DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

From: Hsiaoling Wang
CMC Reviewer
Laboratory of Analytical Chemistry and Blood Related Products (LACBRP)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number 125641/0

Subject: Primary Review Memo for Chemical Assays for Coagulation Factor VIIa (Recombinant), Sevenfact (LR769**)**

Through: Lokesh Bhattacharyya, Lab Chief, CBER/OCBQ/DBSQC
James Kenney, Acting Director, CBER/OCBQ

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

Submission Received by CBER: Oct. 13, 2016

Summary:

A new BLA (STN 125641) was submitted by LFB for Sevenfact, Coagulation Factor VIIa (Recombinant), for use in adolescent and adult for treatment and control of bleeding in patients with hemophilia A or B with inhibitors of Factor VIII and IX.

This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their verification/validations, which are proposed to be used for quality control of the drug substance (DS) and drug product (DP).

1. pH Determination

2. (b) (4) by (b) (4)
3. Impurities of (b) (4)

This reviewer found that these three analytical procedures were adequately described and verified/validated for their intended uses.

Background

Sevenfact is a sterile lyophilized product that is intended for intravenous injection following reconstitution with sterile Water for Injection (WFI). It is supplied in (b) (4) dosage forms containing 1 mg, (b) (4), or 5 mg of LR769 along with syringes filled with 1.1 mL, (b) (4) and 5.2 mL of WFI, respectively.

Documents Reviewed

Original submission STN 125641/0 dated Oct. 13, 2016

- Cover letter
- 2.2 Introduction
- 3.2.S.3.2 Impurities
- 3.2.S.4.1 Specifications of drug substance
- 3.2.S.4.2 Analytical procedures for drug substance
- 3.2.S.4.4 Batch analyses (drug substance)
- Reference standards or materials
- 3.2.P.5.1 Specifications of drug product
- 3.2.P.5.2 Analytical procedures for drug product
- 3.2.P.5.4 Batch analyses (drug product)
- Complement report regarding the method validation for rhFVII LR769 (b) (4)
- Validation report of SOP #10991: (b) (4) of rhFVIIa by (b) (4)
- Final validation report of the analytical method for the determination of (b) (4) RhFVIIa (LR769) by (b) (4)

Amendment 8, dated Jan. 25, 2017

- SOP #11254: Determination of (b) (4) LR769 (RhFVIIa) by (b) (4)

Amendment 19, dated Feb. 28, 2017

- 1.11.1 Quality Information Amendment
- SOP #09545: Use of the pH-meters for GMP production (b) (4)
- SOP #10991: Operating procedure for (b) (4) of rhFVIIa by (b) (4)
- Evaluation method for rhFVII LR769 (b) (4)
- Robustness analysis of rhFVIIa (b) (4) (SOP 10991): sample preparation stability and test of alternative (b) (4)
- Operating procedure rhFVIIa drug product reconstitution (Doc. N° 10246)
- Monitoring of the condition of the analytical columns at the QC Laboratory (Doc. N°14482)

Amendment 33, dated Apr. 19, 2017

- 1.11.1 Quality Information Amendment

Amendment 47, dated June 27, 2017

- 1.11.4 Multiple Module Information Amendment

Amendment 51, dated July 7, 2017

- 1.11.4 Multiple Module Information Amendment

Amendment 54, dated July 31, 2017

- 1.11.1 Quality Information Amendment

Amendment 58, dated August 9, 2017

- 1.11.1 Quality Information Amendment

Review Narrative

1. pH Determination

Method

pH values of (b) (4) reconstituted DP solution are determined by measuring the potential difference between (b) (4) in the solution to be examined according to (b) (4) The pH value is (b) (4) pH units.

The specifications for (b) (4) DP are both (b) (4).

Verification

The pH determination is considered a compendial method, which only requires verification.

The verification is aimed to verify the precision of the method. Considering (b) (4) reconstituted DP samples (b) (4) pH specification, the verification of pH measurement was performed on (b) (4) DP (b) (4). (b) (4) measurements were made by (b) (4) analysts in (b) (4) days. RSDs for repeatability and intermediate precision are (b) (4) respectively, which meet the acceptance criteria of (b) (4) respectively.

Information Request (IR) and Response Review

An IR was sent to the sponsor on Feb. 10, 2017 and the responses were received on Feb. 28, 2017 in the amendment 19.

> Please provide the verification report for the compendial method used for the pH determination of (b) (4) the drug product (DP).

Review of the response
The verification data for pH determination method (SOP 09545) was provided in the response and is summarized in the method verification above. The response is satisfactory.

Conclusion: The analytical procedure of pH determination is adequately described and verified for its intended use.

2. (b) (4) by (b) (4)

Method

(b) (4)

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

(b) (4)

(b) (4)

Review of the response
The LOQ for (b) (4) was determined as per the FDA's suggestion. The results are summarized and reviewed in the Validation section above. The response is satisfactory.

Conclusion: The analytical procedure of (b) (4) by (b) (4) and is adequately described and validated after several IRs and additional experimental data.

3. Impurities of (b) (4)

Method

(b) (4)

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

(b) (4)

(b) (4)

Review of the response
The LOQs were determined as suggested by FDA's. The results are summarized and reviewed in the Validation section above. The response is satisfactory.

Conclusion: The analytical procedure of Impurities of (b) (4) is adequately described and validated.