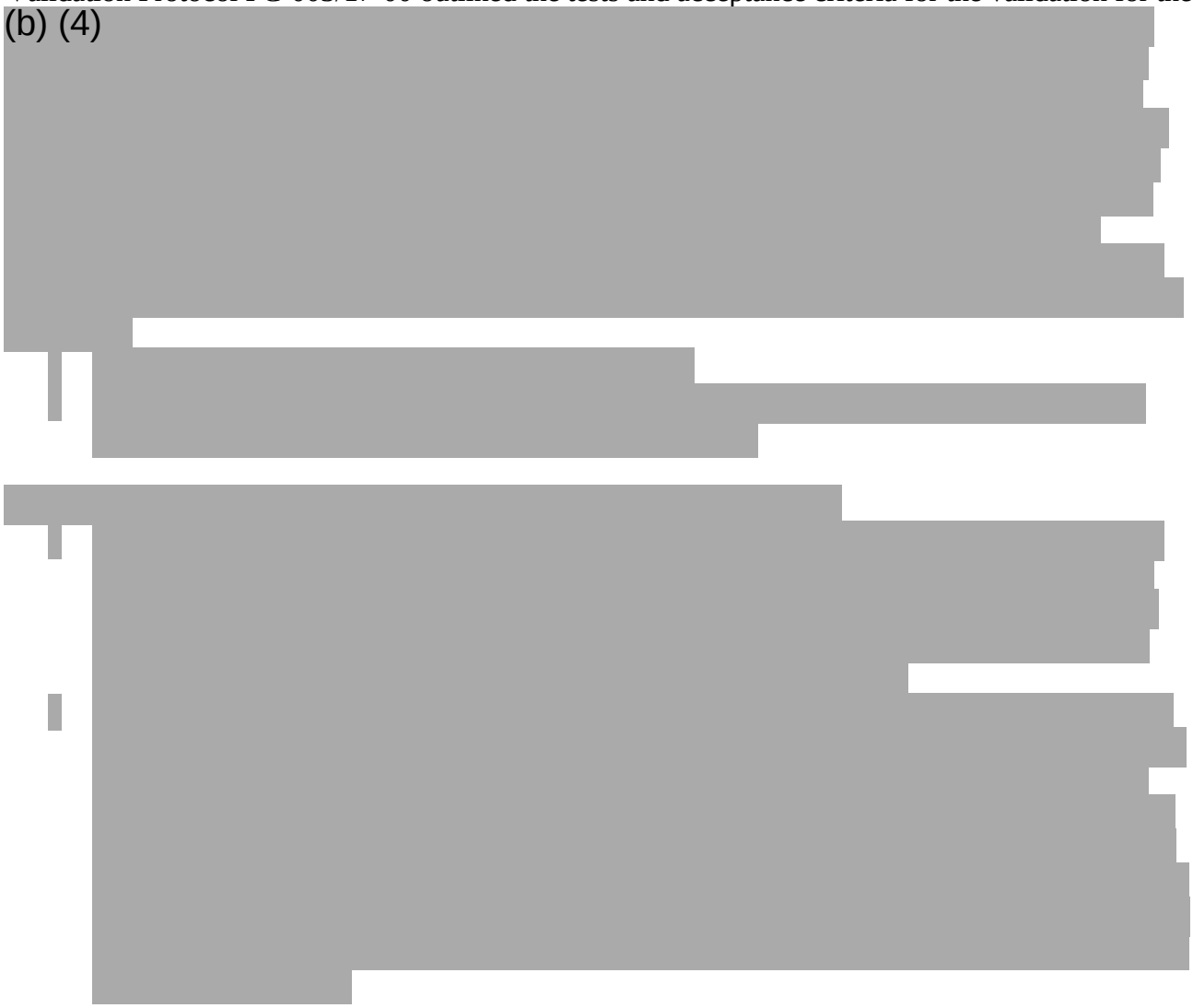
The sterile WFI is packaged in 1.25 mL, (b) (4) or 10 mL capacity syringes (b) (4) syringes, (b) (4) that consist of a syringe barrel, a sterilized stopper and a plastic rigid tip cap (PRTC) with a Luer-Lok as the primary packaging materials. The syringe barrel is made of (b) (4) Type (b) (4) borosilicate glass and is (b) (4) compliant. The plastic rigid tip cap (PRTC) consists of an inner tip cap of (b) (4)

(b) (4) rubber for the 1.25 mL syringe and (b) (4) and 10 mL capacity syringe and an outer shell of (b) (4) ; whereas the Luer-Lok adapter consists of polycarbonate. The plunger stopper is made of (b) (4) elastomer composed of (b) (4) The plunger rod and the backstop are not an integral part of the prefilled syringe, but are provided as accessories. The plunger rod is purchased from (b) (4) and is controlled by (b) (4) according to plunger rod incoming specifications. The backstop is purchased and controlled by (b) (4) .

