

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Wednesday, September 13, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Thursday, August 17, 2017 3:48:00 PM
Attachments: [image013.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:

Your response to the July 25, 2017, Information Request does not address our question about the assessment of leachables in both components of the Final Drug Product (FDP). The submitted study report IG_MA-000678 describes the assessment of four organic compounds as potential leachables from polypropylene. This assessment is insufficient because it does not include the assessment of other materials (filters, membranes, etc.) that are used in close proximity to the respective filling steps at which there is no further purification to remove them. Also, the referenced document does not include data about the limit of detection of the assays for each analyzed compound. Hence, we have the following requests for additional information:

1. For each component of the FDP, please provide an assessment of the leachables from all materials used in the following steps of the manufacturing process for (1) Fibrinogen starting from Step 2.6 to the FDP and (2) Thrombin starting from Step 2.5 to the FDP. In this study, please also include an assessment of extractables and leachables from the applicator device (cannula).
2. Please provide an assessment of the cumulative leachables in the final containers of each component of the FDP performed at the end of its shelf-life stored under either real-time or accelerated condition.
3. Please list the detection limit of the assays for all the analyzed potential leachables, and justify that these assays are sufficiently sensitive to assure safe levels of these compounds in the FDP.
4. Please explain how you identified the (b) (4) of each (b) (4) in the analyses of samples described in document TO-MA-0174-1.
5. Please provide more details on the procedure used in your extractable/leachable studies (reports IG ITEC-002265_ING and IG ITEC-002201_ING). In particular:
 - a. Please clarify if fibrinogen and thrombin components were in contact with the stopper during storage at -20 °C (to create a worst-case condition), or only with the tip (representing normal storage conditions)
 - b. In Report IG ITEC-002265_ING, you state, “one (b) (4) tip cap and one (b) (4) plunger stopper were soaked, separately, in a 10 mL (b) (4) syringe, with different volumes of each product separately.”

Please clarify the duration and temperature condition for the soaking step.

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 13, 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.

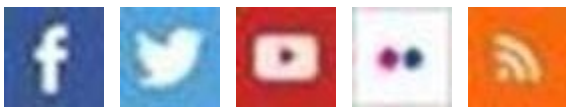
If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

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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