

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Tuesday, May 23, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Monday, May 01, 2017 8:26:00 PM
Attachments: [image001.png](#)
Importance: High

Dear Ms. Robertson:

We are reviewing your original November 3, 2016, submission to BLA 125640 for Fibrin Sealant (Human). We have the following comments and requests for additional information:

Please address the following deficiencies identified with analytical procedures:

1. The document IG_MA-000664_ING *FIBRIN SEALANT IDENTIFICATION* includes the description of two analytical methods: Fibrin Sealant Identification and (b) (4). Because these parameters represent the functionality of the final drug product (FDP) and are included in the release specifications, each analytical method requires validation. In addition, the procedure of the method Fibrin Sealant Identification does not include sufficient details on how to perform the method.
 - a. Please provide a detailed description of the procedure Fibrin Sealant Identification. Please clearly define the acceptance criteria for the test.
 - b. Please validate the analytical procedure for Fibrin Sealant Identification, including an assessment of *Specificity* and submit the results in a validation report. Please include data to support the suitability of the test for its intended purpose (assessment of functionality), as well as the sensitivity of the test to detect changes in the quality attributes of the FDP components (Fibrinogen and Thrombin), e.g., using multiple concentrations of the components, or components that have been subjected to forcible degradation.
 - c. In regard to the (b) (4) test, please clarify how the results will be reported. We note inconsistency in reporting by actual (b) (4) (3.2.P.5.4 Batch Analysis) or as “Pass test” (3.2.P.8.3. Stability Data). If you plan to report the actual (b) (4) (which appears to be implied from the test definition), the test will be considered as a quantitative method requiring validation of *Accuracy*, *Precision*, *Specificity*, *Linearity*, *Range*, and *Robustness*. If this method is considered as an identification test, then the validation should include the assessment of *Specificity* and *Robustness*; in this case, please explain the difference between the Fibrin Sealant Identification and (b) (4) tests. Please submit the validation report. Please also specify the acceptance criteria for this test in the respective SOP.
 - d. In the description of the analytical procedure for (b) (4), please clarify for what “specific studies” the test can be performed with a total product volume of (b) (4). Please provide a detailed description of the

procedure, and the validation data for low-volume testing.

2. We have the following questions/comments regarding the method validation report for the determination of Fibrinogen (Clottable protein) by (b) (4) Method, Document IG_IVMA-000408_ING:
 - a. You have indicated in Section 4.2 that *Linearity* was assessed using Fibrinogen in the range of (b) (4). This range is equivalent to a range of (b) (4) after considering the dilution specified in the test method SOP. Thus, your linearity data do not cover the lower specification limit of (b) (4) for the Fibrinogen component of your product. Please provide additional linearity data to cover the proposed specification range.
 - b. You have evaluated *Accuracy* using only the (b) (4) Standard but not your fibrinogen product. Please provide data using the Fibrinogen FDP to assess *Accuracy* over the proposed range of the assay. Alternatively, please provide data to support the suitability of the use of the standard in the study, e.g., recovery data from the *Precision* study in the proposed range.
 - c. We acknowledge your response to the March 16, 2017, Information Request (IR), regarding the evaluation of *Robustness* of the assay. However, it only includes variations in the equipment used and lots of reagents and standards. Please provide additional data for your method by evaluating the effect of variation of operating conditions and parameters, specifically concentration of calcium and Thrombin and temperature at the extremes of the operational ranges.
3. In regard to your Thrombin secondary standards: in the report IG_IEST-000295_ING and communications EV160930/1 and EV170331/1 (Section 3.2.P.6 *Human Thrombin Reference Standards or Materials*), you reported the extension of the expiry date for Thrombin secondary standard batch (b) (4). Similarly, you reported the extension of the expiry date for Thrombin secondary standard batch (b) (4) (report IG_IEST-000296_ING and communication EV170227/1). However, you have not provided data to support these extensions. Please submit stability data for the Thrombin secondary standards to justify the extension of their expiry dates.
4. In regard to the Secondary standard for Fibrinogen, you provided the report IG_IEST-000441_ING *Preparation and standardization of the Fibrinogen secondary standard lot (b) (4)* and the communication EV151215/16 *Extension of expiry date for (b) (4) secondary standard batch (b) (4)*, you extended the shelf-life of the standard to (b) (4) months, which is beyond the shelf-life of the Fibrinogen component of the FDP (24 months). The extension of the shelf-life of the standard was not justified by real-time stability data. Please provide stability data to justify the extension of the shelf-life of the Fibrinogen secondary standard.
5. In regard to the analytical procedure (b) (4) *in Fibrinogen by (b) (4)* (Fibrinogen Doc: IG MA-000158E_ING) and response to our IR (dated

January 31, 2017) received on February 23, 2017, in Amendment 12, we have the following questions:

- a. In the updated SOP (response to Q1a), you stated that samples must be (b) (4) of (b) (4) in both Sections 4.2 and 4.3. Please provide robustness data to support this practice.
 - b. In response to Q1b, you added an acceptance criterion of (b) (4) number (b) (4) for the (b) (4) of the control as the only system suitability check without other (b) (4) performance checks, such as (b) (4). Please justify this low (b) (4) number for the control, and provide historical data of (b) (4) numbers from your control and FDP samples. Please confirm that this is also the criterion used to decide when to (b) (4).
 - c. In response to Q3a, please explain your rationale in using ((b) (4)) as the X axis in the linearity plot, rather than (b) (4). For a typical (b) (4) assay, linearity is used to demonstrate the range in which (b) (4) of (b) (4) are linear with respect to the amount of (b) (4), and in which the calculated percent of (b) (4) is constant.
6. In regard to *Sterility* testing by (b) (4), please:
- a. Provide results of negative controls used in the sterility qualification study for the Fibrinogen component, *Validation of the Sterility Test* (Doc IG_IVMA-000281_ING).
 - b. Provide a complete sterility qualification report for the Thrombin component. The report should include the type of media used, conformance lot numbers, and incubation conditions and duration, to show the suitability of the *Sterility* test for its intended purpose.
7. In regard to the validation of the *Endotoxin* test for the Fibrinogen component, *Validation of the Endotoxin Test by (b) (4) Method with (b) (4)* (Fibrinogen Doc: IG_IVMA-000168_ING) and *Thrombin component, "Validation of the Endotoxin Test by (b) (4) Method with (b) (4)* (Thrombin Doc: IG_IVMA-000185_ING), please:
- a. Provide the rationale for selecting (b) (4) (for Fibrinogen) and (b) (4) (for Thrombin) testing dilutions. CBER requests re-qualifying the Endotoxin method for both Fibrinogen and Thrombin using a series of dilutions below the (b) (4), and choosing a dilution that provides the optimal Product Positive Control (PPC) % recoveries (e.g., closest to 100%).
 - b. Provide positive control spike concentrations for the results provided in

Table 1, Absence of Enhancement/Inhibition.

Please update the eCTD file for all the above changes.

The review of this submission is ongoing, and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by May 23, 2017, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified. If more time is needed for those items requiring experimentation, please indicate a date in your response as to when the requested data can be generated.

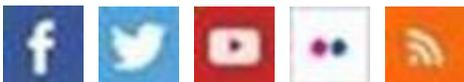
If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is November 3, 2017.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.
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