To: File (STN 125641/0) & Mark Levi, PhD

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

Contents

1. Executive Summary

Laboratoire Français du Fractionnement et des Biotechnologies Société Anonyme (referred to as LFB) submitted an original biologics license application (BLA) for Coagulation Factor VIIa (Recombinant) (also known as rhFVIIa or rFVIIa), on 13 October 2016. SEVENFACT is the proposed proprietary name and *Eptacog beta* (activated) is the International Nonproprietary Name (INN) of this product.

SEVENFACT is a recombinant (r) analogue of human coagulation Factor VIIa (FVIIa), a member of the vitamin K-dependent family of coagulation factors. It is produced by recombinant DNA technology employing site-directed expression of the human Factor VII gene in the mammary gland of genetically engineered rabbits and purified from the rabbit milk.

SEVENFACT final drug product (FDP) has been formulated as a sterile, latex-free, lyophilized dosage form that is to be reconstituted with sterile Water for Injection (sWFI) prior to administration by the intravenous route. It is supplied in three dosage forms (glass vials) containing 1 mg, (b) (4) or 5 mg of

rFVIIa along with sWFI in pre-filled syringes of. The rFVIIa concentration in reconstituted SEVENFACT is 1 mg/mL.

The proposed indication of SEVENFACT is for the on-demand treatment and control of bleeding in adolescent and adult hemophilia A or B patients with inhibitors to Factors VIII or IX.

I reviewed the stability data for the bulk drug substance (BDS) and FDP provided in the original BLA and amendments 37, 44, 51, 53 and 63 dated Oct 13, May 18, June 17, July 7 and 24, 2017, respectively. The proposed BDS and FDP shelf-life and investigated storage conditions, investigation methods and parameters are as follows:

- (b) (4)
- For FDP: 36 months at up to 30°C for the 1, (b) (4) 5 mg dosage strengths
- Reconstituted Product: (b) (4) hours at up to 30°C

The following storage conditions were investigated:

- (b) (4) .

- FDP: 5°C (± 3°C) / (b) (4) RH (proposed real-time storage condition) for 36 months, 25°C (± 2°C) / (b) (4) RH (proposed real-time storage condition) for 36 months, 30 °C / (b) (4) RH (proposed real-time storage condition) for 12 months, (b) (4) RH (accelerated storage condition) for (b) (4) , and reconstitution study at room temperature (max.+25°C) of samples that have been stored for 0, 18, and 24 months.

- (b) (4)

- FDP: The test parameters were Visual Appearance of cake, Visual Appearance of reconstituted solution, identity, pH, (b) (4) , reconstitution time, (b) (4) , sterility, bacterial endotoxins, (b) (4) rFVIIa concentration, rFVIIa potency by (b) (4) , specific activity, trisodium citrate dehydrate, polysorbate 80, arginine HCl, lysine HCl, isoleucine, and glycine.

Reviewer's comment: *Several specification limits for BDS and FDP were changed during the review cycle, and several methods were revalidated. All the stability data were within the specification limits, but there is a potency loss trend for the FDP at* (b) (4) *strength.*

Conclusions and Recommendation:

My review of the stability studies found three deficiencies that need to be addressed:

1) The presented stability data do not support the proposed FDP shelf-life of 36 months when stored at room temperature (30°C) for the (b) (4) dosage strength.

2) The variations in stability data are too large for Potency determination by the (b) (4) assay and Specific Activity measurement to be reliable.
3) The root causes for the presence of visible particulates during stability studies are not adequately investigated and addressed.

2. BDS Stability Studies

(b) (4)

a) BDS Specifications

(b) (4)

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

(b) (4)

(b) (4)

3. FDP Stability Studies

The primary stability studies, supportive stability studies, and simulation of home setting conditions were included in this submission.

a) FDP storage condition

The following storage conditions were investigated to evaluate the stability profile of SEVENFACT FDP:

- Refrigerated storage conditions: 5°C ± 3°C
- Long-term room temperature storage conditions: 25°C ± 2°C / (b) (4) RH (b) (4) RH
- Long-term room temperature storage conditions: 30°C (b) (4) / (b) (4) RH (b) (4) RH
- Accelerated storage conditions: (b) (4) RH (b) (4) RH

b) FDP Specifications

Table 2. SEVENFACT Drug Product Specifications

Parameters	Attribute	Acceptance Criteria
Appearance and description	Visual appearance of cake	White to off-white cake or powder
	Appearance of reconstituted solution: -Opalescence -Color	(b) (4)
	Visual Appearance of reconstituted solution	Clear to slightly turbid colorless solution
	Visual Appearance of reconstituted solution: visible particulates	(b) (4)

Identity	(b) (4)	(b) (4)
Quality	pH	(b) (4)
	(b) (4)	(b) (4)
	Reconstitution time	(b) (4)
	Particulate matter	(b) (4)
	Residual moisture	Release 1 mg vials: (b) (4) (b) (4) 5 mg vials: Shelf-Life 1 mg vials: (b) (4) (b) (4) 5 mg vials:
	Sterility	Sterile
	Bacterial endotoxins	(b) (4)
Purity	(b) (4)	
Impurities	(b) (4)	
	(b) (4)	
	(b) (4)	
Strength, potency	rFVIIa concentration	
	(b) (4)	
	Specific activity	
Excipients	Trisodium citrate dihydrate	
	Polysorbate 80	
	Arginine HCl	
	Lysine HCl	
	Isoleucine	
	Glycine	

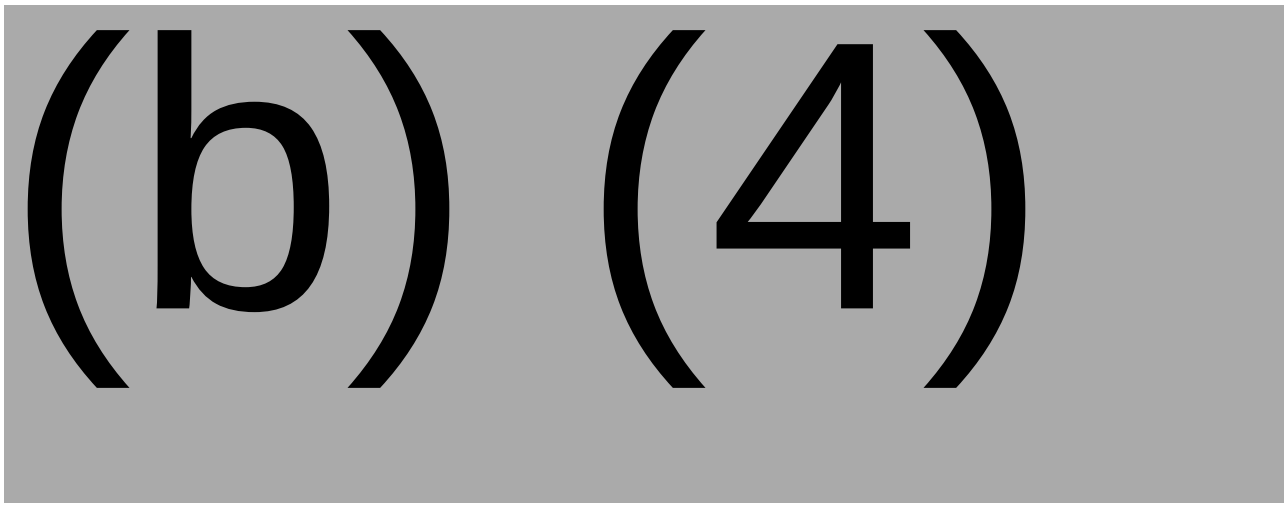
c) Results of FDP Stability Studies:

Primary Stability Studies

(b) (4) PPQ batches of SEVENFACT FDP were evaluated in this stability program: (b) (4) batches of the 1-mg dosage strength (batches (b) (4) of the (b) (4) dosage strength (b) (4) and (b) (4) batches of the 5-mg dosage strength (batches (b) (4)). Nine to 36 months of stability data are available for these batches.

