



MEMORANDUM

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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 125640/0

Subject: (b) (4) Analysis of Fibrinogen in Fibrin Sealant (Human)

Through: Lokesh Bhattacharyya, Lab Chief, CBER/OCBQ/DBSQC
James Kenney, Acting Director, CBER/OCBQ/DBSQC

Applicant: Grifols

Submission Received by CBER: Nov. 3, 2016

Summary:

A new BLA was submitted by Grifols for Fibrin Sealant (Human). This document includes the Primary Review Memo from DBSQC for the analytical method of (b) (4) in Fibrinogen by (b) (4) and its validation, which is proposed to be used for quality control of the drug product (DP). This reviewer found that the procedure was adequately described and validated for its intended use.

Background

Grifols for Fibrin Sealant (Human) product is for use as an adjunct 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) are ineffective or

impractical. The product, provided as a kit, comprises two syringes containing sterile frozen solutions of human fibrinogen and human thrombin assembled on one syringe holder for topical use.

Documents Reviewed

Original submission STN 125641/0 dated Nov. 3, 2016

- Cover letter
- 2.2 Introduction
- 3.2.S.2.3 Control of materials (Human Fibrinogen)
- 3.2.P.1 Description and composition of the drug product
- 3.2.P.5.1 Specifications
- 3.2.P.5.2 Analytical procedures
- 3.2.P.5.3 Validation of analytical procedures
- 3.2.P.5.4 Batch analyses
- SOP (IG_MA-000158E_ING): (b) (4) in Fibrinogen by (b) (4)
- Validation report (IG-IVMA-000041_ING): Validation for Fibrinogen (Sealant) of (b) (4) in Fibrinogen by (b) (4)
- Fibrin Sealant Grifols: Stability Study (IG_IE-000239_ING)
- Fibrinogen (Fibrin Sealant Grifols Component): Characterization Study (IG_IC-000098_ING)

Amendment 12, dated Feb. 23, 2017

- Responses to FDA Information requests in 10&31 Jan17
- Updated SOP (IG_MA-000158E_ING): (b) (4) in Fibrinogen by (b) (4)

Amendment 17, dated Mar. 23, 2017

- (b) (4), Preparation and Standard of the Fibrinogen Secondary Standards Batch (b) (4)

Amendment 28, dated May 23, 2017

- Response to FDA Information request 1 May17

Amendment 31, dated June 20, 2017

- Response to FDA Information request 06 June 17

Amendment 46, dated September 18, 2017

- Response to FDA Information requests Aug. 03, 19 & 29 2017

Review Narrative

Method

(b) (4)

(b) (4)

Information Request (IR) and Response Review

A DBSQC IR was sent to the sponsor as following in the filing notification on Jan. 31, 2017 after initial review. The response was received on Feb. 23, 2017 in amendment 12.

1. Regarding analytical procedure “(b) (4) in Fibrinogen by (b) (4)” (Document No. IG_MA-000158E_ING, Version 7.0):
 - a. Your procedure document instructs, (b) (4) in the Sections 4.2 and 4.3, respectively. These instructions are too vague. Please define acceptable time durations between thawing, sample preparation steps, and sample (b) (4) .
 - b. For an (b) (4) method, acceptance criteria of system suitability test (SST), such as (b) (4) for (b) (4) performance, should be set as part of the system suitability check. Please revise your analytical procedure document to add these acceptance criteria and submit for review.
 - c. In Section 4.1 on page 5, you describe, (b) (4) Is (b) (4) of fibrinogen control sufficient? Please describe the acceptance criterion for (b) (4) .
 - d. You assigned the (b) (4) in the (b) (4) (page 9) as an (b) (4) . Please provide experimental data to support identification of this (b) (4) .
 - e. You described the (b) (4) in the (b) (4) (page 9) as due to an (b) (4) fibrinogen and not due to (b) (4) . Please provide adequate characterization data to support that this (b) (4) is indeed due to an (b) (4) of fibrinogen.

Review of the response

- a. The SOP is updated, which describes that (b) (4) sample must be (b) (4) the in the section 4.3. The response is not justified by the robustness study. A further request was made for the justification of such practice because it prevents samples being (b) (4) .
- b. New section 4.5 “system suitability” was added to the updated SOP, which has an acceptance criterion for (b) (4) of the

fibrinogen control. However, the (b) (4) is a very low requirement for such (b) (4) assay. A follow-up IR was sent to the sponsor for supporting data of this acceptance criterion.

- c. A new section 4.1.1 “(b) (4)” was added to the updated SOP, which specifies how (b) (4) (discussed above in the Method section). The response is satisfactory.
- d. The sponsor stated that the same SOP is also used for another investigational product, which uses (b) (4). The fibrinogen component of the Fibrin Sealant do not contain (b) (4) in the final product. Thus those (b) (4) are not relevant to this product. The response is acceptable.
- e. The sponsor stated that (b) (4)

A further question was sent to the sponsor in the 4th IR.

- 2. Please provide appropriate data to show that no portions of fibrinogen in your product, (b) (4) in the analytical procedure of “(b) (4) in Fibrinogen by (b) (4)” (Document No. IG_MA-000158E_ING, Version 7.0).

Review of the response

Two (b) (4) from other commercial registered Fibrin Sealant (Tisseel® and Evicel®) were presented in the response. They contain (b) (4) respectively. The results showed (b) (4) in these two products. These data did not demonstrate that (b) (4) fibrinogen DP in this BLA are (b) (4). However, accuracy data provided in the validation report showed that DP samples with (b) (4), which demonstrated (b) (4) of (b) (4) from the product (b) (4). Thus, the IR is resolved from the validation data.

