

**From:** Do, Yu  
**To:** [Joan.robertson@grifols.com](mailto:Joan.robertson@grifols.com)  
**Subject:** Information Request (Response Due by Tuesday, May 30, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.  
**Date:** Wednesday, April 26, 2017 12:53:00 PM  
**Attachments:** [image013.png](#)  
**Importance:** High

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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:

Please address the following process-related deficiencies identified during the BLA review and the pre-license inspection (PLI) of your facility:

1. The validation of the aseptic Filling process for Thrombin and Fibrinogen in the manufacture of Fibrin Sealant (Human), as presented in the document IG\_VS-001647 (linked report IG\_IVSP-001658), was found to be incomplete. Please submit an updated Validation Report which should include *all conformance and post-conformance batches manufactured to date* and additional data to address the identified deficiencies. Specifically, please:
  - a. Provide the *time limits* for each phase of aseptic processing, including limits for sterile filtration processes and product exposure on the filling line (time of fill). Please note that the time limits for each phase of aseptic processing should be established and supported by data that include process validation data, in addition to other types of data. In regard to sterile filtration, please note that the total time of product filtration should be limited to an established maximum and supported by the process capability. Please provide an updated version of the validation report IG\_VS-001647 to include the process time limits and results of the process times for each phase of aseptic processing (sterile filtration and filling) for the conformance lots provided to support the BLA submission, in addition to providing an overall process limit for aseptic processing of Thrombin and Fibrinogen.
  - b. Provide *validation data* representative of all fill sizes, including the minimal (1 + 1 mL) and maximal (2 + 2 mL) fill sizes in the 3-mL syringe, and the minimal (3 + 3 mL) and maximal (5+5 mL) fill sizes in the 5-mL syringe. During the PLI, you explained that these data are available. The validation data should include, but not be limited to, in-process controls (IPC) and results of IPC testing, release testing of final containers, assessment of filled batch uniformity by weight and quality parameters, aseptic process monitoring, and actual processing times, as specified in comments 1a and 1d.
  - c. When assessing *consistency of quality parameters* within the batch, perform statistical analysis of the data with pre-defined acceptance criteria, e.g., mean and CV, in addition to the assessment of quality parameters by compliance to the specification ranges.

Establish the processing times for the steps following the filling process

- d. (assembly, packaging, and sterilization) or *the overall processing time* from the start of sterile filtration to the point at which the final product is frozen. Please support the proposed time limits by providing actual processing times for all conformance and post-conformance lots in the report IG\_VS-001647, to demonstrate the process capability.
  - e. Submit *Stability Study Reports* for Fibrinogen and Thrombin that assessed the quality parameters during the overall processing time from the start of sterile filtration until the final product is frozen. If such report is to be submitted separately, please also include this reference in the report IG\_VS-001647.
  - f. Submit updated Production Procedures IG\_MP-000033 FIBRINOGEN FOR FIBRIN SEALANT and IG\_MP-000034 THROMBIN FOR FIBRIN SEALANT to include the validated processing times.
2. Please provide the three most recent media fill study report summaries that include the intervention of the change-over from Thrombin filling to Fibrinogen filling.
3. There was no proposed number of uses indicated in the BLA for Sepharose XL resin used for Thrombin purification. Please note that with the approval of the BLA, you would only be approved for the number of uses supported by the number of runs performed in the process validation. Report IG\_VS-001435 (linked report IG\_IVSP-001620), provided during the PLI, supported (b) (4) runs at full-scale only, whereas the assessment of the number of resin uses in small-scale studies was not performed. With regard to the number of uses for the Sepharose XL resin, please address and note the following:
- a. Please indicate the number of uses for Sepharose XL resin that will be intended for future manufacturing.
  - b. If you plan to extend the number of uses as part of the BLA review, please submit an updated report including *all subsequent purification runs at full scale* that compare column performance parameters against pre-defined acceptance criteria and also include the data relating to the cleaning efficiency, such as monitoring of (b) (4) performed after multiple runs.
  - c. If you intend to extend the number of uses beyond the data provided in the BLA (including the supporting data from subsequent purifications performed at full scale), please note the following: You may submit a Comparability Protocol (CP) as a Prior Approval Supplement, post-approval of the BLA, which provides a protocol for performing small-scale (laboratory-scale) studies covering the proposed, intended lifetime use of the resin for FDA review. The results from small-scale studies can support extension of the lifetime use of the resin before commercial-scale confirmatory studies are to be completed. Submitting a CP will allow a downgraded reporting category to submit the study results as a CBE-30 supplement, provided that the protocol is executed as initially proposed to, and reviewed by, the FDA.

