DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 26 May, 2017

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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 BLA: Review of Bioburden, Sterility and Bacterial Endotoxin Test Methods for SEVENFACT, Coagulation Factor VIIa (Recombinant)

Through James L. Kenney, D.Sc., Chief, LMIVTS
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Applicant Laboratoire Francais du Fractionnement et des Biotechnologies S.A.

Product SEVENFACT, Coagulation Factor VIIa (Recombinant)

Biologics License Application (BLA) Submission Tracking Number (STN) 125641/0

Submission Received by CBER 13 October, 2016

Review Completed 26 May, 2017

Material Reviewed

Method qualifications for: bioburden, sterility and bacterial endotoxin tests performed on the (b) (4) the drug product (DP); and the responses to CBER's Information Requests (IR's), received 25 and 31 January, 6 and 14 February, and 22 May of 2017 were also reviewed.

Executive Summary

After a thorough review of this BLA, and the responses to CBER's IR's (amendments 125641/0.8, 125641/0.10, 125641/0.12, 125641/0.15 and 125641/0.38), this reviewer finds Laboratoire Francais du Fractionnement et des Biotechnologies S.A.'s bioburden, sterility and bacterial endotoxin test methods were qualified in accordance with (b) (4) respectively.

Background

On 13 October, 2016, Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.) submitted this BLA for SEVENFACT, (Coagulation Factor VIIa [Recombinant]) indicated for on-demand treatment of bleeding episodes in adolescent and adult hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. SEVENFACT is produced in and purified from the milk of transgenic rabbits. The unique upstream production process of SEVENFACT utilizes recombinant deoxyribonucleic acid technology to stably integrate the human Factor VII transgene into the rabbit genome. The recombinant human Factor VII transgene is exclusively expressed by the mammary gland under control of a (b) (4) specific promoter. Milk collected from these transgenic rabbits is purified to isolate the recombinant human Factor VII protein, which is subsequently activated to produce Factor VIIa.

SEVENFACT is a sterile, latex free, lyophilized concentrate of recombinant human coagulation Factor VIIa, to be reconstituted with sterile water for injection (WFI) prior to intravenous administration. SEVENFACT is supplied in single-use glass vials containing 1, (b) (4) 5 mg of recombinant human coagulation Factor VIIa alongside pre-filled syringes containing diluent (i.e. filled with 1.1, (b) (4) 5.2 mL of WFI, respectively). Once reconstituted, each vial contains 1 mg/mL of human coagulation Factor VIIa.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission: the confirmatory testing of submitted product samples; review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on LFB S.A.'s bioburden, sterility and bacterial endotoxin test method qualifications to ensure the product matrix is suitable for these intended test methods.

Review

Bioburden Test Qualification for (b) (4) Drug Product (DP)

Bioburden qualification test (b) (4) qualification) was performed on (b) (4) batches of SEVENFACT DP (i.e., (b) (4) at 5mg dosage strength) for (b) (4) and (b) (4) to demonstrate the matrix does not inhibit bacterial and fungal growth. The test was performed using (b) (4) . Note: there is no difference in the matrix between the (b) (4) the DP [freeze-dried powder], which is reconstituted with WFI only. As a result, all test method qualifications were performed on the DP.

(b) (4)

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(b) (4)

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The bioburden results on the conformance DP batches were within their proposed bioburden test specification of (b) (4) . This reviewer finds their proposed acceptance criteria acceptable.

Sterility Test Qualification for DP

LFB S.A. qualified their SEVENFACT DP matrix using the (b) (4) method by performing (b) (4) qualification studies on (b) (4) batches (i.e., (b) (4) to demonstrate the matrix is suitable for the intended test method.

(b) (4)

(b) (4)

thus indicating the SEVENFACT DP matrix is suitable for testing via their compendial (b) (4) sterility test method.

(b) (4) Endotoxin Test (b) (4)) Method Qualification for (b) (4) DP

LFB S.A. qualified their (b) (4) method using (b) (4) batches (all from the 5 mg dosage strength) of SEVENFACT DP (i.e., (b) (4) to verify their product matrix was suitable for the intended test method in accordance with (b) (4)

(b) (4)

(b) (4)

The bacterial endotoxin concentration results found during the (b) (4) testing were all (b) (4) and were within their BET specification of (b) (4) .

Note: based on results from continued development batches, LFB S.A. (b) (4)

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds LFB S.A.'s SEVENFACT (b) (4) DP matrixes are suitable for testing using their bioburden, sterility and bacterial endotoxin testing methods, as these tests were qualified and performed in accordance with (b) (4) , respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose.