Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: File of STN 125641/0 & Seameen Dehdashti CBER/OTAT/DRPM/RPMBI

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

Product: coagulation factor VIIa (recombinant)-jncw [SEVENFACT]

Subject: *Addendum to Review of Stability Studies for the Bulk Drug Substance and Final Drug Product in LFB's original Biologics License Application for Coagulation Factor VIIa (Recombinant)-jncw [SEVENFACT]*

Contents

1. Executive Summary

This memorandum is an addendum to my review of the stability studies for the bulk drug substance (BDS) and final drug product (FDP) in the Biologics License Application (BLA) for Coagulation Factor VIIa (Recombinant)-jncw submitted by Laboratoire Français du Fractionnement et des Biotechnologies Société Anonyme (LFB) on October 13, 2016. The proposed indication is for on-demand treatment of bleeding in adolescents and adults with hemophilia with inhibitors against Factor VIII and Factor IX. LFB's code name for the product is LR769, and proposed proprietary name is SEVENFACT.

A Complete Response Letter (CRL) was issued on October 13, 2017. LFB submitted the complete response to the CRL on October 11, 2019 in an amendment under STN 125641/0.71. I reviewed the information in amendments 71, 73, and 87 dated October 11, October 25, 2019 and March 12, 2020, respectively, on stability studies for the BDS and FDP.

The active ingredient in SEVENFACT is a recombinant analogue of activated human coagulation Factor VII (FVII), which is a vitamin K-dependent protein. The recombinant FVII protein is expressed in and purified from the milk of transgenic rabbits. During the manufacturing process, the recombinant FVII protein is activated to FVIIa. The FDP is a sterile lyophilized powder to be reconstituted with sterile Water for Injection (sWFI) prior to administration via the intravenous route.

There are two dosage forms of FDP containing 1 mg or 5 mg of recombinant FVIIa in single-use glass vials, co-packaged with the diluent in a pre-filled syringe containing 1.1 mL and 5.2 mL of sWFI, respectively.

The proposed BDS and FDP shelf-life and investigated storage conditions are as follows:

- (b) (4)
- For FDP: 36 months at up to 30°C protected from light; and
- Reconstituted product: (b) (4) hours at up to 30°C.

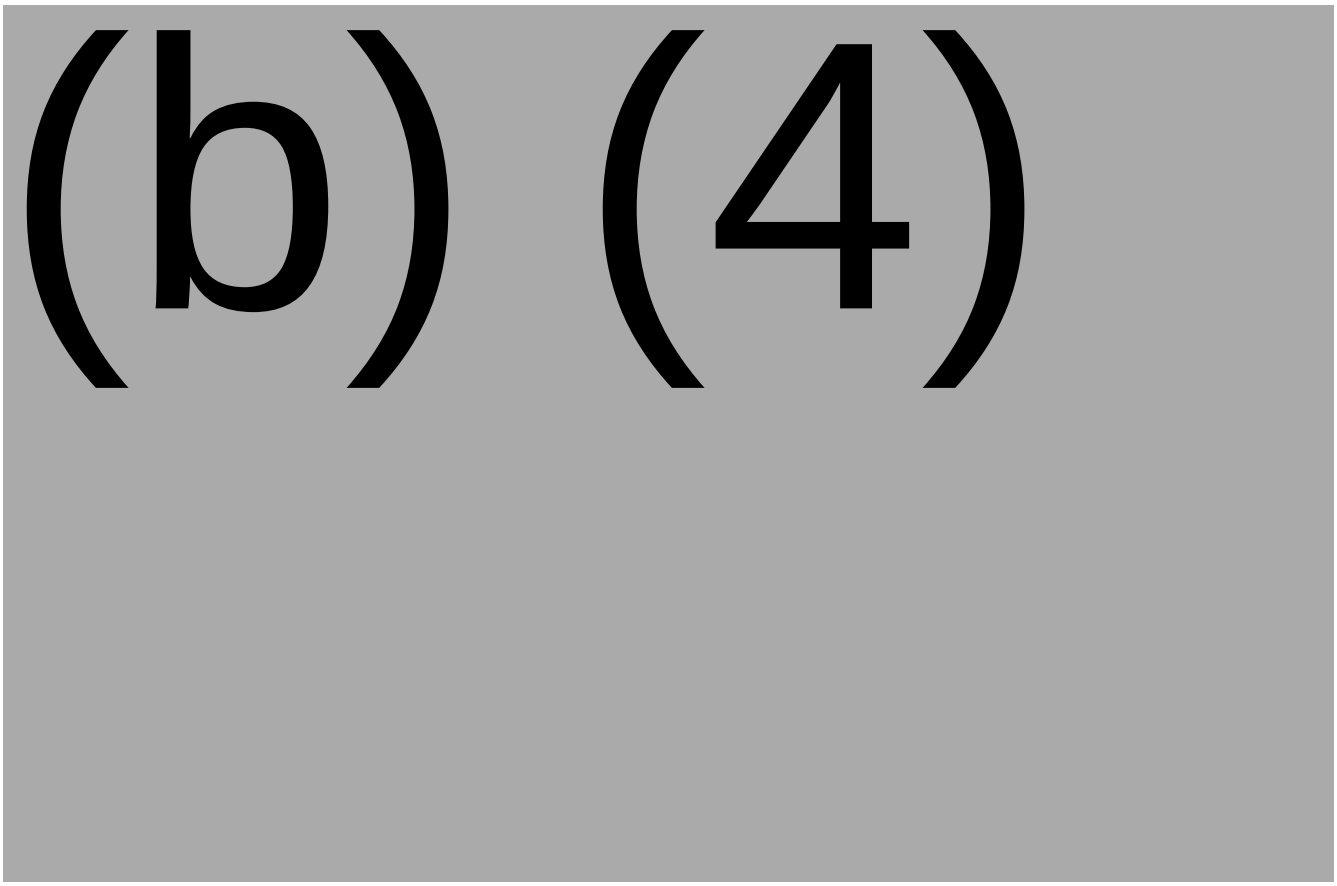
Upon review of all the submitted information related to the BDS and FDP stability studies, the issues raised in the previous review have been resolved, and the data now support the proposed shelf-life. Therefore, I recommend approval of the BLA from the perspective of BDS and FDP stability.