H. Container Closure Integrity Testing

The container closure system (1.25 mL, (b) (4) and 10 mL glass syringe) provides physical integrity to the product from microbiological contamination and prevents loss of water. The suitability of the primary packaging was demonstrated by sterility and endotoxin test results from the stability studies and CCIT. The CCIT utilized the (b) (4) method with (b) (4) .

Validation Protocol PC-003/17-00 outlined the tests and acceptance criteria for the validation for the (b) (4)



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

(b) (4)

.

Review Comments/ Assessment

(b) (4)

In Amendment 57, LFB provided a progress report for the shipping validation with one deviation (#208486) opened. A request will be made for LFB to provide the deviation and associated deviation investigation once completed.

In Amendment 60, LFB stated the shipping validation report would be completed in October 2017 and a request will be made for LFB to provide an in-depth summary of the final report.

10. COMBINATION PRODUCT

Coagulation Factor VIIa (Recombinant) is supplied as a single-use reconstitution kit containing a sterile glass vial of the lyophilized drug product (LR769) along with a needleless PFS of diluent (sterile WFI), a backstop, and a plunger rod for the syringe, and a commercially available FDA 510(k) cleared vial adapter with a 5 µm filter. At the (b) (4) , the drug product vials and WFI diluent PFS are labelled and packaged as a kit with the remainder of the kit's device and device components.

A. Facility

At the (b) (4) packaging facility, the storage and designated packaging line areas are restricted to authorized personnel only through a specific entry under secured conditions (physically separated area, controlled access). These areas are temperature-controlled (b) (4) The packaging line

area is used to manufacture the (b) (4) dosage forms of the kit. Within the packaging line area, there are specific spaces for (b) (4)

B. Manufacturing Process

At the packaging facility, the receipt and primary labeling of the lyophilized drug product in vials and diluent PFS and secondary packing of the combination product kit occur.

- **Component Supply**

Lyophilized Drug Product Vials

(b) (4)

WFI Diluent PFS

(b) (4) .

Vial Adapters

(b) (4)

Other Components

(b) (4) .

Labels are stored in a secured local within the main warehouse. In the main warehouse, (b) (4) compiles the quantity of diluent prefilled syringes barrels, plunger rods, backstops, vial adapters and packaging components requested in the Work Order, and moves these constituent parts to the "storage area".

A Work Order is for a specific dosage form of LR769 and is manufactured with one supplier batch number for each combination product component. All components allocated to a Work Order are verified to have the pharmaceutical status of "Accepted".

Line clearance of the packaging workshop (working area, label printing machines, packaging line) is performed prior to labeling and packaging operations to confirm that the area is clean and free from any other products, materials or documents previously used.

Goods allocated to the work order are then moved to the packaging line area.

Primary Labeling

Lyophilized Drug Product Vials

The primary labeling manufacturing process of the lyophilized powder is performed in (b) (4) steps:

(b) (4)

WFI Diluent PFS

The primary labeling manufacturing process of the diluent prefilled syringes is performed in (b) (4) steps:

(b) (4)

(b) (4)

III. **Secondary Packing**

There is no secondary packaging performed on the individual lyophilized drug product vials and diluent prefilled syringes. They are co-packaged with the vial adapter.

Packaging materials are (b) (4) . A visual and manual inspection is performed on each component of the kit.

(b) (4)

Qualified Person releases these packaging steps and gives data requested by LFB for the final release of the finished product by LFB's Qualified Person.

Review Comments/ Assessment

Please note: In the Filing with deficiencies Letter (#15, CMC), DMPQ requested a description of the manufacturing process for the primary labeling of the lyophilized drug product vials and diluent PFS and secondary packaging for the combination kit. In Amendment 8, LFB provided the requested information. No further action is required.

