U.S. FOOD & DRUG ADMINISTRATION

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

To: Administrative File BLA 125641

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Through: Lori Peters, Acting Branch Chief, OCBQ/DMPQ/MRB1

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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 of the Complete Response Letter dated October 11, 2019 for Biologics License Application (BLA) for Sevenfact®

Due Date: April 10, 2020

RECOMMENDATION: Based on the information provided in the original submission and amendments, approval is recommended. The following Post-Marketing Commitment (PMCs), which were committed to by LFB S.A. via Amendment 125641/0/85 received March 10, 2020, are associated with approval:

1. LFB S.A. will perform a Performance Qualification (PQ) study to demonstrate the robustness of (b) (4) The PQ study final report will be submitted for CBER review as a PMC-Final Study Report.

   Final Report Submission: October 10, 2020

2. LFB S.A. will perform a Performance Qualification (PQ) study to demonstrate the (b) (4) The PQ study final report will be submitted for CBER review as a PMC-Final Study Report.

   Final Report Submission: October 10, 2020

3. LFB S.A. will perform a Performance Qualification (PQ) study to demonstrate the (b) (4) The PQ study final report will be submitted for CBER review as a PMC-Final Study Report.

   Final Report Submission: October 10, 2020

4. LFB S.A. will perform a Performance Qualification (PQ) study to demonstrate the (b) (4). The PQ study final report will be submitted for CBER review as a PMC-Final Study Report.

   Final Report Submission: October 10, 2020

REVIEW MEMO TABLE OF CONTENTS

1. REGULATORY HISTORY

Laboratorie Francais du Fractionnement et des Biotechnologies Société Anonyme (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.

Due to deficiencies in the BLA and amendments, the Agency issued a Complete Response (CR) Letter to LFB S.A. on October 13, 2017, which noted:

- Chemistry, Manufacturing, and Controls (CMC) deficiencies; and
- Outstanding inspection items from the following Pre-License Inspections at:
  - LFB (b) (4)
  - LFB (b) (4)
  - LFB USA, Inc. in Charlton, MA (FEI# 3013501870) conducted on May 8 – 12, 2017.

Note: For additional details regarding the assessment and review of the original BLA submission and amendments as it relates to Chemistry, Manufacturing, and Controls (CMC) and Facilities, please refer to the DMPQ review memos dated September 26 and 27, 2017.

Since the issuance of the CR Letter, LFB S.A. submitted a request for a Type A meeting, which was scheduled for February 9, 2018. LFB S.A.'s questions concerned:

- Process validation activities to demonstrate comparability of the product manufactured from milk sourced from the (b) (4) different rabbit facilities at Charlton Rabbit Facility (Charlton, MA) (b) (4)
- (b) (4)
- Strategy to address the visible particulates observed in the reconstituted Final Drug Product during release, testing, and stability studies;

- Potency assay and the stability studies; and
- Shipping validation program, which includes the Operational Qualification (OQ) and Performance Qualification (PQ) studies.

Based on the written preliminary meeting responses, of which LFB S.A. confirmed receipt, LFB S.A. requested the Type A meeting be cancelled.

On December 27, 2018 FDA's Center for Veterinary Medicine (CVM) approved NADA N-141511-A-0000-OT for Bc2371 rDNA construct in R69 New Zealand white rabbits. Heritable Construct. Domesticated Rabbits. Postmarketing commitments (PMCs) were issued, which are not expected to affect the approvability of the BLA.

On October 11, 2019, LFB S.A. responded to the CR letter action with as Amendment 71, which the Agency designated as a Class 2 resubmission. Since the CR response in Amendment 71, DMPQ follow-up was needed and responses were submitted as:

- Amendment 125641/0/76, received January 23, 2020;
- Amendment 125641/0/80, received February 13, 2020;
- Amendment 125641/0/82, received February 27, 2020; and
- Amendment 125641/0/85, received March 10, 2020.

Note: 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). For additional details, with focus on the lyophilized drug product, please also refer to the other DMPQ review memo prepared by Nicole Trudel.

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

- (b) (4)
- LFB Biotechnologies in Les Ulis, France (FEI# 3003539722); and
- LFB Biomedicaments in Les Ulis, France (FEI # 3003539722).

2. BACKGROUND

Coagulation Factor VIIa (Recombinant), LR769 will be supplied as a single-use co-packaged combination product containing a sterile glass vial of sterilized lyophilized powder LR769 biological drug product, along with sterile Water for Injection (WFI) in a pre-filled syringe (PFS) with a plunger rod and a backstop and a commercially available CE marked ad 510(k) cleared sterile vial adapter (VA) with a 5 µm filter [510(k) number (b) (4) for 13 mm and for 20 mm]. The PFS are fitted with a Luer lock which is compatible with the VA. LR769 is packaged in (b) (4) vial sizes containing 1 mg, (b) (4) or 5 mg of LR769 along with diluent PFS filled with 1.1 mL, (b) (4) and 5.2 mL of WFI, respectively. The DP is to be manually reconstituted with Water for Injection (WFI) immediately prior to administration by bolus intravenous injection. When reconstituted as directed, the concentration of Coagulation Factor FVIIa (Recombinant) is 1 mg (1,000 mcg) per mL.

These components are packaged together with the instructions for use (IFU), into a cardboard box with an inner foam insert and sealed with a tamper evidence.

Note: Per notification in Amendment 70 received June 24, 2019, LFB.S.A. elected to modify their BLA and withdraw the (b) (4) dosage. LFB S.A. indicated that while the (b) (4) , data on the (b) (4) dosage remains within the BLA to support the process validation and stability studies.

