



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology**

**Fibrin Sealant (Human) BLA 125640
Pharmacovigilance Plan Review Memorandum**

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Subject: Pharmacovigilance Plan Review Memorandum

Applicant: Instituto Grifols, S.A.

Proposed Trade Name: Fibrin Sealant (Human)

BLA Submission: Original BLA 125640

Proposed Indication: 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.

Action Due Date: November 3, 2017

1. INTRODUCTION

1.1 Objectives/Scope

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies to evaluate the submitted pharmacovigilance plan for BLA 125640, Fibrin Sealant (Human). The BLA 125640 is seeking initial approval of the product Fibrin Sealant (Human), Instituto Grifols, S.A. The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies, should the product be approved.

1.2 Product Description

Fibrin Sealant (Human), which will hereafter be referred to as “FS Grifols,” is a fibrin sealant product composed of the active substances human fibrinogen and human thrombin. The proposed indication for FS Grifols is as an adjunct to hemostasis for mild to moderate bleeding in adult patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Per the sponsor, FS Grifols is effective in heparinized patients.¹ The human fibrin adhesion system initiates the last phase of the physiologic blood coagulation system, which generates a cross-linked fibrin clot when the components are mixed. The clot then adheres to proteins such as collagen, fibronectin, von Willebrand factor and cell surface receptors, which results in hemostasis and wound healing. FS Grifols is proposed for topical use only, including intra-abdominal use such as use on the surface of the liver. Intravascular administration can lead to thrombosis and is contraindicated.²

FS Grifols is differentiated from existing fibrin sealant products by the addition of 2 steps in the manufacturing process involved in viral inactivation. These two steps include: 1) solvent-detergent treatment and 2) double nanofiltration. Solvent-detergent treatment has a high capacity for inactivation of enveloped viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). Nanofiltration excludes virus particles on a size dependent basis. Per the sponsor, this technique is effective at removing both enveloped and non-enveloped viruses. To minimize the potential transmission of spongiform encephalopathy, FS Grifols contains exclusively non-ruminant origin products.³

The product is delivered by dripping or spraying on the bleeding site and it is packaged with a syringe holder. A spray device (Fibrijets Gas Assisted Applicator)⁴ is to be made available separately. The mechanism of the spray device is similar to existing spray devices packaged with other licensed fibrin sealant products. CDRH has been consulted for evaluation of safety of the spray device. Please refer to the CDRH memo for further discussion on the spray device.

¹ Risk management plan

² Fibrin Sealant Grifols Part I: Product Overview

³ Fibrin Sealant Grifols Risk Management Plan

⁴ 510K # K012868-253999

The required dose is dependent on the size of the area to be treated. When the dripping method of administration is used, FS Grifols is applied to cover the surface area in a 1 mm thick layer. When applied by spraying, FS Grifols is administered to cover the surface area in a thin layer of unspecified thickness. This is a standard method of applying fibrin sealants. The concentrations of the fibrin and thrombin are the same in all kits, specifically, human fibrinogen 80 mg/mL and human thrombin 500IU/mL.

1.3 Regulatory History

FS Grifols has not been approved in any country. There are no post-marketing data to review.

2. MATERIALS REVIEWED

Document Reviewed	Source
1.16.1 Risk Management Plan 5.3.5.1 Clinical Study Reports 5.3.5.3 Integrated Summary of Safety 1.14 Proposed labeling and proposed Package Insert	BLA 125640
Input from Clinical and Statistical reviewers	CBER staff

3. SUMMARY OF CLINICAL TRIAL EXPOSURE

FS Grifols was evaluated in three phase 3 safety and efficacy clinical trials completed at the time of this submission. Subjects were treated during three surgery types, including vascular surgery (IG1101), parenchymous tissue surgeries (IG1102), and soft tissue surgeries (IG1103).

