M E M O R A N D U M

Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research

To: Administrative File for BLA (**STN 125641/0**)
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Subject: Final review of the Analytical Methods and Specification sections in LFB's original BLA for Coagulation Factor VIIa (Recombinant) [SEVENFACT]

Contents

1. EXECUTIVE SUMMARY

This memorandum summarizes the review of the *Analytical Methods* and *Specification* sections in the original BLA submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB) for Coagulation Factor VIIa (Recombinant) (rhFVIIa). The

proposed proprietary name is SEVENFACT, and the proposed indication is for on-demand treatment of bleeding in adolescents and adults with inhibitors against Factor VIII and Factor IX. LFB's internal name for the product is LR769.

At the end of this review cycle, most analytical methods used for the characterization of the identity, purity, quality and safety of the bulk drug substance (BDS) and final drug product (FDP) have been adequately validated to support their intended use in the manufacture of SEVENFACT, and the majority of the specifications for the BDS and FDP were established appropriately based on statistical analysis of manufacturing data.

However, significant deficiencies were found in the design and validation of the potency assay used during the development of SEVENFACT and manufacture of most of the product batches, as well as in stability studies. While a new assay was developed and validated, the lack of sufficient bridging data, and concerns regarding the assay's past performance affect the evaluation of a significant amount of data for process validation and stability studies.

Also, recurring instances of visible particulates were observed in reconstituted FDP, with CAPAs being ineffective to date in eliminating the particulates. The failure of LFB to definitively identify the source of the particulates makes it impossible for us to assess the adequacy of the test method or proposed specification for this parameter.

Finally, LFB was requested to develop a (b) (4) method to control the identity of the SEVENFACT FDP, but it has not been done.

Since the above issues are not yet resolved I recommend issuing LFB a **COMPLETE RESPONSE LETTER** for this BLA.

2. BACKGROUND

SEVENFACT is a recombinant (r) analogue of activated human Factor VII (FVIIa). The zymogen is expressed in the milk of transgenic rabbits, and converted to its activated form, FVIIa, during the manufacturing process.

FVIIa is an enzyme of the blood coagulation system, which activates Factor (F) X. Under normal conditions, this conversion is performed mostly by the intrinsic Xase complex consisting of FVIIIa and FIXa. As such, FVIIa can bypass the Xase complex, and render a therapeutic effect in the treatment of bleedings in the hemophilia A or B patients who have developed inhibitor antibodies against FVIII or FIX, respectively.

The various steps of the SEVENFACT manufacturing process are performed at multiple locations. The milk is collected on rabbit farms in (b) (4) Charlton, MA, USA. The first stage of the manufacturing process, including (b) (4), is conducted at the (b) (4) facility in Charlton, MA, resulting in the (b) (4) . FDP manufacture, including filling, lyophilization and primary packaging, is performed at contract facility (b) (4). The FDP is presented at three nominal dosage strengths of 1, (b) (4) 5 mg of rhFVIIa in single-use glass vials. The FDP is reconstituted in sterile Water for Injection (sWFI) before intravenous administration to the patient.

Several other facilities, all in (b) (4), are also involved in the testing of the BDS and FDP: LFB (b) (4), LFB Biotechnologies and LFB Biomedicaments in Les Ulis, and (b) (4)

3. REVIEW SUMMARY

3.1 Sections reviewed (including relevant documents supplied in appendices and amendments):

3.2.S.2.4 Controls of Critical Steps and Intermediates (limited to testing instructions and method validation reports)
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials

3.2.P.5 Control of Drug Product
3.2.P.6 Reference Standards or Materials

3.2 Review History

The application was submitted on 13 October 2016. The BLA was reviewed under the standard schedule of the PDUFA V program. In the original submission, while many areas of the BLA were missing, most of the information and sections on assays and specifications were sufficiently complete to allow for a meaningful review.

Analytical procedure issues were discussed extensively with the applicant during the pre-license inspections (PLI) of the LFB (b) (4) facility in (b) (4), and the LFB (b) (4) facility in (b) (4). An extensive information request (IR) was sent on 4 May 2017 regarding the justification of specifications and validations of analytical procedures. A partial response to the IR was received on 18 May 2017 in amendment 125641/0.37; with subsequent responses received on 16 June 2015 in amendment 12564/0.44, on 7 July 2017 in amendment 125641/0.51, on 14 July 2017 in amendment 125641/0.52, and on 24 July 2017 in amendment 125641/0.53. The responses adequately resolved most of the issues, but some remain unresolved. The IRs are provided in the appendix of this memorandum. Amendments received after 15 August 2017 were not reviewed.

