

## Late-Cycle Internal Meeting Summary

**Application Type and Number:** BLA, 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.  
**Meeting Date and Time:** August 10, 2017, 1 p.m. to 3 p.m.  
**Date of LCM with applicant:** August 31, 2017  
**Committee Chair:** Natalya Ananyeva, PhD  
**RPM:** Yu Do, MS

### Attendees:

### Review Committee

Discipline	Name/Organization	Attendance
Regulatory Project Manager (RPM)	Yu Do (RPMB1/DRPM/OTAT)	Yes.
Chair (Product/CMC, Validation of Manufacturing Process & Product Quality)	Natalya Ananyeva (HB/DPPT/OTAT)	Yes.
Product/CMC, Adventitious Agents Safety	Ze Peng (HB/DPPT/OTAT)	Yes.
Product/CMC, Analytical Methods and Raw Materials	Svetlana Shestopal (HB/DPPT/OTAT)	Yes.
Chemistry and Identification/Quantification, Extractables/Leachables, Consultant	Andrey Sarafanov (HB/DPPT/OTAT)	Yes.
QC, Test Methods, Thrombin and Heparin Assays	Grainne Tobin (LACBRP/DBSQC/OCBQ)	Yes.
QC, Test Methods, Lot Release Tests, and Method Validation	Ritu Agarwal (LACBRP/DBSQC/OCBQ)	Yes.
QC, Test Methods, CMC, and (b) (4)	Hsiaoling Wang (LACBRP/DBSQC/OCBQ)	No.
Product Quality and Lot Release Protocol/Testing Plan	Varsha Garnepudi (QAB/DBSQC/OCBQ)	Yes.
QC, Sterility and Endotoxin	Karla Garcia (LMIVTS/DBSQC/OCBQ)	Yes.
Facilities and Inspection, Reviewer and Inspector	Christine Harman (BI/DMPQ/OCBQ)	Yes.
DMPQ Consultant, Delivery Device	Deborah Trout (BI/DMPQ/OCBQ)	Yes.

<b>Discipline</b>	<b>Name/Organization</b>	<b>Attendance</b>
DMPQ RPM	Sarah Lee (ARB/DMPQ/OCBQ)	No.
CDRH Consultant, Engineering (Delivery Device)	Rong Guo (DAGRID/ODE/CDRH)	Yes.
CDRH Consultant, Human Factors/Usability	Rita Lin (DAGRID/ODE/CDRH)	Yes.
Pharmacology/Toxicology	John Jameson (PTB2/DCEPT/OTAT)	No.
Clinical Safety and Efficacy	Agnes Lim (GMB1/DCEPT/OTAT)	Yes.
Biostatistics	Min (Annie) Lin (DB/OBE)	Yes.
Bioresearch Monitoring (BIMO)	Bhanu Kannan (BMB/DIS/OCBQ)	Yes.
Pharmacovigilance/Epidemiology	Faith Barash (PB/DE/OBE)	Yes.
Labeling	Alpita Popat (APLB/DCM/OCBQ)	Yes.
Labeling, Proprietary Name Review	Oluchi Elekwachi (APLB/DCM/OCBQ)	No.

### **Additional Attendees**

Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies (OTAT)  
 Kimberly Benton, PhD, Associate Director for Regulatory Management, OTAT  
 Basil Golding, MD, Division Director, OTAT/DPPT  
 Ilan Irony, MD, Deputy Director (Acting), OTAT/DCEPT  
 Renee Rees, PhD, Team Lead, OBE/DB/TEB  
 John (Jay) Eltermann, Division Director, OCBQ/DMPQ  
 Lisa Stockbridge, PhD, Branch Chief, OCBQ/DCM/APLB  
 Tim Lee, PhD, Branch Chief (Acting), OTAT/DPPT/HB  
 Iwen Wu, PhD, Branch Chief (Acting), OTAT/DCEPT/PTB2  
 Ewa Marszal, PhD, Chemist, OTAT/DPPT/PDB  
 Lokesh Bhattacharyya, PhD, Supervisory Chemist, OCBQ/DBSQC/LACBRP  
 Nannette Cagungun, MS, PD, Branch Chief, OTAT/DRPM/RPMB1  
 Ramani Sista, PhD, Division Director, OTAT/DRPM

### **Late–Cycle (internal) meeting agenda:**

#### **1. Introduction and Overview: Application/Product [Natalya Ananyeva]**

Fibrin Sealant (Human) [FS Grifols: company's alternative name] meets the definition of a biologics/device combination product, Type 3, according to 21 CFR Part 3 with the primary mode of action being provided by the biologics (human fibrinogen and human thrombin).

FS Grifols is provided as a kit comprised of two pre-filled syringes containing sterile frozen solutions of Human Fibrinogen (component 1) and Human Thrombin with calcium chloride (component 2), which are assembled in a single syringe holder, intended for topical use. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biologics. When applied, the solutions mix and generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation cascade. An application cannula (Class I device) is co-packaged with the product for application by dripping. An optional spray applicator, a 510(k)-cleared Class II device, is supplied separately.

Both Human Fibrinogen and Human Thrombin are isolated from Source Plasma of U.S. origin, followed by a fractionation process based on the Cohn method and further purification. To ensure product safety, both Drug Substance components are subjected to treatment with organic solvent and detergent validated to inactivate enveloped viruses, and double nanofiltration validated to remove enveloped and non-enveloped viruses.

2. Substantive review issues/major deficiencies raised during review:

CMC: Validation of Manufacturing Process and Product Quality [Natalya Ananyeva]

The review of the assigned CMC information and data in the BLA is in the final stage of completion. No substantive issues with regard to the manufacturing process and product quality have been identified that could preclude approval, or impact the review timeline, of this application.

Process- and specification-related deficiencies identified in the course of review, for the most part, have been adequately resolved through Information Requests (IRs):

<b>IR Date</b>	<b>Response from Instituto Grifols: Amendment STN and Date</b>	<b>Issue</b>
December 15, 2016	125640/0.7 (Dec. 23, 2017); 125640/0.9 (Jan. 11, 2017)	Validation of the assembly of the combination product and Human Factors study reports
January 2, 2017 (Filing Letter)	125640/0.15 (March 9, 2017)	Changes in the manufacturing process (from clinical material to commercial production lots) with comparability reports; hold times
April 4, 2017	125640/0.23 (April 11, 2017)	Additional reports related to the Design History File, including reports on device functionality and usability (Human Factors studies)

April 26, 2017	125640/0.30 (May 30, 2017)	To address process-related deficiencies identified in the course of review and Pre-License Inspection
May 1, 2017	125640/0.28 (May 23, 2017)	To address deficiencies identified with validation of analytical methods
June 15, 2017	125640/0.33 (July 05, 2017)	To address deficiencies identified with Drug Product Specifications

In response to FDA's request, Instituto Grifols (IG) performed additional studies and analyses to validate the aseptic Filling process for Thrombin and Fibrinogen in the manufacture of FS Grifols. IG submitted an updated report which includes: (a) the definitions and time limits for the critical steps of aseptic processing and product assembly which are supported by actual processing times reflecting process capability; (b) the validation data expanded to represent all fill sizes, including the minimal (1 + 1 mL) and maximal (2 + 2 mL) fill sizes in the 3-mL syringe, and the minimal (3 + 3 mL) and maximal (5 + 5 mL) fill sizes in the 5-mL syringe; (c) statistical analysis of the data to confirm consistency of quality parameters of Fibrinogen and Thrombin within the batch ; and (d) the Total Processing Time (Filling and Packaging) until the final product is frozen, which has been established and supported by stability data. The manufacturing procedures were updated to include the validated processing times. This response also addresses the 483 observation #2.

There was no proposed number of uses for SP-Sepharose XL ion-exchange resin in the purification of Thrombin. Assessment of resin lifetime in small-scale studies was not performed, and available data from the full-scale purification runs covered only a limited number of runs ((b) (4)). IG submitted an updated report that contains data supporting the column performance and cleaning efficiency for (b) (4) commercial-scale runs (effective date of May 30, 2017). IG plans to continue concurrent validation at full-scale within the remaining review time to claim the maximum number of (b) (4) runs. The response is not satisfactory in that the Study Protocol for the full-scale validation of resin lifetime was not submitted. A request for an adequate protocol, along with proper recommendations, to allow the release of subsequent commercial lots will be communicated to the applicant via IR, and included in the meeting package before the external Late-Cycle meeting. Further extension on the number of uses would require a small-scale study. Such a study with (b) (4) resins is also warranted to justify the viral clearance capacity of this chromatography step.

The proposed Hold Time of (b) (4) Prothrombin Complex (PTC) of (b) (4) as the starting material for the manufacture of Thrombin was not supported by stability data. In response to FDA's request, IG performed an analysis of the impact of PTC age on the quality and stability of the final Thrombin component. The Hold Time was revised to (b) (4), which is consistent with the longest storage period of PTC used in the validation studies.

The manufacturing procedures for Thrombin and Fibrinogen have allowed for re-processing at the sterile filtration step if the filter integrity test fails. IG was asked to submit data that evaluate the impact of repeated sterile filtration on the quality and stability of Fibrinogen and Thrombin at small and full scales. As no industrial scale lots that underwent re-processing were manufactured, such supporting data are not available, and re-processing may not be allowed.

In response to FDA's request, critical reports related to the Design History File for this combination product, including those related to the functionality of the application device and usability studies, were submitted to the BLA file and are under review by CBER and CDRH reviewers. This addressed the deficiency (lack of usability studies) identified at the filing stage. Through the demonstration of the assembled device during the pre-license inspection and review of usability reports, additional recommendations were formulated to be included in the *Instructions for Use* during the labeling review. IG is committed to verifying/adjusting the measurements of the syringe holder for the 3-mL syringe for a tighter fixation of the syringe in the syringe holder by October 1, 2017. The request for an update will be included in the LCM briefing package.

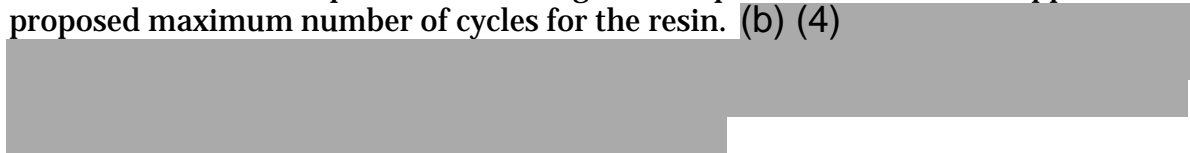
In response to FDA's request, IG included additional parameters to Drug Product Specification (*Total Protein* for Fibrinogen), revised specifications for *Appearance of solution (After Thawing)*, and *Volume* (ranges), and provided more detailed justification of specifications, which appear to be acceptable. *General Safety Test* will be removed based on the FDA Final Rule (Federal Register /Vol. 80, No. 127, July 2, 2015, pages 37971 to 37974).

In-Support testing has been completed in a timely manner by DBSQC, despite the late availability in June of the associated FS Grifols lots.

The remaining deficiencies may be resolved through IRs.

CMC: Adventitious Agent Safety Evaluation [Ze Peng]

No substantive deficiencies have been identified, which could preclude approval, or impact the review timeline, of this BLA. An IR has been recently issued regarding viral clearance studies performed with aged SP-Sepharose XL resin to support the proposed maximum number of cycles for the resin. (b) (4)



CMC: Analytical Methods and Raw Materials [Svetlana Shestopal]

There are no outstanding issues with regard to analytical methods or control of materials that could prevent approval, or impact the review timeline of, this BLA. All of the issues related to protocols and validation of the analytical procedures have been adequately addressed by the applicant via IRs listed below:

IR date	Response from Instituto Grifols: Amendment STN and date	Issue
January 2, 2017	125640/0.15 (March 09, 2017)	Analytical methods in clinical trials
March 16, 2017	125640/0.18 (March 30, 2017) 125640/0.22 (April 10, 2017)	<i>Certificates of Analysis</i> of chromatography resins  Fibrinogen Clottable protein method
March 23, 2017	125640/0.21 (April 07, 2017)	Thrombin activity and (b) (4) determination
May 01, 2017	125640/0.28 (May 23, 2017)	Fibrin Sealant identification/functionality test  Fibrinogen (Clottable protein) method  Thrombin and Fibrinogen secondary standards
June 15, 2017	125640/0.33 (July 05, 2017)	Fibrin Sealant identification test  Thrombin and Fibrinogen secondary standards

Specifically, IG provided clarifications and generated additional data to adequately validate *Clottable protein* assay for Fibrinogen, *Thrombin activity* assay, and *Functionality* test for the final product. One of the issues was the stability/shelf-life of the secondary standards for Thrombin and Fibrinogen. Also, the in-house secondary standards for Thrombin were calibrated against each other without reference to (b) (4) standards. IG performed the testing of the secondary standards for Thrombin, and the applicant is working on the qualification of a new standard for Thrombin. Additionally, this reviewer has reviewed and verified the information on raw materials in the BITS-ABC database.

CMC: Extractables and Leachables (E & L) in the Drug Product [Andrey Sarafanov]  
No substantive issues related to E & L have been identified to date. An IR was issued on July 25, 2017, to request additional information and documents related to methodologies used for the assessment of E & L in the Drug Product, and the applicant's response dated August 03, 2017 (Amendment 37) is currently under review. Based on consensus reached during an internal discussion, the applicant's response appeared to be inadequate and warrants additional information to be requested via IR and included in the meeting agenda for discussion at the external Late-Cycle meeting.

QC, Test Methods: Thrombin and (b) (4) Assays [Grainne Tobin]  
This discipline review is complete, and all of the issues have been addressed satisfactorily via IRs.

QC, Test Methods: Chemistry Assays for Excipients and Impurities [Ritu Agarwal]

There are minor issues that are pending for the following assays, which will be communicated to the applicant via an IR prior to the external Late-Cycle Meeting:

- Fibrinogen components - Glutamic acid (and glycine, arginine, isoleucine), and TNBP
- Thrombin components - TNBP

The issues related to the above assays are minor and should not affect the approval of this BLA.

QC, Test Methods: (b) (4) Analysis [Hsiaoling Wang]

The key issue still pending under this discipline is as follow: inadequate (b) (4) in the validation report for the (b) (4) assay in fibrinogen component of the Drug Product. An IR was issued on August 03, 2017, and its response is currently pending.

QC, Test Methods: Sterility and Endotoxin [Karla Garcia]

The review is complete, and all the pertinent questions have been addressed adequately by the applicant via IRs. The data submitted appear to be acceptable.

QC, Lot Release Protocol, and Testing Plan [Varsha Garnepudi]

This product is subject to the CBER's lot release process. The Lot Release Protocol (LRP) template has been reviewed, and an IR with comments for the template's revision was issued to the applicant on August 3, 2017. The draft of the Testing Plan for this product is a work in progress and will be completed once the LRP template, and the labeling that impact the Testing Plan, have been finalized.

CDRH Device and Human Factors/Usability Review

Device [Rong Guo]

No major issues have been identified regarding the syringe. The essential performance requirements of the syringe, including dose accuracy study and functionality of the syringe, were provided by the applicant. Minor issues raised during review with regard to the device part are as follows:

- There is no stability information for the syringe. The current stability batch is to be marketed as syringe presentation. The applicant should add a parameter of "Volume" in its stability protocol to demonstrate that the syringe can still deliver desired amounts of biological components at expiry.
- Tip cap removal force was not provided.

The applicant is committed to verifying and adjusting the measurements of the syringe holder hook for the 3-mL syringe for a tighter fixation of the syringe in the

syringe holder. *A request for an update on the progress of this investigation will be included in the LCM briefing package.*

Human Factors/Usability [Rita Lin]

The following deficiencies, identified during review, need to be addressed by the applicant:

1. You have provided your list of “parameters” in Table 2 of your Protocol. However, the criteria used to choose your critical tasks are not clear. Of note, since it is difficult to estimate probability of occurrence accurately in the pre-market stage, you should use severity level alone to identify the critical task associated with the subject device. Please describe the severity levels used in your use-related risk analysis in detail. Please provide your complete UFMEA document and present the criteria that you used to identify the critical tasks. If there are no critical tasks associated with the subject combination product, then you can provide the use-related risk analysis results as justification for not including Human Factors data as a part of the pre-market submission.
  - a. In your list of “parameters,” you have listed a few prompts that should be evaluated by use testing or knowledge tasks and not by self-evaluation. For example, “contraindications and warnings are clearly described” and “connection operations are adequately described in preparation instructions” do not give any objective evidence that the contraindications and warnings are clear and that the steps are adequately described. If these are critical tasks, they should aim to challenge the user’s knowledge and/or ability to locate the information. Please provide in more detail if this and like tasks will be evaluated via use testing, through knowledge test, or other applicable test. If appropriate, please conduct additional HF/U testing.
2. You have recruited five surgeons for your final HF/U validation study. However, FDA guidance states that a minimum of 15 participants per distinctive user group should be included in the HF validation study. Please adjust your protocol to include a minimum of 15 participants per distinctive user group and conduct additional HF/U testing as required.
3. You did not describe in detail the planned training provided to the test participants, including the content, delivery modes, and the length of time that will elapse prior to testing (decay window). Because retention of training decays over time, testing should not occur immediately following training; some period of time should elapse. Please provide a description of the planned training, if any, including content and delivery modes.
4. Under your Objective section, you stated that you plan to analyze the usability of the combination product regarding the intended uses “under the expected working conditions.” However, you have not described what the “expected



working conditions” are. The conditions under which simulated-use HF/U validation testing is conducted should be sufficiently realistic so that the testing results are generalizable to actual use. The need for realism is, therefore, driven by the analysis of risks related to the device’s specific intended use, users, use environments, and the device user interface. To the extent that environmental factors might affect users’ interactions with elements of the device user interface, they should be incorporated into the simulated use environment (e.g., dim lighting, multiple alarm conditions, distractions, and multitasking). Please describe your use environment.

5. You did not provide an analysis of known use problems with your predicate device or devices with similar user interfaces. You should address any known post-market human factors issues known to exist for using your device or similar devices. Examples of human factors issues include, but are not limited to, actions requiring substantial dexterity or strength, good visual acuity, or familiarity with uncommon practices. Information on post-market issues may be found by reviewing your internal user complaint files, the published literature, the FDA’s Medical Device Reporting (MDR) system, and FDA Safety Alerts and Public Health Notifications. The findings from this analysis would feed into your use-related risk analysis and ensure that you have done a thorough risk analysis. Please provide this analysis.
6. You did not provide details of how your performance data was analyzed, specifically if you have analyzed all instances of failures, close-calls, and difficulties in performing critical tasks. The protocol should include a subjective assessment portion, testing the user interface using open-ended questions. Please conduct root-cause analysis on the task failures, close calls, and difficulties and provide this analysis as well as proposed mitigations.
  - a. You have noted in your Discussion (page 20) that “there were some comments/suggestions to packaging and involving the Instructions for Use, mainly related to the product preparation.” Please evaluate whether any of these suggestions would mitigate use-related risks, such as being able to quickly and effectively prepare the product for use during surgery. If these suggestions are potential mitigations, please provide an explanation for why they were not pursued.

The following approaches for resolution of HF issues were discussed at the internal Late-Cycle Meeting:

- For FDA assessment of safety of product handling and administration, use the totality of data submitted in the BLA (according to FDA draft guidance on HF studies for combination products, February 2016), including the Risk Analysis report, Usability reports (after obtaining clarifications through IR), data from Part 1 of clinical trial design, and *Instructions for Use (IFU)* to be revised according to FDA recommendations from review and inspection.

- Request the applicant to conduct a new HF study with the revised IFU in order to address the above deficiencies. The review committee agreed that the new HF study can be performed as part of the deferred pediatric study.

*Recommendations for a new HF study and the request for revision of the Study Protocol will be issued to the applicant via IR before the external Late-Cycle meeting. The HF portion of this request will be included in the meeting agenda for discussion during the external Late-Cycle meeting.*

**DMPQ, Facilities and Equipment [Christine Harman]**

From the DMPQ perspective, there are no substantive issues or deficiencies at this time. The applicant's responses to the following IRs are currently under review:

- IR issued on February 6, 2017 (receipt of response on March 27, 2017, as Amendment 13) for additional information relating to equipment qualification and preparation of syringes for (b) (4) sterilization and (b) (4) testing of syringes
- IR issued on April 26, 2017 (receipt of response on May 30, 2017, as Amendment 30) for information relating to the filling process times, column re-use, media fill data, and container closure integrity testing and for clarifications of information discussed during the pre-license inspection
- IR issued on July 25, 2017 (receipt of response on August 1, 2017, as Amendment 36) for further clarification of the response to Observation 1c on the Form FDA 483

The pre-license inspection (PLI) was performed during period from March 13 to March 24, 2017, as a joint inspection with Team Biologics. A single Form FDA 483 was issued to include 17 observations, three of which were specifically associated with PLI. Additionally, some of the observations relating to the Quality System identified by the Team Biologics inspector are also relevant to BL 125640. The applicant provided its responses to the observations in Amendment 24 dated April 12, 2017. The responses were reviewed, and a follow-up IR was issued to seek clarification on the response submitted for Observation 1c. The applicant's response to this IR, submitted on August 1, 2017, as Amendment 36, is still under review. The response, however, appears to be acceptable after a preliminary review. Hence, the inspection will most likely be classified as VAI.

The classification of FS Grifols as a parenteral or non-parenteral product was discussed at the internal Late-Cycle Meeting. It was noted that the current definition of route of administration for fibrin sealant as "topical application" is not absolutely accurate: The definition implies application *onto the body*, while these products are applied onto the surface of organs *inside the body* and can be viewed more as parenteral. However, the risks associated with the use of fibrin sealants appears

lower, compared to parenteral products that are intravenously injected. FS Grifols is intended to be used locally, once per surgery, and in small volumes (10 mL maximum). CBER's current views will be applied during the labeling review and for verifying requirements for particulates during visual inspection of the filled syringes (setting an adequate Acceptance Quality Limit).

Pharmacology/Toxicology [John Jameson]

All nonclinical information submitted to this BLA has been reviewed, and no substantive issues from pharmacology/toxicology have been identified thus far.

Clinical [Agnes Lim]

The review of the clinical information and data in the BLA is in the final stage of completion. No substantive review issues or major deficiencies have been identified to date. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS). No PMRs or PMCs have been identified.

Overall, efficacy data from the three pivotal phase 3 studies (IG1101, IG1102, and IG1103) demonstrate that each study has met its primary efficacy endpoint; thus, study results from all three studies support the use of FS Grifols as an effective local adjunctive hemostatic agent in open surgery. The results of secondary efficacy endpoints in all three studies provide additional support for efficacy. In regard to safety, the collective results from all three studies demonstrate that FS Grifols was reasonably safe and well-tolerated as a local adjunctive hemostatic agent in various surgery types.

Based on review of the clinical information and study data submitted to this BLA, no substantive efficacy or safety issue has been identified from a clinical perspective for FS Grifols as an adjunct to hemostasis in adults for moderate bleeding when intra-operative control of bleeding by standard surgical techniques is ineffective or impractical. As stated at the Mid-Cycle meeting, the phrase “(b) (4) [REDACTED]” should be removed from the proposed indication statement due to deferral of pediatric study, which is a minor issue.

Statistics [Annie Lin]

The three pivotal studies were designed to evaluate the efficacy and safety of FS Grifols in three different surgery types: vascular surgery (Study IG1101, under IND 14988), parenchymous surgery (Study IG1102, under IND 14987), and soft tissue surgery (Study IG1103, under IND 14986).

In Study IG1101, the rate of hemostasis by 4 minutes after treatment application was significantly higher in the FS Grifols group compared to the manual compression group (p-value <0.001), indicating that FS Grifols is superior to manual compression in the ITT population for subjects undergoing vascular surgeries.

In Study IG1102, the rate of hemostasis by 4 minutes after treatment application was significantly higher in the FS Grifols group compared to Surgicel group (p-value =0.01), indicating that FS Grifols is superior to Surgicel in the ITT population for subjects undergoing parenchymous surgeries.

In Study IG1103, the rate of hemostasis by 4 minutes after treatment application in subjects receiving FS Grifols was non-inferior to Surgicel received subjects for patients undergoing soft tissue surgeries.

There is no statistical issue in this submission. The positive efficacy results from the three phase 3 confirmatory studies provided statistical evidence to show the hemostatic effect of FS Grifols and support the application of FS Grifols as an adjunct to hemostasis in surgery.

**Bioresearch Monitoring (BIMO)** [Bhanu Kannan]

To date, all four BIMO inspections are completed. The preliminary review of the inspection reports did not reveal any substantive issues that could preclude approval of this BLA. This discipline review will be completed after all the Establishment Inspection Reports (EIRs) are reviewed.

Bioresearch Monitoring Inspection Assignments for the following studies were issued on March 29, 2017:

**Study IG1101:** *A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis during Peripheral Vascular Surgery*

**Study IG1103:** *A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Soft Tissue Open Surgeries*

<b>Study</b>	<b>Site Number</b>	<b>Study Site</b>	<b>Location</b>	<b>Form FDA 483 issued</b>	<b>Status</b>
IG1101	407	Beer, Simon, William, Moody and Associates	Florence, Alabama	No	NAI*
IG1101	521	University of Belgrade Institute for Cardiovascular Diseases, Clinic for Vascular Surgery	Belgrade, Serbia	No	NAI
IG1103	322	Lotus Clinical Research, LLC.	Pasadena, California	No	NAI
IG1103	722	Clinical Center of Serbia, Urology Clinic	Belgrade, Serbia	No	NAI

\*NAI: no action indicated

Four BIMO clinical investigator inspections verified the data submitted in the BLA including, but not limited to, the protocol deviations, adverse events, and study drug infusions at the inspected clinical sites. All four inspections were classified as NAI.

Epidemiology/Pharmacovigilance [Faith Barash]

There are no significant risks identified from the submitted data, other than those noted below:

- Important potential risks: Tissue Adhesion, Air or Gas Embolism, Anaphylaxis, Thromboembolic Events, and Transmission of Infectious Agent (These are known risks for all fibrin sealant products and for products delivered by spray device.)
- Important missing information: Use in Pediatric populations and Use in Pregnant or Lactating Women

The PMR study is planned to address the use of FS Grifols in pediatric populations. No other PMR studies are anticipated at this time.

Labeling [Alpita Popat]

APLB labeling review memo with recommendations is complete. The first IR with comments for *Prescribing Information*, *Instructions for Use*, and labels is planned to be issued toward the middle of September.

3. Review of upcoming timeline/deadlines **[Yu Do]**

Late-Cycle meeting materials to be shared with IG – August 18, 2017

Late-Cycle external meeting (teleconference) – August 31, 2017

PeRC meeting – September 06, 2017

PMC and labeling review – October 05, 2017

Labeling negotiation – early to middle of September 2017

Completion of supervisory review - October 05, 2017

First action due – November 3, 2017

4. Assess status of the review, including plans for completing outstanding discipline reviews and any other remaining issues. **[Review Committee]**

Please see Item 2 for details.

5. This application will not be presented before the Blood Products Advisory Committee (BPAC). Also, there is no need to draft a BPAC waiver memo with regard to this product/application.
6. There is no anticipation of REMS (Risk Evaluation and Mitigation Strategy) or a PMR (Postmarketing Requirement) study other than the deferred pediatric study.

A potential PMC for the (b) (4)

7. Reach agreement on meeting materials. **[Natalya Ananyeva and Review Committee]**

The meeting package will be prepared by Yu Do and Natalya Ananyeva and routed to the discipline reviewers for review. This material needs to be signed off by the Director of DPPT before issuance.

8. Regulatory Project Manager will meet separately with the Committee Chair and management to reach agreement on agenda items to be discussed during the Late-Cycle meeting with the applicant. **[Yu Do, Natalya Ananyeva, and Tim Lee]**

Drafted: Yu Do / August 18, 2017  
Reviewed: Nannette Cagungan / August 18, 2017  
Revised: Natalya Ananyeva / September 4, 2017  
Reviewed: Deborah Trout / August 18, 2017  
Reviewed: Ilan Irony / August 18, 2017  
Revised: Ze Peng / August 28, 2017  
Reviewed: Andrey Sarafanov / August 31, 2017  
Reviewed: Karla Garcia / August 23, 2017  
Revised: Lokesh Bhattacharyya / August 18, 2017  
Reviewed: Grainne Tobin / August 31, 2017  
Revised: Ritu Agarwal / September 1, 2017  
Reviewed: Bhanu Kannan / August 31, 2017  
Revised: Min (Annie) Lin / August 31, 2017  
Reviewed: Renee Rees / August 31, 2017  
Reviewed: John Jameson / August 21, 2017  
Reviewed: Iwen Wu / August 31, 2017  
Reviewed: Rong Guo / August 23, 2017  
Reviewed: Rita Lin / August 31, 2017  
Reviewed: Alpita Popat / August 31, 2017  
Revised: Tim Lee / September 6, 2017  
Revised: Basil Golding / September 7, 2017  
Revised: Yu Do / September 8, 2017