



## CBER REGULATORY REVIEW MEMORANDUM

**Date** 23 June, 2016

**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 # 125586/0

**Subject** BLA: Review of Bioburden, Sterility and Endotoxin Tests for andexanet alfa

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

**Applicant** Portola Pharmaceuticals (Portola)

**Product** andexanet alfa, recombinant factor Xa (fXa) inhibitor antidote

**Biologics License Application (BLA) Submission Tracking Number (STN)** 125586/0

**Submission Received by CBER** 18 December, 2015

**Review Completed** 23 June, 2016

### Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on andexanet alfa (fXa). In addition, information request responses received 29 January, 29 March, 14 April, 05 May, 26 May and 17 June of 2016 were also reviewed.

### Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility, and endotoxin test methods were qualified in accordance with (b) (4), respectively.

### Background

On 18 December, 2015, Portola submitted this BLA requesting priority review based on the Orphan Drug Designation received 23 February, 2015; which was preceded by a breakthrough product designation received on 22 November, 2013, for an unmet medical need.

fXa is a recombinant modified human factor Xa protein indicated for patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed during life threatening or uncontrolled bleeding (b) (4). The fXa protein is truncated and inactivated to lack physiologic blood coagulation factor activity while retaining its high affinity for direct or indirect fXa inhibitors. The protein has neither pro- nor anti-coagulant activity and lacks catalytic activity due to replacement of active site serine with an alanine. It is directly expressed in Chinese Hamster Ovary (CHO) cells as a functional antidote and requires neither *in-vitro* nor *in-vivo* activation steps for converting native fX to its activated for fXa.

Manufacturing of fXa drug substance (DS) is performed at (b) (4).  
[Redacted]  
[Redacted] The (b) (4)

DS is shipped to Portola where is final DS batch disposition takes place.

Manufacturing of fXa drug product (DP) is performed at (b) (4).  
[Redacted]. The manufacturing is initiated by (b) (4).  
[Redacted]. The (b) (4) batches are (b) (4) and tested for protein, pH and (b) (4) to ensure the solution is homogeneous for protein and excipient distribution. The (b) (4) is then filtered through (b) (4) filters and filled into (b) (4) 20mL glass vials with target fill volume of (b) (4) mL. The vials are partially stoppered and lyophilized followed by capping, labeling and packaging. The final container vials are tested for sterility and endotoxin at (b) (4) and transferred to Portola for DP release.

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 memo covers the review of Portola's bioburden, sterility and endotoxin tests qualification reports to ensure fXa product matrix is suitable for these intended test methods.

**Review**

Bioburden Test Qualification for (b) (4)

(b) (4)  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]

(b) (4) [Redacted text block]

Sterility Test Qualification for DP by (b) (4)  
(b) (4) qualified the fXa DP matrix using the (b) (4) method by performing bacteriostatic and fungistatic qualification study on (b) (4) lots (i.e., lot number: (b) (4)) to demonstrate the DP matrix is suitable for the intended test method. The test was performed according to (b) (4) using the (b) (4) method and (b) (4) indicator microorganisms (i.e., (b) (4)).

The test for each microorganism was performed in (b) (4) using (b) (4) vials of fXa DP in (b) (4) inoculated with (b) (4) of one of the microorganisms indicated above. This inoculation process was repeated for each microorganism and positive control (PC); PCs consisted of microorganism only – no product. The process was also repeated so that negative controls (NC – with product only microorganism) were performed for each medium. (b) (4) bottles were incubated at (b) (4) and (b) (4) bottles (b) (4) for (b) (4) days. Back titrations were performed to confirm the inoculated microorganism counts were less than (b) (4).

Since the fXa DP can cause the media turbid, after (b) (4) days of incubation (b) (4) of inoculated media was transferred into (b) (4) of same fresh media bottle and inoculated for another (b) (4) days at respective temperatures. After incubation, all test media had turbidity comparable between the test sample and their respective PC control, while the NCs showed no growth. The test was performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth; thus indicating that the fXa DP matrix is suitable for testing via their compendial (b) (4) sterility test method.

Baxter submitted sterility test results for several fXa DP lots and results were found to be in compliance with (b) (4).

(b) (4) Qualification for DP by (b) (4)  
(b) (4) qualified their (b) (4) method for fXa DP to verify their product matrix was suitable for the intended test method in accordance with (b) (4).

(b) (4)

The bacterial endotoxin concentration results of (b) (4) generated during their inhibition/enhancement testing were well within their proposed release specification of (b) (4). The test was performed and compliant with (b) (4); thus, indicating the fXa DP matrix is suitable for testing via their (b) (4) method.

Endotoxin test results submitted for (b) (4) fXa DP lots (i.e., (b) (4)), met their endotoxin test specification of (b) (4). CBER finds their proposed release specification acceptable.

**Conclusion**

After a thorough review of the information submitted in this BLA, this reviewer finds Portola fXa drug product matrix is suitable for testing using their sterility and endotoxin test methods; these tests were qualified and performed in accordance with (b) (4), respectively. In addition, the fXa drug substance is suitable for testing using their bioburden and endotoxin test methods and the

qualifications were performed in accordance with (b) (4) [REDACTED], respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.