3.3 Narrative:

This memorandum outlines the issues raised during the review of the BLA and does not contain descriptive information which is provided in the BLA. If the section of the BLA is not mentioned in the review, it is because no issues were identified.

3.3.1 (b) (4) Specification and Analytical Methods

(b) (4)

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

(b) (4)

3.3.3 FDP Specification and Analytical Methods

Please note that the only issues specific to FDP testing are covered in this section. Specifications and test methods applicable to (b) (4) *FDP are described in section 3.3.2 above.*

Visual Appearance of Reconstituted Solution: visible particulates

Multiple recurring out-of-specification results were observed for this test with multiple CAPA being ineffective. More information on this issue may be found in the review memoranda of reviewers from the Division of Manufacturing and Product Quality (DMPQ) and Establishment Inspection Report for the LFB (b) (4) *facility. This review is related to the specification acceptance criteria only.*

For *Visual Appearance of Reconstituted Solution: visible particulates*, the current acceptance criterion (b) (4), referencing (b) (4) was not sufficiently specific, as (b) (4) allows for various testing plans. LFB was requested to revise the acceptance criterion, specifying the number of samples tested per batch size, and the acceptable number of samples with particulates.

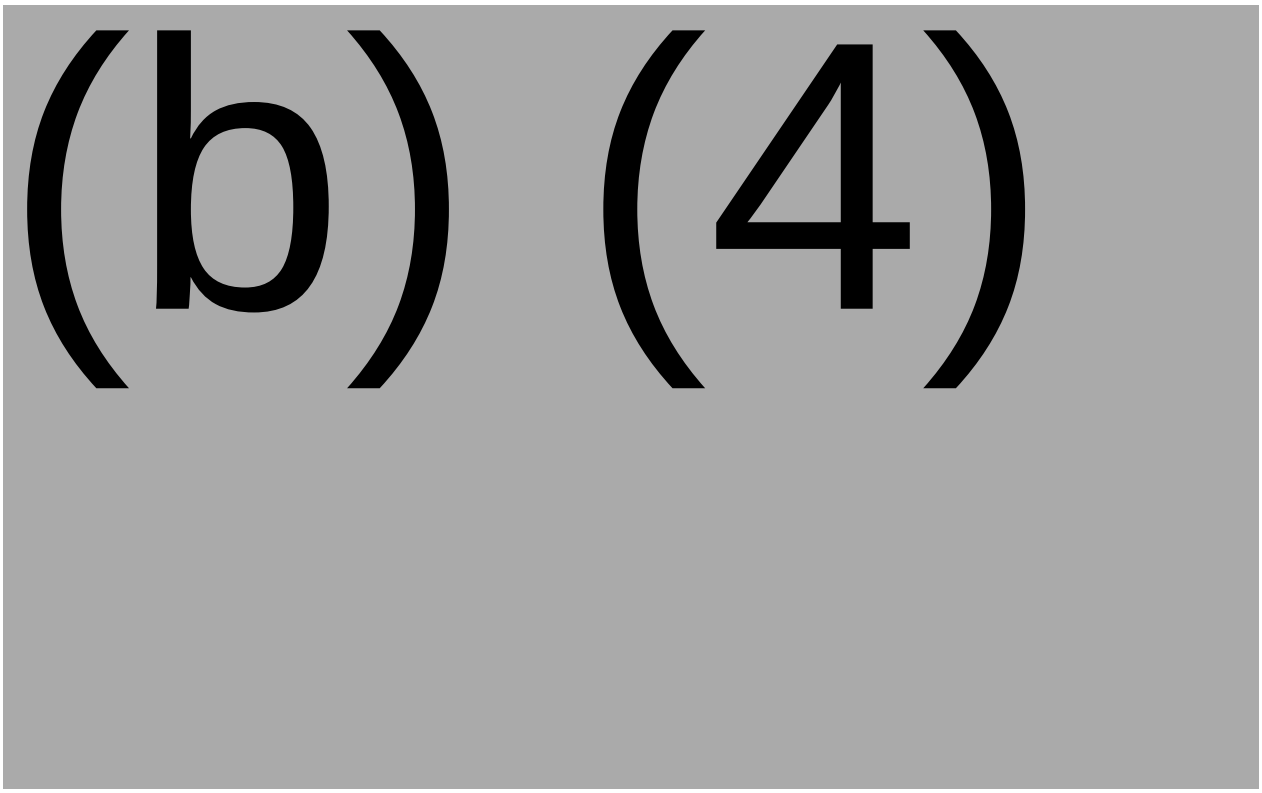
In response, LFB developed the following (b) (4) testing scheme:

(b) (4)

The proposed specification is not adequate as it sets separate acceptance criteria for the (b) (4) *. According to the cited* (b) (4) *standard, when such* (b) (4) *scheme is used, the amount of defects found in each stage need to be added. Moreover, until LFB is successful in identifying the source of particulates and modifying their method to minimize their presence, the adequacy of any acceptance criterion cannot be established.*

Residual Moisture

For *Residual Moisture*, the acceptance criteria were not properly justified. LFB was requested to revise the acceptance criteria addressing the following issues:



LFB agreed to revise the acceptance criteria and introduce separate acceptance criteria for release and shelf-life. LFB included additional stability data in the analysis, which generally confirmed their initial projections on moisture accumulation.

For the 5-mg dosage strength, the method LOQ corresponds to a relative moisture content of (b) (4) and the maximum reported content was (b) (4). An acceptance criterion of (b) (4) is therefore proposed at release.

(b) (4)

For the 1-mg dosage strength, the method LOQ corresponds to a relative moisture content of (b) (4) and the maximum reported content was (b) (4) An acceptance criterion of (b) (4) the LOQ, i.e. (b) (4) is therefore proposed to take into account the variability at the LOQ level.

For shelf-life specification, based on newly available data, LFB agreed to decrease the initial (b) (4) acceptance criteria to (b) (4) for the 1-mg dosage strength, to (b) (4) dosage strength, and to (b) (4) for 5-mg dosage strength.

I found the LFB response acceptable. Characterization studies demonstrated that the batches with over (b) (4) *moisture content at release did not show adverse stability trends after* (b) (4) *months at accelerated conditions.*

pH Test

For the pH test, no data or statistical justification were provided for the acceptance criteria. LFB was requested to provide justification, or revise the acceptance criteria based on statistical analyses of release test results of all FDP lots manufactured at commercial scale.

LFB performed the requested analysis, but the data did not support the change in the acceptance criterion.

I found the LFB responses adequate.

Excipients

For all excipients, LFB used (b) (4) of the mean value of previously tested batches as lower and upper acceptance criteria, which is not statistically justified. LFB was requested to revise the acceptance criteria based on statistical analyses of release test results of all (b) (4) lots manufactured at commercial scale. Additionally, in several cases, the current specification ranges exceeded the validated ranges of the respective analytical methods. As such, LFB was requested to verify that the methods are properly validated to be used with the revised specifications.

LFB performed the requested analysis, and revised the acceptance criteria based on the Mean (b) (4) SD range. Comparison of the original and revised acceptance criteria excipients with the associated validated method ranges can be seen in Table 1.

Table 1. Original and revised acceptance criteria for excipients with associated validated method ranges.

Criteria	Previous Acceptance criteria	Revised Acceptance criteria	Method Validated range
Trisodium Citrate Dihydrate, mg/mL	(b) (4)		
Polysorbate 80, mg/mL			
Arginine HCl, mg/mL			
Lysine HCl, mg/mL			
Isoleucine, mg/mL			
Glycine, mg/mL			

I found the LFB responses acceptable.

