# SUMMARY BASIS FOR REGULATORY ACTION

**Date:** November 1, 2017

**From:** Natalya Ananyeva, PhD, Chair of the Review Committee

**BLA STN:** BL 125640/0

**Applicant Name:** Instituto Grifols, S.A.

**Date of Submission:** November 3, 2016

**Goal Date:** November 3, 2017

**Established Name:** Fibrin Sealant (Human)

**Proposed Indication:** An adjunct to hemostasis for mild to moderate bleeding in adults 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.

**Recommended Action:**
The Review Committee recommends **APPROVAL** of this product.

**Review Office(s) Signatory Authority:**

**Office of Tissues and Advanced Therapies (OTAT) Signatory Authority:**
Wilson W. Bryan, MD, Director

**□ I concur with the summary review.**

**□ I concur with the summary review and include a separate review to add further analysis.**

**□ I do not concur with the summary review and include a separate review.**

The table below indicates the review disciplines and respective review committee members who participated in reviewing this application and developing the SBRA.

| **Discipline/Review Activity** | **Reviewers and Consultants** |
|---|---|
| CMC Reviews<br>• *CMC - Product*<br>• *CMC - Facilities*<br>• *Facility Inspection* | Natalya Ananyeva, PhD, Svetlana Shestopal, PhD, and Ze Peng, PhD (OTAT/DPPT/HB)<br>Christine Harman, PhD (OCBQ/DMPQ/BI)<br>Christine Harman, PhD (OCBQ/DMPQ/BI)<br>Natalya Ananyeva, PhD (OTAT/DPPT/HB) |
| Clinical Reviews<br>• *Clinical*<br>• *Post-marketing safety epidemiological review*<br>• *BIMO* | Agnes Lim, MD (OTAT/DCEPT/GMB1)<br>Faith Barash, MD (OCBQ/DE/PB)<br><br>Bhanu Kannan, MS (OCBQ/DIS/BMB) |
| Statistical Reviews<br>• *Clinical*<br>• *Non-clinical* | Min (Annie) Lin, PhD (OBE/DB/TEB) |
| Pharmacology/Toxicology Reviews<br>• *Toxicology*<br>• *Developmental toxicology*<br>• *Animal pharmacology* | John Jameson, PhD (OTAT/DCEPT/PTB2) |
| Clinical Pharmacology Review | Not Applicable |
| Labeling Review | Alpita Popat, PharmD (OCBQ/DCM/APLB) |
| Additional reviews not captured in above categories<br>• *Extractables/Leachables, Chemistry and Identification/Quantification*<br>• *QC, Test Methods, Product Quality*<br>• *Lot Release Protocol/Testing Plan*<br>• *QC, Sterility and Endotoxin*<br>• *Proprietary Name Review* | Andrey Sarafanov, PhD (OTAT/DPPT/HB)<br><br>Grainne Tobin, PhD, Ritu Agarwal, PhD, and Hsiaoling Wang, PhD (OCBQ/DBSQC/LACBRP)<br>Varsha Garnepudi, MS (OCBQ/DBSQC/QAB)<br>Karla Garcia (OCBQ/DBSQC/LMIVTS)<br>Oluchi Elekwachi (OCBQ/DCM/APLB) |
| Consult reviews<br>• *Delivery Device*<br>• *Engineering, Delivery Device*<br>• *Human Factors/Usability*<br>• *Extractables/Leachables, Toxicological Assessment* | Deborah Trout (OCBQ/DMPQ/BI)<br>Rong Guo, PhD (CDRH/ODE/DAGRID)<br>Rita Lin, MS (CDRH/ODE/DAGRID)<br><br>Evi Struble, PhD (OTAT/DPPT/PDB) |
| Regulatory Project Manager | Yu Do, MS (OTAT/DRPM/RPMBI) |
| Advisory Committee summary | Not presented to an advisory committee |

## 1. INTRODUCTION

Instituto Grifols, S.A. (Grifols) submitted an original biologics license application (BLA) to seek U.S. licensure for Fibrin Sealant (Human). The product 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. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biological components. An application cannula (Class I device) is co-packaged with the product for application by dripping. Fibrin Sealant (Human) is available in 2-mL, 4-mL, 6-mL and 10-mL package sizes. There is no proprietary name for this product.

Fibrin Sealant (Human) is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults 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.

## 2. BACKGROUND

Fibrin sealants recreate the final stage of the blood coagulation cascade via the reaction of thrombin and fibrinogen at the wound site to generate a cross-linked fibrin clot that stops bleeding. These products are generally indicated as an adjunct to hemostasis when control of bleeding by standard surgical techniques is ineffective or impractical. The two-component fibrin sealants, in frozen liquid or lyophilized forms, have a long history of clinical use, including four FDA-licensed products: TISSEEL and ARTISS (Baxter Healthcare Corp.), EVICEL (Omrix Biopharmaceuticals, Ltd., a Johnson & Johnson company), and RAPLIXA (ProFibrix, BV. [The Medicines Company]). In addition, two fibrin sealant patch products, for which thrombin and fibrinogen are embedded into an absorbable backing layer, are licensed in the U.S.: TachoSil by Takeda Pharmaceuticals International and EVARREST by Omrix Biopharmaceuticals. Two thrombin-only products, EVITHROM (Ethicon) and RECOTHROM (Mallinckrodt Pharma IP Trading DAC) are also approved for the same indication.

Grifols' Fibrin Sealant (Human) is another two-component fibrin sealant in a frozen liquid formulation. Fibrin Sealant (Human) meets the definition of a biologics/device combination product (21 CFR Part 3) and was reviewed according to the requirements stipulated in the Final Rule, 21 CFR Part 4 (Subpart A).

Fibrin Sealant (Human) was developed under Investigational New Drug applications (INDs) 14986, 14987, and 14988 submitted by Grifols in January 2012. The safety and efficacy of Fibrin Sealant (Human) was evaluated in prospective, randomized, controlled, single-blind, multicenter clinical trials. To support licensure for the proposed indications, the clinical development program for Fibrin Sealant (Human) included data from:

- **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 IG1102** "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 Parenchymous Tissue Open Surgeries"
- **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"

The hemostatic efficacy data demonstrated superiority of Fibrin Sealant (Human) to manual compression in Study IG1101 and non-inferiority to a licensed comparator product (SURGICEL) in Studies IG 1102 and IG 1103. The results of all three studies demonstrate that Fibrin Sealant (Human) is reasonably safe and well tolerated as a local adjunctive hemostatic agent in various surgery types. The most frequently reported treatment-emergent adverse events in all three studies are typical of open surgeries.

Fibrin Sealant (Human) is not marketed in other countries.

*Regulatory History*

The BLA was received by FDA on November 04, 2016 and reviewed under the standard (12-month) review schedule of the PDUFA V program, and the milestones are listed in Table 1. This product does not have orphan designation.

**TABLE 1: Review Milestones**

| Milestone | Date |
|---|---|
| Received | November 04, 2016 |
| Filed | January 02, 2017 |
| Mid-Cycle Communication | April 25, 2017 |
| Blood Products Advisory Committee | Waived |
| Pediatric Research Committee (PeRC) Meeting | September 06, 2017 |
| Late-Cycle Meeting | August 31, 2017 |
| Action Due Date | November 03, 2017 |

*Review Issues Resolved during BLA Review*

In the course of the review, specific chemistry, manufacturing, and controls (CMC) issues were raised and resolved via information requests (IRs). Per FDA IRs, Grifols:

- performed additional studies and analyses to validate the aseptic filling process and establish time limits for critical processing steps;
- developed a Study Protocol for concurrent full-scale validation of the life-time of the SP-Sepharose chromatographic resin used in the manufacture of Thrombin;
- revised Drug Product Specifications and a post-approval Stability Protocol;

- performed additional experimentation and analyses to complete validation of the analytical methods;
- provided additional information on extractable/leachable substances; and
- modified and qualified the design of the 3-mL syringe holder to ensure tight fixation of the syringes.

One remaining CMC deficiency will be addressed as a Post-Marketing Commitment: Grifols committed to performing a post-marketing study with (b) (4) of this manufacturing step.

All objectionable observations from the Pre-License Inspection have been adequately addressed.

The clinical data on safety and efficacy of Fibrin Sealant (Human) in the adult population did not raise concerns, and clarifications were provided by the Applicant via IRs. The safety and efficacy of Fibrin Sealant (Human) as an adjunct to hemostasis during surgery in pediatric subjects will be assessed in a deferred pediatric clinical trial, which constitutes a Post-Marketing Requirement (PMR) under PREA and is a condition for BLA approval.