C. Equipment Qualifications

There was no equipment qualification for the primary labeling of the lyophilized drug product (equipment (b) (4) and diluent (equipment (b) (4) , because the manufacturing processes require (b) (4) visual check (readability) of all labeled vials and syringes.

Regarding the secondary packaging manufacturing process, operations from Step (b) (4) OQ of this equipment is scheduled in 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 being linked to the BLA review timelines.

Review Comments/ Assessment

Please note: In the Filing with deficiencies Letter (#13e and f, CMC), DMPQ requested the equipment qualification for the primary labeling and secondary packaging and labeling. In Amendment 13, LFB noted the equipment was not qualified as (b) (4) visual check is performed to evaluate the labeling process for the lyophilized drug product vials and diluent PFS.

In Amendment 13, LFB stated an OQ and PQ qualification protocol and report for the serialization secondary packaging would be provided.

D. Shipping

(b) (4)

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

- (b) (4)

(b) (4) :

(b) (4)

(b) (4)

Review Comments/ Assessment

Please note: In the Filing with deficiencies Letter (#17, CMC), DMPQ requested the shipping validation of the final kitted combination product from (b) (4) to HEMA Biologics. In Amendment 8, LFB provided the shipping validation protocol, which appears adequate. The protocol will evaluate the use of the various shipping containers at different configurations to deliver combination kits in an intact manner in the designated thermal conditions, with a visual inspection and CCIT performed to validate the shipping process.

In Amendment 57, LFB provided a progress report for the shipping validation with two deviations (#208488 and 308744) opened. A request will be made for LFB to provide the deviation and associated deviation investigation once completed.

In Amendment 60, LFB stated the shipping validation report would be completed in October 2017 and a request will be made for LFB to provide an in-depth summary of the final report.

E. Device

The co-packaged Coagulation FVIIa drug product vial, the diluent PFS, and vial adapter meet the legal definition of a biologics/device combination product. Please note: The drug product vial and diluent PFS are covered at length in the DMPQ review memos.

Regarding the vial adapter, the 510(k) cleared sterile vial adapters are purchased from (b) (4) and are manufactured by its subsidiary, (b) (4) . The vial adapter is used to facilitate the transfer of the diluent from the PFS into the drug vial and post-reconstitution, facilitate

the transfer of the liquefied drug product into an administration syringe (not provided). Each vial adapter contains a 5 µm filter for particulate filtration and flow aspiration. There are two different sized vial adapters, which are made of the same materials: a 13 mm diameter vial adapter is used for the 1 mg and (b) (4) vials and a 20 mm diameter vial adapter is used for the 5 mg vial.

In *LR769 Combination Product: Overview of Design Controls*, LFB summarized the design and development plan of the combination product and in Doc No. 15259, *General Procedure: Design Control Procedure,* the design inputs, design outputs, design verification design validation, design transfers, and design change procedures were described and an index of the design history file was provided.

- **Design Inputs**

Design Inputs were be developed and maintained for each constituent part to define the system, performance, functional, physical and regulatory requirements, and risk management (safety) requirements according to the intended use.

Combination Product: The design inputs for the co-packaged combination product were integrated into the (b) (4) was used as a comprehensive semi-quantitative quality risk management tool that serves as a basis to establish design outputs. Accordingly, a total of (b) (4) failure modes were evaluated and provided inputs for the design, the labelling and the instructions for use to mitigate the risks.

Constituent Parts: The manufacturers of the vial adapter and PFS provided LFB the design inputs in *Design Input Vial Adapter* (b) (4) and *Report 000146595 Specifications Definition for WFI PFS Developed by* (b) (4), respectively.

Transfer System: The design inputs were also defined for the transfer system.

- **Design Outputs**

Combination Product: A design (b) (4) was used to identify critical design attributes and establish a design verification and validation plan. A total of (b) (4) failure modes were evaluated and the major verification studies were established as follows: (b) (4) The following table presents the design input and output of the combination product:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

III. **Design Review**

During design review there is a documented, comprehensive, systematic examination of a product combination design to evaluate the adequacy of the design requirements, to evaluate the capability of the combination product design to meet these requirements, and identify problems. All documentation are kept in the Design History File (DHF) of the combination product

IV. **Design Verification**

Design verification was conducted both on PFS and on the combination product.