4. The proposed Hold Time of (b) (4) Prothrombin Complex (PTC) of (b) (4) as the starting material for the manufacture of Thrombin is not supported by data. Stability data from the small-scale study indicate approximately a (b) (4) loss of Thrombin activity in PTC (Report IG\_IE-000167 ING) after (b) (4) or as worst-case scenario after (b) (4) of storage at (b) (4). In addition, the conformance lots of Thrombin were manufactured from PTC with the longest storage period of (b) (4). Please:
- Provide data that analyze the impact of the starting PTC age on the quality and stability of the final Thrombin component, and revise the Hold Time for (b) (4) PTC (b) (4) to (b) (4) in the Production Procedure IG\_MP-000034\_ING.
  - Consider storing the PTC at (b) (4) in the future in order to compare stability data for (b) (4) storage conditions. Please specify the container type that will be used for PTC storage for commercial production ((b) (4)).
  - Verify, for consistency with Thrombin, the Hold Time for (b) (4) Fraction 1 against the age of the starting material used in the manufacture of conformance and post-conformance lots of Fibrinogen.
5. The production processes for Thrombin and Fibrinogen include a nanofiltration step. According to your explanation during the PLI, if post-operation filter integrity test fails, re-processing at this step is not possible and not allowed. Please submit the respective SOP where this restriction (no re-filtration) is stated.
6. According to your explanation during the PLI, the manufacturing procedures for Thrombin and Fibrinogen allow for re-processing at the sterile filtration step if the filter integrity test fails. Please submit supporting data (release and stability) that evaluated the impact of repeated sterile filtration on the quality and stability of Fibrinogen and Thrombin.
7. In regard to the viral inactivation step, the acceptance ranges for Solvent/Detergent concentrations are too wide ((b) (4) of the target concentrations) and not centered: for TnBP % (v/v): (b) (4) (target 0.3%) and for Tween 80 % (v/v): (b) (4) (target 1%). Please provide an explanation on how these ranges were established and your justification of their acceptability; in addition, please consider tightening these acceptance criteria based on your accumulated manufacturing data.
8. During demonstration of the assembled syringes at the time of the PLI and examination of the samples provided to the review committee, it was noted that one of the two syringes in the smaller syringe presentation (3 mL fill) is loose and insecure in the syringe holder. Please:
- Provide the timelines for Laboratorios Grifols, S.A. to verify/adjust the measurements for the hook for a tighter fixation of the syringe in the syringe holder, and to implement these changes if needed.

- b. Include, in the visual inspection of the assembled combination product, an additional check for the tight fixation of both syringes in the syringe holder.
9. Please consider performing Container Closure Integrity Testing (CCIT), as part of the Stability Testing Protocol, on stability samples at the end of expiry, in addition to Sterility testing.
10. Please provide a copy of your SOP for batch codification/lot numbering system, and include it in Section 3.2.P.3.2.

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 May 30, 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.

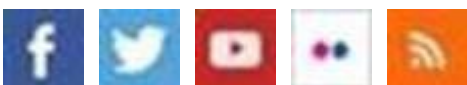
If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

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](mailto:Yu.Do@fda.hhs.gov) if you have any questions.

Sincerely,

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Regulatory Project Manager  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research  
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