U.S. FOOD & DRUG ADMINISTRATION

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

To: Administrative File: STN 125641/0, Coagulation Factor VIIa (Recombinant) (Sevenfact®)

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From: Nicole Trudel, Chair, OCBQ/DMPQ/QA

Through: Lori Peters, Acting Branch Chief, OCBQ/DMPQ/B1

Through: John Eltermann, Division Director, OCBQ/DMPQ

Subject: BLA 2nd Cycle Review Memo for standard 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: Approval

Due Date: April 11, 2020

File History

- Type B Pre-BLA meeting, CRMTS 10181/IND 15183 April 2016
- 125641/0 BLA Complete Response letter issued October 13, 2017

- Type A meeting request package received January 2018 (minutes issued February 7, 2018)
- Amendment 125641/0/71 responded to CRL October 2019

Regulatory Summary

Sevenfact® is a co-packaged combination product with the following co-packaged constituent parts:

- Lyophilized drug product in vial: Drug (Biologic)
- 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

There are two dosage forms (1mg and 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).

One of the reasons for the CR in the first review cycle was a serious particulate issue in that there was an unacceptable quantity of finished drug product units that failed particulate acceptance criteria. This problem has been resolved; the root cause has been identified and corrected, and the visual inspection process has been revised to more robustly inspect finished drug product.

There are (b) (4) manufacturing facilities associated with this BLA. Three PLI were performed during the first review cycle and all EIRs were uploaded to the EDR; another seven inspections were waived. DMPQ performed another assessment of the manufacturing facilities and their respective inspectional status to support the 2nd review cycle and determined that no subsequent inspections are necessary (six were waived). The 2nd cycle inspection waiver memo has been approved and uploaded to the EDR. Based on the information submitted in the CR response, DMPQ has endorsed the three previously conducted PLI as VAI. All issues have been resolved and the file is ready for approval.

PMC

LFB committed to the following PMC in an amendment received March 17, 2020: Laboratoire Francais du Fractionnement et des Biotechnologies SA (LFB S.A.) commits to complete PQ drug product (DP) (b) (4) studies (protocol (b) (4)) evaluating the ability of the (b) (4) The PQ final study report will be submitted for CBER review as a PMC-Final Study Report. Final Report Submission: October 10, 2020.

Source Material Collection

The source material (transgenic rabbit milk) is collected from transgenic rabbits at (b) (4) facilities, LFB USA in Charlton, MA (b) (4) their processes are (b) (4). Animal husbandry was reviewed by the CBER veterinarian during the Charlton PLI and was further reviewed by CVM in the New Animal Drug Application (NADA). I don't have any outstanding issues related to the collection of the transgenic milk. Please refer to my 1st cycle review memorandum, dated September 27, 2017, for a summary of the source material collection process.

Intermediate (IP1) Production

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

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(b) (4)

Facility – LFB USA, Charlton, MA (b) (4) production

I deferred assessment of the HVAC, water systems, pre- and post-viral segregation, and contamination control to the Charlton PLI.

Drug Substance Production

(b) (4)

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

Facility – LFB (b) (4), Drug 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 two presentations of drug product based on 1mg and 5 mg dosage strengths; LFB intends (b) (4) dosage strength.

Receipt and storage of drug substance (DS)

(b) (4)

