

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Friday, April 7, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Thursday, March 23, 2017 3:50:00 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 at this time:

This is in reference to quality control assay for the drug product and the validation reports submitted under STN BL 125640/0.

1. Thrombin Evaluation by Coagulation Using (b) (4) :

a. Regarding Analytical Procedure IG MA-000457A_ING: Thrombin Evaluation by Coagulation using (b) (4) :

- i. In Section 4.1 of your SOP, you state that Thrombin secondary standard is used as both standard and control. If the same lot of the drug product is used as standard and control, it would amount to a circular reasoning. The control should be a different material at least from that of the drug product lot, which is different from the lot used as the standard. Please provide a detailed description of the standard and control used in this assay. If they are from the same lot of drug product, please provide your plan and timeline for qualification of a different lot of drug product to be used as control and submit the qualification data for review.
- ii. Please explain how your Reference Standard and Control and their values are qualified and assigned, respectively. Please provide representative sets of qualification data.

b. Regarding Method Validation Report IG_IVMA-000298_ING: Validation for Thrombin (Sealant) of Thrombin Determination by Coagulation (b) (4) :

i. For linearity, you have measured the slopes and correlation coefficients from the (b) (4) Standard for Thrombin, (b) (4).

Please provide data demonstrating linearity and parallelism between your in-house standard and your drug product.

ii. Please provide data assessing the robustness of your method.

2. (b) (4) Determination by (b) (4) in Fibrinogen Concentrates

- a. Regarding Analytical Procedure IG MA-000185C ING: (b) (4) Determination by (b) (4) in Fibrinogen Concentrates:
- i. Please provide a complete description of the secondary standard used in the assay, including how it is qualified. Please provide representative qualification data for the control.
- b. Regarding Method Validation Report: IG IVMA-FGDI185C_ING: Validation for (b) (4) Fibrinogen of (b) (4) Determination by (b) (4) in Fibrinogen Concentrates:
- i. You have studied linearity using the standard (b) (4) only. However, you have neither evaluated linearity of the drug product nor demonstrated parallelism between (b) (4) and the drug product. Please provide data on the linearity of the drug product and parallelism between concentration versus response plots of (b) (4) and the drug product.
 - ii. Please provide robustness data with respect to variations in critical method parameters.
 - iii. Based on your validation data of accuracy in Table 4 on page 10 of your validation report (IG_IVMA-FGDI185C_ING), the final assay concentration range should be (b) (4), based on the result of your accuracy study. You have studied precision and linearity over a wide range, while accuracy over a narrow range. Therefore, the assay range should correspond with whichever yields the narrower range. However, in the summary of validation report on page 13, you indicated a wider assay range of (b) (4) instead. Please revise page 13 of your validation report to indicate that your assay range is (b) (4) and submit for review.

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 April 7, 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.
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