3. OVERVIEW OF MANUFACTURING AND TESTING FACILITIES

The following table is a list of manufacturing and testing facilities associated with the manufacture of LFB S.A.'s Coagulation Factor VIIa (Recombinant), LR769:

Facility	Manufacturing Activities	Inspection History and Inspection/Waiver/No Inspection
(b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	Inspection not required
LFB USA, Inc. (b) (4) Charlton, MA 01507 FEI: 3013501870	(b) (4)	CBER-DMPQ PLI May 8- 12, 2017 VAI CVM Aug. 21-22, 2017 NAI
(b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	Inspection not required

Facility	Manufacturing Activities	Inspection History and Inspection/Waiver/No Inspection
(b) (4)		
(b) (4)	(b) (4)	Inspection not required
LFB USA, Inc. 175 Crossing Boulevard Framingham, MA 01702, USA FEI: 3003837678	(b) (4)	Inspection not required
LFB Biotechnologies Zone Artisanale de Courtaboeuf 3 avenue des Tropiques Courtaboeuf Cedex Les Ulis, Essonne, 91958, France FEI: 3003539722	(b) (4)	French National Agency for Medicines and Health Products Safety 11/16/2018 Complies Inspection Waiver
(b) (4)	(b) (4)	Inspection not required
LFB (b) (4)	(b) (4)	CBER-DMPQ PLI (b) (4) VAI
LFB (b) (4)	(b) (4))	CBER-DMPQ PLI (b) (4) VAI

Facility	Manufacturing Activities	Inspection History and Inspection/Waiver/No Inspection
LFB Biomedicaments Zone Artisanale de Courtaboeuf 3 avenue des Tropiques Courtaboeuf Cedex Les Ulis, Essonne, 91958, France FEI: 3003539722	(b) (4)	French National Agency for Medicines and Health Products Safety 06/21/2019 Complies
(b) (4)	(b) (4)	ORA inspection (b) (4) VAI Inspection Waiver
(b) (4)	(b) (4)	ORA inspection (b) (4) NAI Inspection Waiver
LFB (b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	ORA Inspection (b) (4) NAI Inspection Waiver
(b) (4)	(b) (4)	Mutual Reliance Agreement Inspection by ANSM (b) (4) VAI Inspection Waiver

In the CR response in Amendment 71, LFB S.A. provided a comprehensive list of manufacturing sites associated with the product. It was noted two facilities identified in the original BLA were no longer identified in the CR response. To reconcile the differences, the following information request was submitted on January 14, 2020:

We noted the original BLA identified the following facilities involved in the manufacture of Coagulation Factor VIIa (Recombinant) that were no longer identified on the comprehensive lists of manufacturing sites in the Reviewer's Guide of Amendment 71.

Please reconcile the following manufacturing facilities and clarify if the facilities continue to be involved in the manufacture of Coagulation Factor VIIa (Recombinant):

Manufacturing Site	***Manufacturing Activity***
(b) (4)	(b) (4)
(b) (4)	(b) (4)

In the IR Item #1 response in Amendment 76 received January 23, 2020, LFB S.A. clarified the (b) (4) facility continues to be involved in the manufacture of Coagulation Factor VIIa (Recombinant) by testing of FVII (b) (4) for female rabbits housed at (b) (4) facility. In Amendment 38, LFB had stated (b) (4) was performed at (b) (4), however, LFB stated no (b) (4) testing is performed at (b) (4). LFB also clarified (b) (4) Quality Control is not involved in the manufacture or testing of Coagulation Factor VIIa (Recombinant).

Review Comments/ Assessment

The IR was issued to ensure an accurate list of manufacturing facilities was provided and reflected in the application for the manufacture of Coagulation Factor FVIIa (Recombinant) as a discrepancy was noted when comparing the CR response in Amendment 71 to the original application and earlier amendments. LFB clarified the involvement of the 2 facilities in question. No further action is required.

The following provides the DMPQ CR Letter administrative items (# 8 – 10) and a summary of the CR Letter response:

CR Item # 8

During the May 2017 inspection of LFB USA, Inc. in Charlton, MA, LFB USA informed that the (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, Inc. in Charlton, MA. Please confirm and update the application to remove reference to the (b) (4) facility, if applicable.

In the CR Item #8 response in Amendment 71, LFB S.A. confirmed (b) (4) in (b) (4), is no longer used as a FVII (b) (4) source material storage facility and was replaced by the storage facility at LFB USA, Inc. in Charlton, MA. The submission was revised to reflect this replacement.

Review Comments/ Assessment

The CR item was issued to ensure the application reflected an accurate list of manufacturing facilities associated with the manufacture of Coagulation Factor FVIIa (Recombinant). LFB verified the facility in question was no longer used. No further action is required.

CR Item # 9
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.

In the CR Item #9 response in Amendment 71, LFB.S.A. provided the same FEI number 3003539722 for LFB Biotechnologies and LFB Biomedicaments in Les Ulis.

To determine if the facilities have to separately identify with separate FEI numbers, criteria includes:

- One or multiple buildings at one geographic location or address if the activities in them are closely related to the same business enterprise;
- Supervision of the same local management; and
- Capability of being inspected by FDA during a single inspection.

The following information request was submitted on January 14, 2020 for clarification to determine if the facilities should separately register to have unique FEI numbers:

In your Amendment 71 response to CR Item 9, you provided the same FEI number 3003539722 for the LFB Biotechnologies and LFB Biomedicaments facilities located in Les Ulis, France. Please clarify if both facilities are under the supervision of the same local management.

Please note: Based on your response for clarification above, if both facilities are not under the supervision of the same local management, the facilities should have a unique FEI number despite being located at the same physical address. Therefore, unless you can provide previous correspondence from the US FDA stating otherwise, please separately register the LFB Biotechnologies and LFB Biomedicaments facilities in Les Ulis and provide the FEI numbers upon registration.

In the IR Item #2 response in Amendment 76 received January 23, 2020, LFB S.A. confirmed the LFB Biomédicament and LFB Biotechnologies facilities are both located at the same physical address in Les Ulis, France, are involved in drug product testing, are under the supervision of the same local management

Review Comments/ Assessment

The IR item was issued to ensure the application reflected accurate information, which includes the FEI #, for the manufacturing facilities associated with the manufacture of Coagulation Factor FVIIa (Recombinant) as it was noted the same FEI # was provided for 2 facilities. LFB's response appeared to confirm the 2 facilities could identify with the same FEI# as the criteria was met. No further action is required.

CR Item # 10
Please provide the FEI number for (b) (4) *facility in* (b) (4)

In the CR Item #10 response in Amendment 71, the FEI number for (b) (4) was provided and included in the facilities table above.

Review Comments/ Assessment

The CR item was issued to ensure the application reflected accurate information, which includes the FEI #, for the manufacturing facilities associated with the manufacture of Coagulation Factor FVIIa (Recombinant). LFB verified the facility in question was no longer used. No further action is required.