2. BDS Stability Studies

(b) (4)

(b) (4)

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



(b) (4)

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3. FDP Stability Studies

SEVENFACT is supplied in three dosage forms (lyophilized powder in glass vials) containing 1 mg, (b) (or 5 mg of rhFVIIa co-packaged with sWFI in pre-filled syringes. The rhFVIIa concentration in reconstituted FDP is 1 mg/mL. The (b) (4) dosage form was removed from the BLA in amendment No. 0073 on October 25, 2019. Data collected for the (b) (4) dosage strength remain within Module 3 to support process validation and stability studies.

In the resubmission, the specification of the FDP was not changed, the potency testing method was re-validated, and some the potency data were obtained using the new potency method.

FDP batches used in the primary and supportive stability studies were manufactured from (b) (4) material at (b) (4) . One FDP batch (b) (4) manufactured from (b) (4) was studied to verify that its stability profile is comparable to that of previous FDP batches manufactured from (b) (4) material.

In total, six types of stability studies were performed on FDP:

a) Primary Stability Studies: (b) (4) FDP PPQ batches were included in the stability study. They include (b) (4) batches of 1 mg, (b) (4) batches of 5 mg, and (b) (4) dosage strengths. These primary stability studies have been conducted in (b) (4) storage conditions 5°C, 25°C, 30°C (b) (4) ; up to (b) (4) months of data were provided.

b) Comparable Stability Studies - (b) (4) Stability Studies
One batch (b) (4), 1 mg) of FDP from (b) (4) was added to the stability study to verify that its stability profile is comparable to that of previous batches manufactured from (b) (4) material.

c) Supportive stability studies: stability studies were conducted on (b) (4) FDP batches manufactured at pilot (b) (4) batches) or industrial scale (b) (4) batches) from Process A or Process B. Up to (b) (4) months of data under refrigerated condition and 36 months of data at room temperature (30°C) are available to support the shelf-life claim of LR769 FDP.

d) Photostability studies: (b) (4) primary registration batches of LR769 FDP were studied at the 1-mg dosage strength. Photostability testing was performed (b) (4)

e) Simulation of home setting conditions: In-use stability data before reconstitution designed to simulate home setting conditions with alternate room temperature and refrigerated storage conditions. This study was conducted on (b) (4) of each extreme dosage strength (1 mg and 5 mg) of FDP.

f) In-use stability study after reconstitution.

The FDP batch information, manufacturing process, available data and storage conditions are listed in Table 5.

