

From: Do, Yu
To: ["Robertson, Joan"](mailto:Joan.Robertson@grifols.com)
Subject: RE: Information Request (Response for Items 1, 3, and 4) Due by Wednesday, March 29, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Thursday, March 16, 2017 1:55:00 PM
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[image018.jpg](#)
Importance: High

That would be fine. Thanks, Ms. Robertson, for letting me know.

Sincerely,

Yu Do, M.S.
Regulatory Project Manager
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration
(240) 402-8343
Yu.Do@fda.hhs.gov



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From: Robertson, Joan [mailto:Joan.Robertson@grifols.com]
Sent: Thursday, March 16, 2017 1:26 PM
To: Do, Yu
Subject: RE: Information Request (Response for Items 1, 3, and 4) Due by Wednesday, March 29, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.

Yu,

I acknowledge receipt. I will get back to you with a date for item 2, which will likely affect the date

for item 3 as the eCTD can't be updated until the response to item 2 is complete.

Thanks,

Joan

Joan Robertson

Grifols Shared Services, NA
Vice President
Regulatory Affairs, Bioscience
Phone: (919) 359-7128
Mobile: (919) 308-9435
Fax: (919) 359-7304
8368 US 70 Bus. Hwy W
Clayton, NC, USA 27520

From: Do, Yu [<mailto:Yu.Do@fda.hhs.gov>]

Sent: Thursday, March 16, 2017 1:19 PM

To: Robertson, Joan

Subject: Information Request (Response for Items 1, 3, and 4) Due by Wednesday, March 29, 2017):
Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.

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:

1. Please provide additional documents related to materials that are used in the manufacture of Human Thrombin.
 - a. *Certificate of Analysis* from the supplier for (b) (4). Please provide the protocol and results, including the examples of (b) (4) test for analysis of (b) (4).
 - b. *Certificate of Analysis* from the supplier for SP Sepharose XL. Please provide the protocol and results, including the examples of spectra, for IR identification test for analysis of SP Sepharose XL.
2. With regard to the analytical procedure FIBRINOGEN (CLOTTABLE PROTEIN) DETERMINATION BY (b) (4) (IG_MA-000888_ING) and VALIDATION FOR FIBRINOGEN (SEALANT) OF FIBRINOGEN (CLOTTABLE PROTEIN) DETERMINATION BY (b) (4) (IG_IVMA-000408_ING, Version 2.0):
 - a. Please provide the description of *Secondary standard for Fibrinogen control*, which is used in the protocol IG_MA-000888_ING. The additional data related to the Secondary standard for fibrinogen control should include the following information:

- i. Preparation, storage, and stability of the standard
 - ii. Calibration against the current International Standard
- b. The system suitability acceptance criteria in the protocol IG_MA-000888_ING include the criterion for CV ((b) (4)) for samples and Fibrinogen control. However, please note that the CV is reflecting only the precision, not the accuracy of the assay. Please add to the protocol an additional criterion for the range of the Fibrinogen control.
- c. Please provide the description, and clarify the usage, of *Secondary standard as (b) (4)* (IG_MA-000888_ING, page 3).
- d. Please provide the description of (b) (4) *standard* (IG_MA-000888_ING, page 3).
- e. Please provide justification for the correction factor (b) (4) used for the calculation of Fibrinogen (Clottable Protein).
- f. Based on the submitted validation report (IG_IVMA-000408_ING), the range of the assay is (b) (4) of Fibrinogen (Clottable Protein). Please add the criterion for each sample after the dilution step to be within the range of the assay in protocol IG_MA-000888_ING. This acceptance criterion is currently not included in the submission.
- g. Specificity
Description of the procedure for Specificity is unclear. Please clarify if you treated the specificity solution (formulation buffer) exactly the same way as the samples. Also, please include in the study the results obtained for clot formation with the formulation buffer (without fibrinogen).
- h. Linearity
In the current version of the validation report IG_IVMA-000408_ING, the parameters in X and Y axes in Tables 2 and 3 are identical and defined as % (w/v) Fibrinogen (clottable protein). Please clarify the definitions of “Concentration” and “Response” and adjust the labeling of axes in the results for Linearity.
- i. Accuracy
In the validation report IG_IVMA-000408_ING, the Accuracy study was performed with (b) (4) Standard for Fibrinogen at (b) (4). Also, the study did not address the effect of excipients on the assay.

Please provide the experimental data to assess the potential effect of excipients in the Final Drug Product formulation on the Accuracy of the assay. Also, please assess the Accuracy at minimum three concentration levels covered by the range of the procedure. Ideally, such tests should be performed in the presence of appropriate concentration of the excipients. Please follow the recommendations in the ICH Q2 (R1) Guidance.

j. Precision

Please clarify how you have determined the acceptance criterion for Precision “(b) (4).”

k. Robustness

Please provide data for evaluation of the robustness of the assay.

3. Please update the relevant documents in the eCTD file after addressing the above requests.
4. Please update the Section 3.2.P.6. Reference standards or Materials with description of all standards, which are in use for Control of Drug Substance and Drug Product.

References:

U.S. Food and Drug Administration, guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (2015).

Guidance Document, International Conference on Harmonization Q2 (R1) *Validation of Analytical Procedures: Text and Methodology* (March 1995; May 1997).

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 to **Items 1, 3, and 4** as an amendment to this file by **March 29, 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.

For Item 2, please estimate time and inform me of the date by which you would be able to provide response.

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
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration
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Yu.Do@fda.hhs.gov

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