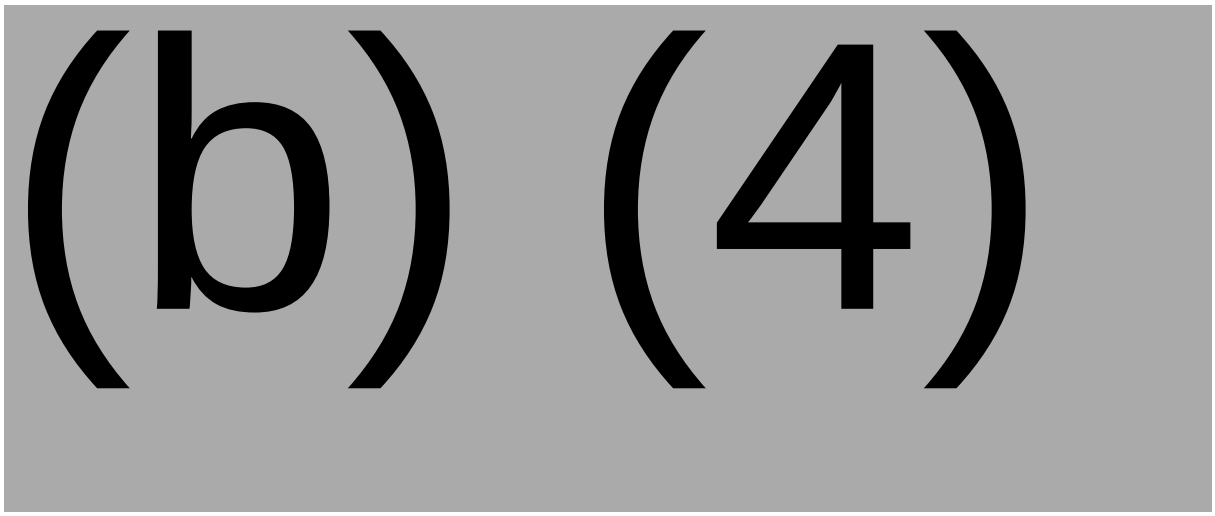
In the primary stability data, all the parameters including *appearance*, *identity*, *quality*, *purity* and *impurities* were within the specification acceptance criteria, except the OOS results for the *Visual Appearance of reconstituted solution: visible particulates.* The Visible Particles are discussed in section *FDP Stability Study Deficiencies* below. The data for *Potency*, *Specific Activity*, (b) (4) presented in a graphical form below.

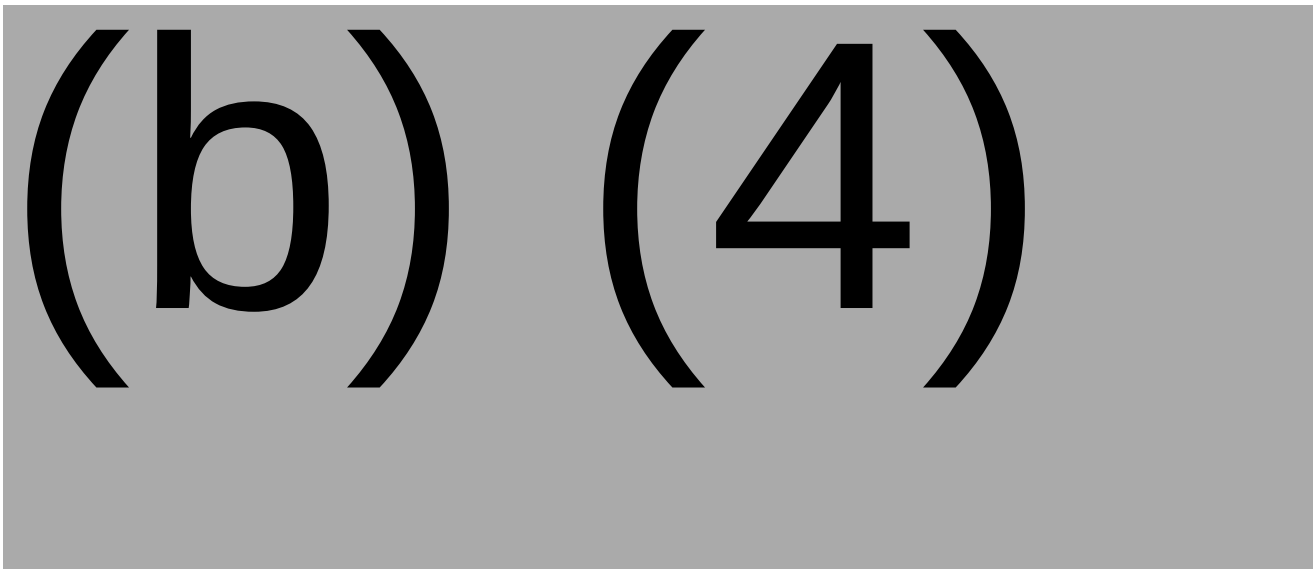
1 page determined to be not releasable: (b)(4)