For the facilities that would require an inspection and could not be waived, a risk-based approach was taken to determine if re-inspections were to be conducted. The three facilities under consideration were: 1) LFB (b) (4) 2) LFB (b) (4) and 3) LFB USA, Inc. in Charlton, MA. During the review of the original BLA, Pre-License Inspections (PLIs) were conducted for the three facilities in 2017 with objectionable items issued on the FDA Form 483 at each facility. Following the issuance of the FDA Form 483 at each PLI, the firms responded to the Form 483s and CBER determined a number of the responses were deficient. The deficiencies were conveyed as outstanding inspection items on the Complete Response Letter issued on October 13, 2017. Based on the nature of the outstanding inspection items from the PLIs, which were predominantly review issues as opposed to quality systems issues, a determination was made to not re-inspect the facilities.

It was noted since CBER's 2017 PLI, LFB (b) (4) was inspected by the French National Agency for Medicines and Health Products Safety in (b) (4) . The (b) (4) inspection was conducted as a follow-up to check the points of Injunction n°16MB134-INJ issued January 26, 2017 and consequently, the site was the subjection of new Injunction n°18MB003-INJ dated May 3, 2018. The following information request was submitted on January 14, 2020:

We noted LFB (b) (4) was issued Injonction N° 18MB003-INJ, dated May 3, 2018, by the French National Agency for Medicines and Health Products Safety / Agence nationale de sécurité du medicament et des produits de santé (ANSM). Please provide the following regarding Injonction N° 18MB003-INJ:

- *Summary of the issues identified;*
- *Scope of the potential impact to BLA 125641; and*
- *List of Corrective and Preventative Actions to address the identified issues and the status of the CAPAs.*

In the IR Item #3 response in Amendment 76 received January 23, 2020, LFB S.A. explained ANSM issued a letter of injunction to the (b) (4) manufacturing facility on May 3, 2018 following a January 15 – 19, 2018 inspection. Deficiencies were identified in the following areas:

- Business Continuity Plan

Issues Identified	CAPA (b) (4)	No.)

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

(b) (4)

LFB explained it had developed a comprehensive and efficient action plan, which ANSM evaluated and verified during a follow-up inspection on May 20 – 24, 2019 and determined was acceptable. The CAPAs have all been closed and ANSM issued a final letter on November 15, 2019 to lift/close the injunction.

LFB Quality Systems conducted full assessments of the Business Continuity Plan, Deviation Management System, Employee Training, and determined all Sevenfact quality system events reported were found to be appropriately identified, investigated and remediated. As such, LFB concluded there was no impact on BLA 125641 cGMP activities.

Review Comments/ Assessment

The BLA 125641 review team had conducted a PLI of LFB (b) (4) . Since the inspection, ANSM had conducted a 2018 inspection and issued an injunction letter. The IR item was issued to obtain more details regarding the injunction letter, which would be assessed to determine if CBER would perform a re-inspection of LFB (b) (4) . The issues identified included areas in business continuity plan, deviation management system, employee training, and manufacturing operations. LFB had developed a plan to address the issues, which included CAPAs. ANSM appeared to agree with LFB's action plan and issued a letter that closed and lifted the injunction. Additionally, LFB had assessed the issues identified and determined there was no impact associated with BLA 125641. No further action is required.

4. SOURCE MATERIAL

(b) (4) LFB USA in Charlton, MA, transgenic rabbits are maintained and milked. The milk from the transgenic rabbits, known as the source material for rhFVIIa, is stored (b) (4).

The following provides the DMPQ CR Letter source material item (#11) and a summary of the CR Letter response with an assessment of the response:

CR Item # 11

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

(b) (4)

(b) (4)

5. INTERMEDIATE

(b) (4)

The following provides the DMPQ CR Letter intermediate items (#12 - 14) and a summary of the CR Letter response with an assessment of the responses:

(b) (4)

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

(b) (4)

6. DRUG SUBSTANCE

(b) (4)

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The following provides the DMPQ CR Letter drug substance items (#15 - 18) and a summary of the CR Letter response with an assessment of the responses:

(b) (4)

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

(b) (4) . No further action is required.

7. DRUG PRODUCT

Regarding the manufacture of the drug product, 24 DMPQ CR items (#19 – 42) were issued and a summary of the CR Letter response with an assessment of the responses were prepared in the review memo by CMC/ facilities reviewer, Nicole Trudel.

8. DILUENT

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

The following provides the DMPQ CR Letter diluent items (#43 - 53) and a summary of the CR Letter response with an assessment of the responses:

CR Item # 43
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)

In the CR Item #43 response in Amendment 71, LFB S.A. confirmed the WFI diluent is filled into syringes and stoppered in Building (b) (4)

Review Comments/ Assessment

The CR item was issued to ensure an accurate description of the filling, stoppering, and terminal sterilization process was provided and reflected in the application for the manufacture of Coagulation Factor FVIIa (Recombinant). LFB confirmed the manufacturing areas associated with the manufacturing process. No further action is required.

CR Item # 44
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)

In the CR Item #44 response in Amendment 71, LFB S.A. provided Deviation DV1405-125, as requested, and explained the deviation was opened due (b) (4)

(b) (4)

LFB S.A. explained when the particle count was exceeded during filling, (b) (4) met established specifications for the filling (b) (4) accepted syringes.

Review Comments/ Assessment

The CR item was issued for additional details regarding a deviation that occurred during process validation while filling the 5.2 mL diluent format. LFB provided the investigation report, which explained the particle count (b) (4) There is agreement the cause of the deviation appears to have been appropriately identified. Additionally, there is agreement sufficient controls, via a visual and (b) (4), are present to ensure personnel segregate and reject products that may be impacted. No further action is required.

CR Item # 45

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.*

In the CR Item #45 response in Amendment 71, LFB S.A. clarified the CCIT samples for the process validation batch were labeled as “sample 12” and (b) (4) samples were assessed for CCIT per each validation batch, which contained approximately (b) (4) syringes. The following table was provided to identify the number of samples tested for each process validation batch:

(b) (4)

(b) (4)

(b) (4)