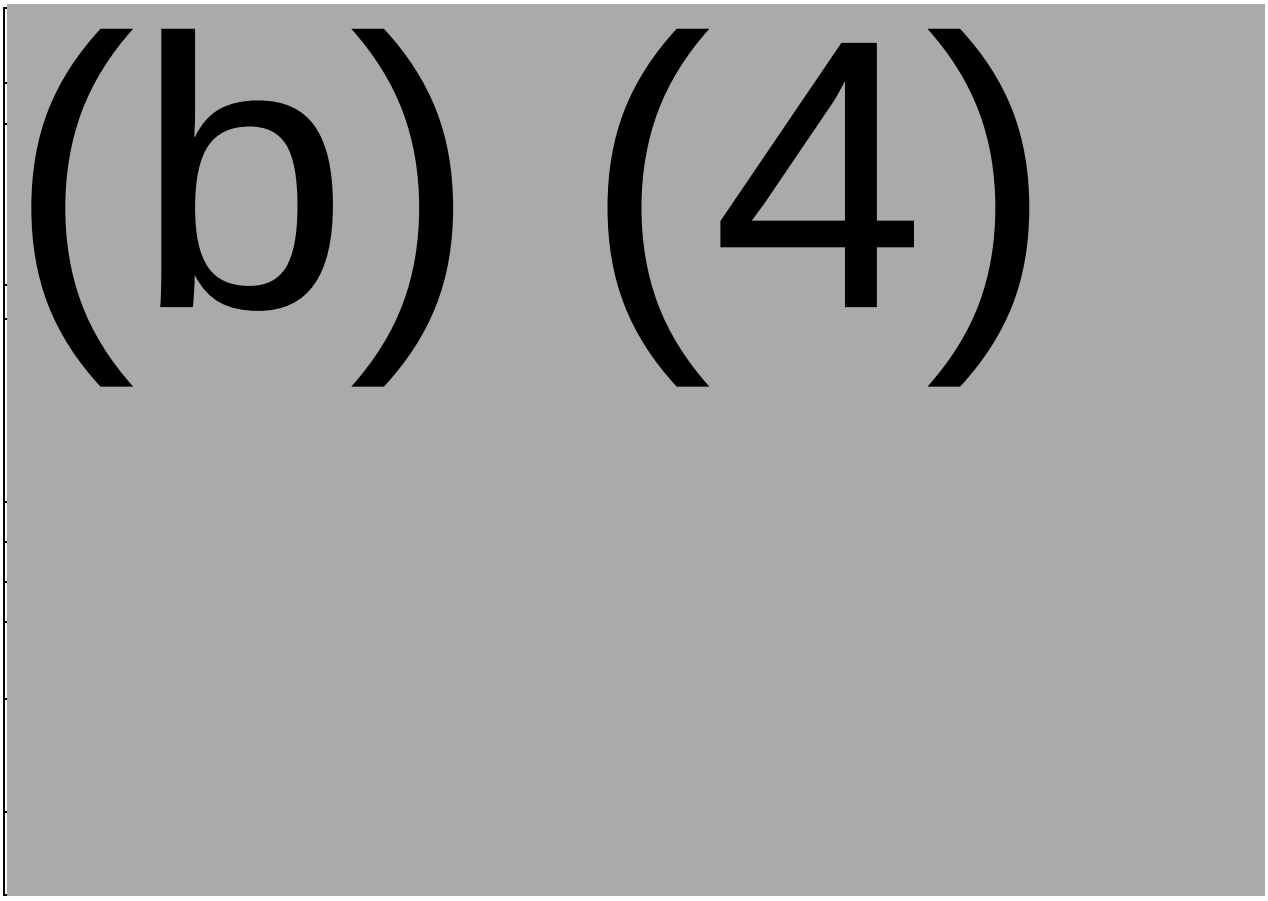
3.3.4 Summary of revisions to BDS and FDP Specifications

Tables 2 and 3 below summarize the proposed changes to the BDS and FDP specifications to SEVENFACT. The proposed changes are in bold. Please note that the specifications were changed for (b) (4) rhFVIIa in (b) (4) and for (b) (4) in FDP. These issues were first discovered by Dr. Jankowski and reviewed in his memorandum. The shaded cells represent specifications which are not acceptable (b) (4) test in (b) (4), which should be replaced with a (b) (4) method; and visual particulates specification, which needs to be re-established after resolving the root cause of failures of this test).

Please note that for the acceptance criteria for shelf-life specification for Residual Moisture, the values were switched for 1- and 5-mg dosage strengths in the tables submitted by LFB in amendments 37 and 53. However, the description of the proposed changes in the text is correct, so the acceptance criteria are represented correctly in Table 3.

Some acceptance criteria listed in the Tables 2 and 3 are not final, considering the limited number of batches manufactured for BDS and FDP. Additional analysis of data generated from more batches may be required to establish the final acceptance criteria. Addressing the issues of incomplete process validation, recurring manufacturing failures, and lack of product manufactured using the milk from the Charlton, MA farm, are also likely to affect the acceptance criteria as more data are likely to be included or excluded from analysis. However, as a Complete Response letter is being recommended for this BLA, these issues will be resolved in the next review cycle.

