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**Cc:** [kelly.smith@grifols.com](mailto:kelly.smith@grifols.com)  
**Subject:** URGENT Information Request (Response Due by Monday, October 30, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.  
**Date:** Thursday, October 26, 2017 4:09:47 PM  
**Attachments:** [image001.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 to continue our review:

We acknowledge receipt of the Amendment 61 dated October 24, 2017, which contains your rationale for the proposed language for the PREA Postmarketing Requirement (PMR) study. To adhere to the agreement reached during the Late-Cycle Meeting, please:

1. Develop a single PREA PMR study protocol, which should include protocols for both the pediatric clinical study and the Human Factors (HF) assessment as in the preliminary stage. Please follow the specific recommendations given below for the HF study when developing these protocols.

2. Propose the language and timelines for the combined PREA PMR study, which should include the following three milestones in a “month-day-year” format:

Final Protocol Submission Date (Submission of final protocol in the March to April 2018 time frame would be acceptable to FDA.)

Study Completion Date

Final Report Submission Date

3. Propose the timelines for the HF assessment within the study protocol, e.g., Study Completion Date and Final Report Submission Date.

You may use the current language for PREA PMR (per Amendment 61) as the basis. The timelines for the HF study, however, will need to be stated in the protocol, not as a separate set of PMR timelines.

### **Specific Recommendations:**

#### Comment 1

Based on your submitted Human Factors/Usability (HF/U) validation protocol of conducting your test in a simulated use environment and based on your proposed timeline, it appears that you intend to conduct the HF/U study separate from the planned pediatric clinical trial instead of as a subpart to the pediatric clinical trial as was previously agreed upon. However, conducting your HF/U study separately may result in classification of this test to be a second PMR. Therefore, we recommend that you conduct a staged HF/U study that follows the phases of the pediatric clinical trial. For example, Phase 1 would include your HF/U test in a simulated use environment, while Phase 2 would include your final HF/U test in an actual use environment, incorporating relevant mitigations, if any, based

on your Phase 1 results.

Comment 2

You have provided in Table 4 (pages 10 to 11) a table of use-related hazards along with their assessed severity levels. You have also stated in Table 5 (pages 12 to 13) that the majority of your critical tasks are mitigated by the Instructions for Use. However, in your test plan and Predetermined Surveys (Annex 1 and Annex 2), you do not directly test the user's comprehension of these critical tasks. As an example to facilitate your understanding, the third line in Table 4 (page 10) states that "thawing temperature exceeding 37 °C" would cause "fibrin clot incorrectly formed." However, it does not appear that you test this critical task in your protocol. The Agency requests in the 2016 Human Factors guidance for industry that those critical tasks that cannot be assessed by simulated use testing should be assessed via knowledge-based comprehensive tasks, so that all critical tasks may be appropriately assessed. Please provide an updated HF/U study plan that includes knowledge-based comprehensive tasks that will appropriately challenge user understanding of relevant critical tasks.

Comment 3

You have stated, "the study will involve at least 10 nurses (Group 1) and 10 surgeons (Group 2) according to their different roles in performing critical tasks correctly for use the product in a safe and effective manner" (page 7). The Agency requests in the 2016 Human Factors guidance for industry that, if the device has more than one distinct population of users, then the validation testing should include at least 15 participants from each user population. The FDA views user populations as distinct when their characteristics would likely affect their interactions with the device or when the tasks they perform on the device would be different. As it appears that surgeons and nurses will have different roles in performing critical tasks, please plan to recruit and test at least 15 nurses and 15 surgeons.

Comment 4

You have provided a description of the training and study overview that you plan to provide to your HF/U participants, which will include "a study presentation with chart-diagrams of product preparation..." (IG\_PETC-000430\_ING v1.pdf, page 7). However, it is unclear whether this study presentation will correspond to real-world training expectations. The 2016 Human Factors guidance for industry states that "the training provided to the human factors validation test participants should approximate the training that actual users would receive" so that study results will be as accurate as possible. Please describe whether your planned training and study overview will be real-world representative; if not, please modify your HF/U protocol to reflect expected training practices.

If you have any questions regarding these comments, please be prepared to ask them at the teleconference scheduled for Friday, October 27, 2017.

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 (language and timelines for PREA PMR) as an amendment to this file by October 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,

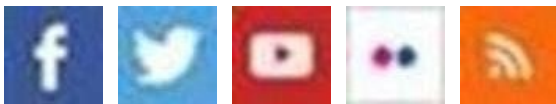
we will notify you in writing.

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,

Yu Do, M.S.  
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Office of Tissues and Advanced Therapies  
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