Review Comments/ Assessment

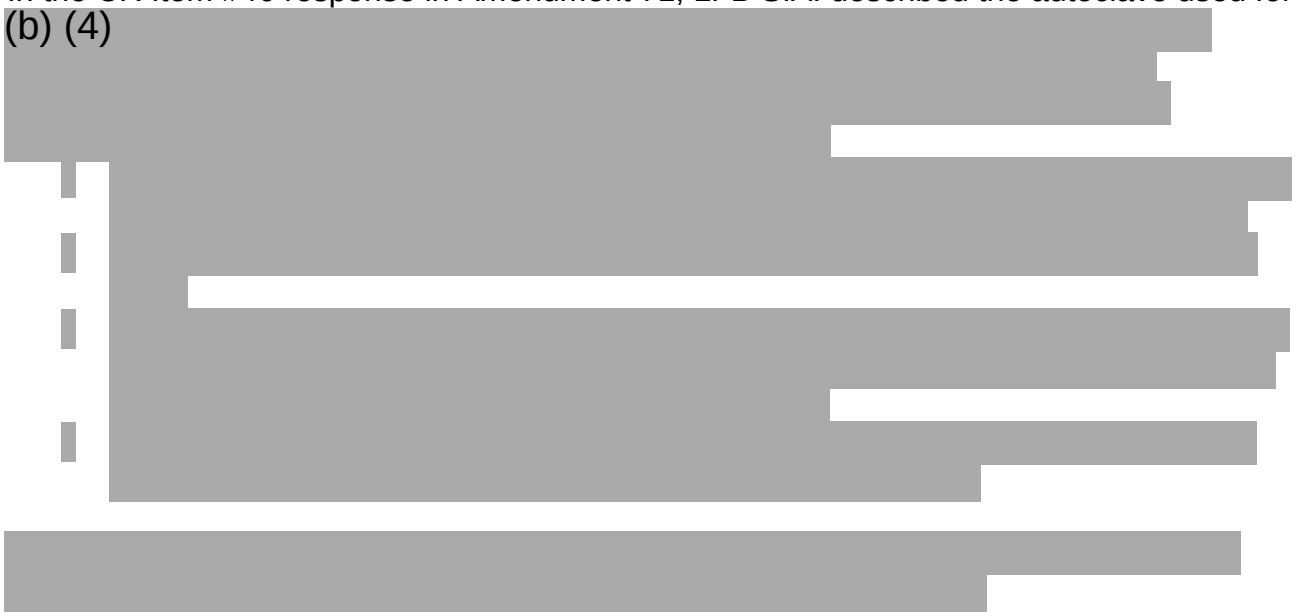
The CR item was issued for a rationale to explain the number of samples collected (b) (4) to be tested by (b) (4) for CCIT, (b) (4) All CCIT samples met the established criteria. There is agreement the number of samples evaluated for CCIT appears adequate to be representative of the batch size. No further action is required.

CR Item # 46

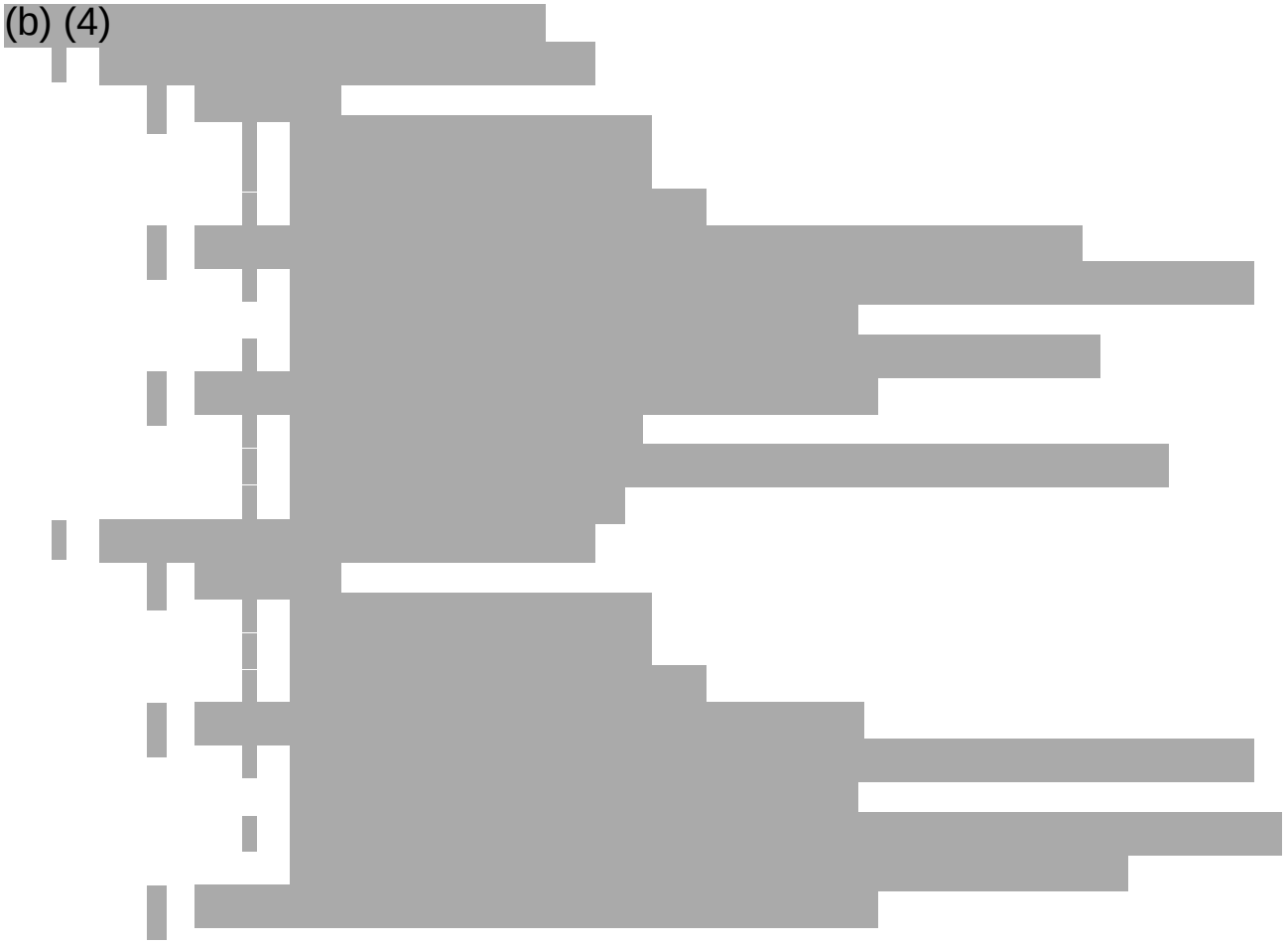
Please provide a description of the sterilizer load configuration, autoclave loading

patterns, and sterilizer hardware (e.g. carts, shelves, trays) used in the (b) (4) *autoclave* (b) (4) *used to* (b) (4)

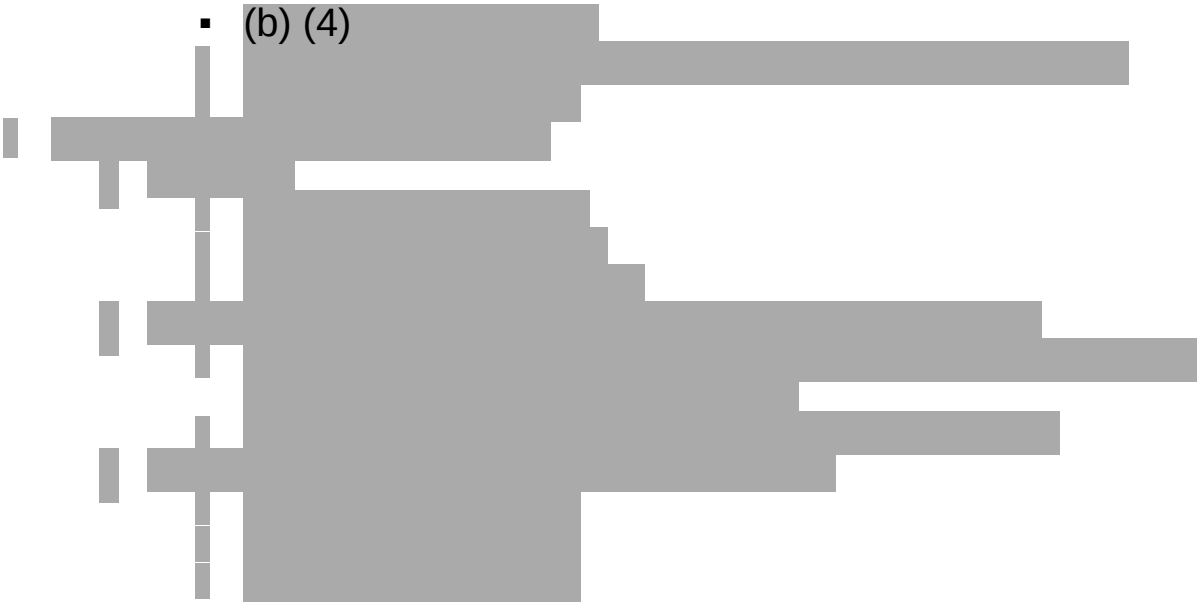
In the CR Item #46 response in Amendment 71, LFB S.A. described the autoclave used for (b) (4)



(b) (4)



- (b) (4)



Review Comments/ Assessment

The CR item was issued to ensure an accurate description of the (b) (4) autoclave (b) (4) used to (b) (4) was provided and reflected in the application, as the information was not previously provided. LFB provided the information, as requested, which would be used to assess if heat distribution and heat penetration studies were adequately performed, as discussed in the subsequent CR items. No further action is required.

CR Item # 47

We acknowledge the (b) (4) *autoclave* (b) (4) *heat distribution (empty chamber) and heat penetration tests were described in Amendment #6 dated December 5, 2016, 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* (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) *.*

(b) (4)

,

(b) (4)

Review Comments/ Assessment

The CR item was issued for the rationale that explains the location of the thermocouples and biological indicators, as applicable, in the heat distribution and heat penetration studies, as it appeared the locations may have been inadequate when previously described. LFB explained the thermocouple locations on the previously provided diagram for the heat distribution were not all-inclusively identified. An updated diagram was provided that identifies all of the thermocouple locations. Additionally, LFB explained a risk assessment had been performed to support the locations of the thermocouples. There is agreement the number of thermocouples and their locations appeared to be sufficient to identify the hot and cold spots within the autoclave. Also, LFB explained the study design of the heat penetration study, which appears to have been adequately executed per the load evaluated. No further action is required.

CR Item # 48

In Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, you describe (b) (4) *. 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)

(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 first and* (b) (4) *steps that support the use of all of the sterilized equipment.*

(b) (4)

(b) (4)

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

(b) (4)

Review Comments/ Assessment

The CR item was issued to ensure an accurate description of the autoclaves and the process used to sterilize equipment that is used in the (b) (4) steps and the associated autoclave validation was provided and reflected in the application, as the information was not previously provided. LFB provided a description of the autoclaves, which included the location of the temperature sensors within the chamber and autoclave control systems. Temperature distribution and heat penetration studies were conducted for each autoclave. For the heat penetration studies, the minimum and maximum loads were evaluated per autoclave and associated load program. The studies appear to have been sufficiently performed with the use of thermocouples and biological indicators as the results for each autoclave and respective load program met the established acceptance criteria to support the autoclaves and sterilization process. No further action is required.

CR Item # 49

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

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Review Comments/ Assessment

The CR item was issued to ensure an accurate description of the (b) (4) process used to sterilize the (b) (4) was provided and reflected in the application and the associated (b) (4) process was validated, as the information was not provided. LFB provided a description of the (b) (4) process and the studies to support the sterilization process validation, as requested. The validation employed (b) (4)

performed, with results meeting the established specifications to support the sterilization process effectiveness. No further action is required.

CR Item # 50

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 and 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) *.*

(b) (4)

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

Review Comments/ Assessment

The CR item was issued for an description of the preparation process for the positive control syringes used in the (b) (4) method for CCIT, as the positive control designs did not appear to incorporate typical leak (b) (4) LFB clarified the positive control designs in question incorporated an LOD of (b) (4), which was (b) (4) than expected, and explained the CCIT method described in the original BLA was not properly validated. As such, LFB validated a new CCIT (b) (4) method, as reported in MVR00737/1, which incorporated positive control vials with (b) (4) defects to evaluate the microbiological and physical-chemical aspects of the (b) (4) method. The results appeared to demonstrate a sensitivity to detect defects in vials with a LOD of (b) (4).