Several deficiencies were identified about the Human Factors (HF)/Usability studies. In response to an FDA IR, Grifols developed a protocol and committed to performing a new HF study as a part of the deferred pediatric clinical trial.

## 3. CHEMISTRY MANUFACTURING AND CONTROLS

### a) Product Quality

**Manufacturing Process for Biological Components**

Fibrin Sealant (Human) is manufactured at the Instituto Grifols, S.A. facility in Barcelona, Spain. Both Human Fibrinogen and Human Thrombin are isolated from pooled human Source Plasma obtained from FDA-licensed plasma collection centers in the United States. A modified Cohn plasma fractionation method is used to obtain Fraction I precipitate, which is the starting material for the production of Fibrinogen, and Prothrombin Complex captured from the supernatant of Fraction I, which is the starting material for the production of Thrombin.

*Manufacture of Fibrinogen Component of Fibrin Sealant (Human)*

Fraction I precipitate is (b) (4) . The (b) (4) undergoes Solvent/Detergent (S/D) treatment with 0.30% (v/v) tri-n-butyl phosphate (TnBP) and 1.0% (v/v) polysorbate-80 (Tween 80) at 27.0 ± 1.5°C for 6.0–6.5 hours to inactivate enveloped viruses. Fibrinogen is further purified through three glycine precipitation steps, and the third glycine precipitate (b) (4)

(b) (4) . After (b) (4) solution undergoes nanofiltration through a series of 35 nm and 20 nm pore size filters to remove enveloped and non-enveloped viruses. The formulated Fibrinogen bulk is sterile filtered and aseptically filled into syringes with 1 mL and 2 mL fill volume for the 3-mL syringes and with 3 mL and 5 mL fill volume for the 5-mL syringes.

*Manufacture of Thrombin Component of Fibrin Sealant (Human)*

Prothrombin Complex (PTC) is obtained from Fraction I supernatant, purified on (b) (4) . Prothrombin in PTC (b) (4) . The (b) (4) solution undergoes S/D treatment with 0.3% (v/v) TnBP / 1.0% (v/v) polysorbate-80 at 25 ± 1°C for 6.0 – 6.5 hours to inactivate enveloped viruses. Thrombin is further purified on an SP-Sepharose XL cation exchange column, (b) (4) , and (b) (4) . The (b) (4) solution is then nanofiltered through two 15 nm pore size filters to remove enveloped and non-enveloped viruses. Calcium (b) (4) The Thrombin solution is then sterile filtered, and aseptically filled into syringes.

*Packaging, Freezing and Storage*

After the Filling process is completed, the syringes are visually inspected and labeled. The Thrombin and Fibrinogen syringes are then assembled with the syringe plungers, syringe holder and plunger link. The assembled units are sealed into a blister, which is then bagged in a thermo-sealed plastic packing and sterilized with (b) (4) . The sterilized product is co-packaged with the applicator tip in a carton box and the kit is frozen and stored at ≤ - 20°C.

**In-Process Controls and Hold Times**

Manufacturing process controls - critical process parameters (CPPs) and in-process control (IPC) tests - were established during process development through extensive experimental evaluation to ensure product purity, quality and safety, to reduce processing times, increase the yield, and optimize conditions taking into consideration the specific properties of the Fibrinogen and Thrombin proteins. Critical quality attributes were established based on process understanding through developmental studies and risk assessments. The operational ranges for the CPPs and acceptance criteria for the IPC tests were initially determined for each unit operation in clinical-scale studies, and the consistency of the manufacturing process at this scale was demonstrated to support the clinical trials. The established IPCs were further verified during process validation at the commercial scale as detailed in the comparability reports. All relevant process and analytical data from process intermediates as well as analytical data from the final product demonstrate that the production processes at clinical and commercial scales are comparable, and allow the manufacture of Fibrinogen and Thrombin in a consistent manner. These data adequately support that the clinical material is representative of the material intended for commercial distribution.

The hold times for process intermediates were established during process development based on stability data, and were validated based on the production of conformance lots and results from additional analyses performed per FDA requests.

In conclusion, the established process parameters and IPC tests provide adequate control of the manufacturing process for Fibrin Sealant (Human).

**Process Validation**

The validation strategy for the commercial manufacturing process of Fibrin Sealant (Human) is consistent with ICH Guideline Q11. The validation studies were performed at Grifols' Barcelona facility, the intended commercial site, under prospective process validation protocols. The validation of the manufacturing process for Fibrin Sealant (Human) was designed as a series of separate studies covering specific manufacturing stages of the Fibrinogen and Thrombin processes and subsequent filling and sterilization of the final product.

The results of the validation of the S/D treatment process demonstrated that the target temperature and concentrations of TnBP and Tween 80 were achieved during the (b) (4) stage and were maintained within their acceptance ranges throughout the treatment duration.

The validation of the manufacturing processes for Fibrinogen and Thrombin was performed by the manufacture of the first three batches of the two proteins, and included assessment of production parameters ((b) (4) ), routine IPC and release testing according to Specifications, and additional characterization of the final product for purity and uniformity of key quality parameters in the entire lot. In both validation studies, all process controls and results of IPC and release testing, as well as additional characterization complied with pre-defined acceptance criteria. FDA identified one deficiency related to the validation of the life-time of the SP-Sepharose XL chromatographic resin used in Thrombin manufacture. Per FDA request, Grifols developed an adequate Study Protocol for concurrent full-scale validation of the SP-Sepharose life-time, which includes controls over (b) (4) , and committed to follow it to manufacture and release subsequent Thrombin lots.

The validation of the aseptic filling process was performed by the manufacture of three batches of Fibrinogen and Thrombin that were filled into syringes with different fill volumes resulting in final product lots of different fill sizes. The validation approach included assessment of aseptic process parameters, routine IPC and release testing of final containers, batch uniformity by (b) (4) and quality parameters, and recording of filling duration times. The results for all parameters for different fill sizes were within the respective pre-defined acceptance criteria.

Per FDA request, Grifols performed additional studies and analyses to more fully validate the aseptic filling process. As an outcome, the scope of the validation studies was expanded to include all available fill sizes; statistical analysis of analytical data was

performed to confirm consistency of quality parameters of Fibrinogen and Thrombin within the filled batch; and time limits were established for critical processing steps – (b) (4) until the final product is frozen for storage.

The heat-sealed blisterpak package containing the assembled Fibrin Sealant (Human) syringes is sterilized using (b) (4). The sterilization process was validated with the use of biological and chemical indicators.

In conclusion, all process and quality controls in the validation studies complied with pre-defined acceptance criteria stated in the protocols, and the results of release testing were within specifications. Based on the evaluation of the manufacturing and analytical data for clinical and conformance lots, the manufacturing process for Fibrin Sealant (Human) was found to be sufficiently controlled, consistent and adequately validated. This approval does not include any reprocessing steps.

**Drug Product Composition and Presentation**

Fibrin Sealant (Human) is available as a kit consisting of two separate packages:

- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions, which are assembled on a syringe holder.
- A package containing an application cannula.

Fibrin Sealant (Human) is available in the following package sizes: 2 mL (1 + 1 mL) and 4 mL (2+ 2 mL) in 3-mL syringes and 6 mL (3 + 3 mL) and 10 mL (5 + 5 mL) in 5-mL syringes. After thawing, the human fibrinogen and human thrombin solutions are clear or slightly opalescent and colorless or pale yellow. Fibrin Sealant (Human) does not contain any preservatives.

Fibrinogen
Component 1 is a sterile solution, pH 6.5 – 8.0, which contains concentrated human fibrinogen (80 mg/mL) and excipients (sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium, and water for injection).

Thrombin
Component 2 is a sterile solution, pH 6.0 – 8.0, which contains purified human thrombin (500 IU/mL) and excipients (sodium chloride, calcium chloride, human albumin, glycine, and water for injection).

The information on the device components of the application system and its functionality and usability was reviewed by CBER/OCBQ and consult reviewers from Center for Devices and Radiological Health (CDRH).

**Device Components: Container Closure and Application System**

Fibrin Sealant (Human) is a biologics/device combination product. The following device components constitute the container closure system for Fibrin Sealant (Human): two syringes with tip caps, stoppers and syringe plungers; syringe holder and plunger link.

Fibrinogen and Thrombin/Calcium Chloride solutions are filled into borosilicate ((b) (4) ) glass syringes (3 mL or 5 mL) with bromobutyl rubber stoppers which are supplied by (b) (4) has established a Biologics Master File for the syringes (No. (b) (4) ) with CBER.

