

Mid-Cycle Meeting 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.
Meeting Date: April 13, 2017
Meeting Time: 2 p.m. to 4 p.m., EDT
Committee Chair: Natalya Ananyeva, PhD
RPM: Yu Do, MS

Review Committee:

Regulatory Project Manager (RPM) - Yu Do (RPM/BI/DRPM/OTAT)
Chair (Product/CMC, Validation of Manufacturing Process & Product Quality) – Natalya Ananyeva (HB/DPPT/OTAT)
Product/CMC, Adventitious Agents Safety - Ze Peng (HB/DPPT/OTAT)
Product/CMC, Analytical Methods and Raw Materials - Svetlana Shestopal (HB/DPPT/OTAT)
QC, Test Methods, Thrombin and (b) (4) Assays - Grainne Tobin (LACBRP/DBSQC/OCBQ)
QC, Test Methods, Lot Release Tests, and Method Validation - Ritu Agarwal (LACBRP/DBSQC/OCBQ)
QC, Test Methods, CMC, and (b) (4) – Hsiaoling Wang (LACBRP/DBSQC/OCBQ)
Product Quality and Lot Release Protocol/Testing Plan - Varsha Garnepudi (QAB/DBSQC/OCBQ)
QC, Sterility, and Endotoxin - Karla Garcia (LMIVTS/DBSQC/OCBQ)
Facilities and Inspection, Reviewer and Inspector – Christine Harman (BI/DMPQ/OCBQ)
DMPQ Consultant, Delivery Device – Deborah Trout (BI/DMPQ/OCBQ)
DMPQ RPM – Sarah Lee (ARB/DMPQ/OCBQ)
CDRH Consultant, Engineering (Delivery Device) – Rong Guo (DAGR/ODE/CDRH)
Pharmacology/Toxicology – John Jameson (PTBII/DCEPT/OTAT)
Clinical Safety and Efficacy – Agnes Lim (GMBI/DCEPT/OTAT)
Biostatistics – Min (Annie) Lin (TEB/DB/OBE)
Bioresearch Monitoring (BIMO) – Bhanu Kannan (BMB/DIS/OCBQ)
Pharmacovigilance/Epidemiology – Faith Barash (PB/DE/OBE)
Labeling - Alpita Popat (APLB/DCM/OCBQ)
Labeling, Proprietary Name Review – Oluchi Elekwachi (APLB/DCM/OCBQ)

Additional Attendees:

Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies (OTAT)
Kimberly Benton, PhD, Associate Director for Regulatory Management, OTAT
Mahmood Farshid, PhD, Deputy Division Director, OTAT/DPPT
Ilan Irony, MD, Branch Chief, OTAT/DCEPT/GMBI
Renee Rees, PhD, Team Lead, OBE/DB/TEB
Laurie Norwood, Deputy Division Director, OCBQ/DMPQ
Lisa Stockbridge, PhD, Branch Chief, OCBQ/DCM/APLB
Timothy K. Lee, PhD, Branch Chief (Acting), OTAT/DPPT/HB
Becky Robinson-Zeigler, PhD, Branch Chief, OTAT/DCEPT/PTBII

After introduction from the meeting participants, Natalya Ananyeva, the Review Committee Chair, provided a brief introduction of the product (FS Grifols - the applicant's internal product name) and moderated discussions addressing review issues from the various disciplines.

According to 21 CFR Part 3, FS Grifols is a biologics-device combination product, Type 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 on a single syringe holder and is 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 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, the manufacturing processes for both Drug Substance components have two virus clearance steps: solvent/detergent treatment for inactivation of enveloped viruses and double nanofiltration for virus removal, including non-enveloped viruses.

Report and Discuss:**1. Reviewer Reports:**

CMC: Validation of Manufacturing Process and Product Quality [Natalya Ananyeva]
The review of the submission is ongoing, and no substantive issues with the manufacturing process or product quality have been identified at this time.

