

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Monday, September 18, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Friday, August 18, 2017 4:30:00 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 to continue our review:

1. We acknowledge receipt of Amendment 30, dated May 30, 2017, to the April 26, 2017 Information Request (Item 3) regarding validation of the lifetime of SP-Sepharose resin, used in the purification of Thrombin. However, we find this response inadequate. We note that Report IG_VS-001435 supports (b) (4) full-scale purification runs, while you plan to extend the maximum number of uses to (b) (4) runs within the BLA review. In order for FDA to grant (b) (4) runs for commercial production to allow release of subsequent lots, please submit for FDA review, as a separate document, a detailed Study Protocol based on the approach used in Report IG_VS-001435. In the Protocol, please:
 - a. Provide clear definitions and justifications of sampling points and controlled parameters, along their acceptance criteria (e.g., (b) (4) (b) (4)”) which are not explained in Report IG_VS-001435 and are not stated in Table 1 of Amendment 30.
 - b. Explain how (b) (4) is defined and calculated in Report IG_VS-001435, and include in the Protocol additional parameter (b) (4) (b) (4), if (b) (4) has a different meaning.
 - c. Clarify the frequency of analysis for (b) (4) in the eluate: Table 1 in Amendment 30 states testing for (b) (4) but testing for (b) (4). However, according to Addendum to Procedure IG_MP-000034 ING, all three parameters are in-process control tests to be performed at (b) (4).
 - d. Include a statement that, in case any of the controlled parameters do not meet the acceptance criteria before run (b) (4) reached, the use of resin should be stopped, and this final run will define the maximum number of runs to be allowed for commercial production.

Please note:

- e. If your testing algorithm will be every (b) (4) runs, then product lots “(b) (4)” can be submitted for CBER release only after lot “(b) (4)” is analyzed.

- f. Please submit an updated report IG_VS-001435 no later than October 1, 2017, with subsequent full-scale purification runs to demonstrate the validity of your protocol.
 - g. Information on the number of runs and results of column performance/cleaning efficiency should be submitted in annual reports until run (b) (4) is reached.
 - h. Small-scale studies may be warranted in the future if you plan a further extension of the maximal number of uses beyond (b) (4). Alternatively, you will need to submit an updated protocol for concurrent validation as a Prior-Approval Supplement.
- 2. The information on critical process parameters (CPP) and in-process control (IPC) tests, although described in the appendices to the Production Procedures and validation reports, is not presented in a consolidated format to adequately describe the manufacturing process in the BLA. To meet the FDA requirements for the eCTD structure, please submit, in a tabular format, lists of CPPs with acceptance ranges and lists of IPC tests with acceptance criteria for each step of the Fibrinogen and Thrombin processes. Please include references to the respective documents that justify the acceptance ranges/acceptance criteria. This information should be included in section 3.2.P.3.4.
- 3. Is the tip cap assembled with the syringe at Instituto Grifols, or are syringes received with tip cap in place? Please clarify. In addition, please provide details on how the tip cap is sterilized.
- 4. For syringes and stoppers which are received (b) (4), you perform a (b) (4) step. Please indicate why you perform a (b) (4) and if there are any detrimental effects on the syringes, stoppers, and components when undergoing (b) (4) (i.e., effects on (b) (4), levels of leachables, and functionality of the container closure system). What testing is performed to ensure there are no detrimental effects on the container closure components due to the (b) (4) step?
- 5. With regard to the applicator cannula, please indicate the incoming testing that is performed, along with its frequency of testing. In addition, please confirm that the supplier of the applicator cannula, (b) (4), is audited every (b) (4), as per SOP IG_MSP-001549_ING "Management of Raw Materials Suppliers."
- 6. You indicated in your response to Information Request (IR) dated February 6, 2017, specifically in regard to the IQ/OQ status of equipment that the (b) (4) will be replaced with a (b) (4) and that this new equipment is an (b) (4). Is this machine intended to perform a different function other than (b) (4)? Please clarify the function of the new equipment to replace the (b) (4).
- 7. During the Pre-License Inspection, we discussed your labeling process in which the syringes are labeled before the AQL for the visual inspection was completed and the potential issue this presents should the AQL fail as a re-inspection would require de-labeling. Please note and acknowledge that the process of de-labeling and re-labeling

syringes is considered as reworking/reprocessing. In your response to Item 5 in IR dated April 26, 2017, in regard to reworking and reprocessing for nanofiltration, you provided SOP IG_MSP-001940 "Procedure for reprocessing/reworking of Instituto Grifols products" for describing reworking/reprocessing for all manufacturing steps for all products. In this SOP, an additional SOP, IG_MSP-001941, was referenced for describing procedures for repackaging/relabeling processes. Please provide SOP IG_MSP-001941 for review. Additionally, please confirm that you are not seeking approval with this BLA for rework/reprocess with regard to labeling. Please note that if you plan to rework/reprocess with regard to labeling, you will need to submit a Prior-Approval Supplement to release the affected lot.

8. In regard to process limit of (b) (4) for the filling of Thrombin and Fibrinogen and the media fill data provided that includes the intervention of the change-over of thrombin and fibrinogen, please provide the time of fill that was simulated in the last five media fills that support the (b) (4) process limit.
9. Please provide the SOP or documentation that demonstrates compliance with the Quality System device regulation *21 CFR 820.20 Management responsibility*.

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 September 18, 2017, except for Item 1f, 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.

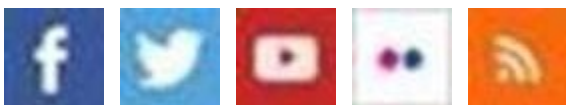
If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

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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