

From: Do, Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Monday, September 25, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Friday, September 08, 2017 1:58:00 PM
Attachments: [image001.png](#)
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, regarding your stability program, to continue our review:

1. We note inconsistency in the description of storage conditions in Report IG-IE-000217_ING (range of -21 (b) (4) °C), Stability Protocol Document IG_PE-000128_ING (range of -20 (b) (4) °C), and the intended long-term storage condition in the description of product shelf-life (temperature of = -18 °C, Section 3.2.P.8.1). Please explain how this proposed long-term storage temperature (= -18 °C) was chosen.
2. In Document IG_PE-000128_ING, please:
 - a. Update the monitored parameters according to the updates made to Drug Product Release Specifications (i.e., adding *Total Protein* test at the “0” and “24-month” time points and removing (b) (4) test). Please also include the parameter “*Volume*” to be tested at the “0” and “24-month” time points to demonstrate that the required amounts of biologics can be delivered at the product expiry.
 - b. Update the description of acceptance criteria for “*Appearance of Solution after Thawing*,” consistent with the Release Specifications. Please use the USP terminology “Colourless or pale yellow solution essentially free of visible particulates” to be consistent with your actual visual inspection. Alternatively, please justify your position not to include the description “visible.” We note that in the Release Specifications, you use a general definition “essentially free of particles.” If you choose to use the USP terminology, then please update the description of this parameter in the Release Specifications as well.
 - c. In Section 1, *Objectives* and Section 6.1, *Samples*, you state that in routine (ongoing) studies, “an (b) (4) lot of product, randomized and alternating in different presentations each year (2 mL, 4 mL, 6 mL and 10 mL) will be studied.” Please revise this statement to reflect the alternation in both fill volumes and syringe sizes, e.g., “an (b) (4) lot of product, randomized and alternating in fill volume and syringe size (b) (4), will be studied: 2 mL (1+1 mL), 4 mL (2 + 2 mL) in 3-mL syringes, and 6 mL (3 + 3 mL) and 10 mL (5 + 5 mL) in 5-mL syringes.” The purpose of this clarification is to ensure that (b) (4) testing of the product in the 3-mL and 5-mL syringes is performed in an alternating manner.
 - d. Please note that results of routine (ongoing) stability testing should be

submitted for FDA review in Annual Reports.

3. In Report IG_IE-000222_ING, *Fibrin Sealant (FS) Grifols. Stability Study after Product Thawing*, you state, “a limit of = (b) (4) is assigned for (b) (4) content in Fibrinogen component immediately after thawing. A limit of = (b) (4) is assigned for the stability ‘in use.’” Please clarify how the limit of = (b) (4) for (b) (4) was established and justify its acceptability.

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 25, 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.

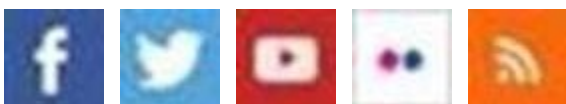
If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

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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