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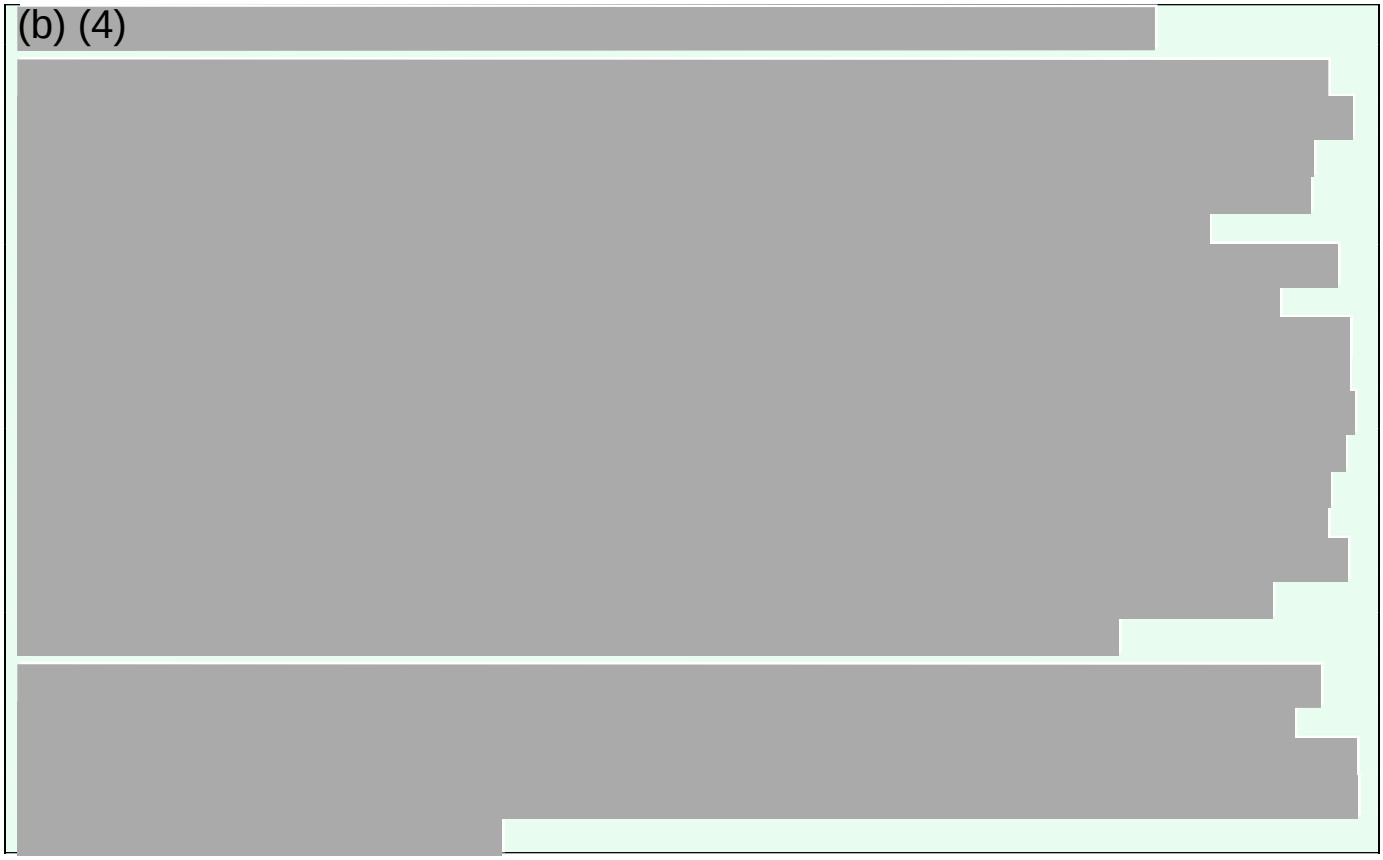
(b) (4)



(b) (4)

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

(b) (4)

Filling

There were no descriptions of either filling line and no performance qualification (PQ) studies or reports to support process validation of the filling process in the original BLA; an IR was included in the December 12, 2017 filing letter as review issue #12, and additional questions were included in the CR letter. The following summary of filling PQ is based largely on information received in Amendment 71, 1.11.1, Response 24:

Information regarding filling machine and their PQ was submitted in Amendment #23 received on March 9, 2017. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

DMPQ Reviewer Assessment: As noted at the beginning of this filling summary, my assessment is based largely on information received in Amendment 71, 1.11.1, Response 24. Per this response, information submitted about the filling procedure and the filling line PQ is complete, and the response is acceptable.

Lyophilization

(b) (4)

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:

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

(b) (4)

(b) (4)

(b) (4)

The lyophilization cycles were not clearly defined and the PQ and PV data were unclear. The following comments/questions were included in the CR letter issued after the first review cycle:

CR Questions regarding the lyophilizer included in the CR letter:

- (b) (4)

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

(b) (4)

DMPQ Reviewer Assessment: The response is acceptable.