The Pre-License Inspection (PLI) of the Instituto Grifols facility in Barcelona, Spain was performed during the period of March 15 to 24, 2017. The inspection was a combined PLI and cGMP inspection with Team Biologics. A single Form FDA 483 was issued on March 24, 2017, which included a total of 17 observations, three of which were specific to the PLI for FS Grifols (detailed by the DMPQ reviewer):

- a. The initiation of documentation of deviations, CAPAs, and change controls are inadequate.
- b. The processing times for critical manufacturing steps, including sterile filtration of Thrombin and Fibrinogen bulk, filling of syringes, and their assembly with plungers and syringe holder, preparation for and sterilization with (b) (4), and secondary packaging up to freezing of the final product, are not established or clearly defined.
- c. Aseptic techniques were not always optimally applied during aseptic operations that include filling.

In addition, two cGMP observations made for the licensed products, IGIV and Albumin, apply to FS Grifols as they fall under the Quality Systems and will need to be resolved in the course of this BLA review (detailed by the DMPQ reviewer).

From the Product Specialist perspective, the following deficiencies were identified during the PLI, which were classified as review issues/discussion items and will be addressed through Information Requests:

- a. The validation of the Filling process for Thrombin and Fibrinogen in the manufacture of FS Grifols was found incomplete in that: (a) there were no clear definitions of processing times; (b) the validation report covered only the minimal fill sizes in the 3-mL syringe, but did not provide data for the 5-mL fill syringe; (c) assessment of the consistency of quality parameters of Fibrinogen and Thrombin within each batch did not include statistical analysis of the data with pre-defined acceptance criteria; and (d) the total processing time, from the start of sterile filtration until the final product is frozen, was not established and not supported by stability data.

Instituto Grifols was informed that it would need to complete the validation to include all fill sizes in the 3-mL and 5-mL syringes and to address the above deficiencies. As Grifols noted that this information was available, this item was classified as a review issue and not as a Form 483 observation.

- b. The proposed Use Time (number of uses) for Sepharose XL resin in the purification of Thrombin was not clearly stated and was not supported by data. The available data from the full-scale purification runs covered only a limited number of runs, whereas assessment of resin Use Time in small-scale studies was not performed. Instituto Grifols was informed that the number of

resin uses may be approved only to the extent supported by actual number of runs performed. At present, Grifols has accumulated data for additional full-scale purification runs and will submit the updated report to the BLA when available. Submission of a protocol for a small-scale study to generate supporting data to extend the number of uses was also discussed.

- c. 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 data. Stability data from the small-scale study indicated approximately a (b) (4) in PTC, and the conformance lots of Thrombin were manufactured from PTC with the longest storage period of (b) (4). Instituto Grifols will be asked to analyze the impact of the starting PTC age on the quality and stability of the final Thrombin component in order to verify/revise this Hold Time.
- d. The manufacturing procedures for Thrombin and Fibrinogen allow for re-processing at the sterile filtration step if the filter integrity test fails. Instituto Grifols will be asked to submit data that evaluated the impact of repeated sterile filtration on the quality and stability of Fibrinogen and Thrombin.
- e. Critical reports related to the Design History File for this combination product, including those on the functionality of the application device and usability studies, were provided for review during the PLI and will be submitted to the BLA. This should address the deficiency (i.e., lack of usability studies) identified during the filing review. During the demonstration of the assembled device, additional recommendations were made to be included in the *Instructions for Use*.

The question of the classification of FS Grifols as a parenteral or non-parenteral product was brought up by the DMPQ reviewer with respect to setting the adequate Acceptance Quality Limit (AQL) for particulates during visual inspection of the filled syringes (see the DMPQ report for more details). Instituto Grifols classifies fibrin sealants as non-parenteral products, according to the European Pharmacopeia, based on their route of administration, which is topical application and not injection or infusion. The applicant reasoned that, unlike true parenteral products for injection (solutions), fibrin sealant components would instantly form a gel upon contact with each other at the wound site. As such, Grifols uses less stringent criteria for the AQL for particulates. In contrast, the clinical colleagues from CBER, who were consulted on the issue, refer to the USP General Chapter <1> and view fibrin sealants as parenteral products considering that their route of administration is the one other than enteral (i.e., through the digestive tract). Additional input will be solicited from the clinical reviewers on whether the risk of particulates (and requirements for the AQL) for fibrin sealant products is comparable to, or lower than, that of parenteral products intended for injections.

