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

To: Administrative File: DATS Login ID #644942, STN 125641/0, Coagulation Factor VIIa (Recombinant) (Sevenfact®)

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Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

Subject: BLA 1st Cycle Review Memo for standard 12-month PDUFA review: New drug product

Indication/ Prod. Info. Lyophilized sterile drug product administered intravenously for on-demand treatment of bleeding in adolescents and adults with hemophilia A or B, w/ diluent prefilled syringe, vial adapter, and other device components (Co-packaged combination Product)

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

Major Facilities LFB USA, Inc. US (b) (4) LFB (b) (4) (b) (4)

Recommendation: Complete Response

Due Date: October 13, 2017

File History
Type B Pre-BLA meeting, CRMTS 10181/IND 15183 April 2016

Regulatory Summary

Coagulation Factor VIIa (Recombinant) (Sevenfact®) is a co-packaged combination product with the following co-packaged constituent parts:

- Lyophilized drug product in vial: Drug
- Sterile WFI diluent in pre-filled syringe: Device
- Vial adapter with filter: Device (This device is 510(k) Cleared)
- Plunger rod: Device component
- Backstop: Device component

The product office is reviewing the applicable design controls of concern as this device only qualifies for aTier-1 CDRH consult; the pre-filled syringe and vial adapter are considered straightforward and fall under the review of the product office. Procedures for design controls, risk assessment and other related documentation to support compliance with CAPA, Management Responsibility, and Purchasing Controls were submitted in Amendment #6. The procedures appear to address all of the constituent parts and finished product. The product office has a CR issue linking design controls to the ongoing problem with particulates in the reconstituted product.

There are three dosage forms (1mg, (b) (4) 5mg; all the same strength: 1 mg/mL). If approved, the U.S. will be the first market approval for this product. This drug would not, however, be the first of its kind; LFB S.A. requested that the subject product be granted orphan drug designation and was denied (Reference Novo Nordisk approval for a recombinant FVIIa product, *NovoSeven* in 1998/1999).

CVM is reviewing the companion New Animal Drug Application (NADA) as there is a domestic rabbit facility for source material collection (milk). CVM will presumably review the environmental analysis as part of the NADA, although the firm requested categorical exclusion per CFR 25.31(c), which appears appropriate. LFB is unable to meet the requirements of the NADA prior to the BLA action due date; therefore, with or without CR issues related to the BLA, the BLA will likely not get approved in the first cycle (NADA must be approved prior to the BLA).

There are (b) (4) manufacturing facilities associated with this BLA. Three PLI were performed, and another seven inspections were waived. Applicable EIRs are finished or scheduled for EDR upload prior to the ADD. The inspection waiver memo has been uploaded.

Issues

- Sterilization, depyrogenation and other data essential for filing were missing from the original BLA. CBER contacted LFB prior to the filing due date and LFB submitted some but not all of this data in Amendment #6, received December 5, 2017 (prior to filing). Numerous other critical data and reports were missing and the BLA was filed with deficiencies. Responses to the deficiencies were submitted throughout the 2nd quarter of the review cycle and beyond. LFB continues to submit amendments; CBER ceased review of any additional amendments received after the late-cycle meeting. Numerous deficiencies with CR letter-ready comments are documented throughout this review memo.
- There is an ongoing particulate issue associated with the reconstitution test method of final product. The product office is conducting a thorough review of this problem.
- CVM cannot approve the NADA until LFB submits validated test methods to support testing and prevention of the transgenic rabbits from entering our food supply; LFB has confirmed that they will not have their test method developed and validated until sometime in 2018.

Categorical Exclusion

A categorical exclusion (CE) for an environmental assessment was provided in eCTD section 1.12.14. The firm claimed categorical exclusion pursuant to 25.31(e), *Action on an IND*.

Issue: 25.31(e) is not applicable to a product pending approval of a BLA.

Resolution: Resolved – The justification for exclusion that was provided appears to meet the criteria for 25.31(c). This issue was identified in question #37 in the December 12, 2016 filing letter; LFB revised their request for categorical exclusion to 25.31(c) per Amendment #9.

Note: CVM is reviewing the associated NADA and presumably will request that LFB submit an environmental assessment (EA) because of the transgenic nature of this product. Submission of an EA would preclude the need for a CE.

Source Material Collection

The process begins with source material (transgenic rabbit milk) collection from transgenic rabbits at (b) (4) facilities, LFB USA in Charlton, MA (b) (4) . The (b) (4) LFB USA rabbit husbandry processes are (b) (4)

Issue: The health of the rabbits impacts the quality of the milk and ultimately that of the drug product. The brief and general summary of the rabbits and associated facilities did not include any procedures or supporting information regarding the care and control of the US (b) (4) transgenic rabbits and the respective Charlton (b) (4) facilities. Floor diagrams were also unclear. These deficiencies were identified in questions #27 and #32 in the December 12, 2016 filing letter.