Reviewer's comments:

1. *Although the Potency and Specific Activity results were within the acceptance criteria limits, Potency and Specific Activity for the* (b) (4) *vial demonstrated a strong decline over time.*
2. *The variation of Potency and Specific Activity data was too large. For example, when Specific Activity was normalized on the value at release (time=0), the specific activity was higher than* (b) (4) *or lower than* (b) (4) *of the initial value in several lots at the 5°C to 30°C storage conditions. Please refer to section "FDP Stability Study Deficiencies" below.*



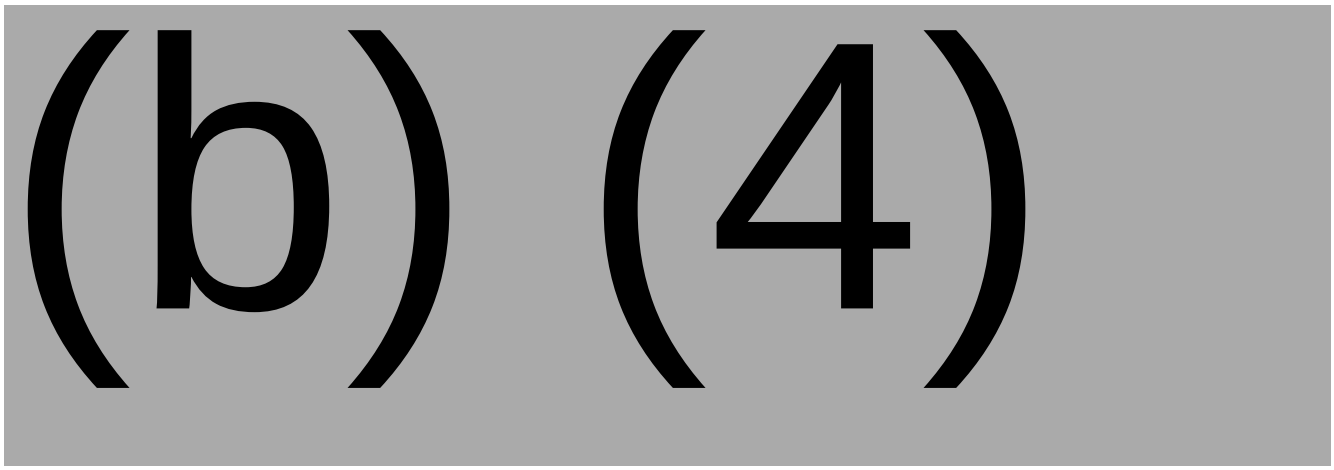


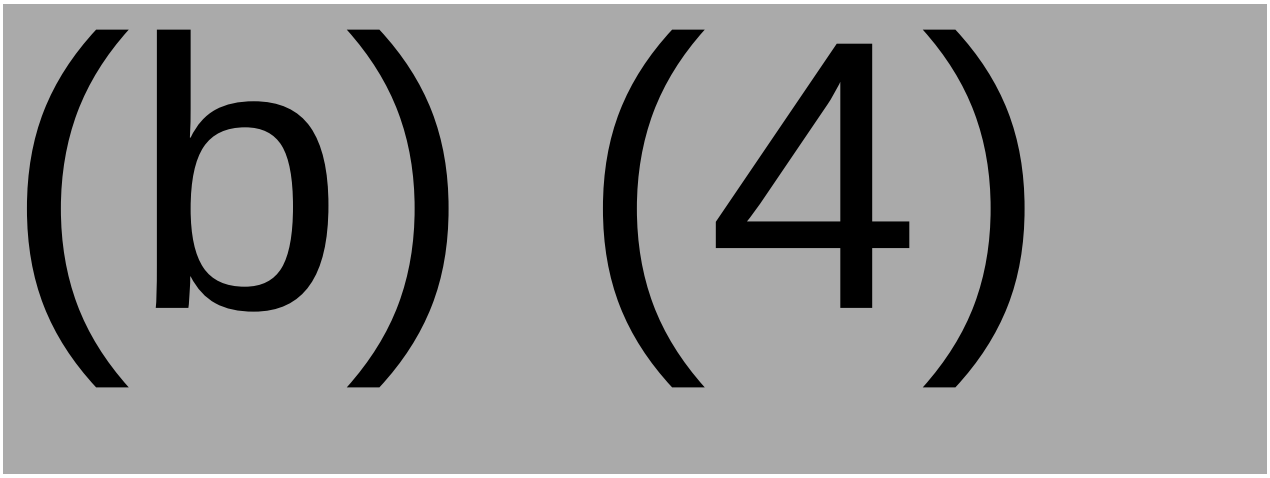
Reviewer's comments: *In the initial submission, a slight increase in the Residual Moisture and* (b) (4) *were observed in the primary stability study, but the data were within the specification limits. However, the updated data presented in Amendment #63 dated September 22, 2017, the Residual Moisture for the 1-mg vial was* (b) (4) *at the 24-month time-point (see figures below), suggesting that the revised stability data may not support the proposed FDP shelf-life. These data will be reviewed in the next review cycle.*

Supportive Stability Studies:

(b) (4) drug product batches manufactured at pilot (b) (4) batches) or industrial scale (b) (4) batches) from Process A or Process B were studied for up to 36 months under refrigerated conditions and up to 36 months under room temperature (30°C) conditions.

- SEVENFACT Potency by (b) (4)





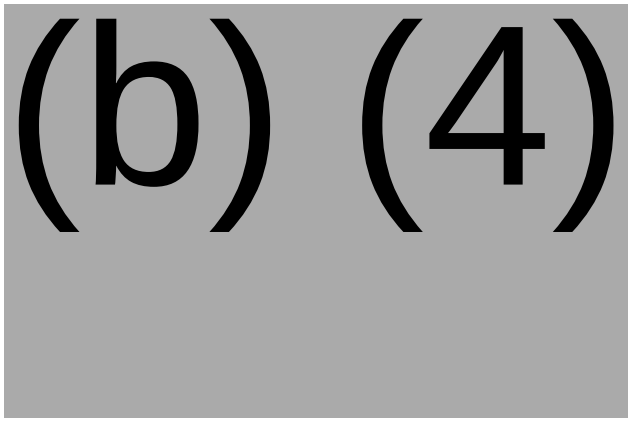
In the supportive stability study, all the parameters including *appearance* (with the exception of visible particles, see below), *identity*, *quality*, *purity* and *impurities* were within the specification acceptance criteria.

Reviewer's comment: *All the parameters were within the specification acceptance criteria and no significant changes in quality attributes over time were observed in stability studies except for the following: (1) loss of potency in several FDP batches, (2) increase of residual moisture in several FDP batches, (3) the Potency data variation was too large, and (4) visible particulates were detected in several FDP batches at several time-points and at different temperatures of storage. These comments are discussed in detail below.*

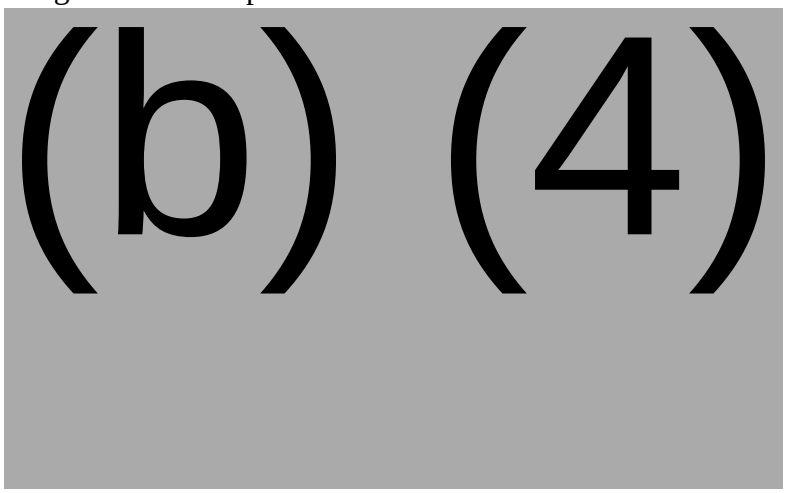
Deficiencies in FDP Stability Studies Identified During Review