Combination Product: The design verification studies on the combination product are conducted by LFB. The studies include (b) (4)

Diluent and Vial Adapter: The development of PFS at (b) (4) was conducted using a (b) (4) approach. (b) (4)

(b) (4)

V. Design Validation

A design validation was conducted to confirm the combination product meets user and intended uses. The validation was assessed via (b) (4) , respectively.

VI. Design Transfer

The design transfer phase is where the design is frozen for the combination product in order for the final production specifications and instructions to be generated. With the design being frozen, the Design History File Index is finalized. For PFS, a technology transfer plan was signed between LFB and (b) (4) in TTP-001/13-00 Technology Transfer Plan. It is noted LFB determined the design transfer was not applicable for the vial adapter as it is a device that is commercially available.

VII. Design Changes

All design changes shall follow the Change Control Procedure (SOP 05781), which involves a team review that includes risk management, testing, and verification and validation records, regulatory impacts prior to making the change.

LFB noted the presence of visible particles after product reconstitution during the stability studies. LFB concluded the (b) (4)

VIII. Design History File (DHF)

LFB provided an index of its design history file which include records for planning, design input, design output, design verification, design validation, design transfer, and project changes for the combination product, PFS, and vial adapter.

In addition to the design controls and procedures, to satisfy the combination device requirements, the purchasing controls and CAPA systems were described:

IX. Purchasing Controls

LFB has a Corporate Quality Policy 14470 *Outsourced Activities and Purchased Materials*, which describes the principles that all LFB Affiliates have to comply with when outsourcing activities and purchasing materials. The principles outlined in the policy apply to the combination product and its constituents throughout the product lifecycle. There are specific procedures in place to identify, select, reference, approve, and monitor the supplier, subcontractor, and service provider. A Quality Technical Agreement established with LFB to define the responsibility of each party. LFB may request and evaluate samples of the items to ensure defined specifications are met. Files are created for each supplier, with audit results and records associated to the criticality of the item. Oversight of the supplier is maintained via batch records review and/or audits.

X. Corrective Action and Preventative Action (CAPA)

LFB has a Corporate Quality Policy 14813 *CAPA Management*, which defines the CAPA related to quality issues. LFB categorizes the quality issues based on the manufacturing phase (deviations, OOS, tends, monitoring); post-marketing phase (product alert, complaint, withdrawal, recall, returned goods, adverse events, audits); and commercial phase. The management of quality issues is based on a description, investigation, and CAPA, with all critical steps reviewed and approved by QA. During the investigation, a risk assessment is conducted to determine the necessity for short term actions to apply corrective actions immediately. Root causes are analyzed to determine and confirm impact. By a risk-based approach, the CAPAs are classified (e.g. critical, major, minor, etc.) per SOP 13609. The CAPAs are managed as a plan between the concerned department and QA and are closed when actions are complete.

Review Comments/ Assessment

Please note: In the communication regarding possible refuse to file issues, DMPQ requested information regarding the combination product, specifically, the design and development plan of the combination product and procedural summaries for the design inputs, design outputs, design review, design verification, design validation, design transfer, design changes, design history file, purchasing controls, and CAPA system. LFB's overview of design controls and SOP 15259 were provided for review, which appears adequate. There is agreement that LFB has fulfilled the requirements of 820.20, 820.30, and 820.100. Specifically, the design inputs included consideration for performance characteristics and expected needs of the end-user and appears to be consistent with the product's intended use. The design inputs appeared to have been used to develop the design outputs, which include product specifications to evaluate against the design inputs. The design inputs and outputs were verified to confirm the initial design requirements were met based on the initial design input via compatibility and stability studies and other studies. The design was validated to under a clinical setting to evaluate the conformity to user needs and intended use. The design transfer was assessed, for example, when bridging the design of the diluent with its manufacturing process. A design

history file was maintained to capture all of the design issues relating to the combined use of the constituent parts. The CAPA program appear sufficiently established with investigations and CAPA performed with risk assessments.

LFB also established corporate SOPs regarding the purchasing controls for the suppliers and products received that are used to manufacture the combination product. Quality Technical Agreements are established between LFB and the supplier with ongoing oversight of the suppliers' activities by (b) (4) audits. The description provided did not explain or identify controls to ensure changes to the product, manufacturing process, or services provided are identified and appropriate measure are taken to verify the design address the change. A request will be made for LFB to address this issue.