The syringe holder and plunger link are manufactured from polycarbonate by Laboratorios Grifols, S.A. and are used to allow for simultaneous application of equal amounts of fibrinogen and thrombin. Grifols conducted the container closure integrity testing on the syringes using a (b) (4) method; all acceptance criteria were met. Two filled syringes (one with Thrombin and one with Fibrinogen) are assembled on the syringe holder. The syringe assembly is packaged into blister packaging and sterilized using (b) (4) . Grifols performed package integrity and seal strength testing of the blister packaging using (b) (4) testing; all acceptance criteria were met.

Fibrin Sealant (Human) can be administered in two ways: dripping or spraying. Dripping: (b) (4) Cannula (b) (4) is co-packaged with Fibrin Sealant (Human). The applicator tip is manufactured by (b) (4) The device was 510(k)-cleared ((b) (4) ) under Irrigating Syringe and this category has since been reclassified as a Class I device.

Spraying: Spraying applicators are not co-packaged. Fibrijet® Gas assisted applicator (with a 510(k) clearance K012868) is recommended by the Applicant, along with other equivalent spray devices (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use.

**Device Components: Functionality and Usability of the Application System**

Grifols provided sufficient information to demonstrate the safety and effectiveness of the device constituent parts.

The functionality of the application systems has been studied by assessing essential performance characteristics such as the delivered amount, application force, consistency of the fibrin adhesive layer, drop size, clotting times, etc. with dripping cannula or spraying applicator. Functionality, viability (stability of performance characteristics during product storage) and compatibility of the application device with the biologic components are sufficiently verified. Per FDA request, the Applicant has modified the design of the syringe holder for the 3-mL syringe to ensure its tight fixation, and qualified it in an additional functionality study.

The Applicant did not provide an adequate Human Factors validation study: the protocol was not clear about critical tasks, use environment, and the approach to analyzing the performance data. In addition, the number of participants was not sufficient. The Applicant committed to conducting a new Human Factors validation study, and incorporate it into the upcoming pediatric clinical trial, which is a Post-Marketing Requirement study under PREA. The Applicant will initiate and complete the Human Factors validation study according to the agreed-upon protocol and within the agreed-upon timelines, and will submit the final report for FDA review.

**Leachable Substances**

Leachables from materials used in the manufacturing processes and container closure system were adequately assessed for both Fibrinogen and Thrombin, using samples from stability studies. The analyzed compounds were those listed by the manufacturers as extractables, representing the worst-case scenario. Toxicological analysis of the data indicated that the levels of the leachable compounds present in the drug product do not pose a safety concern.

**Characterization of Structure and Function**

The characterization program for Fibrin Sealant (Human) used an extensive panel of analytical methods to evaluate physicochemical, biochemical and functional properties of the Fibrinogen and Thrombin components as well as structural characteristics of the fibrin clot made from Fibrin Sealant (Human). The characterization studies were performed on several commercial-scale lots of Fibrinogen and Thrombin.

*Physicochemical/Biochemical Characterization*

The characterization of the Fibrinogen component included the assessment of identity, purity, and structure. Analysis of the integrity of the fibrinogen chains showed the formation of a stable clot in the presence of calcium demonstrating the proper functionality of the fibrinogen molecule. The characterization of process intermediates during commercial scale manufacture of Fibrinogen lots demonstrated robust removal of process- and product-related impurities to either acceptable limits controlled as Drug Product (DP) Specification parameters ((b) (4) , TnBP and Polysorbate 80), or to undetectable or trace levels in the final product.

Biochemical characteristics of the Thrombin component confirmed its identity and demonstrated product purity with no observed thrombin degradation products. The Functionality test showed consistent clot formation when Fibrinogen and Thrombin are mixed. Analysis of process intermediates and/or the final product during commercial-scale manufacture of Thrombin lots confirmed that process- and product-related impurities are consistently removed to undetectable or trace levels in the final product. The residual levels of TnBP and Polysorbate 80 in the final product are controlled to acceptable limits as DP Specification parameters. In addition, the process efficacy to purify Thrombin was demonstrated by an (b) (4) along the manufacturing steps and in the final product.

The uniformity of the results obtained from different lots of Fibrinogen and Thrombin demonstrates that the manufacturing processes are capable of manufacturing consistently high-quality products with integral functional properties.

*In Vitro Clot Structure Characterization*

Per FDA request, Grifols studied the effect of the starting material for Fibrinogen (Fraction I used for this product, versus generally used Cryoprecipitate) on the structural characteristics of the fibrin clot made from Fibrin Sealant (Human). The clot structure was characterized in a series of *in vitro* assays, and the results demonstrated that the Fibrin Sealant (Human) clot characteristics are comparable to those of other licensed fibrin sealant products.

**Analytical Methods**

Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release, and stability monitoring. An acceptable reference standard qualification and maintenance program has been established. The functional activity of the Fibrinogen component is assessed by *Fibrinogen (Clottable Protein)* determination by the (b) (4) method. The activity of the Thrombin component is determined by the coagulation assay using an in-house standard calibrated against the (b) (4) for Thrombin. The quality of the Fibrin Sealant (Human) final product is additionally controlled by the *Fibrin Sealant Identification and Functionality* test to confirm the performance of the combination product. During the review, several IRs were sent to Grifols for additional parameters to adequately validate these three assays, and also assays for (b) (4) *by* (b) (4), and excipients and impurities, and to qualify compendial assays for *Sterility* and *Endotoxin*. As a result, all analytical methods are sufficiently described in the respective Standard Operating Procedures, adequately validated in accordance with ICH Guideline Q2(R1), and suitable for their intended use.

**Drug Product Release Specifications**

The specifications for DP were established in accordance with ICH Guideline Q6B and FDA recommendations provided during BLA review. The parameters were selected from critical quality attributes determined in process development studies and risk assessments. Acceptance ranges/limits are established based on regulatory requirements (European Pharmacopoeia monograph 0903), manufacturing experience (analysis of the release and stability data for clinical and conformance lots), process capability to remove impurities, analytical variability, and previous experience with other licensed Grifols products.

The final DP release specifications in Tables 2-4 reflect revisions made per FDA requests and are considered adequate to control the identity, quality, purity, potency, and safety of Fibrin Sealant (Human).

**TABLE 2: SPECIFICATION FOR DRUG PRODUCT: FIBRINOGEN COMPONENT**

| Attribute | Parameter | Method | Specification |
|---|---|---|---|
| IMMUNO-CHEMICAL CONTROL | IDENTIFICATION | (b) (4) determination by (b) (4) | It complies with the limits of the assay for fibrinogen |
| | FIBRINOGEN (clottable protein) | (b) (4) determination by (b) (4) | (b) (4) |
| | TOTAL PROTEIN | Bradford method | (b) (4) |
| | (b) (4) | (b) (4) | (b) (4) |
| PHYSICO-CHEMICAL CONTROL | APPEARANCE OF FROZEN PRODUCT | Visual inspection | Colorless or pale yellow, opaque solid |
| | APPEARANCE OF SOLUTION (AFTER THAWING) | Visual inspection | Colorless or pale yellow solution, essentially free of visible particulates |
| | pH | pH meter | 6.5 – 8.0 |
| | STABILITY OF SOLUTION (2 hours at 20-25°C) | Visual stability | (b) (4) |
| | ARGININE | (b) (4) | (b) (4) |
| | L-ISOLEUCINE | (b) (4) | (b) (4) |
| | GLUTAMIC ACID (monosodium salt) | (b) (4) | (b) (4) |
| | CHLORIDE | (b) (4) | (b) (4) |
| | SODIUM | (b) (4) | (b) (4) |
| | CITRATE | (b) (4) | (b) (4) |
| | GLYCINE | (b) (4) | (b) (4) |
| | TNBP | (b) (4) | (b) (4) |
| | POLYSORBATE 80 | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) | (b) (4) |
| | VOLUME | Measurement | 1.0 mL (b) (4)<br>2.0 mL (b) (4)<br>3.0 mL (b) (4)<br>5.0 mL (b) (4) |
| MICROBIO LOGICAL CONTROL | STERILITY | (b) (4) | No microbiological growth |
| BIOLOGICAL CONTROL | ENDOTOXINS | (b) (4) | (b) (4) |

**TABLE 3: SPECIFICATION FOR DRUG PRODUCT: THROMBIN COMPONENT**

| Attribute | Parameter | Method | Specification |
|---|---|---|---|
| IMMUNO-CHEMICAL CONTROL | IDENTIFICATION | Coagulation (b) (4) | It complies with the limits of the assay for thrombin |
| | THROMBIN | Coagulation (b) (4) | (b) (4) |
| | ALBUMIN | (b) (4) | (b) (4) |
| PHYSICO-CHEMICAL CONTROL | APPEARANCE OF FROZEN PRODUCT | Visual inspection | Colorless or pale yellow, opaque solid |
| | APPEARANCE OF SOLUTION (AFTER THAWING) | Visual inspection | Colorless or pale yellow solution, essentially free of visible particulates |
| | pH | pH meter | 6.0 – 8.0 |
| | CHLORIDE | (b) (4) | (b) (4) |
| | SODIUM | (b) (4) | (b) (4) |
| | CALCIUM | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) method | (b) (4) |
| | GLYCINE | (b) (4) | (b) (4) |
| | TNBP | (b) (4) | (b) (4) |
| | POLYSORBATE 80 | (b) (4) assay | (b) (4) |
| | VOLUME | Measurement | 1.0 mL (b) (4)<br>2.0 mL (b) (4)<br>3.0 mL (b) (4)<br>5.0 mL (b) (4) |
| MICROBIOLOGICAL CONTROL | STERILITY | (b) (4) | No microbiological growth |
| BIOLOGICAL CONTROL | ENDOTOXINS | (b) (4) | (b) (4) |

**TABLE 4: SPECIFICATION FOR DRUG PRODUCT: FIBRIN SEALANT COMBINATION PRODUCT**

| Attribute | Parameter | Method | Specification |
|---|---|---|---|
| IMMUNO-CHEMICAL CONTROL | IDENTIFICATION | Coagulation method | Clot formation |
| | FUNCTIONALITY (Clot formation (b) (4)) | Coagulation method | (b) (4) |

**Batch Analyses and In-Support Testing**

Process consistency is supported by results of batch analyses for 11 clinical and 10 validation lots of Fibrin Sealant (Human) which were submitted in the BLA or provided during the pre-license inspection. Test results for all parameters and for all batches are within respective specifications.

The Laboratories of the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality (OCBQ), CBER, FDA, performed in-support testing of three Fibrin Sealant (Human) conformance lots of various fill sizes. The results met the acceptance criteria for the assay performance characteristics. In addition, the DBSQC test results for Fibrin Sealant (Human) samples were within the proposed DP specifications and comparable to the results reported by Grifols. The in-support testing confirmed the suitability of critical test methods for their intended use as release specification tests.

**Stability Studies**

The stability program for Fibrin Sealant (Human) included studies under proposed long-term storage (-21 ± 4 °C for (b) (4) months) and accelerated (b) (4) ) conditions. The studies were performed on the conformance DP lots representative of the commercial manufacturing process and encompassed all fill sizes. The studies are now completed, with data meeting specifications for all parameters and all fill sizes throughout storage periods. Based on the data, the proposed shelf-life of 24 months at a temperature of ≤ -18 °C can be granted.

In-use (post-thawing) stability study was performed for Fibrin Sealant (Human) lots at the end of shelf-life which covered all dosage forms. The data support product stability for up to 48 hours at 5 ± 3 °C and up to 24 hours at 25 (b) (4) °C. The storage conditions and handling of Fibrin Sealant (Human) after thawing are accurately described in the labeling.

A Stability Protocol for post-approval testing was revised per FDA request, and is adequate to control DP stability post-approval.

**Evaluation of Safety Regarding Adventitious Agents**

*Viral Safety*

Viral safety of Fibrin Sealant (Human) is based on the control of the starting material (human plasma) and the virus clearance capacity of the manufacturing processes for Human Fibrinogen and Human Thrombin.

The starting material for Fibrinogen and Thrombin is pooled human Source Plasma (21 CFR 640.60) obtained from FDA-licensed plasma collection centers in the United States. All individual plasma donations are tested to be negative for viral serological markers in compliance with the U.S. regulatory requirements stipulated in CFR Subchapter F, Title 21, Part 640, subpart G. All the tests must be non-reactive and the

limit for B19V in each mini-pool must be such to ensure that plasma manufacturing pools do not exceed a titer of $10^4$ IU/mL. The manufacturing plasma pool is also tested and all the tests must be non-reactive.

As described in the previous sections, the potential of viral contamination is further mitigated by inclusion of two validated viral clearance steps, S/D treatment and nanofiltration, in the manufacturing processes for Fibrinogen and Thrombin. The results of these validation studies using viruses with a wide range of physico-chemical characteristics are summarized in Tables 5 and 6 and are sufficient to support effectiveness of viral clearance in the commercial manufacture of Fibrin Sealant (Human):

**TABLE 5. Virus Reduction Factors ($Log_{10}$) For Human Fibrinogen**

| **Manufacturing Step** | **Virus reduction factor ($log_{10}$)*** | | | | | |
|---|---|---|---|---|---|---|
| | **Enveloped viruses** | | | | **Non-enveloped viruses** | |
| | HIV-1 | PRV | WNV | BVDV | HAV | PPV |
| S/D treatment | ≥ 5.33 | ≥ 6.80 | ≥ 5.20 | ≥ 5.60 | n.a. | n.a. |
| Glycine precipitations | n.d. | n.d. | n.d. | n.d. | 5.21 | 2.09 |
| Nanofiltration 35 nm and 20 nm | ≥ 5.57 | ≥ 6.09 | ≥ 4.51 | ≥ 4.53 | 5.22 | 4.37 |
| **Cumulative virus reduction factor ($log_{10}$)** | **≥ 10.90** | **≥ 12.89** | **≥ 9.71** | **≥ 10.13** | **10.43** | **6.46** |

**TABLE 6. Virus Reduction Factors ($Log_{10}$) For Human Thrombin**

| **Manufacturing Step** | **Virus reduction factor ($log_{10}$)*** | | | | | |
|---|---|---|---|---|---|---|
| | **Enveloped viruses** | | | | **Non-enveloped viruses** | |
| | HIV-1 | PRV | WNV | BVDV | HAV | PPV |
| Fraction I precipitation | < 1.0 | 2.13 | 2.78 | 1.34 | 1.18 | < 1.0 |
| S/D treatment | ≥ 5.52 | ≥ 5.85 | ≥ 5.94 | ≥ 5.09 | n.a. | n.a. |
| SP-Sepharose XL chromatography | n.d. | n.d. | n.d. | n.d. | 4.61 | 3.97 |
| Double nanofiltration 15 nm | ≥ 4.03 | ≥ 5.95 | ≥ 5.42 | ≥ 4.93 | 6.56 | 6.14 |
| **Cumulative virus reduction factor ($log_{10}$)** | **≥ 9.55** | **≥ 13.93** | **≥ 14.14** | **≥ 11.36** | **12.35** | **10.11** |

*: Reduction factor below 1 $log_{10}$ is not considered in calculating the global virus reduction;
n.d.: Not done; n.a.: Not applicable;
HIV: human immunodeficiency virus
BVDV: bovine viral diarrhea virus, model for enveloped RNA viruses including HCV;
WNV: West Nile virus, model for enveloped RNA virus;

PRV: pseudorabies virus, model for large enveloped DNA viruses including HBV;
HAV: Hepatitis A virus;
PPV: porcine parvovirus, model for human B19V.

*Non-Viral Pathogen Safety*

The safety with regard to non-viral adventitious agents such as bacteria, fungi, and mycoplasma is ensured through the control of bioburden in source materials, adherence to current good manufacturing practice, validated cleaning/sanitization procedures, in-process control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for Sterility and Endotoxin. The risk of transmissible spongiform encephalopathy (TSE) agents is minimized by excluding donors who are potentially at risk from plasma donation as specified in the current FDA guidance regarding donations collected in the U.S.

(b) (4) raw materials of biological origin are used in the manufacture of Fibrin Sealant (Human). (b) (4) Human albumin, used in the formulation of Human Thrombin, is manufactured by Grifols and licensed in the U.S. for intravenous injections for multiple indications (U.S. License No. 1181).

*Other Raw Materials*

Grifols has established a defined approval and monitoring process for control of raw materials depending on their risk assessment (impact on the production process and product quality). All materials which are in direct contact with the product during manufacture, storage or application (e.g., excipients, primary packaging and other device components) are considered as high risk. Materials with high risk require qualification of both the supplier (collection of documental and historical data, results of latest audits) and material (in-house analysis of product samples). The approved suppliers are monitored by periodic revision of the supplier dossier and audits. In addition to Certificates of Analyses from the manufacturer, Grifols performs in-house all critical tests for each lot of all high-risk materials according to the requirements of USP or/and Ph. Eur in order to release the material for use. For microbiological control, Grifols also performs tests for Endotoxin and Bioburden.

**b) CBER Lot Release**

The Lot Release Protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. A Lot Release Testing Plan was developed by CBER and will be used for routine lot release.

### c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Fibrin Sealant (Human) are listed in Table 7. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

**TABLE 7. Manufacturing Facilities for Fibrin Sealant (Human)**

| Name/Address | FEI number | DUNS number | Inspection/ waiver | Results/ Justification |
|---|---|---|---|---|
| Instituto Grifols, S.A.<br>2 Can Guasch St.<br>Poligono Levante<br>Parets del Valles, Barcelona<br>Spain 08150<br><br>*Drug Substance and Drug Product*<br>Manufacturing, Formulation, Fill/Finish, Labeling and Packaging, Testing | 3002807257 | 465562213 | Pre-License Inspection | CBER March 13 – 24, 2017 Voluntary Action Indicated (VAI) |

CBER performed a pre-license inspection (PLI) of Instituto Grifols from March 13-24, 2017 concurrent with a biennial surveillance inspection by Team Biologics. At the end of the inspection, a single Form FDA 483 was issued that contained observations relating to the PLI and surveillance inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues have been resolved.

### d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

### e) Product Comparability

The Applicant conducted extensive comparability studies for the clinical-scale and commercial-scale processes and provided sufficient process and analytical data to demonstrate that the material used in clinical trials is representative of the material intended for commercial distribution.

### f) Recommendation from the CMC Review

The manufacturing process for Fibrin Sealant (Human) is adequately validated at the commercial scale and sufficiently controlled to assure consistent manufacture of the product that meets acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. The reviewers from Office of Tissues and Advanced Therapies and Office of Compliance and Biologics Quality in CBER and Office of Device Evaluation in CDRH conclude that Grifols has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of Fibrin Sealant (Human).

## 4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The nonclinical program for Fibrin Sealant (Human) consisted of the following studies: 1) assessment of the excipient arginine (Arg); 2) *in vitro* proof-of-concept (POC); 3) pharmacology of drip administration in rabbit and pig models of cardiovascular surgery, and of spray application in a pig model of hepatic surgery; and 4) toxicology of systemic fibrinogen administration in healthy rodents. No animal studies were conducted to evaluate the pharmacodynamics or pharmacokinetics of Fibrin Sealant (Human). No animal studies were performed to assess the potential for carcinogenicity, *in vivo* mutagenicity, reproductive toxicity, or teratogenicity of Fibrin Sealant (Human).

The Arg content in Fibrin Sealant (Human) was similar to that of other approved fibrin sealants. Preliminary POC was demonstrated by applying Fibrin Sealant (Human) onto multiple *in vitro* test surfaces, where similar results for clotting time and surface area coverage were observed for drip and spray applicators. In pharmacology studies conducted in healthy rabbits, drip administration of Fibrin Sealant (Human) was well-tolerated in vascular surgery and reduced surgical time and bleeding (assessed by the change in pre- vs. post-surgery wound dressing mass) compared to sutures alone. In additional pharmacology studies in healthy pigs, drip and spray administration of Fibrin Sealant (Human) during cardiovascular and hepatic surgery, respectively, were well-tolerated without any overt toxicities. The pharmacology results for Fibrin Sealant (Human) were similar to those seen for other approved fibrin sealants.

Acute systemic toxicity studies in healthy mice and rats did not identify any product-related adverse findings following intravenous (IV) bolus administration of the fibrinogen component of Fibrin Sealant (Human). However, this is not the clinical route of administration and only the fibrinogen component was tested. No safety concerns were identified in the resulting data from the nonclinical studies.

## 5. CLINICAL PHARMACOLOGY

This section is not applicable because fibrin sealants exert their effect locally, and there is little (if any) expected systemic exposure to warrant pharmacokinetic assessments.

## 6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

### a) Clinical Program

The clinical program consists of three Phase 3 randomized clinical trials, each evaluating one of three surgery types: vascular surgery, parenchymous (liver) tissue surgery, and soft tissue surgery. In all three trials, the efficacy of Fibrin Sealant (Human) was directly compared with an active control: Manual Compression (MC) in superiority trial IG1101 in vascular surgery, or SURGICEL, an oxidized cellulose hemostasis agent, in non-inferiority trials IG1 102 (parenchymous surgery) and IG1 103 (soft tissue surgery). The three trials are summarized in Table 8.

**TABLE 8: List of All Three Phase 3 Clinical Trials**

| Study no. | Surgery Type | Active Control | Hypothesis testing | Target Bleeding Site Intensity | Primary Efficacy Endpoint |
|---|---|---|---|---|---|
| **IG1101** (N=225) | Vascular Surgery | Manual Compression | Superiority | Moderate | Proportion of subjects achieving hemostasis (Yes/No) at the target bleeding site by 4 minutes (T4) |
| **IG1102** (N=325) | Parenchymous (hepatic) | SURGICEL | Non-inferiority | Moderate | |
| **IG1103** (N=327) | Soft Tissue | SURGICEL | Non-inferiority | Moderate | |

**Study Description**

All three clinical trials were conducted using the same general trial design. The inclusion and exclusion criteria were generally the same except for the type of surgery evaluated in each trial. The key enrollment criteria were males or females of any age who required an elective, non-emergent surgery and an intra-operatively identifiable Target Bleeding Site (TBS) of protocol-defined moderate bleeding intensity. Patients with known sensitivity/reaction to any Fibrin Sealant (Human) component or human blood products, infection at the TBS, or who were pregnant or nursing were excluded. Subjects were eligible to participate after informed consent was obtained.

Each trial consisted of two parts: A Preliminary Part I and a Primary Part II. The purpose of Preliminary Part I of the studies was to ensure that local study teams familiarized themselves with the technique for Fibrin Sealant (Human) application and with intra-operative procedures required by the protocol of the clinical trials. In Study IG1101, all subjects enrolled in Preliminary Part I of the study were treated with Fibrin Sealant (Human); subjects in Primary Part II were randomized in a 2:1 ratio into Fibrin

Sealant (Human) or MC treatment groups. Subjects in Studies IG1102 and IG1103 were randomized in a 1:1 ratio into 1 of 2 treatment groups, Fibrin Sealant (Human) or SURGICEL, in both Preliminary Part I and Primary Part II of the studies.

The primary efficacy endpoint for all three clinical trials was the proportion of subjects in the Primary Part II of the study achieving hemostasis (Yes/No) at the TBS by 4 minutes (T4), following the start of treatment application, without occurrence of re-bleeding and re-application of study treatment after T4 and until the completion of the surgical closure. Secondary endpoints included the proportion of subjects achieving hemostasis at the TBS at 2, 3, 5, 7, and 10 minutes, time to hemostasis (TTH), categorized from ≤2 minutes to ≤10 minutes, and prevalence of treatment failures. Secondary efficacy endpoints were tested per a fixed-sequence testing method. The population for analyses of the primary and secondary efficacy endpoints in all three trials was based on the ITT population in Primary Part II of the trial.

**Clinical Efficacy findings**

In the Primary Part II of Study IG1101, 69.7% (76/109) of the subjects who were randomized to Fibrin Sealant (Human) were male and 30.3% (33/109) were female. In Study IG1102, 53.2% (59/111) of the subjects who were randomized to Fibrin Sealant (Human) in the Primary Part II were male. In the Primary Part II of Study IG1103, 25% (29/116) of the subjects who were randomized to Fibrin Sealant (Human) were male. Overall, across the three trials, of 336 subjects who were randomized to Fibrin Sealant (Human), 48.8% (164/336) were male, maintaining an approximately equal ratio.

In Primary Part II of Studies IG1101, IG1102, and IG1103, the mean age of the subjects who were randomized to Fibrin Sealant (Human) was 64, 60, and 49 years old, respectively.

In Primary Part II, across the three studies, 89.3% (300/336) of the total subjects were White, 8.6% (29/336) were Black, and 2.1% (7/336) were Asian.