Table 5. Summary of Stability Studies for LR769 Final Drug Product (1 mg, 5 mg and (b) (4) Dosage Strengths)

Drug Product	**Manufacturing Process/Scale**	**Batch Designation (Primary/Supportive)**	**Data Available/Study Status**
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 25°C ± 2°C (b) (4) RH/ complete

			(b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 25°C ± 2°C (b) (4) RH/ complete (b) (4) months at 30°C ± (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 25°C ± 2°C (b) (4) RH/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale	Comparability (b) (4)	6 months at 5°C ± 3°C/ ongoing 6 months at 30°C (b) (4) RH/ ongoing (b) (4)
(b) (4) (1 mg)	Process A / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale	Supportive	36 months at 5°C ± 3°C/ complete 36 months at 25°C ± 2°C/ (b) (4) RH/ complete 36 months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (5 mg)	Process B/Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C / complete (b) (4) months at 25°C ± 2°C (b) (4) RH / complete (b) (4) months at 30°C (b) (4) RH / complete

			(b) (4)
(b) (4) (5 mg)	Process B/Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C / complete (b) (4) months at 25°C (b) (4) RH / complete (b) (4) months at 30°C (b) (4) RH / complete (b) (4)
(b) (4) (5 mg)	Process B/Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C / complete (b) (4) months at 25°C ± 2°C (b) (4) RH / complete (b) (4) months at 30°C (b) (4) RH / complete (b) (4)
(b) (4) (5 mg)	Process B/ Pilot Scale	Supportive	36 months at 5°C ± 3°C/ complete 36 months at 25°C ± 2°C/ (b) (4) RH/ complete 36 months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (5 mg)	Process B / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (5 mg)	Process B / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (5 mg)	Process A / Industrial Scale	Supportive	24 months at 5°C ± 3°C/ complete
(b) (4) (5 mg)	Process A / Industrial Scale	Supportive	36 months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (5 mg)	Process A / Industrial Scale	Supportive	24 months at 5°C ± 3°C/ complete
(b) (4) (5 mg)	Process A / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete

			(b) (4)
(b) (4)	Process B / Industrial Scale (PPQ)	Primary	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 25°C ± 2°C/(b) (4) RH/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4)	Process B / Pilot Scale	Supportive	36 months at 5°C ± 3°C/ complete 36 months at 25°C ± 2°C(b) (4) RH/ complete 36 months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4)	Process B / Industrial Scale	Supportive	(b) (4) months at 5°C ± 3°C/ complete (b) (4) months at 30°C (b) (4) RH/ complete (b) (4)
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	Photostability Study
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	Photostability Study
(b) (4) (1 mg)	Process B / Industrial Scale (PPQ)	Primary	Photostability Study
(b) (4) (1 mg)	Process B /Industrial Scale (PPQ)	Primary	Simulation of Home Setting Conditions Study
(b) (4) (5 mg)	Process B/Industrial Scale (PPQ)	Primary	Simulation of Home Setting Conditions Study

Abbreviations: PPQ = Process Performance Qualification

The primary and supportive stability studies are completed, the comparability (b) (4) source material) stability is ongoing.

All tested parameters are within the specification acceptance criteria in the primary and supportive stability studies, including visual appearance of reconstituted solution, identity, pH, (b) (4) , reconstitution time, particulate matter, residual moisture, sterility, bacterial endotoxins, (b) (4) rhFVIIa concentration,

rhFVIIa potency by (b) (4) assay, specific activity, trisodium citrate dehydrate, polysorbate 80, arginine HCl, lysine HCl, isoleucine, and glycine.

In the previous review cycle, the relative moisture content, content in (b) (4) and potency data raised concerns. In the resubmission, the relative moisture content data remained unchanged when stored at 5°C, the data were slightly increased through time up to 36 months when stored at 25°C and 30°C but remained within the specification acceptance criteria. The compilation of relative moisture data generated during the primary stability studies are shown in Section 6, Figure 6 to Figure 8.

The content in (b) (4) remained unchanged at 5°C (Section 6, Figure 9), it increased when storage temperature at 25°C and 30°C (Section 6, Figure 10 and Figure 11) but remained below its specification limit (b) (4) through 36 months. In one batch (b) (4) of 1-mg dosage strength, the content in (b) (4) is above the specification limit after (b) (4) months of storage at 30°C (Section 6, Figure 11), i.e., beyond the proposed shelf life of 36 months. At (b) (4), i.e., above the recommended storage temperature, the increase is more pronounced leading to out-of-specification results after 18 months of storage for the 1-mg vials.

For potency, the stability data met the specification criteria including re-tests with the revalidated potency method under storage conditions at 5°C, 25°C and 30°C through 36 months.