Table 2. Initial and revised Specification for SEVENFACT BDS



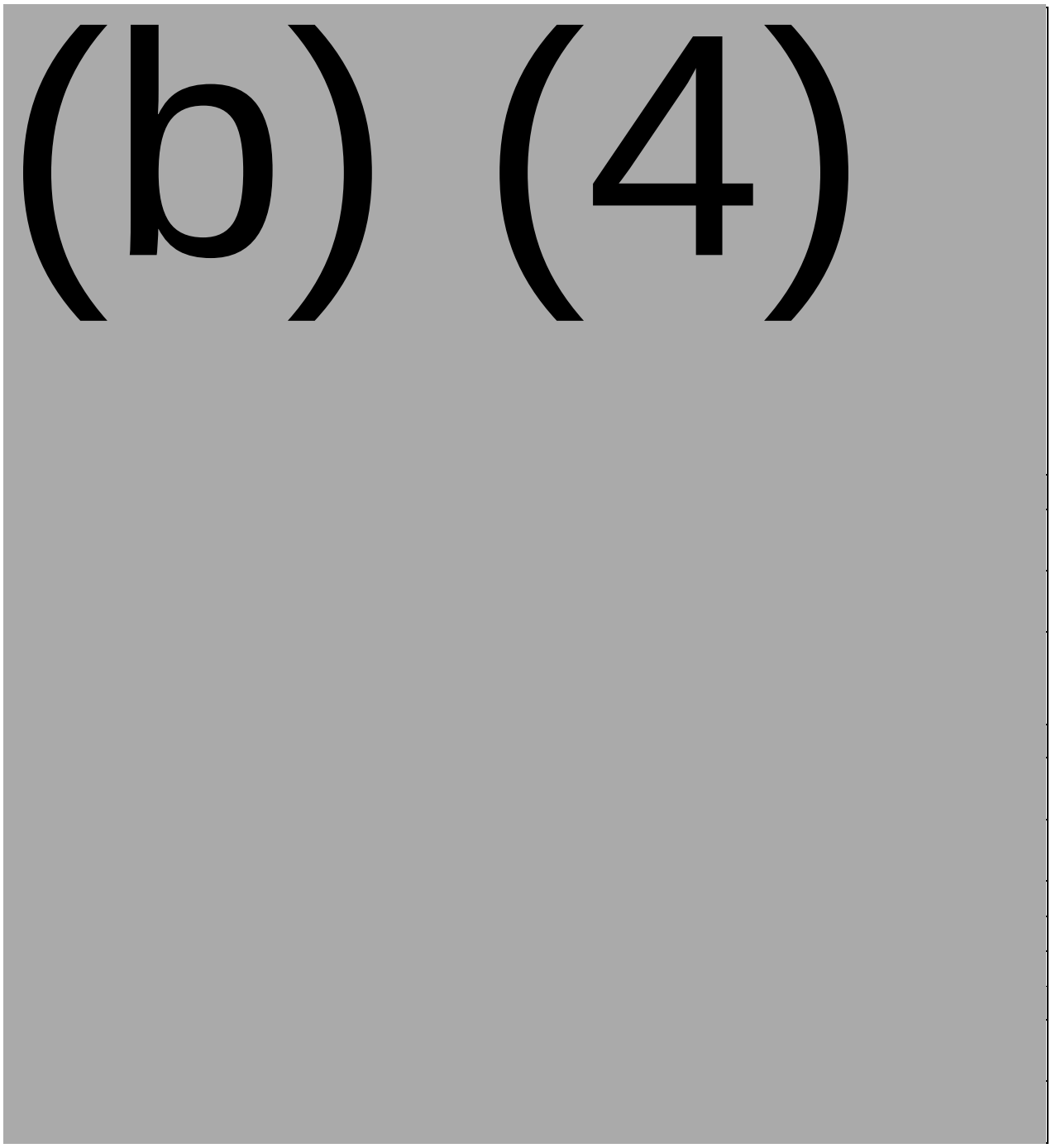


Table 3. Initial and revised Specification for SEVENFACT FDP

Attribute	Test Method	Initial Acceptance Criteria	Revised Acceptance Criteria
Appearance and description			
Visual appearance of cake	Visual inspection	(b) (4)	White to off-white cake or powder