It was noted, though, the SOP 15259 was not in place at time of the combination product design and development, the design and development of the combination product followed the methodology as established under 21 CFR Part 820.30 requirements. LFB has committed to using the SOP as a basis for future combination products design and development.

11. ENVIRONMENTAL ASSESSMENT

LFB claimed an exemption from the requirement of preparing an environmental assessment for the BLA for LR769 in accordance with 21 CFR 25.31 (c). 21 CFR 25.31 (c) allows a categorical exclusion for an action on an application for marketing approval of a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

To support the categorical exclusion, LFB provided the following information for substantiation:

- The LR769 drug product is a recombinant form of the naturally occurring plasma coagulation Factor VII, which is activated during the purification process.
- The recombinant protein is derived from the milk of transgenic rabbits of the R69 line. The rabbit colony, which is used to produce the milk from which the protein is purified, is comprised of transgenic and wild-type rabbits.
- The rabbits are monitored for their health and are maintained in a closed colony in a Specific Pathogen Free barrier facility to prevent the introduction of disease into the colony, milk (source material, which is screened for zoonotic agents), or the environment.
- Collection and disposal of waste adhere to local, state, and federal regulations. Hazardous waste is managed by Environmental, Health, and Safety and or the Rabbit Operations (ROP) Departments.
- No rabbit or rabbit by-products enter the public food supply or are offered for rendering.
- Rabbit carcasses are disposed of in accordance with applicable laws, with a contractor removing the carcasses from the site for complete incineration.

The purified protein is ultimately formulated and lyophilized into the final drug product for use in hemophilia A and B patients. The drug product, when administered to this rare patient population as directed, does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, in accordance with 21CFR 25.31(c).

Review Comments/ Assessment

Please note: In the Filing with deficiencies Letter (#37, Environmental Analysis), DMPQ noted the applicant requested a categorical exclusion under 21 CFR § 25.31 (e), which was not appropriate. DMPQ request the applicant to submit an environmental analysis or if requesting a categorical exclusion, to do so under the appropriate regulation and confirm no extraordinary circumstances exist that would not permit categorical exclusion for an environmental assessment. In Amendment 9, LFB requested a categorical exclusion under the appropriate 21 CFR § 25.31 (c) however did not explicitly state no circumstances existed that would not permit a categorical exclusion to the requirement for a categorical exclusion.

It is noted that while LFB submitted a categorical exclusion under 21 CFR § 25.31(c), CVM will review the environmental analysis as part of the NADA. To receive approval for the BLA, the NADA must be approved prior to the BLA approval unless the applicant withdraws the LFB USA facility. (It is noted the rabbit transgenic milk is also collected at a (b) (4) facility.) It appears the claim for a categorical exclusion of an environmental assessment is negated and a deferment is made to CVM to review the environmental assessment or environmental impact statement in the NADA.

12. INFORMATION REQUEST

The following DMPQ information requests and comments have been communicated to LFB:

A. Prior to Filing

1. The following six comments regarding microbial assurance are based on the Guidance for Industry, for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

    a. Please describe the depyrogenation tunnel and process used for the vials, including physical dimensions, HEPA filters, and flow of product. Time and temperature of exposure, methods and controls for monitoring routine production cycles (e.g., thermocouples) including the number and location of each control, the associated criteria for acceptance and rejection, and a description of the cooling process should also be included. Please include a description of the depyrogenation validation with associated data including heat distribution and penetration study protocols and data, and (b) (4) recovery studies to include the maximum valid dilution.

    b. Please describe the sterilization process used for the lyophilizer (b) (4). Please also include a description of the validation with associated data of this process including heat distribution and penetration summaries, biological challenge studies with microbiological indicators, and routine monitoring procedures.

    c. Please describe the stopper sterilization and (b) (4) removal processes; the submission indicates that these processes are performed with the (b) (4) Please also include a description of the validation with associated data of this process including heat distribution and penetration study protocols and data, biological

challenge studies with microbiological indicators and information about the biological indicators used such as resistance, population, and stability, (b) (4) recovery studies, and routine monitoring procedures. Sterilization data for the stoppers is referenced in the eCTD as being contained in DMF (b) (4); however, the submission indicates that these procedures are performed in-house at (b) (4) and we therefore expect this information to be submitted to the BLA. It is the applicant's responsibility to ensure that the sterilization validation is acceptable and complete.