Table1. List of Clinical Trials

Study no.	Study type	Objective	Design	Population	Treatment	Duration	Exposed FS Grifols	Comparator	Report location
IG1101	Phase 3	Efficacy and safety	Randomized, active-controlled	Vascular Surgery	FS Grifols ≤6 ml vs. MC*	Single intraop	168	Manual compression (57)	5.3.5.1
IG1102	Phase 3	Efficacy and safety	Randomized, active-controlled	Parenchymous Surgery	FS Grifols ≤12 ml vs. Surgicel	Single intraop	163	Surgicel (162)	5.3.5.1
IG1103	Phase 3	Efficacy and safety	Randomized, active-controlled	Soft Tissue Surgery	FS Grifols ≤12 ml vs. Surgicel	Single intraop	169	Surgicel (158)	5.3.5.1

*MC = manual compression

A total of 500 subjects were exposed to FS Grifols over the 3 clinical trials. For vascular surgery, 2 kits were provided per subject. For parenchymal and soft tissue surgeries, 3 kits were provided per subject. The surgeon was permitted to apply ≤6mL for vascular surgery and ≤ 12 mL for parenchymal and soft tissue surgery. A total of 57 subjects in the vascular surgery trial (IG1101) received only manual compression (MC) as a control intervention. A total of 320 subjects received Surgicel (Oxidized regenerated cellulose) as a comparator during two clinical trials (IG1102 and IG1103). Four 4” x 8” sheets of Surgicel were made available for use during the surgery. The number of sheets applied was at the surgeon’s discretion.

4. SUMMARY OF CLINICAL SAFETY

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

This study was intended to demonstrate that the application of FS Grifols provides measurable benefit when compared to hemostasis achieved by mechanical pressure alone. In this study, FS Grifols is administered by topically dripping the product during vascular surgery procedures. A total of 168 subjects were exposed to FS Grifols, while 57 received MC only.

The proportion of subjects in whom treatment-emergent adverse events (TEAEs) were reported was similar between the treatment groups (FS Grifols, 81%; MC, 77.2%). The most commonly reported TEAEs are summarized in the table below:

Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Subjects within a Treatment Group		
Preferred Term	FS Grifols, n=168 (%)	MC, n=57 (%)
Any TEAE	136 (81.0)	44 (77.2)
Procedural Pain	58 (34.5)	21 (36.8)
Pyrexia	19 (11.3)	6 (10.5)
Peripheral Edema	13 (7.7)	1 (1.8)
Body temperature increased	10 (6.0)	4 (7.0)
Anemia	10 (6.0)	2 (3.5)
Nausea	10 (6.0)	2 (3.5)
Post op anemia	9 (5.4)	2 (3.5)
Constipation	7 (4.2)	4 (7.0)
Vomiting	4 (2.4)	3 (5.3)
Vascular Graft Thrombosis	2 (1.2)	3 (5.3)

Of the frequently reported TEAEs, a notable imbalance in the number of subjects who sustained peripheral edema after receiving FS Grifols was observed. This finding was not unexpected given the sustained vascular effects of the product compared to manual compression. All of these AEs were reported to have resolved.

TEAEs graded as severe by Grifols were infrequently reported.⁵ The most commonly reported severe TEAEs observed are summarized in the table below:

Severe Treatment-Emergent Adverse Events Reported in ≥ 2 Subjects		
Preferred Term	FS Grifols n=168 (%)	MC n=57 (%)

⁵ Integrated Summary of Safety 7.1.2 p. 30

Myocardial Infarction	2 (1.2)	1 (1.8)
Post-op wound infection	2 (1.2)	1 (1.8)
Wound infection	2 (1.2)	0
Re-occlusion	2 (1.2)	0
Pneumonia	2 (1.2)	0
Acute Respiratory Infection	2 (1.2)	0

AEs with the outcome of death were infrequently reported (2.4% of FS Grifols subject vs. 0 MC subjects). All deaths were considered unrelated to study drug by the sponsor. Death AEs will be further discussed in Section 4.1.