Appearance of reconstituted solution: • Opalescence • Color	(b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Visual Appearance of reconstituted solution	(b) (4)	(b) (4)	Clear to slightly turbid colorless solution
Visual Appearance of reconstituted solution: visible particulates	(b) (4)	(b) (4)	(b) (4)
Identity			
Identity	(b) (4)	(b) (4)	(b) (4)
Quality			
pH	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Reconstitution time	Visual determination	(b) (4)	(b) (4)
Particulate matter	(b) (4)	(b) (4)	(b) (4)
Residual moisture	(b) (4)	(b) (4)	**Release** **1 mg vials:** (b) (4) (b) (4) **5 mg vials:** **Shelf Life** **1 mg vials:** (b) (4) (b) (4) **5 mg vials:**
Attribute	**Test Method**	**Initial Acceptance Criteria**	**Revised Acceptance Criteria**
Sterility	(b) (4)	Sterile	Sterile
Bacterial endotoxins	(b) (4)	(b) (4)	(b) (4)
Purity			
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Impurities			
(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	**NA**	(b) (4)
Strength, potency			
rhFVIIa concentration	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
Specific activity			
Excipients			
Trisodium citrate dihydrate	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80			
Arginine HCl			
Lysine HCl			
Isoleucine			
Glycine			

4. CONCLUSION & RECOMMENDATION

Significant issues with the analytical methods and specifications used for the characterization of identity, purity, quality and safety of SEVENFACT bulk drug substance and final drug product remain unresolved. I do not recommend approval of the BLA for SEVENFACT from the perspective of analytical methodology and control of Drug Substance and Drug Product.

The following Complete Response Letter comments related to analytical methods and specifications were developed in collaboration with other review team members.

1. *The design of the combination product and validation of its use are deficient as evident by the repeated instances of visible particulates found in the reconstituted Final Drug Product (FDP) during release testing and stability studies. The investigations were not successful in identifying the true root cause(s), e.g., determine the source and origin of the particulates. The proposed CAPAs have so far failed to prevent the recurrence of visible particulates in the FDP.*

   We acknowledge LFB's efforts to minimize environmental particulates, which have not yet been proven to be effective. We also acknowledge LFB's proposals to introduce new kit components in order to address the problem, and a (b) (4) *-tiered testing scheme for Visible Particulates for the release of FDP. However, these proposals are not deemed to be acceptable because they do not address the root cause(s) of the problem, and hence are not considered as effective CAPAs.*

2. *The following assays are not suitable for the control of the* (b) (4) *manufacturing process, FDP* (b) (4) *release, stability studies, and process validation studies:*

   a. *The potency assay is not suitable for its intended use because LFB has not been using a qualified reference standard for the determination of product potency. Specifically, LFB should evaluate*

      i. *The impact of assay variability and lack of results traceability, due to lack of common internal standard, on the determination of product potency at the various stages of process development, product characterization, and in stability studies. So far, the additional provided data are insufficient in addressing the deficiencies, for example,*

         1. *LFB confirmed relative comparability of the results obtained using international standard and standard provided with the kit, but this study was performed using only* (b) (4) *lots of kit and did not fully eliminate concerns regarding assays prior performance.*