Across all three trials, of the total instances where Fibrin Sealant (Human) was applied, 25.7% were vascular surgeries, 37.1% were parenchymous tissue surgeries, and 37.3% were soft tissue surgeries. The mean volume of Fibrin Sealant (Human) applied across all trials was 6.78 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum). The mean volume of Fibrin Sealant (Human) applied in Study IG1 101 was 4.23 mL, with a median of 4.20 mL and a range of 0.3 to 12.0 mL (minimum to maximum). The mean volume of Fibrin Sealant (Human) applied in Studies IG1 102 and IG1 103 combined was 8.07 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum).

**Primary Efficacy Endpoint**

Study IG1 101 was a superiority study, conducted under IND 14988. A total of 166 subjects were randomized in Primary Part II. The proportion of subjects with hemostasis by T4 (Primary efficacy) was 76.1% (83/109 subjects) in the Fibrin Sealant

(Human) group and 22.8% (13/57 subjects) in the MC control group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving Fibrin Sealant (Human) relative to MC was 3.34 (2.01, 5.45). The proportion of hemostasis by T4 was significantly higher in the Fibrin Sealant (Human) group compared to the MC group (p-value <0.001), providing evidence that Fibrin Sealant (Human) is superior to MC and that the primary efficacy objective was achieved in vascular surgeries.

Studies IG102 and IG103 were designed as non-inferiority trials against an approved product (SURGICEL), with a margin of 0.8 for the ratio of proportions of subjects achieving hemostasis by T4.

A total of 224 subjects were randomized to Primary Part II in Study IG1102, under IND 14987. The proportion of subjects with hemostasis by T4 (Primary efficacy) was 92.8% (103/111 subjects) in the Fibrin Sealant (Human) treatment group and 80.5% (91/113 subjects) in the SURGICEL treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving Fibrin Sealant (Human) relative to SURGICEL was 1.15 (1.04, 1.28), providing evidence that Fibrin Sealant (Human) is non-inferior to SURGICEL. The proportion of subjects achieving hemostasis by T4 was significantly higher in the Fibrin Sealant (Human) group compared to the SURGICEL group (p-value = 0.010). Because the lower limit of the 95% CI is above 1, the study provides evidence that Fibrin Sealant (Human) is superior to SURGICEL in parenchymous tissue open surgeries.

A total of 224 subjects were randomized to Primary Part II in Study IG1103, under IND 14986. The proportion of subjects achieving hemostasis by T4 (Primary efficacy) was 82.8% (96/116 subjects) in the Fibrin Sealant (Human) group and 77.8% (84/108 subjects) in the SURGICEL group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving Fibrin Sealant (Human) relative to SURGICEL was 1.06 (0.93, 1.21), providing evidence that Fibrin Sealant (Human) is non-inferior to SURGICEL in soft tissue open surgeries. However, the proportion of hemostasis by T4 was not statistically superior in the Fibrin Sealant (Human) group compared to the SURGICEL group because the lower limit of the 95% CI is less than 1.

There were no missing data in any of the three studies. Results of the primary efficacy endpoint, hemostasis by T4, for the three studies are summarized in Table 9.

**Secondary Efficacy Endpoints**

Secondary endpoints included the proportion of subjects achieving hemostasis at the TBS at 2, 3, 5, 7, and 10 minutes, time to hemostasis (TTH), categorized from ≤ 2 minutes to ≤10 minutes, and prevalence of treatment failures. Overall, in all trials, results of secondary endpoints were supportive of the primary efficacy endpoint.

**TABLE 9: Primary Efficacy (Hemostasis by T4) in Primary Part II of the Three Phase 3 Trials**

| Study No. | Fibrin Sealant (Human) % (n/N) | Control % (n/N) | Risk Ratio* (95% CI) | p-value | Efficacy Result |
|---|---|---|---|---|---|
| IG1 101<br><br>Vascular | 76.1<br>(83/109) | MC<br>22.8<br>(13/57) | 3.34<br>(2.01, 5.45) | <0.001 | Fibrin Sealant (Human) was superior to MC |
| IG1 102<br><br>Liver | 92.8<br>(103/111) | SURGICEL<br>80.5<br>(91/113) | 1.15<br>(1.05, 1.28) | 0.010 | Fibrin Sealant (Human) was non-inferior to SURGICEL** |
| IG1 103<br><br>Soft Tissue | 82.8<br>(96/116) | SURGICEL<br>77.8<br>(84/108) | 1.06<br>(0.93, 1.21) | 0.401 | Fibrin Sealant (Human) was non-inferior to SURGICEL |

*Risk Ratio (RR): Estimated ratio of the proportion of subjects meeting the primary efficacy endpoint in the two treatment groups in Primary Part II: Fibrin Sealant (Human) relative to MC or SURGICEL
** The lower limit of the 95% CI above 1, provides evidence that Fibrin Sealant (Human) is superior to SURGICEL.

**Efficacy Conclusions**

All three Phase 3 trials met their designated primary endpoint: one was a superiority trial in vascular surgery against manual compression (MC), the other two were non-inferiority trials against SURGICEL in parenchymal surgery (Study IG1 102) and soft tissue surgery (Study IG1 103). In the second trial (IG1 102), Fibrin Sealant (Human) met the primary efficacy non-inferiority endpoint, and Fibrin Sealant (Human) was statistically superior to SURGICEL at hemostasis by T4. The secondary efficacy endpoints results also provided additional support for Fibrin Sealant (Human) as an effective adjunct local hemostatic agent in all three Phase 3 trials.

**Bioresearch Monitoring**

Bioresearch Monitoring inspections were issued for two clinical study sites, one domestic and one foreign, that participated in the conduct of Study IG1101, and two additional clinical study sites, one domestic and one foreign, that participated in the conduct of Study IG1103. The inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

### b) Pediatrics

Fibrin Sealant (Human) as an adjunct to hemostasis during surgery was not sufficiently evaluated in pediatric subjects. Of the 11 pediatric subjects treated with Fibrin Sealant (Human) across the three Phase 3 trials, there was no pediatric subject enrolled in Study IG1 101 and only one pediatric subject was randomized to Primary Part II (Study IG1 103). The Applicant has agreed to conduct a postmarketing (PMR) pediatric trial to provide additional safety and effectiveness data in the pediatric population. The initial Pediatric Study Plan (iPSP) and the pediatric clinical trial protocol (Study IG1 405) were previously reviewed and approved by FDA under IND 14986. There is no substantive modification to the pediatric protocol included in the BLA submission. In this study, the different types of surgeries (parenchymous and soft tissue) will be evaluated in a single trial, with the stipulation that at least 50% of surgeries must be hepatic. Because there is a low prevalence of pediatric patients undergoing vascular surgery, it was not considered feasible to include pediatric subjects.

In addition, a new human factors study will be conducted to address deficiencies identified in the initial human factors study completed in February 2017. The new human factors study, IG-PETC-000430_ING, will be conducted as a subpart of the pediatric trial. This modification to the pediatric trial is not expected to substantively impact the pediatric trial design or risk to subjects. The Applicant has agreed to conduct the new human factors study at the same centers participating in the planned pediatric clinical trial in the United States. Study IG1 405 is summarized below.

Study Title: "A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects"

The multicenter Phase 3b trial will enroll a total of 172 subjects, randomized in a 1:1 ratio to Fibrin Sealant (Human) vs. control (EVICEL) as the comparator group. EVICEL is a 2-component (fibrinogen and thrombin) fibrin sealant solution, approved for topical use as an adjunct to hemostasis during surgery. The study was designed to demonstrate non-inferiority if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of the proportion of subjects achieving hemostasis by T4 exceeds 0.8. The key study entrance criteria are:

Pre-operative:

1. <18 years of age
2. Requires an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure

Intra-operative:

1. Presence of an appropriate target bleeding site (TBS) identified by the investigator surgeon
2. TBS is of Grade 1 (mild) or Grade 2 (moderate) bleeding intensity, rated using a 5-point validated bleeding severity scale

The iPSP includes deferrals for all pediatric age groups, from newborn to 17 years of age (inclusive). The age groups included in the study are summarized in Table 10:

**TABLE 10: Study IG1 405: Pediatric Age Groups**

| Age Group | Number of Subjects Planned |
|---|---|
| Adolescents (12 to 17 years) | 100 |
| Children (2 to 11 years) | 50 |
| Infants and toddlers (28 days to 23 months) | 16 |
| Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) | 6 |
| The first 24 subjects to be enrolled in the study will be adolescents (age range 12 to 17 years). | |

Assessments will be performed at baseline, Day 1, Day 4 and Day 30. Intraoperatively, hemostasis will be evaluated at T4 (primary efficacy endpoint) from start, and at T7 and T10 as secondary efficacy endpoints. Safety will be monitored by adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), adverse reactions (ARs), discontinuations due to AEs, clinical laboratory panels, physical examinations, and vital signs.

