
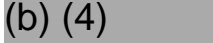

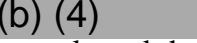

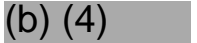
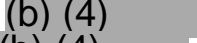
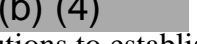



From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Thursday, May 25, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Friday, May 05, 2017 3:08:00 PM
Attachments: [image001.png](#)
Importance: High

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 related to analytical methods for the determination of excipients and process-related impurities in your product, Fibrin Sealant (Human):

Fibrinogen Component

1. **Determination of Glutamic Acid, Glycine, Arginine, and Isoleucine by (b) (4)**

 - a. For the (b) (4)  procedure described in your SOP IG_MA-000358C_ING, please provide: (1) the composition of (b) (4) ; (2) the (b) (4) ; (3) (b) (4) ; and (4) composition of the control sample and the details of the qualification of the control.
 - b. Regarding the Method validation report, document IG_IVMA-FGD1358C_ING:
 - i. Please provide a representative (b) (4)  of fibrinogen drug product, and (b) (4)  of the four amino acids in fibrinogen product, and the (b) (4)  of the corresponding amino acids in the standard solutions to establish both identity and specificity of your assay.
 - ii. Please establish range of your assay for each amino acid based on the linearity, accuracy, and precision data obtained from the fibrinogen samples, and update your validation report accordingly.
 - iii. Please provide the robustness data by evaluating the effect of variations of critical method parameters.
2. **Citrate Determination by (b) (4)  Method**
 - a. Regarding your testing instruction document IG_MA-000170B_ING, please provide the details of composition of the control sample used to assess the validity of citrate assay.
 - b. Regarding the Method validation report, document IG_MA-000381_ING:
 - i. You have demonstrated linearity and accuracy of your assay using the data obtained from citrate standards only. Please provide data for the validation characteristics using representative fibrinogen drug product

samples. Also, for linearity, please include an assessment of parallelism between the standard and sample regression lines of the plots of analyte concentration (or dilution) versus response.

- ii. For your specificity study, please provide results obtained with fibrinogen drug product sample formulated with all other excipients, except citrate, and a comparison of the results obtained with the actual representative drug product formulation that contains citrate.
- iii. Please provide the results of the robustness evaluation for your assay.

3. **Determination of Chloride by (b) (4) Method**

- a. Section 6.0 of your SOP (document IG_MA-000016A_ING) includes the assay validity criteria based on the control. Please provide the composition of the control sample.
- b. Regarding the Method validation report document IG_IVMA-000367_ING: For your method robustness, please provide details of the parameters varied and their effect on the measured chloride concentration.

4. **Determination of Polysorbate 80 by (b) (4) Method**

- a. Regarding your testing instruction document IG_MA-000403C_ING: Please provide composition of the control sample mentioned in Section 4.2 of your test method SOP.
- b. Regarding the Method validation report, document IG_IVMA-FGD1403C_ING:
 - i. For your linearity studies, you have evaluated the results obtained using polysorbate 80 standard, but not the fibrinogen drug product sample. Please provide linearity data for your fibrinogen product over the proposed assay range, and demonstrate parallelism between the plots of analyte concentration (or dilution) versus response for the standard and your drug product.
 - ii. You have concluded that the LOQ of the assay is (b) (4), based on polysorbate 80 standard curve. However, you have not provided accuracy, precision, and linearity data at LOQ. Please provide accuracy, precision, and linearity data from fibrinogen samples to support the LOQ of your assay.
 - iii. Please provide the robustness data to show that your method is not susceptible to deliberate variations in analytical conditions.

5. **Determination of Tri-n-Butyl Phosphate (TNBP) by (b) (4)**

- a. Regarding your method SOP IG_MA-000281A_ING, please provide composition of the sample used as an assay control.

b. Regarding the Method validation report, document IG_IVMA-000261_ING:

- i. For your specificity study, please provide (b) (4) of TNBP (b) (4) from the drug product and reference standard to establish (b) (4) identity and method specificity.
- ii. You have not provided accuracy data to support accuracy of your method at the upper specification limit of (b) (4). Please provide accuracy data at this concentration level.
- iii. You have calculated the LOQ of your assay as (b) (4) based on TNBP standard curve. However, you have not provided accuracy, precision, and linearity data at LOQ in your validation report. Please provide accuracy, precision, and linearity data from fibrinogen samples to support the LOQ of your assay.
- iv. Please provide robustness data for your method by evaluating the effect of variation of different (b) (4) parameters.

6. **Sodium Determination by (b) (4)**

- a. Regarding your testing instruction document SOP IG_MA-000005A_ING: Please revise your SOP to include a detailed description or composition of the sodium secondary standard used as an assay control and submit for review.
- b. Regarding the Method validation report, document IG_IVMA-000373_ING:
 - i. The linearity and accuracy of your assay was validated with the use of sodium standards only. Please provide data on linearity and accuracy using actual drug product samples at concentration levels covering the range of the assay.
 - ii. Please provide data obtained from fibrinogen drug product samples prepared without sodium-containing excipients (e.g., replacing sodium by potassium) to substantiate your conclusion that the method is specific.
 - iii. Please provide robustness data for your method by evaluating the effect of variation of different operating parameters of your assay.

Thrombin Component

7. **Determination of Glycine by (b) (4)**

- a. For the (b) (4) procedure described in your SOP IG_MA-000358A_ING, please provide: (1) the composition of (b) (4); (2) (b) (4) conditions; (3) (b) (4); and (4) description and qualification details of the control sample.