d. For each autoclave and (b) (4) system, including the lyophilizer (b) (4) system, that is used in preparation of equipment and components used in the finished sterile drug product, please provide the following:

   i. A description of the sterilization process, including the type of cycle (e.g., (b) (4)), the cycle parameters such as time, temperature, and pressure, and performance specifications to include minimum and maximum f_0. Please include methods and controls for monitoring routine production cycles (e.g., thermocouples) including the number and location of each control, and the associated criteria for acceptance and rejection. For the autoclaves, please also describe production load patterns.

   ii. A description of the associated sterilization validation including heat distribution and penetration study protocols and data, information about thermal monitoring and other controls for the validation cycles, thermal mapping of the chamber to include minimum and maximum f_0 values, a description of the validated cycle as compared to the production cycle, biological challenge studies with microbiological indicators and information about the biological indicators used such as resistance, population, and stability. For autoclaves used for the sterilization of product contact equipment please also include loading patterns of the validation runs, and a comprehensive list of all equipment items that these validations support.

   iii. Identity of each specific autoclave unit and lyophilizer unit to include the manufacturer, model/model#, any internally assigned equipment identification numbers, and physical location (building and room or suite).

e. For terminal sterilization (diluent), please provide the following:

   i. A description of the sterilization process, including the type of cycle (e.g., (b) (4), the cycle parameters such as time, temperature, and pressure, and performance specifications to include minimum and maximum f_0. Please include methods and controls for monitoring routine production cycles (e.g., thermocouples) including the number and location of each control, and the associated criteria for acceptance and rejection.

ii. A description of the associated sterilization validation including heat distribution and penetration study protocols and data, information about thermal monitoring and other controls for the validation cycles, thermal mapping of the chamber to include minimum and maximum f_0 values, a description of the validated cycle as compared to the production cycle, biological challenge studies with microbiological indicators and information about the biological indicators used such as resistance, population, and stability.

iii. Specifications (alert and action levels) for (b) (4) should be provided. A description should be included of the program for routinely monitoring (b) (4) to ensure that validated and established limits are not exceeded (e.g., frequency of analysis and methods used in (b) (4) screening). The methods provided should be specific.

f. Please submit the microbial retention studies for the (b) (4) filters that are used for sterile filtration of the finished drug product.

2. Coagulation Factor VIIa, the prefilled syringe (diluent), and vial adapter meet the legal definition of a drug/device combination product (21 CFR Part 3). As you know, 21 CFR Part 4 (Subpart A) addresses the Current Good Manufacturing Practice (CGMP) requirements for all combination products; this final rule was codified on January 22, 2013. Prior to this final rule, manufacturers of co-packaged combination products had to comply with all of the CGMPs associated with each of their constituent parts. 21 CFR 4.4(b) serves as a regulatory option for such manufacturers, which eliminates some of the redundancies associated with the establishment of multiple CGMP operating systems, and thus provides some regulatory relief to co-packaged combination product manufacturers. Please also note that use of a 510(k) cleared device does not preclude the requirement for the applicant to assess the design, suitability, and compatibility of the cleared device to ensure it meets the design requirements of the combination product. Design controls as promulgated per 820.30 still apply. Please address the following:

a. Please provide the design and development plan(s), or a summary of the plan(s), for the combination product under review as per CFR 820.30(b). Your design and development plan(s) or summary, should describe or reference, and assign responsibility for the implementation of the following elements:

- Design Inputs
- Design Outputs
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Design History File

b. Please provide a summary of the procedures used for the identification and control of design inputs as per CFR 820.30(c). Information provided should include how design inputs are documented, reviewed and approved.

c. Please provide a summary of the procedures used to define and document design outputs in terms that allow an adequate and measurable evaluation of conformance to design inputs as per CFR 820.30(d). Information provided should contain design output acceptance criteria. In addition, please explain the mechanism used to ensure that you identified those design outputs that are essential for proper function of the combination product.

d. Please provide a summary of the procedures that define and control the design reviews as per CFR 820.30(e). Information provided should explain how formal design reviews are planned and how you ensure that formal design reviews are conducted at appropriate stages of the design and development process.

e. Please provide a summary of the procedures used to verify the combination product design as per CFR 820.30(f). Information provided should describe the process that confirms the design outputs meet the design input requirements and the mechanism for resolving any discrepancies.

