



CBER REGULATORY REVIEW MEMORANDUM

Date 12 February, 2016

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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 # 125591/0

Subject BLA: Review of Review of Bioburden, Bacterial Endotoxins Test and Sterility Qualifications for rVIII-SingleChain (Antihemophilic Factor [Recombinant], Single Chain).

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

Applicant CSL Behring

Product rVIII-SingleChain (Antihemophilic Factor [Recombinant], Single Chain).

Biologics License Application (BLA) Submission Tracking Number (STN) 125591/0

Submission Received by CBER 29 May, 2015

Review Completed 12 February, 2016

Material Reviewed

Method qualifications for: 1) bioburden; (2) endotoxin; and 3) sterility tests performed on (b) (4) drug product (DP) for rVIII-SingleChain.

Executive Summary

After a thorough review of this BLA, and the response to CBER's Information Request (IR) (Amendments 125591/0.6 and 125591/0.20 received on 29 October, 2015 and 29 January, 2016, respectively), this reviewer finds CSL Behring's bioburden, endotoxin, and sterility test methods were qualified in accordance with (b) (4) respectively, by demonstrating the rVIII-SingleChain matrix is suitable for these intended test methods.

Background

On 29 May, 2015, CSL Behring submitted a BLA for rVIII-SingleChain (Antihemophilic Factor [Recombinant], Single Chain [rVIII-SingleChain]) with a proposed proprietary name of 'AFSTYLA™'. rVIII-SingleChain is a recombinant, single-chain, human coagulation factor VIII (FVIII) molecule indicated as replacement therapy for adults and children with hemophilia A for the following: 1) control and prevention of bleeding episodes, 2) routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes, and/or 3) peri-operative management (surgical prophylaxis).

rVIII-SingleChain is produced in Chinese Hamster Ovary Cells and is expressed as a single chain human FVIII molecule with the majority of the B-domain and 4 amino acids of the adjacent acidic a3 domain removed (amino acids 765 to 1652). A covalent linkage between the heavy and light chains results in increased stability of the protein itself and increased affinity for the von Willebrand Factor, which contributes to improved pharmacokinetics thereby allowing less frequent dosing than with the full length recombinant FVIII products.

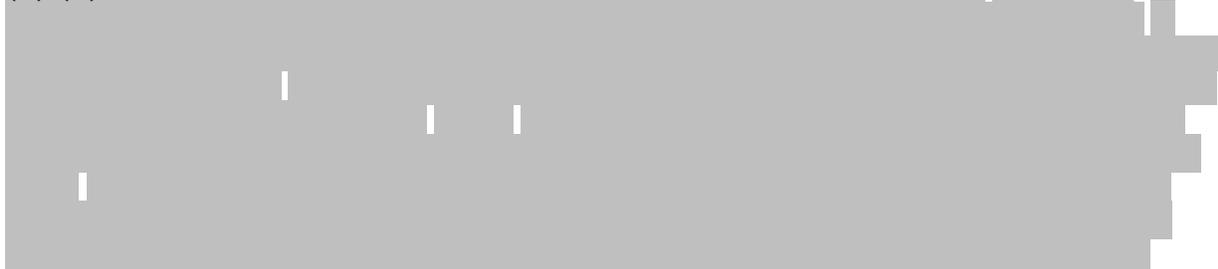
The final product is a sterile, non-pyrogenic, preservative free, slightly yellow lyophilized powder presented in two fill sizes (2.5 and 5.0mL) and administered following reconstitution in sterile water for injection. The 2.5 mL fill size produces vials containing potencies of 250, 500, and 1000 IU/vial (corresponding to dosage strengths of 100, 200 and 400 IU/mL, respectively); whereas the 5.0 mL fill size produces vials containing potencies of 2000 and 3000 IU/vial (corresponding to dosage strengths of 400 and 600 IU/mL, respectively). The final product also contains: Sucrose, Sodium and Calcium Chloride (b) (4), L-Histidine (b) (4) and Polysorbate 80 (b) (4). rVIII-SingleChain is intended for a single use intravenous administration and the dose administered is based on the body weight (kg) x the desired Factor VIII rise. The recommended starting regimen is 20-50 IU/Kg administered 2 to 3 times weekly and this regimen may be adjusted based on the patient's response.