- 3. Regarding “Validation for Fibrinogen (Sealant) of (b) (4) in Fibrinogen by (b) (4)” (Document No. IG_IVMA-000041_ING, Version 2.0):
 - a. Please provide your results to demonstrate the (b) (4).
 - b. We do not agree with the LOQ determination in your validation report, in which you obtained σ and S values for $10\sigma/S$ from the (b) (4). Please recalculate and submit the result for review.
 - c. Please provide results of the robustness evaluation of the method.

Review of the response

- a. (b) (4) study were provided in the response. Using %Fibrinogen (b) (4). A further IR was sent to the sponsor for clarification.
- b. The LOQ is recalculated as suggested and is (b) (4). The response is satisfactory.
- c. A retrospective evaluation of robustness has been performed from the data during method development stage and summarized in the method validation above. The response is satisfactory.

Second IR and response review

The 2nd IR was sent to the sponsor on May 1, 2017 and the responses were received on May 23, 2017 in amendment 28.

1. In the updated SOP (response to Q1a), you stated that samples must be (b) (4) in both sections 4.2 and 4.3. Please provide relevant robustness study data to support this practice.

Review of the response

Samples stability study was conducted (b) (4)

The response is acceptable.

2. In response to Q1b, you add an acceptance criterion of (b) (4) number (b) (4) of the control as only system suitability check without other important (b) (4) check such as (b) (4). Please justify this (b) (4) number for the control and provide historical data of (b) (4) numbers from your control and DP samples. Please confirm this is also the criterion used to decide (b) (4).

Review of the response

The sponsor provided historical (b) (4) numbers (N) of both control and DP samples. The ranges of N are (b) (4), respectively from results of (b) (4) of the control and (b) (4) of the DP lots. The N from the DP is significantly higher than that of the control from (b) (4). The sponsor also stated that N of the control is also used as a criterion to decide to (b) (4). The heterogeneity of human fibrinogen is well known [cf. M.W. Mosesson, Fibrinogen and fibrin structure and functions, J. Thromb. Haemost. 3 (2005) 1894-1904]. The historical (b) (4) data indicates that the (b) (4) from DP is less heterogeneous than that of the control. The response is satisfactory.

3. In response to Q3a, please explain the rationale in using (b) (4)

(b) (4). For a typical (b) (4) assay, (b) (4)
(b) (4), and in which the calculated percent of
(b) (4) is constant.

Review of the response

(b) (4) are provided in the response.
Correlation coefficient (R) from (b) (4) independent runs for (b) (4) of (b) (4) is
(b) (4), which meets the acceptance criterion of (b) (4). The response is acceptable.

Third IR and response review

The 3rd IR was sent to the sponsor on June 6, 2017 and the response was received on June 20, 2017 in the amendment 31.

Your current Fibrinogen control (Lot (b) (4) from (b) (4) Human plasma Fibrinogen) has the established (b) (4) limits of (b) (4), which is below the LOQ of your assay (b) (4). Therefore, you cannot measure (b) (4) of this control with adequate accuracy and precision. Please establish a new control that has (b) (4) above your LOQ for the accuracy check of this assay and submit results for evaluation.

Review of the response

The LOQ is re-evaluated with the deviation of (b) (4) of a DP sample with (b) (4)
(b) (4). The determined (b) (4) LOQ is (b) (4) from three independent experiments. We consider this LOQ value is adequate for the intended purpose because both accuracy and precision at LOQ level are acceptable. The response is acceptable.

Fourth IR and response review

The 4th IR was sent to the sponsor on Aug. 3, 2017 and the response was received on Sep 18, 2017 in the amendment 54.

1. Your response, submitted on February 23, 2017 (Amendment 12), to item 1e of the January 31, 2017, Information Request is not acceptable. Please provide adequate characterization data to support that (b) (4) is due to an (b) (4) fibrinogen. The (b) (4) and (b) (4) analyses of the (b) (4) may provide such information.

Review of the response

In response, the sponsor explained that (b) (4) and (b) (4) analyses were conducted under (b) (4) for (b) (4) from (b) (4) different DP lots. For the (b) (4) test, a (b) (4) were used for the (b) (4) detection. (b) (4) and (b) (4) results showed (b) (4),

corresponding to (b) (4) of fibrinogen, which are constituents of the (b) (4) probably corresponding to (b) (4) of fibrinogen. (b) (4) and (b) (4) results showed (b) (4) : one corresponding to fibrinogen (b) (4) fibrinogen. In addition, the fibrinogen purity was also assessed by (b) (4) in (b) (4) according to method IG MA-000009B_ING. In all three lots, only (b) (4), which corresponds purity (b) (4). The experimental data support that (b) (4) consists of fibrinogen (b) (4). The response is acceptable.

2. You stated, "(b) (4) of fibrinogen are (b) (4)." Please provide supporting data or literature references to support this claim.

Review of the response

The results of (b) (4) in the fibrinogen characterization study (IG_IC-000098_ING) and percentage of (b) (4) fibrinogen against (b) (4) is (b) (4) in the stability study (IG IE-000239_ING). This demonstrates at least that (b) (4) in the fibrinogen (about (b) (4) from (b) (4) test) is clottable. The response is acceptable.

Conclusion

The analytical procedure of (b) (4) in Fibrinogen by (b) (4) is adequately described and validated for the intended use.