All deficiencies discussed above can be addressed through Information Requests which are in preparation.

CMC: Adventitious Agent Safety Evaluation

[Ze Peng]

The viral clearance data from down-scale studies estimating the overall inactivation/removal capacity of the manufacturing process for six model viruses – HIV-1, PRV, BVDV, WNV, HAV, and PPV – were reviewed, and no substantive issues have been identified in this regard.

The following Information Request will soon be conveyed to Instituto Grifols:

- a. To better estimate the potential virus load in the starting material, please submit the *Limit of Detection* of each of the Nucleic Acid Tests (NAT) used for the detection of Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus, Hepatitis A Virus, or Parvovirus B19 (B19V) in the (b) (4) [REDACTED], as well as the manufacturing plasma pool.
- b. In Section 3.2.S.2.3. Control of Materials (Human Fibrinogen or Human Thrombin), you stated that the (b) (4) [REDACTED] and the manufacturing plasma pools have been tested and found to be non-reactive for viral markers of infection, including B19V. Please provide the acceptance limits for the level of B19V DNA in the (b) (4) [REDACTED] and manufacturing pool, and the results of all the plasma pools tested so far based on your quantitative NAT for B19V.

CMC: Analytical Methods and Raw Materials

[Svetlana Shestopal]

No substantive issues regarding analytical methods and raw materials have been identified at this time. However, there are deficiencies in the validation of several analytical methods including *Fibrinogen (Clottable Protein)*, *Fibrin Sealant Identification (Identification and (b) (4) [REDACTED])*, *Thrombin activity*, and (b) (4) [REDACTED]. The SOP for *Fibrin Sealant Identification* (the main functionality test) is not sufficiently detailed. In addition, the qualification information for some secondary standards is missing. Some secondary standards expired, and the extension of their shelf life is not adequately justified.

Issues identified with regard to analytical methods will be addressed through Information Requests. In addition, the request will be made for an estimation of time for submission of validation and qualification reports for the assays and standards.

QC, Test Methods: Thrombin and (b) (4) [REDACTED] Assays

[Grainne Tobin]

Information Request regarding linearity, robustness, range, and reference standards for the *Thrombin activity* and (b) (4) [REDACTED] assays was issued on March 23, 2017. Grifols' response, received on April 7, 2017, is currently under review.

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

All assigned sections have been reviewed. The method validation for the assays noted below is found incomplete:

- Fibrinogen component: Fibrinogen/Clottable Protein, Glutamic Acid (also Glycine, Arginine, and Isoleucine), Citrate, Chloride, Polysorbate 80, TNBP, and Sodium
- Thrombin component: Glycine, (b) (4), Chloride, Polysorbate 80, TNBP, Sodium, and Calcium

Specifically, the applicant has not submitted the linearity and accuracy data from representative drug product samples. Furthermore, the validation package does not include the robustness data. The identified deficiencies will be communicated via Information Request which is currently in preparation.

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

Information Request regarding analysis of (b) (4) for Fibrinogen was issued on January 31, 2017, and included questions on the SOP and Method Validation report. The SOP request asked for details on performing the analytical procedure, system suitability criteria, justification for (b) (4), and addressing sample stability issues. The Validation report did not include adequate evaluation of linearity, range, and robustness. The responses, received on February 23, 2017 (Amendment 12), were reviewed and found incomplete. Additional Information Requests are currently in preparation.

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

Information on the *Sterility* and *Endotoxin* assays in Sections 3.2.P.5.2 and 3.2.P.5.3 for both Human Fibrinogen and Human Thrombin has been reviewed thus far. The request will be made in the near future for additional information regarding sterility qualification and bacterial endotoxin qualification, to demonstrate suitability of the test methods for the intended purposes.

