

RECORD OF TELEPHONE CONVERSATION

Submission ID: BL 125640/0
Review Office: Office of Tissues and Advanced Therapies (OTAT)
Product: Fibrin Sealant (Human)
Proposed Indication: An adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Fibrin Sealant (Human) is effective in heparinized patients.
Applicant: Instituto Grifols, S.A. (IG)

Date/Time: October 27, 2017, 10 AM, EDT
Initiated by FDA? Yes.
Telephone Number: 1-213-204-8852, Conference ID 15219902
Author: Yu Do
Purpose: To have discussion and reach consensus with the applicant, regarding the language for PREA PMR in which a new Human Factors study is to be a part of the planned pediatric clinical trial.

FDA Participants:

Natalya Ananyeva, PhD, Division of Plasma Protein Therapeutics, Office of Tissues and Advanced Therapies (OTAT)
Yu Do, MS, Division of Regulatory Project Management, OTAT
Rita Lin, MS, Office of Device Evaluation, Center for Devices and Radiological Health
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IG Participants:

Salvador Grancha, Vice President, Research & Development
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Sònia Amorós, Director, Global Regulatory Affairs
Joan Robertson, Vice President, Regulatory Affairs
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Summary of Discussion

FDA acknowledged receipt of Amendment 61, dated October 24, 2017, and stated that the proposed PREA PMR language, which references two different protocols [for pediatric clinical trial and Human Factors (HF) validation study] and includes two separate sets of timelines, implies two independent post-marketing studies. FDA stated

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that this would be contrary to the agreement reached during the Late-Cycle Meeting (LCM) on August 31, 2017, in that the HF study was supposed to be a part of the pediatric clinical trial. Two options were proposed to the applicant by FDA for consideration:

1. To combine the protocols for pediatric study and HF assessment into a single protocol, which will be considered by FDA as a single PREA PMR, with the HF study being conducted during the preliminary stage of the study. This option is consistent with the agreement reached during the LCM.
2. To perform the HF study as an independent, stand-alone study, which will constitute another reportable PMR (considering it is related to the safety of the device) with a separate set of timelines, in addition to the deferred PREA PMR pediatric clinical trial.

The applicant recognized the consequences of performing two separate studies and chose to have one PMR, instead, under a single consolidated protocol, as this makes the process more streamlined and efficient. The applicant stated that the HF component (in a simulated use environment) would be conducted in the initial or preliminary stage. The applicant will proceed to a clinical use setting with patients only if no issues or problems arise. Otherwise, the HF portion must be repeated until its outcome is satisfactory, and the clinical study will be modified in accordance with the results obtained from this portion of the protocol. In summary, the study with patients will commence only after the HF assessment has been successfully completed.

FDA emphasized that the applicant should state the three milestone dates (Final Protocol Submission, Study Completion, and Final Report Submission) as part of the PREA PMR language and be sure to include the timelines for the HF validation study within the combined protocol. The applicant acknowledged and agreed to submit the revised language for PREA PMR on Monday, October 30, 2017.

Furthermore, FDA offered the following comments to provide guidance for the HF study design:

The Table 4 (pages 10 to 11) in the submitted Human Factors/Usability validation protocol provided a litany of use-related hazards along with their assessed severity levels. The applicant stated in Table 5 (pages 12 to 13) that majority of the critical tasks are mitigated by the Instructions for Use. In the test plan and Predetermined Surveys (Annex 1 and Annex 2), however, the applicant does not appear to directly test the user's comprehension of these critical tasks. 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. The applicant needs to update the HF/U study plan to include knowledge-based comprehensive tasks that will appropriately challenge user understanding of relevant critical tasks.

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The study involving at least 10 nurses (Group 1) and 10 surgeons (Group 2) in accordance with their different roles in performing critical tasks correctly for use of the product in a safe and effective manner (page 7) is not adequate. 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. 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, the applicant should plan to recruit and test at least 15 nurses and 15 surgeons.

A description of the training and study overview that the applicant plans to provide to its HF/U participants is unclear in terms of whether this study presentation would correspond with 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. The applicant should describe whether its planned training and study overview will be real-world representative; if not, it needs to modify the HF/U protocol to reflect expected training practices.

Signature: _____

Drafted: Yu Do/November 1, 2017

Reviewed: Natalya Ananyeva/November 1, 2017

Reviewed: Rita Lin/November 1, 2017

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