Resolution: *Resolved* – LFB submitted revised floor diagrams in Amendment #8 (Jan 25). In section 1.11.4 of Amendment #9 (Jan 27), LFB indicates that they have animal husbandry and biosecurity practices with QA oversight (not described). LFB further indicates that all applicable animal husbandry information will be submitted to CVM in the New Animal Drug Application (NADA). Animal husbandry was reviewed during the Charlton PLI by the CBER veterinarian; I will defer to the animal husbandry review as documented in that EIR, as well as to the CVM review of the NADA.

According to the BLA narrative, the health of the rabbits is closely monitored and controlled, and all rabbits are tested for transgenic status (minimum required amount of FVII) (b) (4) . The rabbits are also tested for a variety of virus, bacteria, and parasites on a (b) (4) basis as described in Table 1 of 3.2.S.2.3. The source material is tested prior to further processing.

(b) (4)

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

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

Facility – LFB (b) (4) **Substance production**

A pre-license inspection was performed at this facility. DMPQ reviewed the HVAC, environmental monitoring, water systems, and contamination control during this inspection. Please see the applicable EIR for this information.

Drug Product Production

The finished drug product is manufactured at (b) (4) The drug product is aseptically filled into glass vials which are (b) (4) stoppered prior to lyophilization. The lyophilized vials are capped and stored at (temperature?) before being shipped to LFB (b) (4) visual inspection. There are three presentations of drug product based on 1mg, (b) (4) and 5 mg dosage strengths.

Receipt and storage of drug substance (DS)

(b) (4)

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

(b) (4)

(b) (4)

Filling

There were no descriptions of any of the (b) (4) filling lines and no performance qualification (PQ) studies or reports to support process validation of the filling process in the original BLA; the following IR was included in the December 12, 2017 filing letter as review issue #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.*

Information regarding filling machine PQ was submitted in Amendment #23 received on March 9, 2017.

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The following letter-ready IR for filling PQ/PV (product) should be included in the CR letter:

- (b) (4)

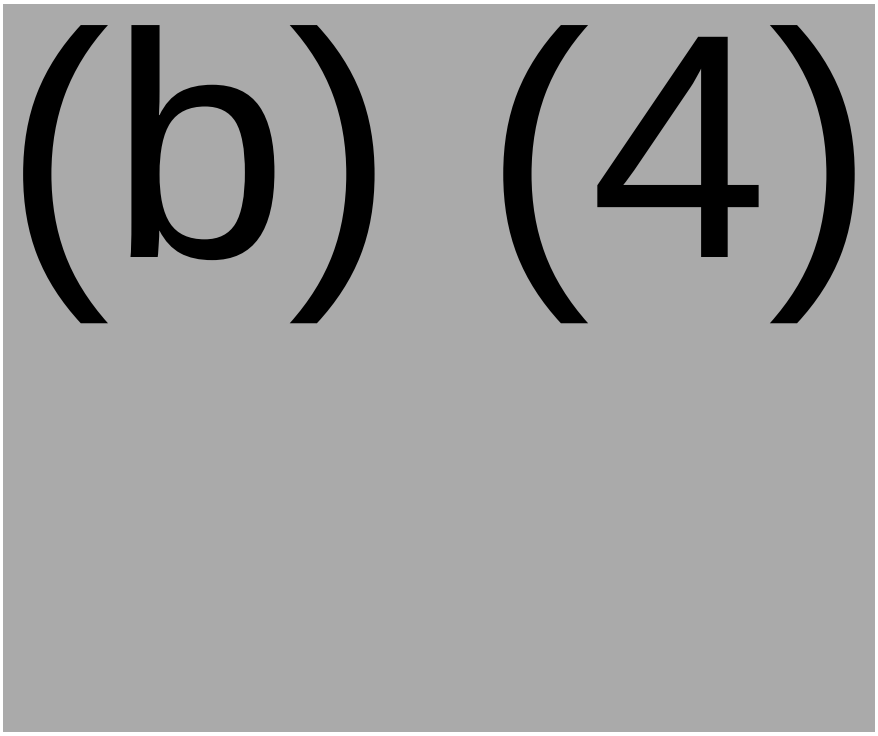
Lyophilization

The original BLA contained a general overview of process validation of the lyophilizers in 3.2.P.3.5; there were no PQ studies, reports or data. The following IR was included in the December 12, 2017 filing letter as review issue #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*