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: 1) bioburden method performed on the (b) (4) bacterial endotoxin (b) (4) test method performed on the (b) (4) DP, and 3) sterility method performed on the DP.

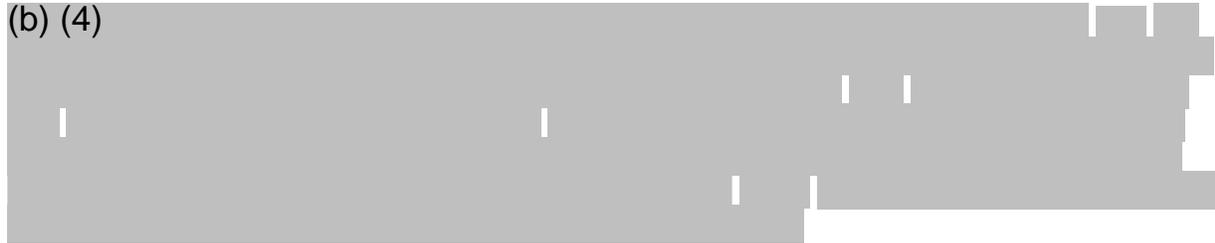
Review

Bioburden Test Qualification

The bioburden test method qualification was performed on (b) (4) representing the worst case scenario to demonstrate the rVIII-SingleChain matrix does not inhibit bacterial and fungal growth. The test was performed according to (b) (4)



(b) (4)



Endotoxin Test Qualification for (b) (4)

CSL Behring qualified their (b) (4) test method using (b) (4) of their rVIII-SingleChain^{(b)(4)}, to demonstrate their (b) (4) is suitable for the intended test method.

(b) (4)



(b) (4)



Endotoxin Test Qualification for Drug Product

CSL Behring qualified their (b) (4) test method using (b) (4) (b) (4) respectively representing the rVIII-SingleChain lowest (250 IU) and highest (3000 IU) potencies, to demonstrate their DP matrix is suitable for the intended test method.

Samples were tested (b) (4) times each at a (b) (4) resulting in the following respective (b) (4)

[Redacted]

Table 1: DP (b) (4)

Matrix	Endotoxin-	(b) (4)
(b) (4)	(b) (4)	(4)
Drug Product 250 IU	(b) (4)	(4)
Drug Product 500 IU	(b) (4)	(4)
Drug Product 1000 IU	(b) (4)	(4)
Drug Product 2000 IU	(b) (4)	(4)
Drug Product 3000 IU	(b) (4)	(4)

Table 2: DP FVIII:C Activity and Release Specification per DP Concentration

Matrix	Determined FVIII:C activity	Endotoxin Release Specification (b) (4)
Drug Product 250 IU	(b) (4)	(4)
Drug Product 500 IU	(b) (4)	(4)
Drug Product 1000 IU	(b) (4)	(4)
Drug Product 2000 IU	(b) (4)	(4)
Drug Product 3000 IU	(b) (4)	(4)

All test qualification parameters were compliant with the requirements in (b) (4) . The bacterial endotoxin concentration results found during the (b) (4)

[Redacted], respectively, which were within their release specification of (b) (4) . CBER finds their release specification acceptable as it is representative of their production process capability. CBER finds CSL Behring's (b) (4) method was qualified in accordance with (b) (4) by demonstrating their DP matrixes are suitable for the intended test method.

Sterility Test Qualification

CSL Behring qualified their rVIII-SingleChain DP matrix using the (b) (4) method by performing (b) (4) to demonstrate their DP matrixes are suitable for the intended test method.

(b) (4)

[Redacted]

(b) (4)

[Redacted]

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds CSL Behring's bioburden, (b) (4) and sterility, methods were qualified in accordance with (b) (4), respectively, by demonstrating the matrix for (b) (4) DP is suitable for these intended test methods.