An additional study using the validated positive control preparation process was performed to verify the CCIT of the PFS. The study appears to be adequately conducted with the use of a worst-case syringe ((b) (4)

(b) (4)

CR Item # 51

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)

(b) (4)

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

(b) (4)

[redacted]

Review Comments/ Assessment

The CR item was issued because the diluent shipping studies were incomplete and did not adequately evaluate the shipping container's ability to maintain product integrity and storage temperatures while in transit. LFB explained a new OQ study was performed. There is agreement the study was adequately performed with 3 runs at the minimum and maximum loads and challenged with worst-case transport durations and transport thermal conditions when exposed to (b) (4)

[redacted]

(b) (4)

Additionally, in the CR response, LFB (b) (4)

The PQ protocol design appeared adequate. LFB (b) (4)

Given the OQ study results and deviations observed, it is recommended the PQ results be closely reviewed to ensure the product can withstand the routine packaging and shipping process. (b) (4)

CR Item # 52

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.*

(b) (4)

(b) (4)

Review Comments/ Assessment

The CR item was issued for the validation of the temperature-controlled trucks that are used to transport the diluent manufactured at (b) (4) to the kit packaging and labeling facility at (b) (4). LFB provided the truck validations, as requested. The validations appear to be adequately performed with the worst-case load (b) (4), to be representative of a maximum shipment. Also, temperature probes appear to be sufficiently located to provide thermal conditions of the product within the vehicle and the environmental thermal conditions outside of the vehicle. The results appear to support the qualification of the vehicles. Additionally, a description of the trucks was provided, which included temperature sensors that appear to provide adequately controls to monitor shipment temperatures. The results of the vehicle qualification appear to support the use of the trucks. No further action is required.

CR Item # 53

We acknowledge you provided a progress report of the shipping validation ((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).

(b) (4)

(b) (4)

Review Comments/ Assessment

The CR item was issued for an explanation of the deviation that occurred during the OQ protocol. LFB provided an explanation of the deviation, as requested. It is noted the deviation and CR item appears to be irrelevant because a new OQ protocol was executed, as described above in CR Item #51. For additional details, please reference CR Item #51. No further action is required.

9. COMBINATION PRODUCT

The following provides the DMPQ CR Letter combination product items (#54 - 55) and a summary of the CR Letter response with an assessment of the responses:

CR Item # 54

We acknowledge that 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.*

(b) (4)

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

(b) (4)

[redacted]

Review Comments/ Assessment

The CR item was issued because the combination product shipping studies were incomplete and did not adequately evaluate the shipping container's ability to maintain product integrity and storage temperatures while in transit. LFB explained a new OQ study was performed. There is agreement the study was adequately performed with 3 runs at the minimum and maximum loads and challenged with worst-case transport durations when exposed to (b) (4)

[redacted]

(b) (4)

.

Additionally, in the CR response, LFB (b) (4)

The PQ protocol design appeared adequate. LFB (b) (4)

.

Given the OQ study results and deviations observed, it is recommended the PQ results be reviewed to ensure the product can withstand the routine packaging and shipping process. Distribution would not be recommended if the PQ results, (b) (4)

CR Item # 55

We acknowledge that 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.

(b) (4)

(b) (4)

Review Comments/ Assessment

The CR item was issued to ensure LFB has proper control of the final product if changes were made to the combination. LFB provided a SOP explaining that before a supplier may make a change to the product, the supplier must provide written notification to LFB. The changes are evaluated by a LFB panel and if the changes to the combination product have the potential to impact the product quality, validations, and/or regulatory documentation, a risk analysis is performed to establish a risk-based action plan to monitor the impact of action implementations at set times. LFB provides final notification of acceptability of the change before it may be implemented. Other measures by which LFB monitors changes to the combination product include the Annual Product Review / Product Quality Review and supplier audits. LFB appears to have established a procedure by which it maintains control of any changes that could impact the final combination product through notification from the supplier before the changes are implemented and conducting its own risk analysis and action plan to evaluate the changes before they are implemented. No further action is required.

10. OUTSTANDING INSPECTION ITEMS

Three PLIs were performed during the review of BLA 125641. The inspection team on each PLI issued a Form FDA 483 at the close-out of each PLI. While the facilities responded to the objectionable items, the inspection team found some of those responses to be deficient. The following provides the CR Letter outstanding inspection items (#56 – 70) and a summary of the CR Letter response with an assessment of the responses:

LFB Biomédicaments

CR Item # 56

Regarding Observation 3, LFB Biomédicaments was cited for not preparing the test sample (for the visual appearance of reconstituted solution: visible particulates) in accordance with end-user (patient) instructions. FDA acknowledges LFB proposals to prepare (b) (4) *per batch in accordance with end-user instructions (Amendment #29 dated April 4, 2017), to change the test operating conditions as documented in the proposed test protocol (Amendment #52 dated July 14, 2017) and test report (Amendment #54 dated July 28, 2017), and to introduce a* (b) (4) *-tiered testing scheme for this supplemental test to the* (b) (4) *visual inspection process (Amendment #37 dated May 17, 2017). Please address the following questions regarding the visual inspection of reconstituted FDP:*

a. *Please confirm that these supplemental test samples are pulled from the passing Acceptance Quality Limit (AQL) sample set of the* (b) (4) *visual inspection.*

b. *Please clarify the quantity of additional samples in the second sampling plan of the supplemental test; presumably, the total sample size is* (b) (4) *units from the first supplemental sampling plus an additional* (b) (4) *units in the second supplemental sampling plan for a total of* (b) (4) *units.*
c. *Please clarify the acceptance criteria for the second sampling plan, and confirm that the total number of vials with particulates includes any vials with particulates detected in the first* (b) (4) *vials, plus any detected in the additional* (b) (4) *(or* (b) (4) *vials.*
d. *Please confirm that the acceptance criteria limits for the supplemental testing apply only to intrinsic particulates, and that any extrinsic particulates would require a thorough investigation.*
e. *Please provide a rationale for proposing a double sampling plan with the same AQL* (b) (4) *vs. a normal sampling plan with a tightened AQL for the second supplemental inspection.*

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by Nicole Trudel.

LFB (b) (4)

CR Item # 57

Regarding FDA Observation 4a, please submit the revised specifications for the (b) (4) *and any supporting documentation to demonstrate that the supplier is meeting these new specifications.*

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by Nicole Trudel.

CR Item # 58

Regarding FDA Observation 4b, please provide the revised specifications for the (b) (4) *, and any supporting data to demonstrate that the supplier has been appropriately qualified.*

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by Nicole Trudel.

CR Item # 59

Regarding FDA Observation 6: In the documents "1.11.1 Quality Information Amendment" submitted in Amendment #31 dated April 14, 2017, on pages 21-22 of 41, and Report No. 000236286 (V 1.0) "Report on validation of the (b) (4) *following* (b) (4) *submitted in Amendment #52 dated 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 T0 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)

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 6 was issued to LFB (b) (4) because the container closure integrity of the (b) (4) was not tested. Specifically, (b) (4) was not validated to prevent (b) (4) To address the 483 Observation, LFB provided a response that described 2 qualification studies it would perform to:

- (b) (4)

The qualification results of the lowest (b) (4) appeared acceptable. For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 4, 2017.