1. ***Potency decrease, batch*** (b) (4)

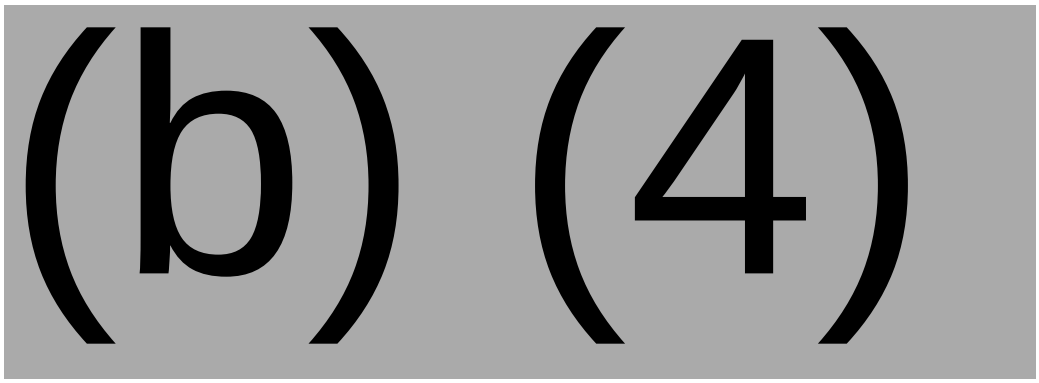
Adverse trends in product *Potency* were observed in stability data for (b) (4) presented in the initial submission; these conclusions were confirmed by additional stability data provided by LFB to Dr. Alexey Khrenov in April, 2017 during the Pre-License Inspection of LFB facilities in (b) (4). The figure below shows the extrapolation of the data presented in the initial submission and the reports obtained during the inspection. The *Specific Activity* is projected to fall below the low specification limit of (b) (4) before 30 months of storage at room temperature.



The adverse *Specific Potency* trends were slightly corrected in the recent Amendment #63 dated September 22, 2017. To achieve this, LFB recalculated the *Specific Potency* using the revised *rFVIIa Concentration* data, i.e., LFB replaced the *rFVIIa Concentration* values obtained in a stability study with a single "corrected" value. LFB's back-calculation of *Specific Potency* will be reviewed in the next review cycle for this BLA. The approach does not appear acceptable at this time because it contradicts the description of *Specific Potency* assay in the original Stability Study protocol. This revision of *Specific Potency* data resulted in a slightly reduced negative trend, but the data still do not support LFB's proposed shelf-life. The figure below shows the extrapolation of the initial (STN 125641/0) and revised (STN 125641/0/0.63) data. Extrapolation of the revised data suggests that the Specific Activity will reach the low specification limit by 34 months of storage at room temperature.



(b) (4)



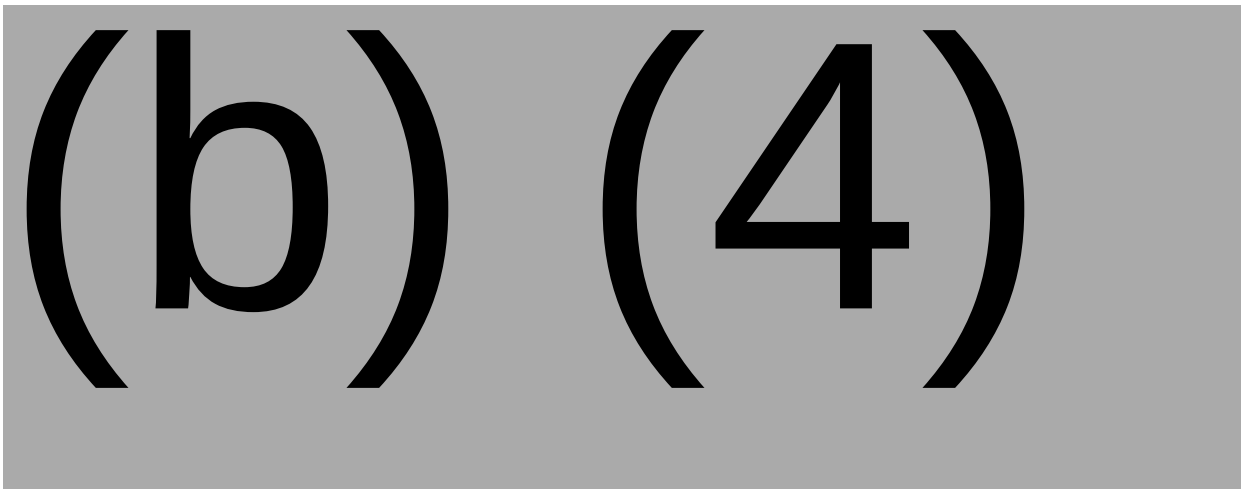
2. Elevated Moisture in the 1-mg SEVENFACT dosage form

In Amendment #63 dated September 22, 2017, the residual moisture of the 1-mg batches (b) (4) exceeded the specification limit of (b) (4) LFB did not provide an explanation for these OOS results. At this time, the results do not support the proposed FDP shelf-life of 36 months.

Reviewer's comment: *Because these data were received very late in the review cycle, I was not able to conduct a substantive review of the validity of these new findings. These results will be reviewed in the next review cycle for this BLA.*

3. Variability of Potency Data

The FVIII and FIX concentrate products are usually considered stable when factor activity remains within the (b) (4) range of the potency value printed on the vial at release. SEVENFACT is dosed by mass, unlike the FVIII and FIX products which are dosed by factor activity. However, consistency of dosing is maintained by the release assay *Specific Activity*. To evaluate the relative changes in SEVENFACT *Specific Activity*, I normalized all *Specific Activity* values at different stability time points on the initial value at release (time=0). The specific activity was higher than (b) (4) or lower than (b) (4) of the initial value in several SEVENFACT batches, see figures below. The lowest Specific Activity value was (b) (4) and the highest was (b) (4) the initial value. This indicates that either the FDP is unstable or the Specific Activity and Potency methods are not robust.



4. Detection of Visible Particles in the Reconstituted Product

In the original submission BLA STN 125641/0, LFB reported that the presence of visible particles after product reconstitution was detected in 4 FDP batches during stability studies, at different time-points and temperatures of storage. These results are reported as "not conforms" in stability tables. LFB claims that these observations occurred regardless of the dosage form, the temperature of storage and randomly over time without any increasing trend. LFB suggested that the vial adapter (VA) is the probable root cause. The following explanation was provided[1]:

(b) (4)

[1] See "3.2.P.8.3 Stability Data" in STN 125641/0

(b) (4)

LFB also stated[1] that the following Corrective and Preventive Action was implemented:

(b) (4)

However, during the BLA review cycle, LFB reported that the particles continued to be detected in stability studies at multiple time-points, e.g.,[2]

- 3 months: (b) (4) Process B Lot (b) (4) at +5°C ± 3°C
- 9 months & 18 months: (b) (4) Process B Lot (b) (4) at 25°C ± 2°C, (b) (4) RH (b) (4) RH
- 3 months & 9 months: (b) (4) Process B Lot (b) (4) at 30°C (b) (4) (b) (4) RH (b) (4) RH
- 18 months: 1 mg Process B Lot (b) (4) at 30°C (b) (4) RH (b) (4) RH
- 3 months: 1 mg Process B Lot (b) (4) at 25°C ± 2°C, (b) (4) RH (b) (4) RH
- 24 months: 5 mg Process B Lot (b) (4) at 25°C ± 2°C, (b) (4) RH (b) (4) RH
- 24 months: 5 mg Process B Lot (b) (4) at 25°C ± 2°C, (b) (4) RH (b) (4) RH
- 18 months: 5 mg Process B Lot (b) (4) at 25°C ± 2°C, (b) (4) RH (b) (4) RH
- 24 months: 1 mg Process B Lot (b) (4)
- 3 months: 1 mg Process B Lot (b) (4)
- 9 months: (b) (4) Process B Lot (b) (4)
- 24 months: 5 mg Process B Lot (b) (4)
- 3 months: (b) (4) Process B Lot (b) (4) at +30°C (b) (4) RH (b) (4) RH
- 24 months: 5 mg Process B Lot (b) (4) at +30°C (b) (4) RH (b) (4) RH
- 36 months: 5 mg Process B Lot (b) (4) at +30°C (b) (4) RH (b) (4) RH
- 3 months: (b) (4) Process B Lot (b) (4)
- 24 months: 5 mg Process B Lot (b) (4)

