

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Wednesday, July 5, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Thursday, June 15, 2017 4:46:00 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 determined that the following information is necessary to continue our review:

Please provide clarifications and address the following deficiencies identified with Drug Product (DP) Specifications:

1. Please include the parameter *Total Protein* in the Specifications for Fibrinogen, to be consistent with your characterization, validation, and stability studies. Including this parameter in the Fibrinogen Specification will provide a tool (% Clottable Protein) with which to monitor process consistency and product quality during commercial manufacturing.
2. Please revise the Specification for *Appearance of Solution* (both components) as follows: "Colourless or pale yellow solution, essentially free of visible particles."
3. Since your proposed acceptance criteria for *Fibrinogen (Clottable Protein)* and *Thrombin Activity* are wide, please re-evaluate these acceptance criteria based on statistical analysis of available manufacturing data, and tighten the ranges accordingly.
4. We note that the specification for Polysorbate 80 ((b) (4)) is much higher than that for TnBP ((b) (4)). Please justify this limit based on the capability of the assay and risk assessment of Polysorbate 80 level at the highest application dose.
5. The specification for *Volume* is stated as a limit of ((b) (4)) (depending on the fill size). Please express the acceptance criterion as a range based on your overfill studies.
6. Please note the FDA Final Rule regarding General Safety Test (GST) which removes 21 CFR §§ 610.11, 610.11a, and 680.3(b) regulations as duplicative of requirements of BLAs (Federal Register /Vol. 80, No. 127, July 2, 2015, page 37971 to 37974). You may submit a request with justifications to remove the *Abnormal Toxicity* test from the Drug Product Specification and Stability Program based on demonstration of GST compliance, adequate safety controls, and analytical techniques ensuring product safety.
7. We acknowledge your May 23, 2017, response related to the validation of the *Identification* test and *Verification of Functionality* test (Question 1). You demonstrated the specificity of these tests by replacing one or both components

with the specificity solutions to confirm absence of clotting. However, you did not provide data to demonstrate test applicability (i.e., sensitivity) within the entire ranges of *Thrombin Activity* and *Fibrinogen (Clottable Protein)*, which are wide (Question 3). Please perform additional studies with concentrations of both components at the lower limits of their specification ranges to justify that the proposed acceptance criterion for the (b) (4) can be met under worst-case conditions.

8. We acknowledge your May 23, 2017, response related to the extension of the shelf-life of your Thrombin secondary standards (Question 3). Please clarify if you used the (b) (4) Standard for Thrombin (b) (4) as the reference standard in the stability study for your Thrombin secondary standards.
9. We acknowledge your May 23, 2017, response related to the extension of the shelf-life of your Fibrinogen secondary standard (Question 4). The stability study for your Fibrinogen secondary standard batch (b) (4): communication EV151215/16 included the period from June to November 2015, whereas the shelf-life was extended to July 2017. Please provide the latest *Fibrinogen (Clottable Protein)* test result for this lot. Please include a requirement of periodic (e.g., annual) testing of your Fibrinogen secondary standard in protocol IG_IEST-000441_ING for standard qualification.
10. Please clarify if release testing of the product lot is performed immediately after DP assembly and sterilization, or after the final drug product has been frozen, and the kit is then thawed for testing.

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 5, 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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