The timelines for the pediatric study are:

- Final Protocol Submission Date: March 30, 2018
- Study Completion Date: June 30, 2023
- Final Report Submission Date: June 30, 2024

The Applicant's pediatric study protocol and deferral request for the trial were approved at the September 6, 2017 meeting of the Pediatric Research Committee (PeRC). The Protocol will be updated to include a Human Factors validation study as part of the pediatric clinical trial.

### c) Other Special Populations

A total of 172 subjects aged 65 years or older were treated with Fibrin Sealant (Human) across the three trials. Overall, there was no pattern suggesting a unique safety concern for the elderly subjects.

## 7. SAFETY

### Safety Population

Because the trial designs of all three clinical trials were similar and demographics across the trials were generally similar, the safety evaluations for this BLA were based on the pooled safety population, defined as all subjects enrolled in Preliminary Part I plus Primary Part II of the studies. A total of approximately 500 subjects were treated with

Fibrin Sealant (Human), 320 subjects were treated with SURGICEL, and 57 subjects were treated with MC over the three Phase 3 trials. The safety and tolerability of Fibrin Sealant (Human) was assessed by analyzing adverse events (AEs), adverse drug reactions (ADRs), laboratory values (including virus safety assessments and immunogenicity), vital signs, and physical assessments. All reported AEs were coded and summarized by system organ class (SOC) and preferred term (PT) per MedDRA version 16.0.

**Common Treatment Emergent Adverse Events (TEAEs)**

The most common Treatment Emergent Adverse Events (TEAEs) reported in ≥5% of Subjects by Preferred Term within a treatment group in the three treatment groups were similar (Tables 11 and 12):

- Fibrin Sealant (Human): procedural pain (41.8%), nausea (13.4%), and pyrexia (10%)
- SURGICEL: procedural pain (45.9%), nausea (17.5%), anemia (12.5%), pyrexia (10.9%), constipation (10.6%), and procedural nausea (10.0%)
- MC: procedural pain (36.8%) and pyrexia (10.5%)

Overall, across all trials, the most frequently reported TEAEs were procedural pain, nausea, and pyrexia.

**TABLE 11: Summary of Adverse Events by Treatment Group in All 3 Studies (Safety Population)**

| Adverse Events Categories | Pooled Safety Fibrin Sealant (Human) N=500 n (%) | Pooled Safety SURGICEL N=320 n (%) | MC N=57 n (%) |
|---|---|---|---|
| Subjects with any TEAE<br>Total number of TEAEs | 419 (83.8)<br>1763 | 278 (86.9)<br>1263 | 44 (77.2)<br>104 |
| Subjects with any Adverse Drug Reaction (ADR)<br>Total number of ADRs | 64 (12.8)<br>128 | 27 (8.4)<br>65 | 3 (5.3)<br>5 |
| Subjects with any ADR attributable to application technique<br>Total number of ADRs attributable to application technique | 1 (0.2)<br>2 | 0<br>0 | 0<br>0 |
| Subjects with any SAE<br>Total number of SAEs | 81 (16.2)<br>167 | 41 (12.8)<br>65 | 11 (19.3)<br>14 |
| Subjects with any TEAE with outcome of death | 13 (2.6) | 4 (1.3) | 0 |
| Subjects with any serious ADR<br>Total number of serious ADRs | 9 (1.8)<br>15 | 0<br>0 | 1 (1.8)<br>1 |
| Subjects with any AE leading to withdrawal<br>Total number of AEs leading to withdrawal | 0<br>0 | 0<br>0 | 0<br>0 |

Source: Table 5.3 (Module 5.3.5.3); BLA submission

**TABLE 12: Treatment-Emergent Adverse Events Reported in ≥5% of Subjects by Preferred Term within a Treatment Group in All 3 Studies (Safety Population)**

| Preferred Term | Fibrin Sealant (Human) N=500 n (%) | SURGICEL N=320 n (%) | Manual Compression N=57 n (%) |
|---|---|---|---|
| Procedural pain | 209 (41.8) | 147 (45.9) | 21 (36.8) |
| Nausea | 67 (13.4) | 56 (17.5) | 2 (3.5) |
| Pyrexia (fever) | 50 (10.0) | 35 (10.9) | 6 (10.5) |
| Anemia | 45 (9.0) | 40 (12.5) | 2 (3.5) |
| Constipation | 46 (9.2) | 34 (10.6) | 4 (7.0) |
| Hypotension | 36 (7.2) | 15 (4.7) | 3 (5.3) |
| Hypertension | 35 (7.0) | 24 (7.5) | 1 (1.8) |
| Oedema (swelling) peripheral | 30 (6.0) | 14 (4.4) | 1 (1.8) |
| Vomiting | 29 (5.8) | 26 (8.1) | 3 (5.3) |
| Incision site pain | 28 (5.6) | 18 (5.6) | 1 (1.8) |
| Procedural nausea | 24 (4.8) | 32 (10.0) | 0 |
| Tachycardia | 23 (4.6) | 31 (9.7) | 1 (1.8) |
| Pruritus | 23 (4.6) | 22 (6.9) | 0 |
| Body temperature increased | 11 (2.2) | 2 (0.6) | 4 (7.0) |
| Hyperglycemia | 9 (1.8) | 18 (5.6) | 0 |
| Hypophosphatemia | 9 (1.8) | 16 (5.0) | 0 |
| Vascular graft thrombosis | 2 (0.4) | 0 | 3 (5.3) |

**Serious Adverse Events**

Serious Adverse Events were reported in 81/500 (16.2%) subjects in the Fibrin Sealant (Human) treatment group, 41/320 (12.8%) subjects in the SURGICEL treatment group, and 11/57 (19.3%) subjects in the MC treatment group (Table 11). Of the SAEs in the Fibrin Sealant (Human) group (72/81 subjects), FDA reviewers determined that the majority were unrelated to study treatment in all except 9 subjects (9/81 subjects). The following SAEs reported from four subjects are at least possibly related to study treatment: cellulitis, parvovirus B19 (B19V) test positive (determined not to be treatment-emergent viral infection), abdominal wound dehiscence, and peritonitis. No subject in any of the three studies had an AE leading to withdrawal. SAEs included 13/500 (2.6%) deaths in the Fibrin Sealant (Human) treatment group, 4/320 (1.3%) deaths in the SURGICEL treatment group, and no deaths in the MC treatment group. Deaths are further discussed in the Adverse Events of Special Interest section below.

All SAEs in the SURGICEL and MC treatment groups were determined by FDA reviewers to be unrelated to study treatment.

Overall, there were no substantial differences noted in SAE incidences among treatment groups, when these SAEs were reviewed within the context of known potential risk of the class of fibrin sealant products.

Safety Review Issue: In Study IG1 102, SAEs of pulmonary embolism and deep vein thrombosis reported in a subject were assessed by investigators and the Applicant to be unlikely related to Fibrin Sealant (Human). Because fibrin sealants as a class may be thrombogenic (if accidentally administered intravascularly), the FDA clinical and pharmacovigilance reviewers determined that these SAEs could be possibly related to the product.

**Adverse Events of Special Interest**

The thrombogenic nature of fibrin sealant products makes thromboembolic events – deep vein thrombosis, pulmonary embolism, and myocardial infraction – of special interest.

**Thromboembolic Events**

Cardiac and thrombotic SAEs occurring after exposure to fibrinogen and thrombin are suspicious for being possibly related, depending on when the event occurred after the time of exposure. Overall, the number of thromboembolic events reported across the three trials was relatively small. Additionally, the review of these events for Fibrin Sealant (Human) was performed within 1) the context of the known thromboembolic risks of the fibrin sealant product class, 2) the fact that the comparators inherently carry lower risks: manual compression only or SURGICEL, a cellulose hemostat sheet applied topically as compared to the dripping or spraying route of administration of the Fibrin Sealant (Human) liquid solution, and 3) the nature of the surgeries and underlying conditions of the subjects. These factors are taken into consideration in concluding that the safety data for Fibrin Sealant (Human) do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery.