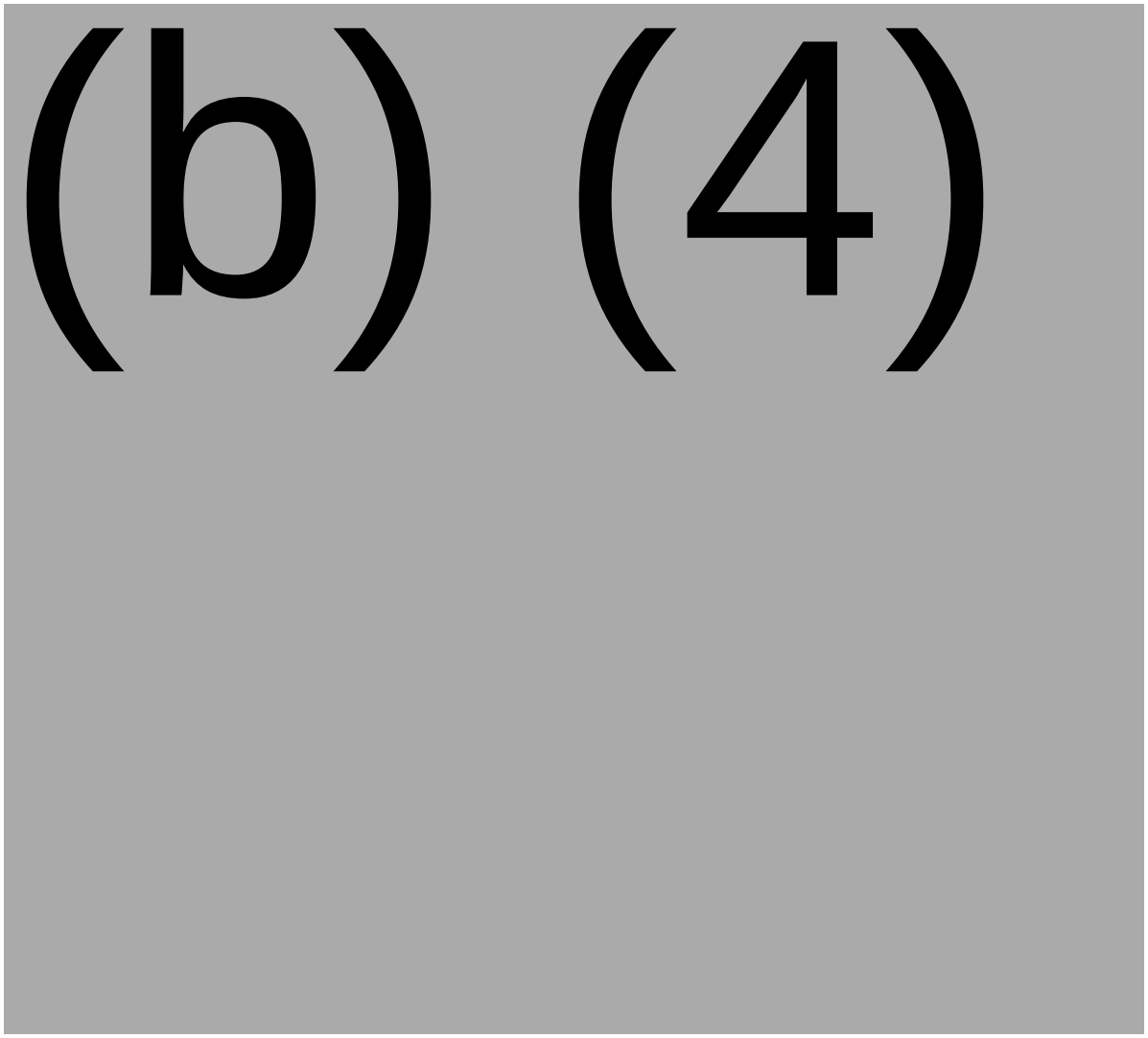
well as during routine production. The PQ should support demonstration that each phase of the cycle is complete prior to commencing the next phase. Please include qualification data to demonstrate capacity of the condenser and its ability to support your maximum batch size. The qualification should include 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.

LFB submitted a summary of the Lyopherizer performance qualifications (PQ) for (b) (4) in Amendment 23, received March 9, 2017. The following table describes the capacity of the lyophilizers and their condensers, as compared to the maximum batch sizes:



(b) (4)

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



* these results are not consistent with the acceptance criteria and are unclear (see CR comment)

The lyophilization cycles are not clearly defined and the PQ and PV data are unclear. The following CR comments summarize my concerns with the lyophilization process:

Letter-ready CR comments regarding lyophilization:

- (b) (4)

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

(b) (4) lyophilizers are shared equipment. The lyophilizers are (b) (4) with (b) (4)

Issue: There is no information in the submission or applicable amendments regarding the routine (b) (4) procedure or the validation of the (b) (4) process; there is no information regarding the procedure to address a worst-case spill.

