

From: Do.Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Thursday, October 12, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Thursday, October 05, 2017 4:18:11 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 to continue our review:

We acknowledge receipt of Amendment 44 (eCTD Sequence No. 43) dated September 13, 2017, which summarized study reports and results of risk assessments of potential extractables/leachables from product-contacting surfaces during the manufacture, and from the container closure system and application device. Please provide the following information to justify the validity of your study results:

1. Your study reports for assessment of leachables in the product containers and application device do not have information about assessment of recovery of organic compounds from aqueous solutions upon extraction into the organic phase for further analysis, and whether the respective factors were applied to calculate the concentrations in the parental samples. In particular, a low recovery factor can result in underestimation of the respective leachable in the drug product, which, in turn, would result in incorrect assessment of the risk for patients.

Therefore, please provide such information for each potential leachable and confirm that the respective correction factors were applied for quantitation and safety assessments.

2. In your response to our question 3 (Amendment 44, dated September 13, 2017), you stated that the detection limits of (b) (4) identified organic leachables from final containers were (b) (4) (i.e., (b) (4)), Table 4, page 14), which were likely applicable to other (non-detected) organic compounds. From our experience, using (b) (4) methods for analysis of organic compounds, the detection limits are typically (b) (4) (i.e., (b) (4)) that generally result in detection of a significantly higher number of leachables. Indeed, in your study of leachables from the application device, the concentrations of identified compounds were in the range of (b) (4) (i.e., (b) (4)), report IG_ITEC-002666_ING, Tables 8 to 11).

Therefore, please comment on the relevance and sensitivity of your analytical methodology for the intended purpose, particularly with regard to the possibility that other leachables, while being present in the product, were not detected in your studies performed on final containers.

3. It appears that you have applied the correction factor twice for the non-volatile leachables. According to pages 13 and 14 of 31 in report IG_ITEC-002666_ING, the calculation of (b) (4) was performed by applying a “(b) (4)”

(b) (4)

. However, in Table 11 (on page 18 of 31) under “Corrected concentration ($\mu\text{g/L}$),” an additional correction factor, due to pre-concentration, is applied. Please check the calculations for accuracy.

- a. If the amounts are adjusted upward, please submit a complete toxicological assessment of the leachables identified. Links to peer-reviewed publications should be accompanied by critical assessment of the studies performed by qualified toxicologist(s).
4. Please indicate sections in the BLA that discuss potential leachables from the storage containers of the starting materials and process intermediates (Fraction I, 3rd Glycine Precipitate, (b) (4) PTC Eluate, and Thrombin (b) (4) Solution), or summarize this information 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 12, 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





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