Lyophilizer (b) (4)

(b) (4) lyophilizers are shared equipment. The lyophilizers are (b) (4) with (b) (4) . There was no information in the submission or applicable amendments regarding the routine (b) (4) procedure, validation of the (b) (4) process, or the procedure to address a worst-case spill.

CR Questions regarding the lyophilizer (b) (4) included in the CR letter:

- (b) (4)

(b) (4)

. **DMPQ Reviewer Assessment**: The information is complete and the response is acceptable.

Lyophilizer (b) (4)

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

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

Reviewer Assessment: The response is acceptable.

- (b) (4)

DMPQ Reviewer Assessment: The response is acceptable.

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)
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

(b) (4)

(b) (4)

CR question regarding vial washing included in the CR letter: There is no description of the vial washing process or the associated vial washers, and there are no 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' ability to remove particulates and other contaminants.

DMPQ Reviewer Assessment: (Per Amendment 71, 1.11.1, pages 268-280) The vial washers were qualified under worst-case conditions for the removal of visible particulates and residues. A sufficiently robust sample size was challenged in each of the runs and the acceptance criteria appear adequate. The washers are requalified (b) (4) with the worst-case vial presentation. The response is acceptable.

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. This information was requested in the November 29, 2017 IR communication as question #1a. Vial depyrogenation data was submitted in Amendment #6 received on December 6, 2017.

(b) (4)

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

(b) (4)

. **DMPQ Reviewer Assessment**: The response is acceptable.

(b) (4)

Filling Component Prep – Stoppers

A translated description of the stopper (b) (4) and its performance qualification was submitted in Amendment #6, received December 6, 2017. Stoppers are (b) (4)

(b) (4)

(b) (4)

(b) (4)

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

Caps

The (b) (4) of the cap-(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)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

DMPQ Reviewer Assessment: The response is acceptable.

Sterilization of critical product contact equipment

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

(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)

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

(b) (4)

(b) (4)

(b) (4)

CR comments regarding the (b) (4) **used to sterilize the lyophilizer trays**

- (b) (4)

and the response is acceptable.

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)

(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)

CR comments regarding the EMPQ of the drug product aseptic filling area

- **CR Comment 41**: I requested information about the current environmental monitoring procedure

and asked for supporting data from the EMPQ. I also requested data to support control of particulates in the (b) (4)

LFB Response: (Per Amendment 71, 1.11.1, Request 41 page 424): LFB confirmed and provided supporting data to demonstrate that a robust EMPQ was performed under dynamic conditions on the filling lines, including the surrounding Class (b) (4) areas, and the (b) (4) (not previously performed). Testing was conducted in conjunction with media fills and other process runs. Particulate acceptance criteria were in accordance with ISO (b) (4) and ISO (b) (4) as applicable. Surface and personnel microbial monitoring was also performed for critical areas. Current routine EM procedures include monitoring for viables and particulates at (b) (4) These locations are supported with viable and non-viable data on numerous additional locations throughout the filling line. Operators are routinely monitored on (b) (4)

DMPQ Reviewer Assessment: The current EM procedures appear acceptable and are supported by EMPQ data; the response is acceptable.

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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CR comments regarding general contamination control of the drug product facility

- **CR Comment 42**: I requested information about the facility sanitization and disinfectant effectiveness studies, to include information about facility isolates; I also asked about the physical separation of Class (b) (4) and Class (b) (4) space, and routine facility sanitization. **LFB Response**: (Per Amendment 71, 1.11.1, Request 42 page 438): (b) (4) data provided); the routine cleaning procedures are considered validated against these organisms. **DMPQ Reviewer Assessment**: The current EM procedures appear acceptable and are supported by EMPQ data; the response is acceptable.

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 fro (b) (4) A robust qualification of the HVAC filtration system appears to have been done and filters are requalified (b) (4)

Water Systems

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

at a temperature range of (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)

CR Question 42 e: Please identify the locations in which (b) (4) are used for the (b) (4) drug product manufacturing site. Please describe the frequency of (b) (4)

(b) (4)

DMPQ Reviewer Assessment: The response is acceptable.

