

**From:** Do, Yu  
**To:** [Joan.robertson@grifols.com](mailto:Joan.robertson@grifols.com)  
**Subject:** Information Request (Response Due by Friday, July 21, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.  
**Date:** Monday, July 10, 2017 2:53:00 PM  
**Attachments:** [image001.png](#)  
**Importance:** High

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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 to continue our review:

This is in reference to your submissions dated May 10 and 25 of 2017:

### **Fibrinogen and Thrombin Components**

#### Multiple Analytical Methods for Fibrinogen and Thrombin Components

1. With regard to the lot release testing of fibrinogen and thrombin components, you have described only the components of the control sample for the following assays:
  - a. Assay for Chloride in fibrinogen and thrombin products (document IG\_MA-000016A\_ING)
  - b. Assay for TNBP in fibrinogen and thrombin products (document IG\_MA-000281A\_ING)
  - c. Assay for Polysorbate 80 in fibrinogen and thrombin products (document IG\_MA-000403C\_ING)
  - d. Assay for Sodium in fibrinogen and thrombin products (document IG\_MA-000005A\_ING)
  - e. Assay for Citrate in fibrinogen product (document IG\_MA-00170B\_ING)
  - f. Assay for (b) (4) in thrombin product (document IG\_MA-000456A\_ING)
  - g. Assay for Calcium in thrombin product (document IG\_MA-000359A\_ING)

Please provide data to show that the control sample used in each of the above assays is adequately qualified or standardized in your laboratory against an appropriate primary or secondary standard.

#### Determination of Tri-n-Butyl Phosphate (TNBP) by (b) (4)

2. With regard to the Method validation reports for the determination of TNBP in fibrinogen product (Document IG\_IVMA-000261\_ING) and thrombin product (Document IG\_IVMA-000237\_ING):
  - a. In response to Information Request dated May 05, 2017, regarding the robustness of the assay, you have submitted data wherein the effects of

analytical parameters were evaluated by calculating the resolution between the TNBP (b) (4), using calibration standards only. Please provide data for demonstrating robustness of the assay by evaluating the effect of variation of (b) (4) parameters on TNBP results from your fibrinogen and thrombin products.

- b. You have concluded that the LOQ of the assay is (b) (4) based on the analysis of the standard. However, you did not provide the data from fibrinogen and thrombin product samples in support of LOQ of this assay. Please provide linearity and accuracy data using the drug product to show that (b) (4) is the LOQ of your assay.

### **Fibrinogen Component Only**

#### Determination of Glutamic Acid, Glycine, Arginine, and Isoleucine by (b) (4)

3. With regard to the Method validation report, Document IG\_IVMA-FGD1358C\_ING:
  - a. Your response to Information Request dated May 25, 2017, and submitted linearity data are acceptable for the quantitation of glutamic acid, arginine, and isoleucine. However, glycine is quantitated as an impurity in this assay. Please provide your results for linearity and accuracy evaluation for glycine in the interval between LOQ and the specification limit of (b) (4).
  - b. In your method validation for the glycine assay, the range of assay based on the linearity, accuracy, and precision results is (b) (4). Thus, the LOQ, which is the lowest concentration assessed with acceptable accuracy and precision, is (b) (4). However, you stated that the LOQ was (b) (4). Please provide data to show the accuracy and precision of the method at (b) (4) or correct your validation report to indicate (b) (4) as the LOQ.

#### Determination of Chloride by (b) (4) Method

4. With regard to the Method validation report, Document IG\_IVMA-000367\_ING:

You have demonstrated linearity and accuracy of your assay using the data obtained from chloride standards only. Therefore, you have not validated the assay adequately. Please provide linearity and accuracy data using representative fibrinogen samples. Also, for linearity please include an assessment of parallelism between the standard and sample regression lines.

### **Thrombin Component Only**

#### Determination of Glycine by (b) (4)

5. With regard to the Method validation report, Document IG\_IVMA-THROMB358A\_ING:

The glycine (b) (4) obtained from the standard and product samples are (b) (4) (original submission) and (b) (4) (response to Information Request dated May 05, 2017), respectively. These two (b) (4) are significantly different. Please explain the discrepancy and provide justification for confirmation of glycine identity from your results.

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 July 21, 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 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](mailto:Yu.Do@fda.hhs.gov) if you have any questions.

Sincerely,

Yu Do, M.S.  
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Center for Biologics Evaluation and Research  
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