Letter-ready CR comments regarding lyophilizer (b) (4)

- (b) (4)

Lyophilizer (b) (4)

(b) (4) lyophilizers are shared equipment. After (b) (4), the lyophilizers are (b) (4) with (b) (4)

Issue: The following IR was submitted to LFB on November 29, 2016 as item number 1d: *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:*

- *A description of the sterilization process…*
- *A description of the sterilization validation…*

Resolution: Information regarding lyophilizer (b) (4) was submitted in Amendment #6.

(b) (4)

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

- (b) (4)

Filling Component Prep

The following table summarizes the primary container closure components:

Dose	Vial (Type (b) (4) borosilicate glass)	Stopper (Bromobutyl Lyo stopper (b) (4) rubber formulation)	Filling line
1mg	3 mL, 13 mm opening	13 mm	(b) (4)
(b) (4)			
5mg	10 mL, 20 mm opening	20 mm	

Issue: The cleaning, sterilization, depyrogenation, and (b) (4) validation data for the primary container closure components were not included in the original BLA. This information is critical and these deficiencies were communicated to the sponsor in a pre-filing information request, to inform LFB that the BLA could not be filed without this data.

Resolution: Some but not all of this data was submitted in Amendment #6 received on December 5, 2016; please see letter-ready comments throughout this section.

Filling Component Prep – Vials

Vial Washing

Vials are washed with (b) (4)

CR (letter-ready) comment for vial washing: There is no description of the vial cleaning process, the associated vial washers and performance qualification (PQ) data, cleaning validation (CV) acceptance criteria, CV protocols, or reports. Please submit the vial washer PQ protocols and reports to demonstrate the vial washers' abilities to remove particulates and other contaminants.

Vial Depyrogenation

There were no descriptions of the depyrogenation tunnels or processes in the original BLA; there were also no studies or reports to demonstrate performance qualification of the tunnels. The following IR was included in the November 29, 2017 IR communication as question #1a:

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.*

Vial depyrogenation data was submitted in Amendment #6 received on December 6, 2017. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Vial Depyrogenation CR comments: There are numerous gaps in the description of the routine production cycle and the performance qualification. The following comments were sent to the sponsor in the Late Cycle Meeting Materials letter dated August 4, 2017 as substantive review issues # 2b viii-xii, respectively:

(b) (4)

The depyrogenated vials are (b) (4)

Filling Component Prep – Stoppers

A translated description of the stopper (b) (4) and its performance

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) **of stopper-filled** (b) (4) **CRs:** The following comments were sent to the sponsor in the Late Cycle Meeting Materials letter dated August 4, 2017 as substantive review issues # 2b xxviii-xxxvi, respectively:

(b) (4)

(b) (4)

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Caps

The (b) (4) of the cap-filled (b) (4) was validated with the (b) (4) . The caps are applied after the primary container is fully closed, thus I have no further comments.

Cleaning of critical product contact equipment

The following table summarizes the product-contact equipment used in the (b) (4)

(b) (4)

(b) (4)

The response was included in Amendment #12 received on February 6, 2017. The cleaning procedure for the dosing groups is described as manual.

Issues: There is no further description of the cleaning procedure, an established dirty hold-time, or an established clean hold-time; there is also no mention of periodic verification of cleaning, given the manual nature of the routine cleaning procedure. See CR comments at the end of this section.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Letter-ready CR comments regarding cleaning of critical equipment (should be included as contamination control issues in the CR letter):

- (b) (4)

(b) (4)

Sterilization of critical product contact equipment

(b) (4)

(b) (4)

The following IR was submitted to LFB on November 29, 2016 as item number 1d: *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:*

- *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.*
- *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.*

- *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).*

A response to the IR was received in Amendment #6 on December 6, 2016. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

No information was provided regarding empty chamber mapping or identification of cold spots.

Letter-ready CR comments regarding the (b) (4) **autoclave PQ and sterilization of critical equipment**:

- (b) (4)

(b) (4)

The following table lists the critical equipment items that are sterilized with (b) (4) prior to use:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