f. Please provide a summary of the procedures used to validate the design for the combination product under review as per CFR 820.30(g). Information provided should define the method of recording design validation for the design history file and should include:

    - Validation results
    - Identification of the design
    - Validation methods
    - Date(s) of validation
    - Individual(s) performing the validation

g. Please provide a summary of the procedures for purchasing controls as per CFR 820.50. Information provided should describe your supplier evaluation process and describe how you will determine type of and extent of control you will exercise over suppliers; how you maintain records of acceptable suppliers; and how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. For additional guidance on the relationship between purchasing controls and receiving acceptance activities, see the Quality System regulation preamble comment #99. [61 FR 52624]

h. Please provide a summary of the procedures for your corrective and preventive action (CAPA) system as per CFR 820.100. Information provided should explain how your CAPA system is tied to your risk management program. For additional discussion on this topic, see the QS regulation preamble comment #159. [61 FR 52633-52634]

B. Filing

CMC

7. (b) (4)

8. Please submit the equipment performance qualification protocols and data to include mixing studies and temperature control studies that support process validation of the (b) (4)

9. Please submit the equipment performance qualification protocol and data that support the (b) (4)

10. Please submit the equipment performance qualification protocol and data that support the process validation of each of the (b) (4) steps. The qualifications should include monitoring and control of critical process parameters (b) (4)

11. We acknowledge that some aspects of the lyophilization process validation were described in sections 3.2.P.3.5.2.6 and 3.2.P.3.5.2.7. Please submit equipment performance qualification protocols and data that support the process validation of the

LR769 lyophilization process for the (b) (4) should be included. Qualification should include empty and loaded chamber temperature distribution studies, and should describe how the temperature and other critical parameters are monitored and controlled during PQ as well as during routine production. The PQ should support demonstration that each phase of the cycle is complete prior to commencing the next phase. Please include qualification data to demonstrate capacity of the condenser and its ability to support your maximum batch size. The qualification should include a detailed description for each lyophilizer including: manufacturer, model/model#, size/dimensions, number of shelves, number of trays, size of trays, and number of vials that can be loaded on each tray and shelf; a description of the condenser, the heating system, and the vacuum pump should also be included. Please describe the batch size and loading patterns for each PQ run as compared to your minimum and maximum production run scales. Additional information and data may be requested at a later time pending further review.

12. Please submit the equipment performance qualification protocols and data that support the process validation of the LR769 filling processes for the (b) (4) Qualifications should address critical process parameters such as filling line speed, pressure, and other adjustable settings with specified acceptable operating ranges to demonstrate that critical quality attributes, e.g., fill volume, fill weight, head space, etc. meet the pre-established acceptance criteria.

    We acknowledge that some performance qualification data was provided for the (b) (4) filling machine used to fill the diluent pre-filled syringes, to include minimum and maximum filling speeds and corresponding fill volume and head space results for each of the three presentations (1.1 mL, (b) (4), and 5.2 mL); additional information and data may be requested at a later time pending further review.

13. Please submit equipment qualification performance qualification data for all equipment used in the manufacture of LR769 drug substance and drug product to include the following:
    (b) (4) (used for (b) (4)
    e. Primary labeling for the lyophilized drug product and diluent
    f. Secondary packaging and labeling for the lyophilized drug product, diluent, and combination product.

14. Please submit the cleaning validation protocol and data for the following equipment:
    (b) (4)

(b) (4)

15. Please submit a description of the manufacturing process for the primary labeling of the lyophilized vials, the primary labeling of the diluent pre-filled syringes, and secondary packaging for the lyophilized powder, diluent, and combination product performed at (b) (4).

16. Please submit the 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; please also submit the test method validation protocol and results for the leak test method that was also used on the diluent pre-filled syringe. Test method validations should include qualification of visual inspectors and instrumentation as applicable, used to detect a critical leak. For the (b) (4) test method used for the drug product vials, please correlate the (b) (4) as determined by your risk analysis, and explain how the (b) (4) characteristics of (b) (4) were quantified.

17. We acknowledge that your shipping validation study for the final kitted combination product from (b) (4) to the HEMA distributors as summarized in in 3.2.P.7.4.2 was ongoing at the time of submission of the BLA. Please submit this shipping validation protocol and data, including the location(s) of the HEMA distributors.

