



**CBER REGULATORY REVIEW MEMORANDUM**

**Date** 19 August, 2015

**From** Dr. Hyesuk Kong  
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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 # 125577/0

**Subject** BLA: Review of Bioburden, Sterility, and Bacterial Endotoxin Test Method  
Qualifications for recombinant von Willebrand Factor (rVWF) company code  
BAX111

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

**Applicant** Baxter Healthcare Corporation (Baxter)

**Product** Recombinant von Willebrand Factor (rVWF)

**Biologics License Application (BLA) Submission Tracking Number (STN)** 125577/0

**Submission Received by CBER** 19 December, 2014

**Review Completed** 19 August, 2015

**Material Reviewed**

Method qualifications for: 1) burden test performed [REDACTED] at the rVWF drug product (DP) manufacturing stage; 2) sterility, and bacterial endotoxin test using [REDACTED] method (b) (4) performed on the DP; and Baxter's response to CBER's Information Requests (IRs: amendments 125577/0/3 and 125577/0/7; received on 30 March and 28 May of 2015, respectively).

**Executive Summary**

After a thorough review of this BLA and the response to CBER's IRs, this reviewer finds Baxter's bioburden, sterility, and [REDACTED] methods were qualified in accordance with [REDACTED] and [REDACTED] respectively, by demonstrating the rVWF matrix is suitable for these intended test methods.

## Background

Baxter Healthcare Corporation (Baxter) submitted this BLA on 19 December, 2014 for Recombinant von Willebrand Factor (rVWF) for the prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand Disease (VWD). Recombinant VWF is formulated as a lyophilized powder for intravenous injection after reconstitution with sterile water for injection in single-use vials containing nominally 650 or 1300 international units (IU) VWF: Ristocetin cofactor (RCo) per vial. ADVATE (STN 125063/0 approved on 25 July, 2003), Baxter's recombinant FVIII (rFVIII), is to be co-administered with the first dose of rVWF if low FVIII levels are present.

Recombinant VWF protein is expressed in Chinese Hamster Ovary (CHO) cells. (b) (4) by the use of recombinant Furin. This (b) (4) production of recombinant VWF (b) (4) is performed at Baxter's (b) (4) facility in (b) (4). Then the rVWF (b) (4) Baxter's Thousand Oaks facility in California for rVWF final DP formulation and final container packaging; to include: (b) (4), filling, lyophilization, labeling and packaging operations. The bioburden test is performed (b) (4) at the rVWF final DP product manufacturing stage and the final container DP is tested for endotoxin and sterility.

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 rVWF DP, to indicate if the product matrix is suitable for testing using the intended test methods.

## Review

Bioburden Test Qualification for rVWF (Report No. TO-65-0776O001, Rev.2 and TO-65-71830 Rev. 0)

The bioburden test method qualification was performed on (b) (4) of rVWF (i.e., (b) (4)) of the formulated BDP (b) (4) at the rVWF DP manufacturing stage to demonstrate their rVWF does not inhibit bacterial and fungal growth. The test was performed according to (b) (4)



[REDACTED]

[REDACTED]

The bioburden results on their conformance BDP batches [REDACTED], which was within rVWF BDP proposed bioburden test specification [REDACTED].

Sterility Test Qualification using [REDACTED] Method for rVWF DP

Baxter qualified their rVWF DP using their [REDACTED] sterility [REDACTED] method by performing bacteriostatic and fungistatic (B&F) qualification studies on [REDACTED] of rVWF DP in a 650IU/vial [REDACTED] ) and [REDACTED] in a 1300 IU/vial [REDACTED] ) to demonstrate these DP matrix is suitable for the intended test method. Baxter reported these results in their validation report (OR-1200005-CVRTVA.03).

[REDACTED]

[REDACTED] The test was performed and compliant with [REDACTED] and the test results indicate there is no product inhibition on microorganism growth; thus indicating rVWF DP matrix is suitable for testing via their [REDACTED] sterility test method.

