

**From:** Do, Yu  
**To:** ["Robertson, Joan"](#)  
**Subject:** RE: Information Request (Response Due by Friday, December 2, 2016): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.  
**Date:** Tuesday, November 22, 2016 12:26:00 PM  
**Attachments:** [image007.png](#)  
[image013.png](#)

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Thanks, Ms. Robertson, for your acknowledgement.

Please note the correction in the subject line.

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](mailto:Yu.Do@fda.hhs.gov)



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**From:** Robertson, Joan [mailto:Joan.Robertson@grifols.com]  
**Sent:** Tuesday, November 22, 2016 12:22 PM  
**To:** Do, Yu  
**Subject:** RE: Information Request (Response Due by Friday, November 28, 2016): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.

I acknowledge receipt.

Thanks

**Joan Robertson**

Grifols Shared Services, NA  
Vice President  
Regulatory Affairs, Bioscience

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**From:** Do, Yu [<mailto:Yu.Do@fda.hhs.gov>]  
**Sent:** Tuesday, November 22, 2016 12:15 PM  
**To:** Robertson, Joan  
**Subject:** Information Request (Response Due by Friday, November 28, 2016): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.  
**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 request for additional information to continue our review:

1. For all three studies, IG1101, IG1102, and IG1103, the Legacy SDTM dataset define files open only as a xml file.

Please provide these files as define.pdf for all three study data.

2. The Fibrin Sealant Grifols meets the legal definition of a biologics/device combination product (21 CFR Part 3). As you know, 21 CFR Part 4 (Subpart A) addresses the Current Good Manufacturing Practice (CGMP) requirements for all combination products; this final rule was codified on January 22, 2013. Prior to this final rule, manufacturers of co-packaged combination products had to comply with all of the CGMPs associated with each of their constituent parts. 21 CFR 4.4(b) serves as a regulatory option for such manufacturers, which eliminates some of the redundancies associated with the establishment of multiple CGMP operating systems, and thus provides some regulatory relief to co-packaged combination product manufacturers. Please address the following items with regard to the device constituent parts of the Fibrin Sealant Grifols:
  - a. Please provide the design and development plan(s), or a summary of the plan(s), for the device under review as per CFR 820.30(b). Your design and development plan(s) or summary should describe/reference and assign responsibility for the implementation of the following elements:
    - Design Inputs
    - Design Outputs
    - Design Review
    - Design Verification
    - Design Validation
    - Design Transfer
    - Design Changes
    - Design History File

- b. Please provide a summary of the procedures used for the identification and control of design inputs as per CFR 820.30(c). Information provided should include how design inputs are documented, reviewed, and approved.
- c. Please provide a summary of the procedures used to define and document design outputs in terms that allow an adequate and measurable evaluation of the conformance to design inputs as per CFR 820.30(d). Information provided should contain design output acceptance criteria. In addition, please explain the mechanism used to ensure that you have identified those design outputs that are essential for proper function of the device.
- d. Please provide a summary of the procedures that define and control the design reviews as per CFR 820.30(e). Information provided should explain how formal design reviews are planned and how you ensure that formal design reviews are conducted at appropriate stages of the design and development process.
- e. Please provide a summary of the procedures used to verify the device design as per CFR 820.30(f). Information provided should describe the process for confirming that the design outputs have met the design input requirements, and the mechanism for resolving any discrepancies.
- f. Please provide a summary of the procedures used to validate the device design for the device under review as per CFR 820.30(g). Information provided should define the method of recording design validation for the design history file and include:
  - Validation results
  - Identification of the design
  - Validation methods
  - Date(s) of validation
  - Individual(s) performing the validation
- g. Please provide a summary of the procedures for purchasing controls as per CFR 820.50. Information provided should describe: your supplier evaluation process; how you will determine type and extent of control you will exercise over suppliers; how you maintain records of acceptable suppliers; and how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. For additional guidance on the relationship between purchasing controls and receiving acceptance activities, please see the Quality System (QS) regulation preamble comment #99 [61 FR 52624].
- h. Please provide a summary of the procedures for your corrective and preventive action (CAPA) system as per CFR 820.100. Information provided should explain how your CAPA system is tied to your risk management program. For additional discussion on this topic, please see the QS regulation preamble comment #159 [61 FR 52633-52634].

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 December 2, 2016, 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.  
Regulatory Project Manager  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research  
Office of Medical Products and Tobacco  
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