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 (b) (4)

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

(b) (4) All results passed. **DMPQ Reviewer Assessment**: The more recent media fills are representative of the actual production scale as compared to the clinical batch size data that was previously submitted. The protocols and acceptance criteria are appropriately representative of the process and all results passed; the response is acceptable.

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 light or dark particulates. The lamps were current on their calibration schedule.

VI Operators are trained in (b) (4). The (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 enough 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 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 could not be evaluated during the first review cycle.

CR comments regarding visual inspection

CR Comments 37 and 56: In Comment 37 CBER requested the following 1) 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) 2) The master batch record (or detailed narrative) for the reconstituted solution supplemental testing; and 3) At least one executed batch record for the (b) (4) and supplemental visual inspection testing. In Comment 56 CBER requested clarification on the procedure, AQL, and acceptance criteria for the supplemental testing.

LFB Response: (Per Amendment 71, 1.11.1, Request 37 page 414 and submitted batch records in 3.2.R.1): According to the submitted batch records, LFB has established the following defect categories and AQLs:

(b) (4)

DMPQ Reviewer Assessment: The categories of defects are comprehensive and conservative for critical defects, erroring on the side of caution/patient safety, thus I find the defect categories acceptable. The AQL sample size (according to the master and executed batch records) is (b) (4) units for both the 1 mg and 5 mg dosage strengths, and the critical defect acceptance criterion is (b) (4) which correlates to (b) (4). It should be noted that the batch size range is (b) (4) vials for the 1 mg dosage and (b) (4) vials for the 5 mg dosage.

All of the master and executed batch records submitted in response to Comment 37 indicate that the AQL sample size for all dosage forms is (b) (4) vials, taken from vials that passed the initial (b) (4) visual inspection. The narrative response to Comment 56 (specifically in Amendment 71, 1.11.1., page 509 of 570) LFB notes that "A subset of (b) (4) vials which passed the (b) (4) visual inspection is then subjected to AQL…" Either scenario is acceptable.

Because the drug product is lyophilized, LFB performs a supplemental visual inspection test for visible particulates in reconstituted solution; this supplemental test also includes the (b) (4) was previously identified as a potential root cause of the long-running particulate problem (Reference CRL Comment #2). The supplemental test is a destructive test; LFB follows (b) (4) The original sampling plan (b) (4) Due to the previous ongoing particulate issue, LFB 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 (b) (4) To clarify, this allows for an overall acceptance criterion of (b) (4) vials with particulates for the total (b) (4) vials subjected to supplemental testing. The visual inspection process is sufficiently robust and all issues related to visual inspection and particulates have been resolved.

Container Closure Integrity

CCIT Test Method Validation:

CR comments regarding CCIT

Issue: There were no studies or reports to support the brief narrative regarding container closure integrity testing (CCIT) in the original BLA; an IR was included in the December 12, 2017 filing letter as review issue #16. LFB submitted the requested information in Amendment 12 (response to request 16), received on February 6, 2017. An initial study using the (b) (4) method was performed for (b) (4)

DMPQ Reviewer Assessment: The (b) (4) method is not appropriate for lyophilized products, which are sensitive to air and moisture. The (b) (4) method is acceptable and has been implemented for routine testing; however, more importantly, LFB performs (b) (4) testing on (b) (4). This testing is more meaningful for lyophilized drug products since failures would be indicative of breaches that could occur at much (b) (4). I have no additional issues or questions regarding CCIT.

Drug Product 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)

(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) .

Issue: The CR letter included several questions regarding shipping studies. LFB (b) (4) received March 17, 2020: Laboratoire Francais du Fractionnement et des Biotechnologies SA (LFB S.A.) (b) (4) .

Diluent Production

I defer to Nicole Li on review of the diluent; likewise, she defers to me on review of the lyophilized DP.

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 three 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) A visual check is performed for readability of all labeled vials.

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* (b) (4) *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) labeling. 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.