18. Please submit the shipping validation for the unlabeled vials of lyophilized drug product from (b) (4).

19. Please submit the shipping validation for the unlabeled diluent pre-filled syringe from (b) (4).

20. Please submit executed batch records for the diluent.

Facility

26. We acknowledge that LFB is in the process of registering all the manufacturing facilities; please provide FEI numbers for all applicable manufacturing sites upon registration.

27. The LFB USA floor diagrams provided in Section 3.2.A.1 LR 769 – LFB USA, as Appendices 1 to 8, are not sufficiently clear. Please resubmit the diagrams to permit the visualization of flow for the drug substance so that areas or room proximities that may be

of concern for a particular operation, room numbers, and other unique identifiers are clear.

28. For all areas in which operations for the drug substance manufacturing are performed, the information concerning precautions taken to prevent contamination or cross-contamination is not sufficient. While the air quality classification was identified, it was unclear if the air quality classification was validated and measured during operations. Please confirm that the identified air quality classifications at the two drug substance facilities (LFB USA and LFB (b) (4) were validated and measured during operations.

29. The description of LFB (b) (4) Water System provided in 3.2.A.1 Facilities and Equipment – LFB (b) (4) is incomplete. You state there are (b) (4) (b) (4) .

30. The Purified Water System in (b) (4) diagram, provided as Appendix 9 in Section 3.2.A.1 – Facilities and Equipment – LFB (b) (4) is not clear. Please re-submit a clear diagram so all identifiers can be read.

31. In Section 3.2.A.1 Facilities and Equipment – (b) (4) , you provided four facility or floor plan diagrams as Appendices 1 to 4. However, these diagrams were not clear and some were not in English. Please resubmit the diagrams in English so that all unique identifiers are clear.

32. Please provide all details of rabbit husbandry and animal facility biosecurity. Please let CBER know when you plan to submit the application to CVM for the transgenic rabbit development.

Combination Product

33. We acknowledge receipt of the design control data for the various device constituent parts in your December 5, 2016 submission, in response to the November 29, 2016 information request. Please submit data to demonstrate compliance with design history file requirements as specified per CFR 820.30 (j) for the combined product.

34. Please submit data to demonstrate that the devices used for the combination product were developed according to an approved design plan as per CFR 820.30(b). The design plan is the responsibility of the applicant of the combination product and should include: design inputs, design outputs, design review, design verification, design validation, design transfer, design changes, and the design history file.

    Please note that design inputs for the devices should relate to the combination product and are the responsibility of the applicant; it is not sufficient to submit design inputs for

the various constituent parts developed by the respective constituent part manufacturers. Likewise, vendor drawings of the devices do not fulfill the design output requirements per CFR 820.30 (d).

35. Please submit data to demonstrate the recording and tracking of any changes to the devices and how the changes impacted product development and the overall design plan for the combination product. For example, previously the combination product (b) (4)

36. We acknowledge receipt of the design control overview in your December 5, 2016 submission, in response to the November 29, 2016 information request. This document does not address design verification requirements; please submit data to support design verification requirements as per CFR 820.30 (f).

Environmental Assessment

37. It is noted that a request for categorical exclusion was submitted to the BLA (25.31(e) Action on an IND); this categorical exclusion is not applicable to a product under review in a biologics license application. Please submit an environmental assessment as outlined in 21 CFR Part 25 or a request for a categorical exclusion with the appropriate basis for exclusion for your BLA, as outlined in 21 CFR Part 25.31. Please confirm that no extraordinary circumstances exist that would not permit categorical exclusion to the requirement for an environmental assessment.

C. Late Cycle

Please note that critical equipment and facility information was received very late in the review cycle and is still under review. The following is a list of issues discovered thus far; additional issues may be identified as the review progresses.

Regarding the diluent:

i. FDA found the qualification of the (b) (4) autoclave (b) (4) , which issued to (b) (4) to be inadequate. Specifically:

(b) (4)

.

(b) (4)

(b) (4)

Regarding the drug product – depyrogenation:

(b) (4)

(b) (4)

(b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

.

Regarding the drug product – stopper washing:

(b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Regarding the drug product – stopper sterilization:

(b) (4)

(b) (4)

Regarding the drug product – (b) (4) *of stopper-*(b) (4)

(b) (4). (b) (4)