- b. Regarding the Method validation report, document IG_IVMA-TROMB358A_ING:
 - i. Please provide the (b) (4) of formulated thrombin product, and the (b) (4) of glycine in thrombin product and glycine standard solution to establish (b) (4) identity and specificity of your assay.
 - ii. Please establish range of your assay based on the linearity, accuracy, and precision data obtained from the thrombin samples, and update your validation report accordingly.
 - iii. Please provide robustness data by evaluating the effect of deliberate variations of critical method parameters.

8. **(b) (4) Determination by (b) (4) Method**

- a. Regarding your testing instruction document SOP IG_MA-000456A_ING, please provide the composition of the control sample used to assess the validity of the (b) (4) assay.
- b. Regarding the Method validation report, document IG_IVMA-THROMB456A_ING:
 - i. You have demonstrated linearity of your assay using the data obtained from (b) (4) standards only. Please provide linearity data and plots of analyte concentration (or dilution) versus response using representative thrombin samples, and include an assessment of parallelism between the standard and sample regression lines.
 - ii. For your specificity study, please provide results obtained from thrombin drug product sample formulated with all other excipients, except (b) (4).
 - iii. You have not submitted the robustness data for your method. Please provide the results to permit a complete review of your assay.

9. **Determination of Chloride by (b) (4) Method**

- a. Regarding your testing instruction document IG_MA-0000016A_ING, Section 6.0 includes assay validity criteria based on the control. Please provide the composition of the control sample.
- b. Regarding the Method validation report, document IG_IVMA-000374_ING:
 - i. Please provide data to show linearity and accuracy of chloride response in your thrombin drug product.
 - ii. Please provide the data obtained from thrombin drug product formulated without chloride-containing excipients to demonstrate method

specificity.

- iii. For your method robustness, please provide details of the parameters varied and their effect on chloride concentration.

10. Determination of Polysorbate 80 by (b) (4) Method

- a. Regarding your testing instruction document SOP IG_MA-000403C_ING, please provide composition of the control sample mentioned in Section 4.2 of your test method SOP.
- b. Regarding the Method validation report, document IG_IVMA-000401_ING:
 - i. For your linearity studies, you have evaluated the results obtained using polysorbate 80 standard, but not the thrombin drug product sample. Please provide linearity data for your thrombin product over the proposed assay range, and demonstrate parallelism between the standard and your drug product regression plots of analyte concentration (or dilution) versus response.
 - ii. You have concluded that the LOQ of the assay is (b) (4), based on polysorbate 80 standard curve. Please provide accuracy, precision, and linearity data from thrombin samples to support the LOQ of your assay.
 - iii. Please provide robustness data to show that your method is not susceptible to variations in assay conditions.

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

- a. Regarding your method SOP IG_MA-000281A_ING, please provide composition of the sample used as an assay control.
- b. Regarding the Method validation report, document IG_IVMA-000237_ING:
 - i. For your specificity study, please provide (b) (4) and (b) (4) of TNBP (b) (4) from the drug product and reference standard.
 - ii. You have not provided accuracy data to support accuracy of your method at the upper specification limit of (b) (4). Please provide accuracy data at this concentration level.
 - iii. You have calculated the LOQ of your assay as (b) (4) based on TNBP standard curve. However, you have not provided accuracy, precision, and linearity data in your validation report. Please provide accuracy, precision, and linearity data from thrombin drug product samples to support the LOQ of your assay.
 - iv. Please provide robustness data for your method by evaluating the effect of variation of different (b) (4) parameters.

12. **Sodium Determination by (b) (4)**

- a. Regarding your testing instruction document SOP IG_MA-000005A_ING, please revise your SOP to include a detailed description or composition of the secondary standard used as an assay control.
- b. Regarding the Method validation report, document IG_IVMA-000415_ING:
 - i. The linearity and accuracy of your assay was validated with the use of sodium standards only. Please provide linearity and accuracy data using actual drug product at concentration levels covering the range of the assay.
 - ii. Please provide data obtained from thrombin samples prepared in specificity solution (without sodium-containing excipients) to substantiate your conclusion that the method is specific.
 - iii. Please provide robustness data for your method by evaluating the effect of variation of different analytical parameters of your assay on sodium concentration.

13. **Determination of Calcium by (b) (4)**

- a. Please revise your SOP (document IG_MA-000359A_ING) to include: (i) the composition of the assay control and (ii) procedure for sample (b) (4) using (b) (4) and submit for review.
- b. Regarding the Method validation report, document IG_IVMA-000062_ING:
 - i. The linearity and accuracy of your assay was validated with the use of calcium standards only. Please provide linearity and accuracy data using actual drug product samples at concentration levels covering the range of the assay.
 - ii. To support your method specificity, please provide data obtained from thrombin drug product samples prepared without calcium-containing excipients.
 - iii. Please provide robustness data for your method by evaluating the effect of variation of different analytical parameters of your assay on calcium concentration.

The review of this submission is ongoing, and issues may be added, expanded upon, or modified as we continue to review this submission. As the identified deficiencies require experimentation, please provide the *timeline* as to when the requested data can be generated and submitted to FDA for review as a consolidated response. Please submit the *timeline* as an amendment to this file by May 25, 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 if you have any questions.

Sincerely,

Yu Do, M.S.
Regulatory Project Manager
Office of Tissues and Advanced Therapies
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Office of Medical Products and Tobacco
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