**Deaths**

Across all three trials, there were 13 deaths reported with use of Fibrin Sealant (Human) (13/500 [2.6%]) as compared to 4/320 [1.3%] in the SURGICEL group. Deaths were more frequently reported in Study IG1 102; of the 13 deaths reported for Fibrin Sealant (Human), 7 deaths occurred in the IG1 102 trial. The investigator and Applicant assessed all the deaths, including all deaths in the IG1 102 trial, to be unrelated to study treatment. Of the deaths reported in subjects who were treated with Fibrin Sealant (Human), 4 deaths occurred less than 1 week after Fibrin Sealant (Human) administration. Safety data for Fibrin Sealant (Human) were reviewed within the context of known risks of products in the fibrin sealant class - including thromboses, air embolus, adhesions - and the nature of the surgeries and underlying conditions of the subjects. Although there were more deaths with Fibrin Sealant (Human) than with the comparator SURGICEL, most of the deaths occurred more than one week after the time of exposure, and no discernable pattern was detected from review of the death

narratives for possible relatedness. Except for Subject 2072001 (Vena Cava thrombosis occurring 5 days post-exposure), which may be possibly related, the deaths are considered by FDA reviewers unrelated to the study drug. The safety data do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery.

**Immunogenicity (Safety)**

No immunogenicity occurred from the treatment with Fibrin Sealant (Human).

**Pharmacovigilance**

Fibrin sealants have been available and in use for many years, and are generally considered to be a safe adjunct to hemostasis in surgical procedures. Safety data for Fibrin Sealant (Human) do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery that have not been previously identified for fibrin sealants as a class. The Applicant proposes routine pharmacovigilance for post-market safety monitoring. However, the submitted data do not provide evidence of safety of Fibrin Sealant (Human) as compared to any other available fibrin sealant product. A clinical trial is currently being planned to assess the efficacy and safety of Fibrin Sealant (Human) as an adjunct to hemostasis during surgery in pediatric subjects (Study IG1405). Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Study IG1405, comparing safety and efficacy of Fibrin Sealant (Human) with EVICEL in pediatric subjects, may fulfill PREA requirements, as well as provide additional post-marketing study data of use with a fibrin sealant as a comparator. The primary efficacy objective is to evaluate if Fibrin Sealant (Human) is non-inferior to EVICEL in obtaining hemostasis with no occurrence of rebleeding. The study is planned to include 172 pediatric subjects (86 in the Fibrin Sealant (Human) group and 86 in the EVICEL comparator group, with a 1:1 randomization ratio). Safety will be monitored for Fibrin Sealant (Human) and EVICEL. The protocol was submitted on February 6, 2017. The Applicant also committed to conducting a new Human Factors validation study, and incorporate it into the upcoming pediatric clinical trial. The final protocol for the combined study will be submitted in March 2018 and the study will be completed in June 2023. The Division of Epidemiology (DE) agrees with the pharmacovigilance activities proposed by the Applicant. The submitted pharmacovigilance plan is acceptable.

**Safety Conclusions**

The safety data for Fibrin Sealant (Human) were reviewed within the context of known risks of products in the fibrin sealant class, including thromboses, air embolus, and adhesions. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS). In addition, the Applicant has agreed to

conduct a (deferred) postmarketing prospective, randomized, controlled pediatric trial that will further evaluate safety (and efficacy), comparing Fibrin Sealant (Human) to another frozen 2-component (fibrinogen and thrombin) fibrin sealant (EVICEL) as active control. The trial will include a subpart for a new human factors study. This pediatric trial will provide additional postmarketing safety data.

The safety data from all three studies demonstrated that Fibrin Sealant (Human) was reasonably safe and generally well tolerated as a local adjunct hemostatic agent and do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery.

## 8. ADVISORY COMMITTEE MEETING

The Division of Plasma Protein Therapeutics and the Division of Clinical Evaluation and Pharmacology/Toxicology in the Office of Tissues and Advanced Therapies reviewed the information in this application and determined that referral to the Blood Products Advisory Committee prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The new molecular entity (NME) provision does not apply to Fibrin Sealant (Human) as it does not represent a novel product class. Fibrin sealants have been used as an adjunct to hemostasis since the late 1970's in Europe and since 1998 in the United States.

- The mechanism of action of fibrin sealants (fibrinogen/thrombin products) and their function in blood coagulation and control of local hemorrhage are well studied and understood.

- The Fibrinogen and Thrombin components of Fibrin Sealant (Human) are adequately characterized and demonstrate expected physicochemical, biochemical and functional properties and clot structure characteristics.

- Product safety with regard to adventitious viruses is provided by the adequate control of the starting materials and the virus clearance capacity of the manufacturing processes for Human Fibrinogen and Human Thrombin.

- The design of the clinical studies to evaluate the safety and efficacy of Fibrin Sealant (Human) for the proposed indications was adequate and the efficacy and safety results of the studies did not raise any concerns.

- Review of information submitted in the BLA for Fibrin Sealant (Human) did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

## 9. OTHER RELEVANT REGULATORY ISSUES

This application is not affected by the Application Integrity Policy. The notable issues raised during the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences.

## 10. LABELING

### a) Proprietary Name

The proposed proprietary name, VERASEAL, was reviewed by the Advertising and Promotional Labeling Branch (APLB). The proposed name was found to be misleading and fanciful within the meaning of 21 CFR 201.10(c)(3), 202.1(e)(5)(i), and 202.1(e)(6)(i). The proposed name may cause medication errors due to its high phonetic and orthographic similarity to other currently marketed products within the meaning of 21 CFR 201.10(c)(5). VERASEAL was determined to be unacceptable as the proprietary name for the product by the Agency and this determination was provided to the Applicant on February 3, 2017. There is no proprietary name for the product.

### b) Prescribing Information/Carton and Container Labels

The prescribing information, product package and container labels were reviewed, commented on, and revised by the appropriate discipline reviewers, and by APLB from a promotional and comprehension perspective. Notable issues that were discussed and resolved include description of product handling, assembly, and administration and presentation of clinical trials results.

FDA comments regarding the product labeling were conveyed to the Applicant on October 3, 18, and 25, 2017. The final version of Full Prescribing Information (FPI) submitted on October 27, 2017 was determined to be acceptable. Carton and container labels submitted to the BLA on October 11, 2017 were considered acceptable. A copy of the FPI is attached.

## 11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

### a) Recommended Regulatory Action

The CBER review committee recommends **APPROVAL** of this BLA for Fibrin Sealant (Human). The manufacturing process for Fibrin Sealant (Human) is considered adequately validated and controlled. Efficacy and safety clinical data for Fibrin Sealant (Human) support a favorable benefit/risk determination for its topical use as an adjunct to hemostasis for mild to moderate bleeding in adults 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.

### b) Benefit/Risk Assessment

All three Phase 3 trials met their primary efficacy endpoint of achieving hemostasis at the Target Bleeding Site by 4 minutes. The benefit consistently shown was rapid hemostasis during a variety of elective surgical procedures to mitigate bleeding complications during surgery. The potential risks (thromboses, adhesions and air embolism), are expected to be rare if administered per labeling instructions and precautions. The nature and frequency of these risks are consistent with those in the fibrin sealant product class and were not higher with Fibrin Sealant (Human) than other similar fibrin sealant products. Thus, the benefits of Fibrin Sealant (Human) justify its risks.

### c) Recommendation for Postmarketing Activities

The CBER review committee agrees with the pharmacovigilance activities proposed by the Applicant. The submitted pharmacovigilance plan described in section 7 is acceptable. The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS) or a required post-marketing (PMR) study, other than the deferred pediatric clinical trial and a new Human Factors study as a subpart of the pediatric trial under PREA.

**Postmarketing Studies subject to reporting requirements UNDER SECTION 506B**

As stated in Amendment 64 dated October 30, 2017, Instituto Grifols commits to the following to fulfill PREA requirement:

1. Instituto Grifols, S.A. commits to evaluating the safety and efficacy of FIBRIN SEALANT (Human) as an adjunct to hemostasis during surgery in pediatric patients < 18 years of age in the deferred pediatric clinical trial under protocol IG1405 entitled “A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects.” Instituto Grifols, S.A. also commits to conducting a study of the Human Factors assessment as part of the pediatric trial. The timelines for the combined PREA PMR study are as follows:

   Final Protocol Submission Date: March 30, 2018
   Study Completion Date: June 30, 2023
   Final Report Submission Date: June 30, 2024

**Postmarketing Studies not subject to reporting requirements UNDER SECTION 506B**

As stated in Amendment 53 dated October 5, 2017, Instituto Grifols commits to the following:

1. Instituto Grifols, S.A. commits to providing results from small-scale studies for the (b) (4)

   The final results will be submitted as a "Postmarketing Study Commitment - Final Study Report" by December 31, 2018.

   Final Report Submission Date: December 31, 2018