



CBER REGULATORY REVIEW MEMORANDUM

Date 17 July 2015

From Simleen Kaur
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
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 # 125582/0

Subject BLA: Review of Bioburden, Sterility and Endotoxin tests for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)

Through Dr. James L. Kenney, Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
Dr. William M. McCormick, Director, DBSQC/OCBQ/CBER/FDA

Applicant CSL Behring (CSL)

Product Idelvion™, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)

Biologics License Application (BLA) Submission Tracking Number (STN) 125582/0

Submission Received by CBER 5 December, 2014

Review Completed 17 July, 2015

Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on (b) (4) drug product for Idelvion™, recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP). In addition, information request response received 03 February, 13 March, 14 April, 30 April, 18 May and 30 June of 2015 and information conveyed during a teleconference with the sponsor on 15 April, 2015 were also reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility and endotoxin test method were qualified in accordance with (b) (4) respectively, for Idelvion™ rIX-FP and the product matrix is suitable for the intended test methods.

Background

On 5 December, 2014, CSL Behring (CSL) submitted a biologics license application for production of Idelvion™ rIX-FP. Idelvion™ is an antihemophilic factor indicated for patients with hemophilia B for routine prophylaxis to prevent or reduce the frequency of bleeding episodes, control and prevention of bleeding episodes and control and prevention of bleeding of perioperative setting.

The active ingredient, rIX-FP, is a purified protein derived from a Chinese Hamster Ovary (CHO) cell line and produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to recombinant coagulation factor IX. rIX-FP remains intact in the circulation until FIX is activated followed by albumin cleavage releasing activated FIX (FIXa) only when it is needed for coagulation. The Idelvion™ drug product is a lyophilized powder in single-use glass vials containing 250, 500, 1000 or 2000 International Units (IU) of the active ingredient and three dosage strengths of 100, 200 and 400 IU/mL.

The drug substance (DS) (b) (4)



For drug product (DP) manufacturing, (b) (4)

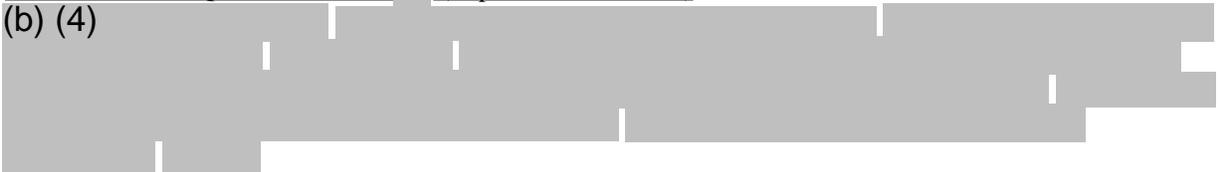


The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and 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 the qualification of bioburden, sterility and endotoxin test performed on Idelvion™, to indicate if the product matrix is suitable for testing using the intended test methods.

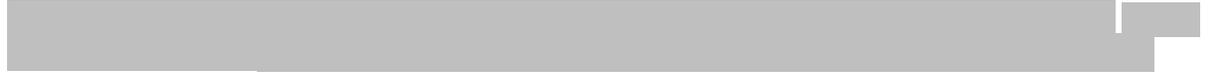
Review

Bioburden Test Qualification for (b) (4) (Report No. REP-8104)

(b) (4)

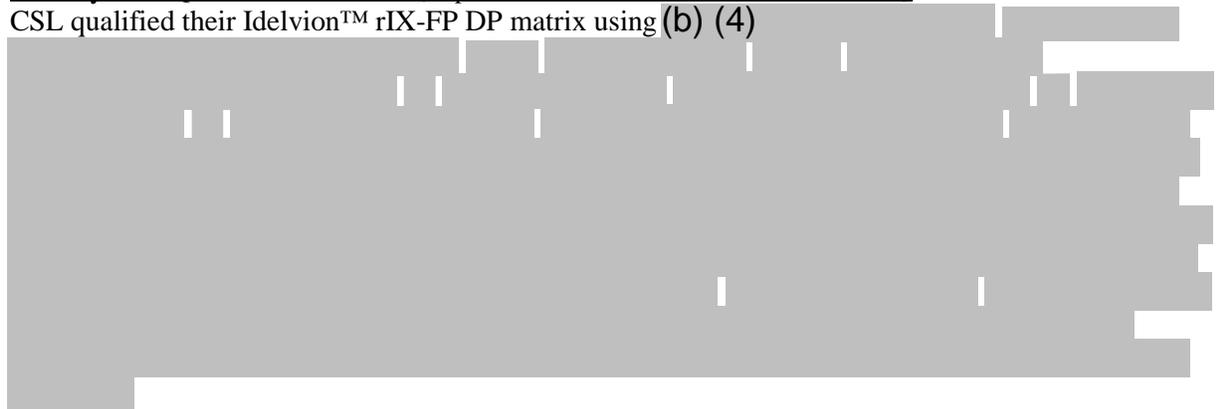


(b) (4)



Sterility Test Qualification for DP (Report No. MVR-25-002-rIX-FP version 3.0)

CSL qualified their Idelvion™ rIX-FP DP matrix using (b) (4)



(b) (4)



CSL performed sterility test on several clinical, pilot and commercial Idelvion™ rIX-FP DP batches produced using the compendial sterility (b) (4) method and were reported to meet their specification of (b) (4)

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



(b) (4)

[Redacted]

[Redacted]

CSL submitted endotoxin results on several clinical, pilot and commercial DP batches, which met their endotoxin test specification of (b) (4) .

Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds CSL Idelvion™ product matrix is suitable for testing using their sterility and endotoxin testing methods; these tests were qualified and performed in accordance with (b) (4) respectively. In addition, the Idelvion™ (b) (4) is suitable for testing using their bioburden and endotoxin testing methods and these qualifications were performed in accordance with (b) (4) respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.