(b) (4)

CR Item # 60

Regarding FDA Observation 7: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #31 dated 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.*

In the CR Item #60 response in Amendment 71, LFB S.A. referenced CR Item #14, which provided the OQ shipping study that evaluated the (b) (4) on the product and packaging during transport. For additional details, please reference CR Item #14.

Review Comments/ Assessment

The FDA 483 Observation 7 was issued to LFB (b) (4) because the shipping validation study for the (b) (4) was not adequately completed as the studies did not evaluate the (b) (4) to ensure integrity of the product during transport. To address the 483 Observation, LFB provided a response that explained a new OQ would be conducted that would evaluate (b) (4) and ability to maintain the product storage temperature to ensure product integrity. The OQ protocol appeared acceptable. For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 4, 2017.

The CR item was issued for the OQ study results, as the results were not provided prior to the CR letter issued on October 13, 2017. Please refer to the OQ study, which was evaluated in the CR Item #14.

CR Item # 61

61. Regarding FDA Observation 11, please submit the approved protocols and final stability reports for the (b) (4) *.*

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by Nicole Trudel.

CR Item # 62

Regarding FDA Observation 13: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #31 dated 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.*

(b) (4)

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 13 was issued to LFB (b) (4) because the freezer equipment qualifications were incomplete. Specifically, the empty chamber mapping tests and the maximum load temperature distribution tests were not performed for all freezers. To address the 483 Observation, LFB provided a response that described the qualification plans and associated protocols. LFB also explained if equivalency was not established for all of the freezers via the empty chamber mapping test, then the temperature distribution test would be performed for all of the freezers. If equivalency were established, the existing temperature distribution results on one freezer would be acceptable and determined to be representative of all of the freezers. LFB's plan appeared acceptable. For additional

details regarding the 483 Response, please refer to the 483 Response Memo dated October 4, 2017.

The CR item was issued because the empty chamber mapping results for all fothe freezers were outstanding. LFB conducted the temperature mapping for all of the freezers and the results met the established specifications. There is agreement the mapping study appeared to be adequately conducted with the use of thermal probes at geometric (b) (4) and evenly throughout the freezer. There is also agreement the results support the establishment of equivalency as the specifications were met and the hot and cold spots were in similar spots of the freezer. No further action is required.

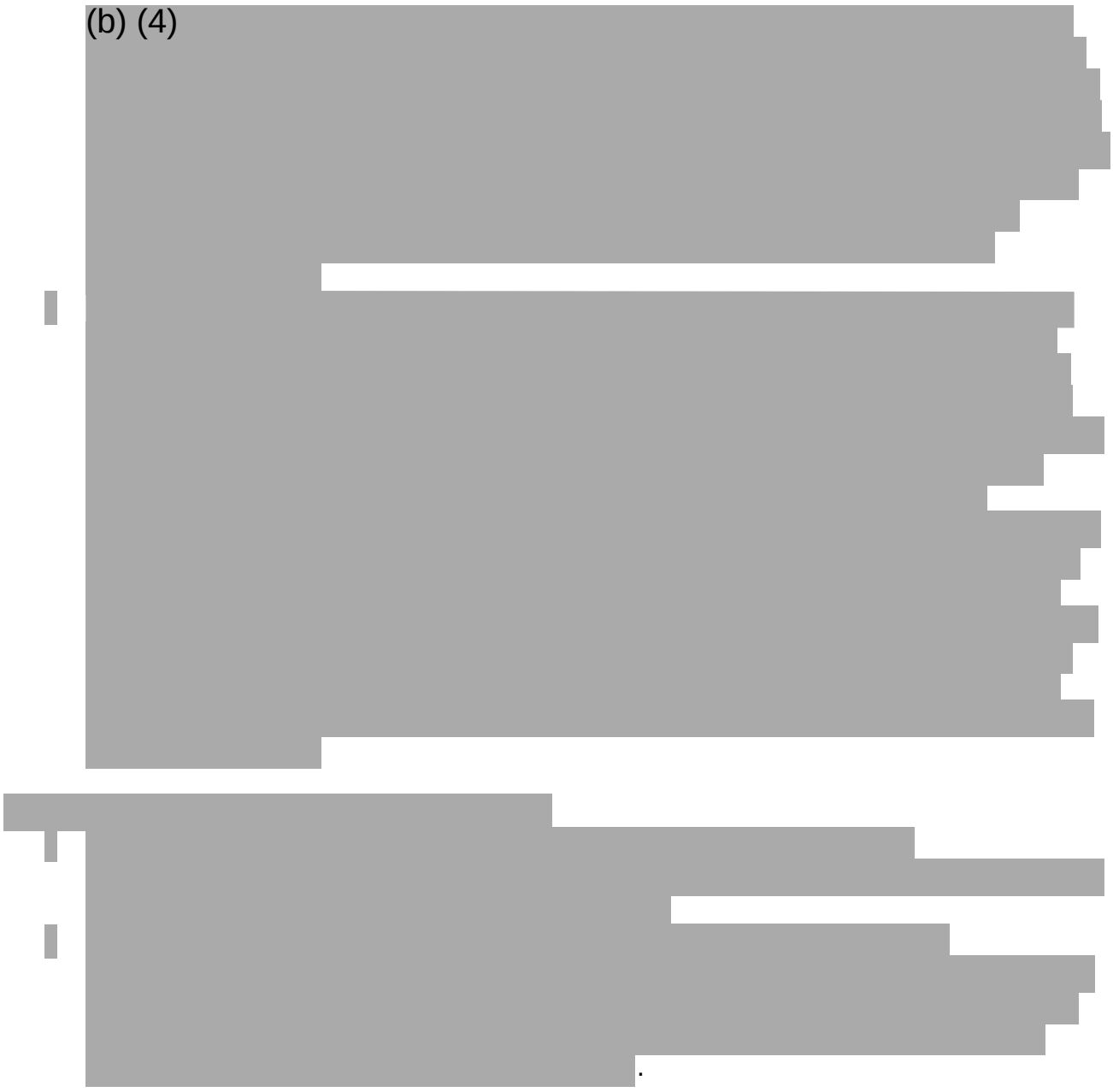
CR Item # 63

Regarding FDA Observation 15: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #31 dated 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.

(b) (4)

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

(b) (4)



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Review Comments/ Assessment

The FDA 483 Observation 15 was issued to LFB (b) (4) because the disinfectant effectiveness studies were not performed to support the facility cleaning method. To address the 483 Observation, LFB provided a response that described the study to qualify the disinfectants, which appeared acceptable. For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 4, 2017.

The CR item was issued because the results of the disinfectant effectiveness study were outstanding. LFB conducted the study and provided the results, as requested. There is agreement the study appears to have been sufficiently performed as the

agents were evaluated on (b) (4) [redacted] No further action is required.

CR Item # 64

Regrading Observation 16, please submit the final environmental monitoring performance qualification protocol and report for the (b) (4) *.*

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by Nicole Trudel.

LFB USA, Inc.

CR Item # 65

With reference to item # 1 in the Form FDA 483 issued at the end of the Pre-License Inspection of LFB USA, Inc. on May 12, 2017, please provide the following:

a. *Regarding FDA Observation 1a, the final report for process validation that includes data on 3* (b) (4) *batches manufactured using milk sourced from the Charlton Rabbit Facility.*
b. *Regarding FDA Observation 1b, the final report for the accelerated stability study.*
c. *Regarding FDA Observation 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) [redacted] *.*
d. *Regarding FDA Observation 1d, the final report on the study that establishes the acceptance ranges for the storage conditions of the* (b) (4) [redacted]

Review Comments/ Assessment

A summary and assessment of the response can be found in the Review Memo by the Product Office.

CR Item # 66

Regarding FDA Observation 4: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #54 dated 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)

(b) (4)

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

- (b) (4)

Review Comments/ Assessment

The FDA 483 Observation 4 was issued to LFB USA, Inc. because there were no studies done to demonstrate (b) (4) recovery of (b) (4)

(b) (4) test method. To address the 483 Observation, LFB committed to performing a (b) (4) study on samples (b) (4) for at least (b) (4) For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 5, 2017.

The CR item was issued for clarification regarding the long-term effects of (b) (4)

(b) (4)

No further action is required.

CR Item # 67

Regarding FDA Observation 5: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #41 dated 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 the 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)

In the CR Item #67 response in Amendment 71, LFB S.A. provided the qualification study conducted for (b) (4)

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 5 was issued to LFB USA, Inc. because the process to prepare samples for (b) (4) testing was inadequate. Specifically, (b) (4)

To address the 483 Observation, LFB provided a plan to perform a

qualification study of its sampling procedure to assess the (b) (4) . For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 5, 2017.

The CR item was issued because qualification study results for the (b) (4) testing was outstanding. Additionally, in LFB's 483 response, LFB stated the (b) (4) would be assessed in the qualification study to evaluate sampling for (b) (4) testing. The CR item was also issued for LFB to provide clarification for the relationship between (b) (4) . In the CR response, LFB explained (b) (4) studies that were performed to assess the (b) (4) No further action is required.

CR Item # 68

Regarding FDA Observation 6: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #41 dated 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.*

(b) (4)

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 6 was issued to LFB USA, Inc. because a study was not performed to support the (b) (4) To address the 483 Observation, LFB provided a plan to evaluate the (b) (4), which appeared to be acceptable. For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 5, 2017.

The CR item was issued for outstanding results from the (b) (4) study. LFB provided the results, as requested. The tests appeared to be adequately performed with the application (b) (4) No further action is required.

CR Item # 69

Regarding FDA Observation 11:

a. *In the document "1.11.1 Quality Information Amendment" submitted in Amendment #41 dated 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 in Amendment #41 dated 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.*

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 11 was issued to LFB USA, Inc. because deficiencies were identified in equipment qualifications of freezers and incubators. To address the 483 Observation, LFB described a temperature recovery study and power failure test that would be performed on several freezers, as the qualification tests were not performed as part of the initial qualification. The response regarding the incubator appeared acceptable (b) (7)(E) For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 5, 2017.

The CR item was issued for outstanding results from the temperature recovery and power failure test. LFB provided the results, as requested. The tests appeared to be adequately performed with data collected to provide times when alarms would be triggered and times the sensors and temperature controller to return back to the specified ranges. No further action is required.

CR Item # 70

Regarding FDA Observation 12: In the document "1.11.1 Quality Information Amendment" submitted in Amendment #41 dated 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. *In your response, you noted that there was a power outage on August 13, 2016 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.*

(b) (4)

Review Comments/ Assessment

The FDA 483 Observation 12 was issued to LFB USA, Inc. because an inadequate change control on a freezer at the facility. Specifically, the set point temperature of the freezer has been changed a couple of times after the freezer qualification. To address the 483 Observation, LFB provided the change controls and explained a power failure had occurred wherein the freezer reverted to the factory default setting. For additional details regarding the 483 Response, please refer to the 483 Response Memo dated October 5, 2017.

The CR item was issued for additional details regarding the power failure and its impact on equipment performance to ensure equipment remain in their controlled, qualified states. LFB confirmed the freezer reverted back to the default state

because of a malfunctioning battery and explained preventative maintenance measures were updated to include a (b) (4) as corrective action. LFB also explained an assessment is performed on critical utilities and temperature controlled units that would be impacted by a power outage. There appears to be adequate control as the critical entities are either monitored or capable of returning to normal operations. An exception was the cold units wherein an update SOP required documented confirmation the affected the units returned to the validated set point temperatures, which appears to be acceptable. No further action is required.

11. ADDITIONAL COMMENTS

Over the course of the submission, the following deficiencies or CR Letter additional comments (#72 – 78) were identified for clarification and completeness of the information submitted but would not impact the final decision on the application:

CR Item # 72
What is the time limit for the (b) (4) *process (step* (b) (4)

CR Item # 73
Please clarify what the (b) (4) *is tested for at the conclusion of Step* (b) (4)

CR Item # 74
What is the time limit of manufacture for (b) (4) *(step* (b) (4)*, and does this include the* (b) (4)

CR Item # 75
Regarding (b) (4) *(step* (b) (4)*, what are the minimum and maximum* (b) (4) *step? Only the set-points were provided in the BLA.*

CR Item # 76
Regarding the (b) (4) *Please clarify the* (b) (4) *critical process parameter (identified as* (b) (4) *in 3.2.S.2.4) with regard to the* (b) (4) *steps described above, and specify the minimum and maximum* (b) (4)*.*

CR Item # 77
Is there a validated hold-time (b) (4)

CR Item # 78
(b) (4)

Review Comments/ Assessment

A summary and assessment of the responses for CR Items 72 - 78 can be found in the Review Memo by Nicole Trudel.