In the comparability stability study of FDP from (b) (4) sources, (b) (4) at storage conditions from 5°C to (b) (4); six months stability data are available. All tested stability parameters were within specification limits. The residual moisture and (b) (4) data stored at 30°C and (b) (4) are shown in Section 6, Figure 12 and Figure 13. The 6-month stability data indicate that batch (b) (4)

Reviewer's comments:
Potency were re-tested with the revalidated method, and the data were within the specification limits for up to (b) (4) months when stored at up to 30°C. Specific Activity results met the acceptance criteria, Potency and Specific Activity for the (b) (4) vial demonstrated a strong decline over time to 24 months but return to normal at 36 and (b) (4) months indicated method variability. The content in relative moisture, (b) (4) remained unchanged at 5°C, they were increased at higher temperatures of storage but remained within the specification limits for up to 36 months at 25°C and 30°C. All other testing parameters were within the specification acceptance criteria in the set of long-term stability data generated through (b) (4) months at 5°C to 30°C, supporting the proposed shelf life of 36 months at a temperature not exceeding 30°C.

4. CRL Items

Review of CRL responses:

Request 4

The proposed shelf-life for the FDP is not supported by stability data. Please provide the following:
a. ***The potency results of all stability samples, determined using a fully validated Potency assay.***

Summary of LFB Response:
The revalidated potency assay with the implementation of a working standard and a Quality Control (QC) sample was introduced in July 2017, reported in amendment No. 0053. At that time, the PPQ batches (except batch (b) (4)) had already been analyzed at their 24-month time-point and the stability program of development batches (pilot and engineering batches) was completed.

The revalidated potency assay was therefore used to analyze PPQ batches starting at the 36-month time-point (24 months for batch (b) (4)). Additional engineering batches manufactured after the PPQ batches were placed on stability and additional potency data generated with the revalidated method are available from these batches. All potency and specific activity results meet the acceptance criteria for up to 36 months under long-term storage conditions (5°C to 30°C) and (b) (4) months under accelerated conditions (b) (4) The (b) (4)-month results available for one batch (b) (4) also meet acceptance criteria under long-term conditions.

Reviewer's Comments: *The answers are acceptable.*

b. ***The investigation reports for all the out-of-specification (OOS) results in Potency and Specific Activity for FDP release and stability evaluation against the proposed acceptance limits.***

Summary of LFB Response:
There was no out-of-specification potency or specific activity result as shown in response to request 4a, including for batch (b) (4) for which an apparent loss of potency was detected at the 23-month time-point. Because of the variability of the method, fluctuating results were sometimes generated, therefore no investigation was triggered as they remained within specification limits. For commercial batches, a trending analysis has been implemented with an alert limit set at (b) (4) standard deviations to detect out-of-trend results.

Reviewer's Comments:
The data are within the specification accept criteria through a full set of long-term real-time stability study under different storage conditions up to 30°C. The previously observed adverse stability trends, noted in my primary memorandum, were likely caused by the data variation caused by method variability. This answer is acceptable.

c. ***The investigation report for the declining trends in Potency as shown in the stability studies for the (b) (4) FDP presentation. Specifically, the updated stability data presented in Table 26 of Amendment #53 dated July 24, 2017, demonstrate that after storage for 23 months under the recommended conditions, Potency of batch (b) (4) is decreased by (b) (4) and its Specific Activity by (b) (4). At this rate, the Potency is projected to be OOS at 30 months of storage, 6 months before the proposed shelf-life.***

Summary of LFB Response:

Long-term stability data up to 36 months are now available for batch (b) (4) and do not show a loss in potency. Overall, the full set of long-term stability data generated through 36 months at three temperatures of storage (5, 25 and 30°C) on batch (b) (4) as well as on (b) (4) other PPQ batches indicates a satisfactory stability profile in a temperature range from 5°C to 30°C. This real-time data support the proposed shelf life of 36 months at a temperature not exceeding 30°C.

Reviewer's Comments

The Specific Activity of batch (b) (4) *was steadily decreasing by the 24-month time-point and clearly showed a negative trend even if it was within the specification. As shown in my previous memorandum, the projected data would fall below the low specification limit of* (b) (4) *before 30 months of storage at room temperature based on the provided 24 months data. In the resubmission, the trend disappeared after adding the 36- and* (b) (4) *-month data-points, indicating that the negative trend was due to method variability. The answer is acceptable.*

5. Conclusion and Recommendation

The data from the stability studies for BDS and FDP are acceptable, and support the proposed shelf-life as follows:

(b) (4)

For FDP: 36 months at 5 to 30°C protected from light

- There were no significant changes, except relative moisture content, the content in (b) (4) remained unchanged at 5°C, and increased when storage temperature at 25°C and 30°C but remained below its specification limit (b) (4) through 36 months, supporting the shelf-life of 36 months at 5 to 30°C.
- Exposure to light had an impact on purity, (b) (4) and specific activity. FDP storage in its (b) (4) package is needed.

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