Reviewer's comment: *LFB claims that the presence of visible particulates during stability studies is not related to changes in the FDP during storage. LFB concluded that the origin of the particles was environmental and not related to the manufacturing process or stoppers, and therefore it was not related to FDP stability. I defer to the primary product reviewer to determine the validity of these root cause investigations.*

d) Home Use Stability Study:

The alternate room temperature and refrigerated storage conditions were studied before reconstitution to simulate home setting conditions. (b) (4) of each dosage strength, 1 mg and 5 mg, was studied.

[2] These data were taken from the revised section "3.2.P.8.3 Stability Data" which was submitted in Amendment #63 dated September 22, 2017. This amendment was not reviewed because it was received after the Late-Cycle Meeting.

The results of the in-use stability studies are acceptable. All parameters were within the specification acceptance criteria, demonstrating the stability of FDP when exposed to alternate room temperature (+30°C) and refrigerated (5°C) storage conditions for (b) (4)

e) Study of Reconstituted FDP

The SEVENFACT reconstituted with sWFI was studied for up to (b) (4) hours of storage at + 30°C (b) (4) RH (b) (4) RH. All results were within the acceptance criteria and no trend was observed.

Although stability was demonstrated for (b) (4) hours at + 30°C, LFB is recommending an immediate use of reconstituted SEVENFACT. This approach is acceptable because SEVENFACT contains no preservatives.

f) Post-Approval Stability Study Commitment

i. Several on-going long-term stability studies at 5°C, 25°C, 30°C, and (b) (4) on (b) (4) primary batches and on additional supportive batches will be continued through the proposed shelf-life of 36 months and up to (b) (4) months.

ii. (b) (4) each of the extreme FDP dosage strengths (1 mg and 5 mg, (b) (4) will be placed on stability at 30°C each (b) (4). All stability studies will be performed on the FDP in the primary packaging components.

Reviewer's Comment: *The proposed* (b) (4) *is not supported with provided data because* (b) (4) *batch* (b) (4) *showed adverse stability trends which were not observed in 1-mg and 5-mg stability studies. LFB should include* (b) (4) *vials in all studies.*

4. History of Changes in Specification Criteria

I noted that LFB has submitted three revisions of specifications for the BDS and FDP. The history of the changes in specifications is listed in Table 3.

Table 3. History of changes of specifications in the BLA

a) History of changes in specification for BDS		
Version	Amendment #	Date of submission
Initial	01	Oct 13, 2016
2nd	37	May 18, 2017
3rd	53	July 24, 2017
b) History of changes in specification for FDP		
Initial	01	Oct 13, 2016
2nd	37	May 18, 2017
3rd	53	July 24, 2017

LFB re-evaluated their stability data using the revised FDP release limits in Amendments #37 and #53. Specifically, data were re-evaluated using the revised specification limits for *Relative Moisture,* (b) (4) *, rFVIIa concentration by* (b) (4) *and Specific Activity*. The specifications for (b) (4) was also revised but the stability data were not re-analyzed.

5. Conclusion and Recommendations

The results and information on SEVENFACT stability are not sufficient to support the proposed shelf-life for SEVENFACT FDP, i.e., 36 months at 30ºC, because:

1) The presented stability data demonstrate that the *Specific Activity* of the (b) (4) dosage strength is decreasing and will not comply with the specification limits for the full duration of the proposed shelf-life of 36 months stored at room temperature.

2) Residual Moisture in the 1-mg FDP is increasing and does not comply with the upper specification after 24 months of storage. These data were submitted too late (Amendment #63 dated September 22, 2017) to allow a substantive review.

3) *Potency* and *Specific Activity* data are too variable, suggesting that either the product is unstable or the Potency method is not suitable for its intended use.

4) The re-occurrence of visible particulates in the reconstituted FDP during stability studies is not adequately investigated and addressed.