[REDACTED] Method Qualification for rVWF DP

Baxter qualified their [REDACTED] for the rVWF DP matrix by testing [REDACTED] of rVWF DP at rVWF final drug product at a concentration of 1300 IU/mL [REDACTED] ) to verify their matrix is suitable for the intended test method in accordance with [REDACTED]

[REDACTED]

[REDACTED] test results met their qualification acceptance criteria to qualify their product matrix for their [REDACTED] method in accordance with [REDACTED]

[REDACTED]

CBER performed licensing support bacterial endotoxin testing using a [REDACTED] method on their DP conformance lots (i.e., [REDACTED] at 650 IU/vial and [REDACTED], [REDACTED] at 1300 IU/vial) using Baxter's proposed [REDACTED] sample testing dilution. CBER's licensing support BET results support those of Baxter's qualification report and this licensing support test result memo is included in the STN file. Thus, CBER finds Baxter's proposed [REDACTED] sample testing dilution as a routine release testing acceptable.

The bacterial endotoxin specification of [REDACTED] for rVWF DP was calculated based [REDACTED]

[REDACTED]

[REDACTED]. Based on this information, this reviewer finds Baxter's proposed BET release specification of [REDACTED] for DP acceptable.

Regarding Baxter's Response (# 3.3: amendments 125577/0/3) to FDA received on 30 March, 2015, CBER sent an additional IR to Baxter on 14 May, 2015, requesting details on clarification of their primary sample dilution for their routine release testing; Baxter's response (Amendment 125577/0/7) is documented below in *italic font*:

FDA Question: In your response # 3.3, you clarified the [REDACTED] dilution is the primary sample dilution for your routine release testing. However, you indicated higher validated dilutions [REDACTED] may be used to dilute the product samples when the primary sample dilution [REDACTED] resulted in an invalid test due enhancement by product sample matrix. CBER expects a method suitability test to be performed on each product concentration (650 IU/vial and 1300 IU/vial), as their product matrixes are different; thus, the individual testing dilution selected for each product concentration should result in a qualified test performed each time. CBER will not accept an option to retest if the release test does not meet its qualifications the first time, as CBER performs confirmatory release testing of products and uses the specific testing dilution specified for each product in their license application. A product is expected to pass its release test using the testing dilution qualified as suitable for the product matrix, if the test is not valid – one could assume the product matrix has changed; which would indicate a major change in the production process. Please perform method suitability testing for each product concentration and provide CBER a specific testing dilution(s) that should result in a qualified release test, even if you need to assign different testing dilutions for each product concentration.

*Baxter would like to clarify that rVWF Final Drug Product (FDP) is manufactured in two different dosage strengths (650 and 1300 IU VWF: RCo/vial); however, the nominal potency after reconstitution (130 IU VWF: RCo/mL) and the sample matrix of both strengths are identical.*

*Suitability of Quantitative Determination of Endotoxin [REDACTED] in rVWF FDP samples under actual conditions of use (method suitability for a specific product) was demonstrated according to the procedures described in [REDACTED] [REDACTED] [REDACTED] [REDACTED]*

Additionally, the suitability of the [REDACTED] method for every single test run (i.e. the validity of the test run) is demonstrated prior to reporting the endotoxin level in rVWF FDP samples by meeting the following measures. For further details please refer to Section 5.3 in OR1300043-CTPTV\_FDP.03:

- The acceptance criteria of the standard calibration curve.
- The acceptance criteria of sample, including positive control samples [REDACTED] [REDACTED] which are included in every test run.

[REDACTED]

[REDACTED]

<sup>1</sup>: As a result of the agency's pre-licensing inspection that was held in [REDACTED] manufacturing facilities from [REDACTED], Baxter received an observation (483, No.1) with regard to deficiencies identified in laboratory investigation procedures for various test methods. To resolve these deficiencies and as part of the response to this observation, a global laboratory investigation procedure is being developed for all test methods.

Baxter indicates that if a primary dilution [REDACTED] is invalid, a deviation will be initiated and the impact on the product process capability will be investigated. All testing procedures, including those for retesting are specified in their SOP. Therefore, CBER finds their proposed testing dilution and their proposed retesting procedures acceptable according to applicable regulatory guidance.

## Conclusions

After a thorough review of the information submitted in this BLA and the response to CBER's information requests (amendments 125577/0/3 and 125577/0/7) received on 30 March and 28 May, 2015; this reviewer finds Baxter's bioburden, sterility, and [REDACTED] methods were qualified in accordance with [REDACTED] respectively, by demonstrating the rVWF product matrix is suitable for these intended test methods. Therefore, I recommend approval of the bioburden, sterility and bacterial endotoxin test methods for testing of the rVWF drug product.