

## Mid-Cycle Communication Summary

**Application Type:** Original Biologics License Application (BLA)  
**Tracking Number:** BL 125640/0  
**Product Name:** Fibrin Sealant (Human)  
**Proposed Indication:** An adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) 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. (Grifols)  
**Meeting Date:** April 27, 2017  
**Meeting Time:** 10 a.m. to 11 a.m., EDT  
**Committee Chair:** Natalya Ananyeva, PhD  
**RPM:** Yu Do, MS

**Purpose:** To provide a status update on the BLA review.

Your application is subject to “The Program” under PDUFA V, and the Mid-Cycle Communication is part of the PDUFA V “Program.” In accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the PDUFA V Program.

The Program evaluation for PDUFA V is now complete. Therefore, ERG will not be in attendance at this meeting.

### FDA Attendees:

Natalya Ananyeva, PhD, HB/DPPT/OTAT/CBER  
Yu Do, MS, DRPM/OTAT/CBER

### Instituto Grifols Attendees:

Sebastián Gascón, VP, Quality, Regulatory Compliance & Technical Director  
Juan Carlos Sánchez, Deputy Qualified Senior Manager  
Salvador Grancha, VP, Research & Development  
Maite López, Senior Manager, Laboratory and R&D Coordination  
Núria Jorba, VP, Manufacturing  
Jaume Ayguasanosa, Senior Manager, Clinical & Medical Affairs  
Jordi Navarro, Global Clinical Research Leader  
Junliang Chen, Director, Biostatistics and Data Management  
Sònia Amorós, Director, Global Regulatory Affairs  
Joan Robertson, VP, Regulatory Affairs

### Discussion Summary:

1. Any significant issues or major deficiencies identified by the review committee to date:

- No significant issues or major deficiencies have been identified by the review committee to date.
- Pre-License Inspection of Instituto Grifols' facility in Barcelona, Spain was performed on March 15 to 24, 2017. Grifols' resolution plan to address the Form FDA 483 observations, received on April 12, 2017, is currently under review.
- To date, only one Fibrin Sealant (Human) lot was provided for CBER in-support testing. Please verify when the two additional lots will be shipped to FDA.

**Additional Discussion:**

Grifols stated that it will complete the release testing and associated documents of the two additional lots within the next two weeks. Grifols clarified that these lots are manufactured strictly for CBER in-support testing, and will not be released for sale.

FDA asked Grifols to submit the relevant documents associated with these two lots in an amendment to the BLA by May 15, 2017. After review of the information, FDA will request samples of these two lots for testing and provide the shipping address.

Grifols agreed to the proposed plan.

2. Information regarding major safety concerns:

- No major safety concerns have been identified at this time.
- As stated in the February 3, 2017, *Proprietary Name Non-acceptance Letter* and clarified during the April 25, 2017, teleconference, the proposed proprietary name VERASEAL was found unacceptable due to its potential to pose high risk of medication errors and its promotional tone.

**Additional Discussion:**

Grifols will discuss internally and inform FDA of its decision on whether to propose an alternative proprietary name, or to use only the proper name for the remainder of this BLA review cycle. Grifols acknowledged its understanding that a proprietary name is not required for approval.

3. Preliminary review committee thinking, regarding risk management:

- The current thinking of the review committee is that a *Risk Evaluation and Mitigation Strategy* (REMS) would not be required. However, additional pharmacovigilance activities may be recommended.

4. Information Requests (IRs) issued:

- CMC IR regarding testing of plasma for viral markers was communicated to Grifols on April 18, 2017.

Response to this IR, received on April 26, 2017, is currently under review.

- Clinical/Statistical IR regarding subgroup analysis in clinical trials IG1101, IG1102, and IG1103 was communicated to Grifols on April 19, 2017.

Response to this IR, received on April 26, 2017, is currently under review.

- Responses submitted in Amendments 15 through 24 are currently under review as well.

5. Any new Information Requests to be communicated:

- CMC (process-related): To address deficiencies in the validation of the filling step for Fibrinogen and Thrombin; for additional media fill studies that cover the change-over between the filling of Thrombin and Fibrinogen; and for validation data to support use time for Sepharose XL chromatography resin, hold times, and re-processing at the sterile filtration step.

This IR was issued on April 26, 2017, and Grifols acknowledged receipt.

- CMC (analytical): To address deficiencies in the validation of several analytical methods and revisions to the *Lot Release Protocol*.

These IRs are in preparation and will be issued in early May of 2017.

- The review is ongoing, and additional IRs may be issued as the need arises.

FDA advised Grifols to request a CMC-specific teleconference if clarification is warranted regarding these IRs.

6. Proposed date for the Late-Cycle Meeting (LCM):

- Instituto Grifols and FDA agreed to hold the LCM on Thursday, July 20, 2017, from 10:30 a.m. to 12 p.m., EDT. The format of the LCM (face-to-face or teleconference) will be determined by Grifols.

Grifols will inform FDA regarding the format of the LCM after discussing it internally.

7. Updates regarding plans for the Advisory Committee meeting:

- The current thinking of the review committee is that this BLA will not be presented at the *Blood Products Advisory Committee* meeting.
8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:
- The action due date for this BLA is Friday, November 03, 2017.