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

During the December 7, 2016, teleconference, the applicant stated that there was only one Drug Product (DP) lot (IBND6L3MP1 in 10-mL fill size) available at that time for CBER's in-support testing. This lot was received and is currently used to perform the following tests: Fibrin Sealant Identification (functionality test), Total Clottable Protein, Thrombin Activity, (b) (4) for Fibrinogen, Stability of Fibrinogen solution, pH, Appearance, and Endotoxin.

In the January 3, 2017 Amendment, the applicant committed to manufacturing two additional DP lots, providing their release testing data, and making them available for CBER's in-support testing by May of 2017. Therefore, the timeline of in-support testing is dependent on the actual time at which additional DP lots are shipped to CBER.

The Lot Release Protocol is currently under review. The Testing Plan will be finalized once the Lot Release Protocol template and labeling impacting the Testing Plan have been finalized.

Device Consultative Review

[Rong Guo]

Evaluation of the design of the device constituent parts of Fibrin Sealant Grifol is in progress. An Information Request for additional device-related information was issued on March 30, 2017, to provide gliding force (initiating and sustaining) specification and verification, the verification study for the delivered volume for both drug product components, and full biocompatibility report for the plastic syringe holder. The response is pending.

A potential design issue was noted for the smaller syringe presentation (3 mL fill) where fixation of syringes in the syringe holder is loose and insecure. This concern was conveyed to the applicant during the PLI. The Human Factors/Usability studies were also suggested to the applicant at the filing stage, and have been completed as stated by the applicant during the PLI. The study report will be requested. A separate Inter-Center Consult Request will need to be communicated to CDRH to evaluate the performance and usability of the device (double syringe, syringe holder and the applicator cannula).

The Instructions for Use (IFU) need to be written more clearly on the correct way to attach the application cannula to the double syringe. This will be addressed during the labeling review.

The specification for Volume is (b) (4) or X mL; however, this should either be given as an acceptance *range* or be in compliance with USP General Chapter, in order to ensure the 1:1 ratio for the Fibrinogen and Thrombin components during application.

Extractables/Leachables of all product-contact components of the syringe, including the cannula, should also be evaluated by the CMC and Toxicology reviewers.

DMPQ: Facilities and Equipment

[Christine Harman]

From the perspective of DMPQ, there are currently no substantive issues or deficiencies at this time.

The Pre-License Inspection (PLI) performed from March 15 to March 24 was a combined PLI and cGMP inspection with Team Biologics. A single Form 483 was issued on March 24, 2017, at the close-out that included the combined observations from the PLI and cGMP inspection. A total of 17 observations were made, three of which were specific to the PLI for Fibrin Sealant. The following issues were noted during the PLI:

- a. The initiation of documentation of deviations, CAPAs, and change controls are inadequate. The following support this overall observation: (a) batch

record instructions were crossed out with no reporting changes to instructions as a deviation; (b) Blisterpak machine was not qualified before use in manufacturing the conformance lots during 2013 - 2014 period; (c) no deviation was initiated to review impact on lots manufactured prior to qualification of this instrument that occurred in December 2015; (d) unplanned maintenance of equipment and facilities are not reported as deviations and not tracked or reviewed by QA in terms of impact on manufacturing; and (e) there is no SOP that describes the initiation documenting equipment failures as deviations.

- b. The processing times for critical manufacturing steps, including sterile filtration of Thrombin and Fibrinogen bulk, filling of syringes, and their assembly with plungers and syringe holder, preparation for and sterilization with (b) (4), and secondary packaging up to freezing of the final product are not established or clearly defined.
- c. Aseptic techniques were not always optimally applied during aseptic operations that include filling. The following supported this observation:
 - (a) neither operators sanitized gloves all the time after touching surfaces such as wall control panels nor were glove changes observed during change-over operations and
 - (b) one operator was observed leaning against table with gown touching in several places in the aseptic area.