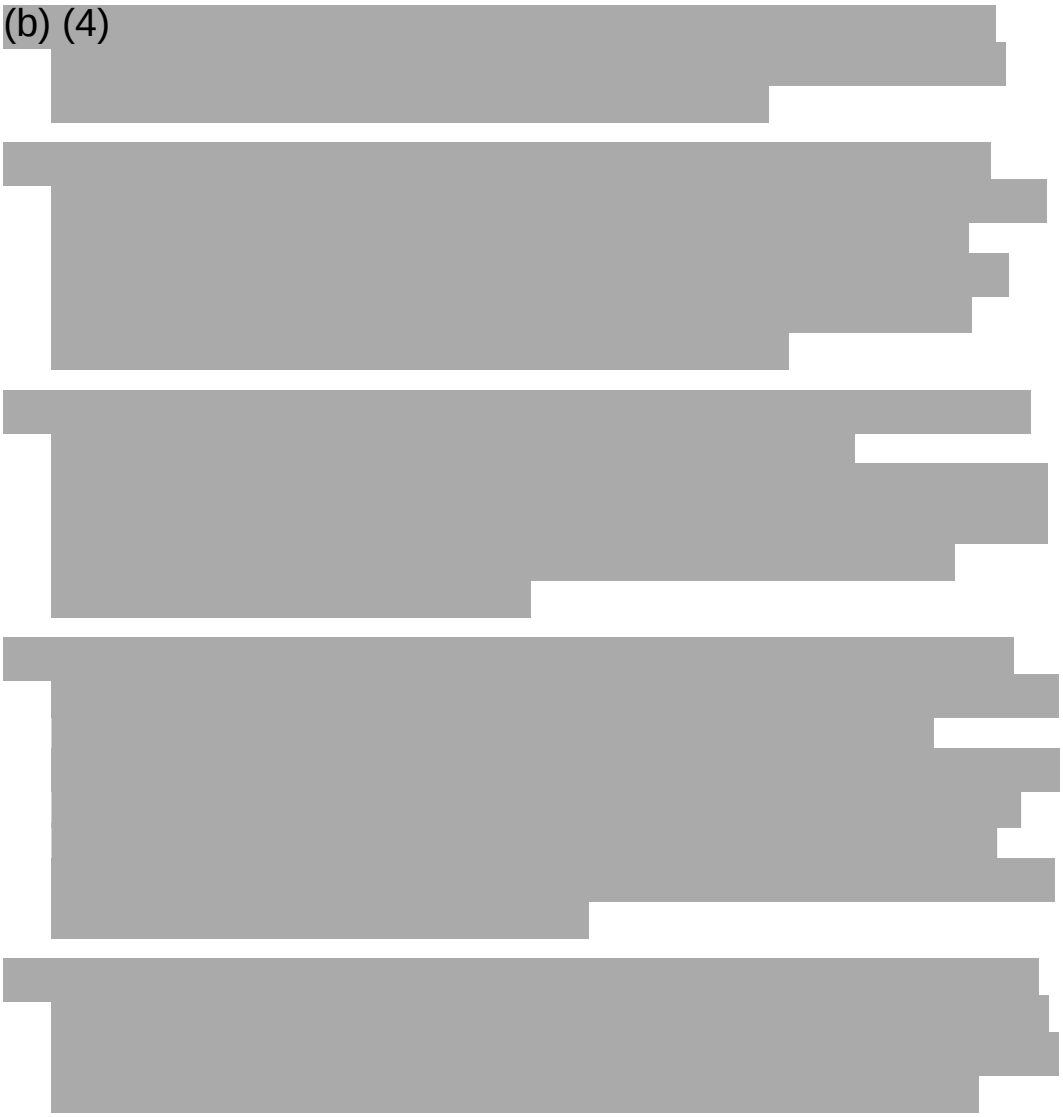
         2. *The observed higher recovery of Process B materials in the Process A and Process B bridging PK Study No. RB-FVIIa-06-013 were not addressed evaluation of retained samples of lots used in clinical studies by the validated Specific Activity and Potency assays, which should include those lots that have expired.*

         3. *LFB claimed that the potency of product lots was not impacted by the temperature of storage therefore retesting of all in-date lots can be used to support new release specifications for Potency and Specific Activity. However, the data presented in Tables 24 and 26 of amendment 53 dated July 24, 2017 demonstrate an inverse correlation between the rate of potency decline and the temperature of storage as evidenced from a decrease in Specific Activity of lot* (b) (4) *at 24 months of storage to* (b) (4) *when stored at 5°C±3°C,* (b) (4) *when stored at 25°C±2°C, and* (b) (4) *when stored at 30°C* (b) (4) *compared to* (b) (4) *at release.*

      ii. *The stability of the proposed product-specific reference standard. Please establish stability program for product-specific standard.*

   b. *The current* (b) (4) *method is not sensitive enough to detect minor* (b) (4) *changes and is not sufficient to control the Identity of recombinant proteins. Please develop a* (b) (4) *method for Identity testing.*

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



3. Please revise the release specifications of the *final drug product* (FDP), and the associated BLA sections, including "Justification of Specifications" and test methods. Specifically,