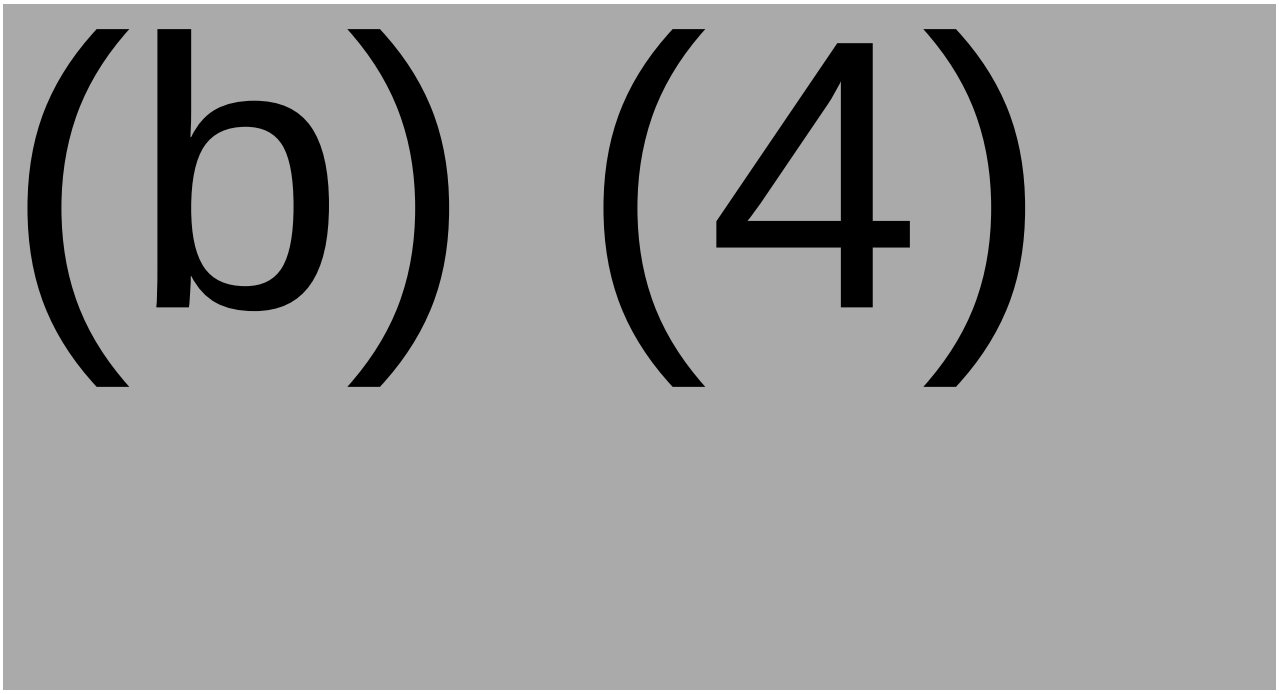
The following letter-ready CRs for the (b) (4) should be included in the CR letter:

- (b) (4)

Environmental Monitoring

The filling line is maintained under (b) (4) Class (b) (4) conditions within a Class (b) (4) suite. There is no description of any physical barrier between the Grade (b) (4) and Grad (b) (4) areas. Please refer to the letter-ready IRs under Contamination Control. Per the facilities appendix in 3.2.A.1, the filling area environment is continuously monitored throughout the filling and lyophilization processes. The following table describes the general types of routine microbiological monitoring and associated alert/action levels for the LR769 product areas:

(b) (4)



(b) (4)

(b) (4)

The following IR was included in the December 12, 2017 filing letter as deficiency # 13c: *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) .

A response was included in Amendment #23 received on March 9, 2017. The initial qualifications for each of the (b) (4) . Each qualification included (b) (4)

The following letter-ready comments summarize my EMPQ concerns and should be included in the CR letter as contamination control issues:

- Please submit the environmental monitoring performance qualification protocol and report for the LR769 drug production facility. The EMPQ should be robust enough to support the established routine environmental monitoring procedures to include the type of sampling performed, the number of sampling points, the sampling point locations, and the frequency. Please include the acceptance

criteria for all classifications.

- Please submit a detailed description of the environmental monitoring procedures for the LR769 drug product production facility. Details should include the type of sampling performed, the number of sampling points, the sampling point locations, and the frequency. This information was not included in the BLA.
- Regarding the (b) (4) none of the requalification summarizes included demonstration of acceptable control of viable particulates. The requalification studies also appear to have been done at rest, vs. under dynamic conditions (production). The original qualifications were in some cases performed more than 20 years ago. Please submit the most recent studies with data to support viable and non-viable particulate control under dynamic conditions.
- Please provide a description of the sampling locations for each type of sample, and a justification for sampling only (b) (4)

Contamination Control

The (b) (4) site is a multi-product facility; the following table summarizes the other products manufactured in the drug product facility, and the affected manufacturing areas:

(b) (4)

(b) (4)

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Letter-ready CR comment regarding Contamination Control:

- Please describe the barrier separating the Class (b) (4) and Class (b) (4) areas of the (b) (4) for each of

the (b) (4) filling lines.