The firm was informed that response to the observations made during cGMP inspection (for licensed products IGIV and Albumin), which may be applicable globally as those observations from the Quality Systems, will also be considered in the review of this BLA as part of the 483 response. The specific issues conveyed in the observations relating to the Quality System include:

- Visual inspection: If product lot fails visual inspection, labels must be taken off to perform re-inspection, and then vials are re-labeled. The firm is not approved to perform this reworking process.
- Facility and equipment failures, such as HEPA filter integrity failures, equipment stoppages, validation failures/excursions, and calibration failures, are not included in the batch record review for lot release.

An additional issue (not an observation on Form 483 and downgraded to discussion item,) was noted during inspection: Instituto Grifols does not consider the Fibrin Sealant product as a parenteral, which has implications in regard to visual inspection and the Acceptance Quality Limit (AQL) for particulates. Grifols sets an AQL for major defects (covering particulates) of (b) (4) since they do not consider the Fibrin Sealant to be a parenteral product because it is not “injected or infused.” Their rationale was based on the product’s route of administration (topical application); they referenced European Pharmacopeia, which indicates higher limits with regard

to particulates for subcutaneous or intramuscular injection as appropriate and classified the Fibrin Sealant in this category of risk in their internal SOPs.

Because Grifols does not consider the Fibrin Sealant a parenteral (which Grifols defines as injected or infused), a higher than typical AQL (for parenteral products) is used for major defects, i.e., particulates, whereas the USP General Chapter <1790> indicates, for injected parenterals, a typical AQL range for major defects as 0.10 to 0.65, taking into consideration the risk of particulates with injected parenterals. Grifols is currently using an AQL of (b) (4) for their Fibrin Sealant product, which is less stringent. Based on the definition of parenteral stated in USP General Chapter <1>, Fibrin Sealant is considered a parenteral (i.e., route of administration other than enteral), thus differing from what Grifols consider as a parenteral. There are several USP Chapters that describe limits for visual inspection in regard to parenteral, but these chapters seem to specifically focus on parenterals that are injected or infused. The language is vague in regard to other routes of administration, particularly those that are topically applied, but are used inside the body (in open surgeries as in case with fibrin sealants). Feedback from the clinical group would be needed to: (1) define what an injectable parenteral is, as opposed to a non-injectable parenteral, and (2) assess the risk of particulates with regard to parenterals that are used similarly to the Fibrin Sealant products so as to properly advise Instituto Grifols on the AQL for major defects (particulates).

The resolution plan to address FDA Form 483 observations was submitted by Instituto Grifols on April 12, 2017, and is currently under review. An Information Request for additional information and clarifications, currently in preparation, is related to the following:

- To provide more specifics and updated information in regard to the filling validation (process parameters, definition of process times for sterile filtration and, time of filling with respective acceptance criteria).
- To provide most recent media fill simulations to validate the aseptic filling process. These recent media fills, reviewed on inspection, incorporate the significant intervention that includes the change-over from Thrombin to Fibrinogen filling; thus, these media fill studies need to be part of the BLA.

Pharmacology/Toxicology

[John Jameson]

The following preclinical studies have been submitted for review: one *in vitro* coagulation study using a drip applicator, five *in vivo* safety pharmacology studies, six *in vivo* toxicology studies in mice (3) and rats (3), and risk assessment of arginine.

All preclinical information has been reviewed, and no substantive issues from pharmacology/toxicology have been identified.

Clinical

[Agnes Lim]

Three pivotal phase 3 studies, Study IG1101 (vascular surgery), IG1102 (parenchymous surgery [liver resections]) and IG1103 (soft tissue surgery), were submitted in the original BLA. All three studies were prospective, randomized, controlled, single-blind, multicenter studies with a two-part design: Part I to familiarize the local teams with the product and the clinical study protocol and Part II to assess the safety and efficacy of FS Grifols. The overall data from these pivotal studies demonstrate hemostatic efficacy of FS Grifols and support its use as an effective local adjunctive hemostatic agent in surgery. The results of all secondary efficacy endpoints in all three studies provide additional support.

From a clinical safety standpoint, the results of all three studies demonstrate that FS Grifols is reasonably safe and well tolerated as a local adjunctive hemostatic agent in various surgery types. The most frequently reported treatment-emergent adverse events (TEAEs) by treatment in the safety population in all three studies are reasonably considered as typical of open surgeries. The most common TEAEs ($\geq 10\%$ of subjects by MedDRA preferred term) in the three treatment groups were generally similar: FS Grifols - procedural pain (41.8%), nausea (13.4%), and pyrexia (10%); Surgicel, the control in Studies IG1102 and IG1103 - procedural pain (45.9%), nausea (17.5%), anemia (12.5%), pyrexia (10.9%), constipation (10.6%), and procedural nausea (10.0%); and manual compression (MC), the control in Study IG1101 - procedural pain (36.8%) and pyrexia (10.5%). No substantial differences in TEAE incidences were noted between treatment groups. The majority of TEAEs in all treatment groups were either mild or moderate in severity (FS Grifols: 92.5%; Surgicel: 95.9%; and MC: 91.3%).

The clinical review of the clinical data is ongoing. No substantive issues have been identified thus far for FS Grifols to be used as an adjunct to hemostasis in adults for moderate bleeding when intra-operative control of bleeding by standard surgical techniques is ineffective or impractical. The phrase “(b) (4) [REDACTED]” should be deleted from the proposed indication statement due to deferral of the pediatric study, but this is a minor issue that will be addressed later in the review cycle.

Statistics

[Annie Lin]

The three pivotal studies, IG1101, IG1102, and IG1103, 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).

The statistical review of efficacy evaluations for all three studies has been completed, and no substantive statistical issues have been identified at this time. In Study IG1101, the rate of hemostasis by 4 minutes after treatment application was significantly higher in the FS Grifols group compared with 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 with 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 that of the subjects receiving Surgicel for patients undergoing soft tissue surgeries.

The evaluation of safety analysis and integrated analyses for all three studies are ongoing, and there are no substantive statistical issues at this time regarding the submission.

The following Information Request will soon be conveyed to Instituto Grifols, regarding the subgroup analyses:

- a. You have submitted the subgroup analyses by age group and sex for Study IG1101. Please also provide the subgroup analysis by race group using the ITT analysis set.
- b. You have submitted the subgroup analyses by age group for Study IG1102 and IG1103. Please also provide the subgroup analyses by race group and sex using the ITT analysis set.

Bioresearch Monitoring (BIMO)

[Bhanu Kannan]

BIMO inspections for two clinical investigators for Study IG1101 and two clinical investigators for Study IG1103 are pending. BIMO 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

Study	Site Number	Study Site	Location	Status
IG1101	407	Beer, Simon, William, Moody and Associates	Florence, Alabama	Inspection pending
IG1101	521	University of Belgrade Institute for Cardiovascular Diseases, Clinic for Vascular Surgery	Belgrade, Serbia	Inspection pending

IG1103	322	Lotus Clinical Research, LLC.	Pasadena, California	Inspection Pending
IG1103	722	Clinical Center of Serbia, Urology Clinic	Belgrade, Serbia	Inspection pending

To date, the inspections and inspection reports are pending, and the review committee will be notified of any substantive issues or significant findings when the pending inspections and review of inspection reports are completed.

Epidemiology/Pharmacovigilance

[Faith Barash]

The available data do not suggest any safety concerns that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), Postmarketing Commitment (PMC), or Postmarketing Requirement (PMR) specifically designed to evaluate safety as a primary endpoint.

There are no critical risks or potential risks identified thus far, stemming from the clinical use or clinical studies, other than the following identified risks: tissue adhesion, air or gas embolism, anaphylaxis, thromboembolic events, transmission, or infectious agent. No safety concerns have been raised for immunogenicity of the biological components: the product is available for topical application only, and no immunogenicity response was observed in patients treated with FS Grifols in the three pivotal studies. However, information regarding use in pediatric population and pregnant or lactating women is missing.

Discuss:

2. This application will not be presented at the Blood Products Advisory Committee (BPAC) meeting.
3. The review committee identified no need for Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs), or a Risk Evaluation and Mitigation Strategy (REMS) at this time. [Faith Barash]
4. No substantive deficiencies have been identified thus far with regard to National Drug Codes (NDCs). The NDCs are in a 5-4-1 configuration, and its labeler code, 61953, correctly belongs to Grifols USA, LLC. [Yu Do]
5. The proper name of this product is Fibrin Sealant (Human). The proposed proprietary name, VERASEAL, has been found unacceptable, as of February 3, 2017, due to its high risk of medication errors and promotional tone.
6. Status of Pre-License, cGMP, and BIMO inspections is updated under Item 1 (see DMPQ and BIMO sections, respectively, for details).

Confirm:

7. The Data Abstraction Team (DAT) has been notified of this original BLA. The ABC Component Information submitted under this BLA was abstracted into BITS-ABC database and reviewed by QC on November 28, 2017. Svetlana Shestopal will review the information in BITS-ABC later during this review cycle. [Yu Do]
8. New facility information from the application has been entered into RMS-BLA. The facility information entry in RMS-BLA will be checked for accuracy and completeness. [Christine Harman/Yu Do]
9. The samples of one of the three lots (IBND6L3MP1 in 10-mL fill size) were requested on February 23, 2017. There will be potential delays in in-support testing due to issues regarding availability of two additional FS Grifols lots (end of April or May 2017) and discontinuation of (b) (4) for the determination of (b) (4) for Fibrinogen.

The Lot Release Protocol is currently under review. The Testing Plan is being drafted and will be completed after the Lot Release Protocol template and labeling impacting the Testing Plan have been finalized. [Varsha Garnepudi]

10. Unique Ingredient Identifier (UNII) codes (for Fibrinogen and Thrombin) have been assigned to this product on April 5, 2017, and will be conveyed to the applicant in the near future. [Yu Do]
11. PeRC presentation date for this original BLA is set for September 6, 2017. The Regulatory Project Manager will work with the Clinical reviewer, Agnes Lim, to prepare and submit PeRC forms and other review materials two weeks in advance of the scheduled meeting. The Clinical reviewer will address the *Agreed Initial Pediatric Study Plan* and request for deferral. [Yu Do]
12. The Regulatory Project Manager will meet with the Committee Chair, Natalya Ananyeva, separately to reach agreement on the information to be conveyed during Mid-Cycle Communication with the applicant. No substantive issues should be discussed at the Mid-Cycle Communication. The Mid-Cycle Communication is only for applications that qualify under the PDUFA V “Program.” [Yu Do]

Review:

13. Pending dates of major targets and milestones:

Mid-Cycle Communication outline – April 21, 2017
Mid-Cycle Communication – April 27, 2017
Late-Cycle internal meeting – June 20, 2017
Late-Cycle meeting materials - July 07, 2017
Late-Cycle external meeting – July 20, 2017

Advisory Committee Meeting (if needed) – August 04, 2017 (pending)
PeRC meeting – September 06, 2017
PMC and labeling review – October 05, 2017
Completion of supervisory review - October 05, 2017
First action due – November 3, 2017

14. Please see Item 1 for details regarding the current status of review for each discipline, inspection, and EIR.
15. A labeling review meeting for Fibrin Sealant Grifols should be scheduled on or after August 04, 2017.

Action Items:

The Mid-Cycle Communication (MCC) has been scheduled for April 27, 2017.

Meeting to reach an agreement on the information to share during MCC will be held during the week of April 17, 2017. [Yu Do and Natalya Ananyeva]

Drafted: Yu Do/April 20, 2017
Revised: Natalya Ananyeva/May 11, 2017
Reviewed: Christine Harman/May 12, 2017
Revised: Agnes Lim/May 11, 2017
Reviewed: John Jameson/May 4, 2017
Revised: Bhanu Kannan/May 11, 2017
Reviewed: Faith Barash/May 11, 2017
Revised: Karla Garcia/April 21, 2017
Reviewed: Basil Golding/May 5, 2017
Revised: Varsha Garnepudi/May 5, 2017
Revised: Lokesh Bhattacharyya/May 11, 2017