

From: [Do, Yu](#)
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Monday, October 23, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Wednesday, October 18, 2017 5:09:52 PM
Attachments: [image001.png](#)
[FDA Annotated Labeling Text Version October 18 2017 IG.docx](#)
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:

Please revise the Prescribing Information according to the attached annotated version of the labeling and as follows. Please accept all those tracked changes with which you agree, but insert your own comments where further discussion is warranted. Please indicate clearly, point by point, whether you would accept each change or not. If not, please provide briefly your rationale or justification. Also, please be sure to submit in your response both clean and annotated versions of the revised labeling in Word and PDF files.

General recommendations are stated below, while more specific changes are proposed within the text of the Prescribing Information.

Section 2.2 Preparation and Handling:

- There are numerous bolded sub-headings throughout the PI. To avoid confusion with the numbered sections/sub-sections, please use underline, italics, or bullet point for these sub-headings as exemplified below:

“2.2 Preparation and Handling

Prepare and administer the product only according to the instructions and with the recommended devices.

Thawing

-

Room temperature

Thaw FIBRIN SEALANT (Human) at room temperature (20 °C - 25 °C, [68 – 77 °F]) for approximately eighty (80) minutes for the 2 mL and the 4 mL package sizes and one hundred twenty (120) minutes for the 6 mL and the 10 mL package sizes...

OR

2.2 Preparation and Handling

Prepare and administer the product only according to the instructions and with the recommended devices.

Thawing

- Room temperature

Thaw FIBRIN SEALANT (Human) at room temperature (20 °C - 25 °C, [68 – 77 °F]) for approximately eighty (80) minutes for the 2 mL and the 4 mL package sizes and one hundred twenty (120) minutes for the 6 mL and the 10 mL package sizes...”

- Please explain the rationale for spelling out numbers for time intervals, e.g., thirty (30) minutes. Please consider removing the spelling and leaving numbers only for time.

Section 2.2 Preparation and Handling and Section 2.3 Administration:

- For improved readability and clarity, please place each explanatory figure directly below the associated step, and improve the quality of all figures.
- Please double-check the movement direction for syringes (clockwise or counterclockwise) and indicate it by ARROWS in Figs. 5 and 6. Please verify which HAND would be optimal for the end-user to hold the syringe to allow such movement. In Figs. 5 and 6, same hand should hold the syringe if the movements are the same for the drip and spray applicators (currently shown in the right hand in Fig. 5 and left hand in Fig. 6). It is not clear whether Fig. 6 relates to the spray applicator, or is the next step to Fig. 5 for the drip application.
- Please revise Fig. 7 to show that the syringe is already connected to the applicator tip at this stage.

Section 4 Contraindications:

- Please delete the phrase regarding endoscopic and laparoscopic procedures for clarity/brevity: The latter part of the statement is sufficient to communicate the concern about maintaining the recommended distance from the bleeding site. Please revise the same sentence in the Highlight section under CONTRAINDICATIONS accordingly.

Section 5.2 Gas or air embolism:

- The deleted sentence was confusing. Please change this entire sentence to “Do not spray in confined spaces.” Please change the same sentence in the Highlights section accordingly.

Section 6.1 Clinical Trials Experience:

- In all Adverse Reactions tables, the System Organ Class columns are not informative for health care providers or patients. Please use only MedDRA preferred terms and whenever feasible, a term easier for patients to understand [e.g., pyrexia (fever) or hypokalemia (low serum potassium)].

Section 8.1 Pregnancy:

- Please delete the statement of systemic absorption in favor of the sentence that

describes the background risks of birth defects/miscarriage. Per the PLLR Guidance, this statement should only be included when there are data to demonstrate that the product is not systemically absorbed. You did not evaluate systemic absorption in nonclinical studies.

Please note FDA may have additional comments, based on review of the revised labeling included in your response.

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 October 23, 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.
Regulatory Project Manager
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration
(240) 402-8343
Yu.Do@fda.hhs.gov



"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the

content of this communication is not authorized. If you have received this document in error, please immediately notify the sender by e-mail or phone."