- Please identify the worst-case soil (product) with respect to cleaning and sanitization of shared equipment and facility production areas. Please confirm that the worst-case products have been incorporated into the applicable validations of the cleaning of shared equipment.
- CBER understands that the drug product production areas are sanitized with (b) (4) Please provide a description of the facility cleaning procedure to include the frequency, cleaning agent exposure times, and disinfectant effectiveness studies.
- Please submit a list of any facility isolates, and the procedure for identifying facility isolates.

Utilities

HVAC

This HVAC review is limited to the critical areas used in the aseptic operation, and the sterile support operations to the aseptic process. Filters of concern include those located in the (b) (4)

The entire staging, gowning, filling and lyophilizer loading areas are (b) (4) . The following table summarizes the (b) (4) pressure within the production facility.

(b) (4)

HEPA filter air velocity criteria range from (b) (4) A robust qualification of the HVAC filtration system appears to have been done and filters are requalified (b) (4)

Letter-ready CR comment regarding Contamination Control: It appears that particulate testing in operation (dynamic conditions) for the Grade (b) (4) areas is not performed. Please clarify.

Water Systems

Purified water is produced on-site (b) (4)

(b) (4) Purified water is distributed to the points of use (b) (4)

The entire system is served by an automatic control system that provides control and alarms for (b) (4) The purified water (b) (4)

Water for injections (WFI) is produced via (b) (4)

The WFI is produced (b) (4) at a temperature range of (b) (4)

The water is maintained in (b) (4) at a temperature of (b) (4)

Qualification strategy:

(b) (4)

All the acceptance criteria are in accordance with the (b) (4) for purified water and WFI. Points are sampled for (b) (4).

Compressed gases

(b) (4)

Letter-ready CR comments regarding Contamination Control: Please identify the locations in which (b) (4) are utilized (b) (4) drug product manufacturing site. Please describe the frequency of (b) (4)

(b) (4) .

Aseptic process validation

The following IR was included in the December 12, 2017 filing letter as review issue #7: *The description of the media fill process for LR769 provided at 3.2.P.3.5.1.7 is a short summary of the LR769 production process and does not provide critical details regarding the media fill procedure. Please submit the media simulation protocol and data that support the aseptic process performed at* (b) (4) *The protocol should be comprehensive to include the number of units filled, worst-case conditions and interventions, durations of hold-times, identification of the container and closure components, equipment settings, environmental conditions, growth promotion studies, qualification of personnel including visual inspectors of filled and incubated vials, and other supporting details to demonstrate validation of the approved aseptic process. Reconciliation of the total number of units filled, rejected, and incubated should also be provided, with justification for any units not incubated. Please also include a summary of any deviations, investigations, determination of root cause, and corrective actions. You can refer to the 2004 Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. Additionally, CBER acknowledges that you set the frequency of microbiological monitoring during media fills based on the method of sampling. However, you did not specify the frequency. Please provide the frequency for each method of sampling for the microbiological monitoring program.*

Media fill protocols and reports were submitted in Amendment #12, received February 6, 2017. According to the protocols submitted, the aseptic process validations for each (b) (4)

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(b) (4)

