



## CBER REGULATORY REVIEW MEMORANDUM

**Date** 30 October, 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** Biological License Application Submission Tracking Number #125640/0

**Subject** BLA: Review of Sterility and Bacterial Endotoxin Test Method Qualifications for Fibrin Sealant (Human)

**Through** James L. Kenney, D.Sc., Chief, LMIVTS  
Maryna Eichelberger, Ph.D., Director, DBSQC

**Applicant** Instituto Grifols

**Product** Fibrin Sealant (Human)

**Biologics License Application (BLA) Submission Tracking Number (STN)** 125640/0

**Submission Received by CBER** 4 November, 2016

**Review Completed** 30 October, 2017

### Material Reviewed

Method qualifications for sterility and bacterial endotoxin tests (BET) performed on Fibrin Sealant (Human). In addition, the responses to the information request sent on 01 May and 21 September of 2017 was also reviewed.

### Executive Summary

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

## Background

On 4 November, 2016, Instituto Grifols submitted this BLA for Fibrin Sealant (Human) indicated as an assist to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Fibrin Sealant (Human) is effective in heparinized patients.

The human plasma-derived fibrin sealant Grifols (FS Grifols) is a frozen sterile solution contained in two syringes with two components: human fibrinogen (component 1) and human thrombin with calcium chloride (component 2). The syringes are assembled on a syringe holder and one applicator cannula is provided with the product and supplied in sizes 2, 4, 6, and 10 mL. When applied, the solutions mix and generate a cross-linked fibrin clot that mimics the last stage of the human coagulation system.

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 endotoxin release specifications to ensure they reflect process capability and are regulatory compliant. 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 per their product's licensed test method specifications. Therefore, this review will focus on the (b) (4) sterility and BETs for the two components of FS Grifols drug product (DP).

## Review

### Sterility Test Qualification for Human Fibrinogen and Human Thrombin Components

The human fibrinogen and thrombin components of the DP matrix were qualified using the sterility (b) (4) to demonstrate the matrixes are suitable for the intended test method. The sterility test for both components was performed using (b) (4) indicator microorganisms (i.e., (b) (4)

on (b) (4) of 5 mL (i.e., lot numbers: (b) (4)) and (b) (4) lots of 3 mL (i.e., lot numbers: (b) (4)), according to validation report (i.e., IG\_IVMA-000281\_ING) for human fibrinogen and (b) (4) of 5 mL (i.e., lot numbers: (b) (4)) and (b) (4) lots of 3 mL (i.e., lot numbers: (b) (4)), according to validation report (i.e., IG\_IVMA-000203\_ING) for the human thrombin component. On 21 September, 2017, CBER requested Grifols qualify their sterility test using known environmental isolates from their Barcelona Spain facility, Grifols replied (125640/0.50), they will requalify their sterility test to include known environmental isolates once their product manufacturing process becomes regular. CBER finds this proposal acceptable and expects these results to be submitted in their pertinent annual report.

The test for each microorganism was performed using (b) (4) bottles of Fibrinogen (80 mg/mL) 3 mL, and before performing the test for human thrombin 3 and 5 mL of Thrombin (500 IU/mL) units were placed in a 37°C incubator to thaw. Each microorganism was tested (b) (4)

(b) (4)

(b) (4)

. The tests were performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth; thus, indicating that the human fibrinogen and human thrombin component matrixes are suitable for testing via their compendial (b) (4) sterility test method.

(b) (4)

BET (b) (4)-BET) Method Qualification for Human Fibrinogen

Grifols qualified their (b) (4)-BET method for Human fibrinogen 3 mL lots (i.e., lot numbers:

(b) (4)

) according to validation report (i.e., IG\_IVMA-000168\_ING) to verify their human fibrinogen component matrix was suitable for the intended test method in accordance with (b) (4).

The maximum valid dilution (MVD) was (b) (4)

(b) (4)

BET (b) (4)-BET) Method Qualification for Human Thrombin

The same type of (b) (4)-BET qualification was used for the human thrombin component and it was tested as mentioned above with the same release specifications and MVD. According to their validation report (i.e., IG\_IVMA-000185\_ING) (b) (4) 3 mL lots (i.e., lot numbers: (b) (4) ) were used to verify the human thrombin component matrix was suitable for the intended test method in accordance with (b) (4)

All test parameters met their preapproved bacterial endotoxin qualification requirements and were compliant with (b) (4).

This reviewer finds the human fibrinogen and thrombin components of the DP matrix were qualified appropriately and found suitable for testing using Grifols' (b) (4)-BET method. In addition, CBER finds their endotoxin release specifications acceptable.

### Conclusions

After a thorough review of this BLA and the responses to CBER's IRs, this reviewer finds the method qualifications for sterility and bacterial endotoxin release testing (BET) performed on FS Grifols' fibrinogen and thrombin component matrixes suitable for their proposed test methods, as they were qualified and performed in accordance with (b) (4) and (b) (4). Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.