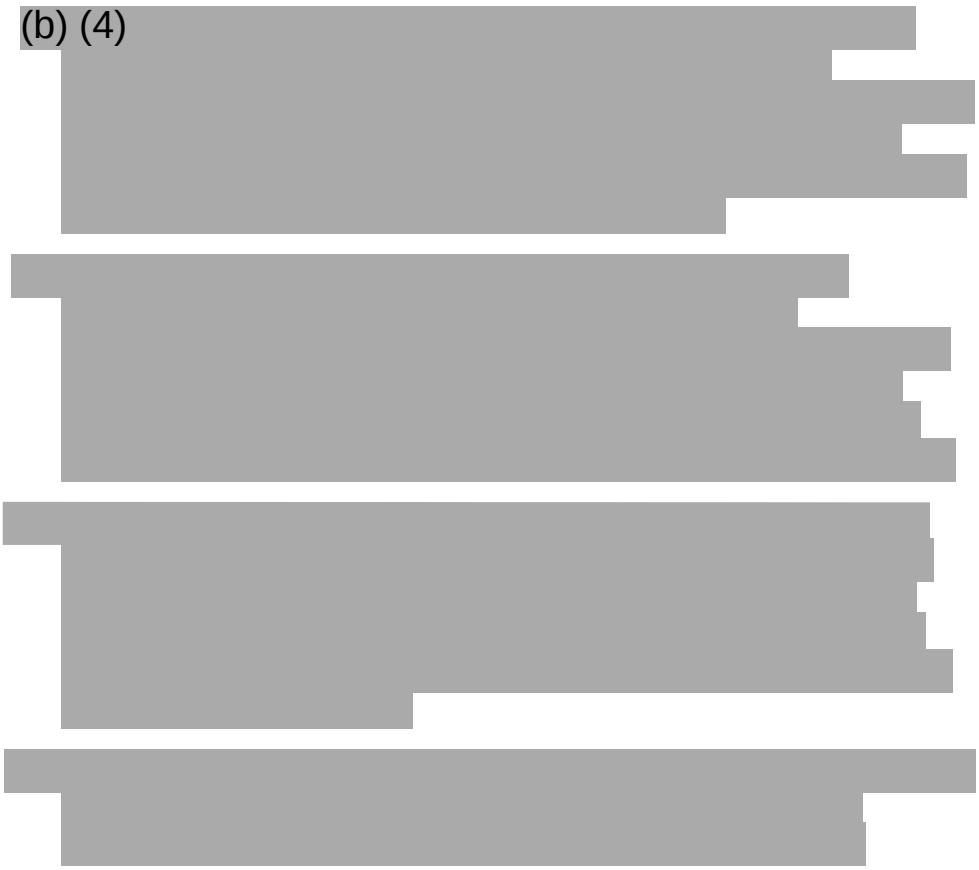
    a. For *Visual Appearance of Reconstituted Solution*, the current acceptance criterion (b) (4) is not sufficiently specific, as (b) (4) allows for various testing plans. Please revise the acceptance criteria, specifying the number of samples tested per batch size, and the acceptable number of samples with particulates.

    b. For the *Visual Appearance of Reconstituted Solution* test, please provide validation data along with justification for setting the acceptance criteria at the current levels. Please note that (b) (4) is not legally recognized in the USA.

    c. For the *Identity* test by (b) (4), the current acceptance criterion ("Identity Confirmed") is not sufficiently specific to be meaningful, and does not describe the attributes or procedure used to confirm identity. Please revise it accordingly.

d. For *Residual Moisture*, the current acceptance criteria are not properly justified. Please revise the acceptance criteria addressing the following issues:

(b) (4)



e. For the *pH* test, no data or statistical justification were provided for the acceptance criteria. Please revise the acceptance criteria based on statistical analyses of release test results of all FDP lots manufactured at commercial scale.

f. For the (b) (4) test, no data or statistical justification were provided for the acceptance criteria. Please revise the acceptance criteria based on statistical analyses of release test results of all FDP lots manufactured at commercial scale. Please provide the method validation report for the (b) (4) test.

g. For (b) (4), please revise the FDP specification according to item 1.d. in the IR dated 1 May 2017 for the (b) (4) specification for these parameters.

h. For *rFVIIa* concentration by (b) (4), please revise the acceptance criteria in the same manner as requested for the (b) (4) specification in item 2.k. of this IR.

i. For *Specific Activity*, please revise the acceptance criteria in the same manner as requested for the (b) (4) specification in item 2.l. of this IR.

j. For *Activity by* (b) (4) *Assay*, please reestablish the acceptance criteria based on the data derived from the modified *Activity* assay as described in your responses to the Form FDA 483 issued at the inspection of the (b) (4) manufacturing facility.

(b) (4)

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Please respond by 17 May 2017 by providing FDA with a plan to address the aforementioned issues, and identify the dates when the requested documents will be submitted.