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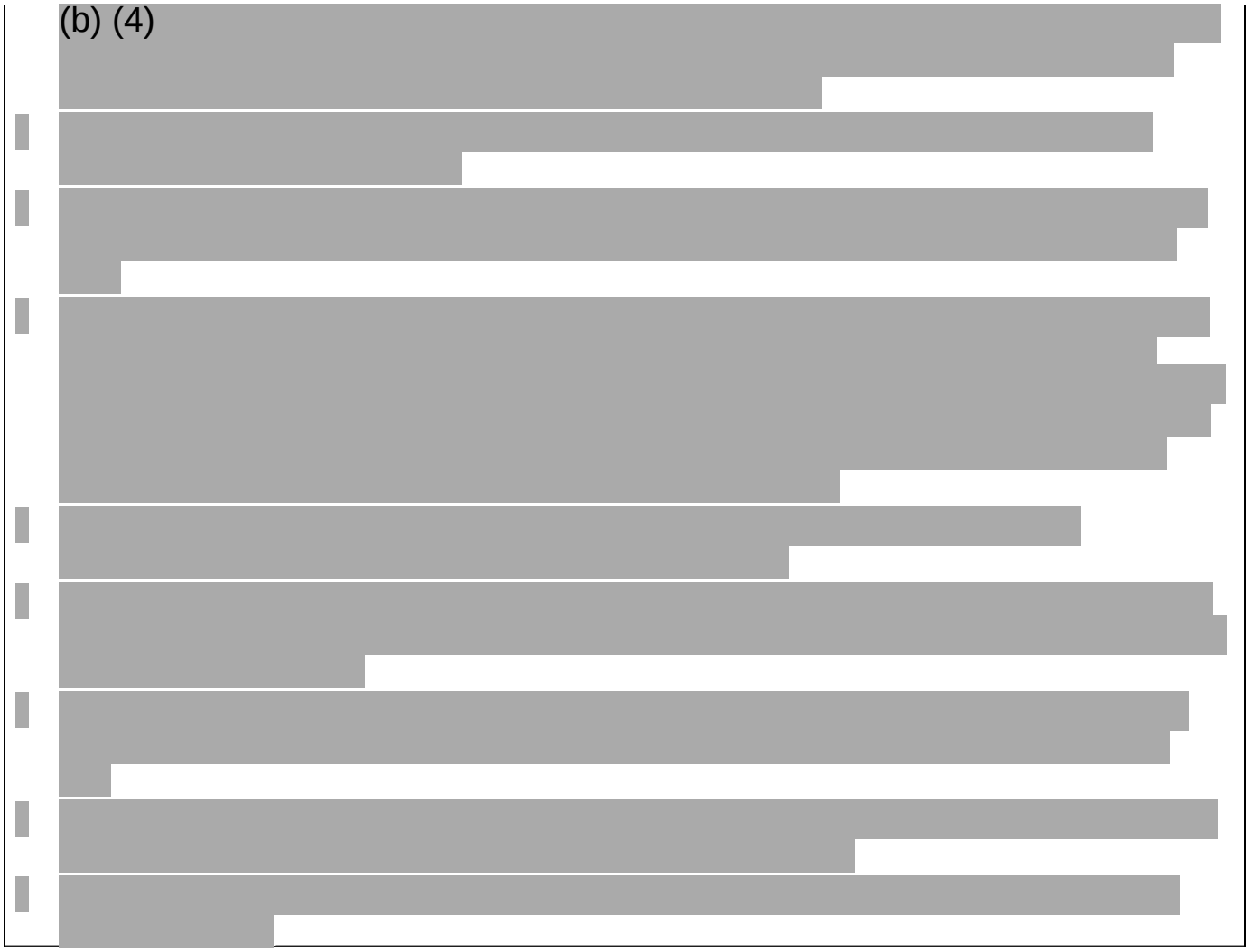

Visual Inspection

The (b) (4) visual inspection (VI) of finished drug product is performed at LFB (b) (4) .

CBER performed a one-day pre-license inspection on (b) (4) . CBER was unable to observe the VI process during the PLI as there was no VI scheduled. CBER reviewed the training, and inspected the VI room. VI is performed manually in room (b) (4) . CBER noted that the room was equipped with the required (b) (4) and appeared to have proper illumination for detection of potential (b) (4) particulates. The lamps were current on their calibration schedule.

VI Operators are trained in (b) (4)

(b) (4)

VI operators must undergo an (b) (4) visual examination. VI operators must also be re-qualified after an (b) (4) all results were passing.

There was not sufficient time to complete the review of applicable documentation during this one-day to inspection. Rejects, reject categories, AQL and other aspects of the (b) (4) visual inspection process were be reviewed in the applicable batch records submitted to the BLA. I subsequently determined that there were no master or production batch records associated with the (b) (4) visual inspection process submitted to the BLA. The acceptance criteria, including those for AQL cannot be evaluated.

Letter-ready CR comments regarding visual inspection: Please note that the batch records submitted thus far are incomplete; the visual inspection batch records are missing. Please submit at least one master batch record (or a detailed narrative) for the (b) (4) visual inspection of the finished drug product, performed at LFB (b) (4). Please include the master batch record (or detailed narrative) for the reconstituted solution supplemental testing. Please also submit at least one executed batch record for the (b) (4) and supplemental visual inspection testing.

Because the drug product is lyophilized, LFB performs a supplemental visual inspection test for visible particulates in reconstituted solution. This is a destructive test; thus, LFB follows (b) (4) LFB has proposed a new sampling plan for the supplemental test (per Amendment #37 received May 18, 2017). Per Amendment #37, LFB states that their new sampling scheme is in accordance with (b) (4)

The new sampling plan allows (b) (4). I have the following issues and questions regarding their revised supplemental testing scheme:

- (b) (4)

(b) (4)

Container Closure Integrity

CCIT Test Method Validation:

There were no studies or reports to support the brief narrative regarding container closure integrity testing (CCIT) in the original BLA; the following IR was included in the December 12, 2017 filing letter as review issue #16:

Please submit the test method validation protocol and results for the (b) (4) *container closure integrity test method for the lyophilized powder vial; the test method validation should include qualification of visual inspectors and instrumentation as applicable, used to detect a critical leak. Please also correlate the* (b) (4) *as determined by your risk analysis, and explain how the* (b) (4) *characteristics of* (b) (4) *were quantified.*

LFB submitted the requested information in Amendment 12 (response to request 16), received on February 6, 2017.

An initial study was performed for (b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

CCIT CR items:

- (b) (4)

CCIT Process Validation Results:

(b) (4)

Letter-ready CR comments regarding CCIT process validation results:

- (b) (4)

Shipping

Per 3.2.P.3.3.5 and 3.2.P.3.5.5.2, the (b) (4) drug product vials are packed into (b) (4) .

The BLA is silent regarding shipment of the drug product from the (b) (4) warehouse to the LFB (b) (4) test facility (visual inspection) as well as from LFB to the (b) (4) labeling and packaging facility.

The shipping validation studies were discussed in 3.2.P.3.5.5. These studies were performed solely to qualify (b) (4) during shipping. The intent of the shipping qualification was to incorporate worst-case conditions, as well as to capture the impact of typical distance, climate (b) (4) procedures.

(b) (4)

Section 3.2.P.3.5.5.2 indicated that additional shipping studies would be performed to test integrity of the (b) (4) Studies were to be performed on the 1 mg and 5 mg doses. The following question was included in the December 12, 2017 filing letter with deficiencies as item #18: *Please submit the shipping validation for the* (b) (4) *vials of lyophilized drug product from* (b) (4)

Amendment #8 included Protocol #16-SCBP-0016-GLL for drug product transportation from (b) (4) . Testing would be performed in accordance with standard (b) (4) to challenge shipments of drug product with the temperature and mechanical stresses of routine and presumably worst-case conditions. Studies were in-progress at the time of the Amendment 8 submission, and reports were to be available in July 2017 (5 mg) and October 2017 (1 mg).

The studies were to include (b) (4)

(b) (4)

Letter-ready CR comments regarding shipping validation for drug product:

- Please clarify all of the transportation steps of the finished drug product vials, starting from (b) (4) and concluding with (b) (4) where they are labeled and kitted with the final product. Please include any transportation steps to and from the (b) (4) warehouse.
- Please confirm that the shipping validation studies performed to support shipping of finished drug product support all of the transportation steps of the drug product vials.
- Please compare the durations of time for the qualification studies to that of the actual shipping for the maximum length of shipment. It is not clear if the studies incorporated the worst case shipping time to challenge the maintenance of acceptable temperature.
- Please specify the (b) (4) , for each of the shipping studies.
- Section 3.2.P.3.5.5.2 indicated that vials would be subjected to integrity testing after the mechanical shipping studies were performed. Was the (b) (4) test method used to test container closure integrity on vials subjected the simulated shipping conditions? Please submit the results.
- Please submit the shipping validation reports for the lyophilized drug product vials.

Diluent Production

I am deferring to Nicole Li for review of the diluent; likewise, she is deferring to me for review of the lyophilized drug substance.

Primary Labeling and Secondary Packaging

The original BLA did not include any information regarding labeling and packaging of the lyophilized drug product vials; the following deficiency was included as item #15 in the December 12, 2016 filing letter with deficiencies: *Please submit a description of the manufacturing process for the primary labeling and secondary packaging of the lyophilized powder vials performed at* (b) (4) . LFB responded in Amendment #8 received January 25, 2017.

(b) (4) Each lot of LR769 is labeled on a campaign basis; the line is used for all (b) (4) dosages. Access to the storage area and packaging line area is controlled and restricted to authorized personnel. The packaging/labeling areas are temperature-controlled (b) (4) .

Upon receipt of the drug product vials, a visual check is performed for identification and container integrity. The QC Unit verifies the Certificate of Conformity and Certificate of Analysis. Drug product vials are stored in the controlled storage area until labeling occurs. Pre-printed labels and other packaging components are purchased by (b) (4) from their approved suppliers according to requirements defined by LFB. (b) (4) controls incoming components per internal procedures. Labels are stored in a secured warehouse location.

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

(b) (4)

The following question was included in the December 12, 2016 filing letter as item #13 e: *Please submit equipment qualification performance qualification data for all equipment used in the manufacture of LR769 drug substance and drug product to include primary labeling [equipment] for the lyophilized drug product.* Per Amendment 13 section 1.11.1, there is no performance qualification for the equipment used in primary labeling of the lyophilized drug product vials, given that the vials are subjected to a (b) (4) visual inspection (b) (4) . This appears acceptable, assuming acceptability of training and applicable procedures. The pre-approval inspection of the (b) (4) facility was waived.

The finished labeled drug product vial is placed inside a three-holed foam insert during final packaging/kitting of the combination product (reviewed by Nicole Li).

Kitting

I defer to Nicole Li's review of the kitting process, including shipment of the final kit.