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

This study was designed to evaluate the safety and efficacy of FS Grifols versus Surgicel in subjects undergoing open surgical procedures where bleeding was present on parenchymal tissue. In this study, FS Grifols was topically administered by spraying. 163 subjects were randomized to receive FS Grifols, and 162 received Surgicel. A total of 11/163 subjects (6.7%) experienced TEAEs that were possibly related to treatment per the sponsor, compared to 3/162 (1.9%) in the Surgicel group. The most frequently reported TEAEs, occurring in more than 5% of subjects, were procedural pain (36.2% in FS Grifols vs. 37.7% in the Surgicel group), nausea (20.9% vs. 23.5%), and hypotension (14.1% vs. 6.2%). The most commonly reported TEAEs are summarized in the table below:

Treatment-Emergent Adverse Events Reported in \geq 5% of Subjects within a Treatment Group		
Preferred Term	FS Grifols, n=163 (%)	Surgicel, n=162 (%)
Any TEAE	134 (82.2)	139 (85.8)
Procedural Pain	59 (36.2)	61 (37.7)
Nausea	34 (20.9)	38 (23.5)
Hypotension	23 (14.1)	10 (6.2)
Pyrexia	17 (10.4)	20 (12.3)
Tachycardia	14 (8.6)	24 (14.8)
Hypertension	14 (8.6)	12 (7.4)
Peripheral Edema	14 (8.6)	11 (6.8)
Vomiting	13 (8.0)	17 (10.5)
Pruritus	12 (7.4)	12 (7.4)
Incisional site pain	12 (7.4)	11 (6.8)
Pleural effusion	12 (7.4)	9 (5.6)
Atelectasis	11 (6.7)	10 (6.2)
Abdominal Pain	11 (6.7)	3 (1.9)
Procedural Hemorrhage	9 (5.5)	4 (2.5)
Dyspnea	3 (1.8)	11 (6.8)

Treatment-emergent adverse events described as severe by Grifols were reported in 18.4% of the FS Grifols subjects and 14.2% of Surgicel subjects.

Severe Treatment-Emergent Adverse Events Reported in ≥ 2 subjects within a Treatment Group		
Preferred term	FS Grifols, n=163 (%)	Surgicel, n=162 (%)
Acute Renal Failure	3 (1.8)	1 (0.6)
Respiratory Failure	3 (1.8)	1 (0.6)
Hypotension	3 (1.8)	1 (0.6)
Sepsis	2 (1.2)	2 (1.2)
Hepatic Failure	2 (1.2)	1 (0.6)
Thrombocytopenia	2 (1.2)	0
Pneumonia	2 (1.2)	0
Pleural Effusion	2 (1.2)	0
Pulmonary Embolism	3 (1.8)	2 (1.2)

In Study IG1102, AEs with the outcome of death were more frequently reported in FS Grifols subjects (7 FS Grifols vs. 3 Surgicel subjects). All were considered by the sponsor to be unrelated to study drug. Due to the imbalance in number of deaths related to FS Grifols, an information request was submitted, requesting details of the 7 deaths reported. Requested information included operative reports, date of death relative to exposure date, and concomitant medications or medical history. The death reports were reviewed, and no patterns in the causes of death or case histories were noted. Please see section 4.1 for further discussion about death reports.

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

This study was intended to evaluate safety and efficacy of FS Grifols as used in retroperitoneal and pelvic surgeries, and during mastopexies and abdominoplasties. 167 subjects were randomized to receive FS Grifols, and 158 were randomized to receive Surgicel. 18.9% of the FS Grifols group and 15.2% of the Surgicel group experienced AEs. The most frequently reported TEAEs were procedural pain (54.5% v. 54.4%), and nausea (13.6% v.11.4%).

Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Subjects within a Treatment Group		
Preferred Term	FS Grifols, n=169 (%)	Surgicel, n=158 (%)
Procedural Pain	92 (54.4)	86 (54.4)
Nausea	24 (14.2)	31 (19.6)
Constipation	19 (11.2)	11 (7.0)
Pyrexia	14 (8.3)	15 (9.5)

Anemia	13 (7.7)	14 (8.3)
Hypertension	13 (7.7)	12 (7.1)
Vomiting	12 (7.1)	9 (5.7)
Hypotension	11 (6.5)	5 (3.2)
Pruritus	9 (5.3)	10(6.3)
Incisional Pain	9 (5.3)	7 (4.4)
Cervicitis	9(5.3)	6 (3.8)
Urinary Tract Infection	1 (0.6)	9 (5.7)

TEAEs described as severe by Grifols were infrequently reported, and no imbalances of concern are observed. The most commonly reported severe TEAEs observed re summarized in the table below:

Severe Treatment-Emergent Adverse Events Reported in ≥ 2 subjects within a Treatment Group		
Preferred term	FS Grifols, n=169 (%)	Surgicel, n=158 (%)
Anemia	1 (0.6)	4 (2.5)
Pyelonephritis	0	3 (1.9)
Sepsis	2 (1.2)	1 (0.6)
Procedural Pain	1 (0.6)	2 (1.3)
Hypocalcemia	2 (1.2)	1 (0.6)
Ileus	2 (1.2)	0
Respiratory failure	2 (1.2)	0

AEs with the outcome of death were infrequently reported (2 FS Grifols subjects vs. 1 Surgical subject). All were considered by the sponsor to be unrelated to study drug. Death AEs will be further discussed in Section 4.1.

4.1 Death Reports

The following table summarizes deaths which occurred in study participants. The reported “Event Day” refers to the day that death occurred, with day 0 being the day of exposure.

Subject	Study	Product	Preferred Term	Event Day
1321004	IG1101/vascul.	FS Grifols	Death (not otherwise specified)	11
1491002	IG1101/vascul.	FS Grifols	Myocardial Infarction	42
4091003	IG1101/vascul.	FS Grifols	Gastrointestinal hemorrhage	35
5001032	IG1101/vascul.	FS Grifols	Multi-organ failure	3
2072001	IG1102/parench.	FS Grifols	Respiratory failure, vena cava	4

			thrombosis, Cardiac Arrest	
2072004	IG1102/parench.	FS Grifols	Hypotension, Respiratory failure, Hepatic Failure	5
2312001	IG1102/parench.	FS Grifols	Septic Shock	39
2322013	IG1102/parench.	FS Grifols	Brain Injury(anoxia)	23
6202008	IG1102/parench.	FS Grifols	Hepatic necrosis, Liver Abscess	31
6202028	IG1102/parench.	FS Grifols	Abdominal wound dehiscence, intestinal perforation, Wound evisceration, Sepsis	36
6212010	IG1102/parench.	FS Grifols	Deep Vein Thrombosis	52
3073009	IG1103/soft tiss.	FS Grifols	Cardiac Arrest	27
4053011	IG 1103/soft tiss.	FS Grifols	Respiratory Fail	5

In total, there were 13 deaths reported with use of FS Grifols across all three studies (13/500 [2.6%]) as compared to 4/320 [1.3%] in the comparator groups (Surgicel and manual compression). Although there were more deaths reported in FS Grifols patients than with controls, many of the deaths occurred more than two weeks after product exposure, and there were no observable patterns or similarities in the case histories of subjects who died following exposure to FS Grifols. Review of the case narratives demonstrates no clear attributability to the product.

5.0 Integrated Summary of Safety

As noted above, three phase 3 clinical trials for safety and efficacy have been completed using Fibrin Sealant Grifols as an adjunct to hemostasis during vascular surgery, parenchymous tissue surgery and soft tissue surgery. The safety data is evaluated within the context of several known risks of products in the fibrin sealant class, which include thromboses, adhesions, and air embolus when administered via spray device. Of note, there were no cases of either adhesion or air embolism reported in these study data.

The overall number of TEAEs was similar for the FS Grifols group (83.8%), the Surgicel group (86.9%), and the manual compression group (77.2%). The most commonly reported TEAEs occurred with similar incidence in both groups.

The thrombogenic nature of fibrin sealant products makes thromboembolic events (TEEs), including deep vein thrombosis, pulmonary embolism, and myocardial infarction, events of special interest. An information request was sent to the sponsor to determine the total number of TEEs that occurred during all clinical trials, regardless of severity or sponsor’s assessment of attributability to the product. The sponsor’s response is summarized in the table below:

Thromboembolic Events in the Clinical Safety Database

Preferred Term	FS Grifols N=500 N (%)	Surgicel N=320 N (%)	Manual Compression N=57 N (%)
Deep vein thrombosis	5 (1)	2 (0.6)	0
Pulmonary embolism	5 (1)	2 (0.6)	0
Myocardial infarction	2 (0.4)	0	1 (1.8)

Note: For each preferred term, subjects are counted only once.

The number of TEEs observed in the trials was small, and the proportion of subjects in the treatment groups that sustained these AEs was similar. This reviewer considers TEEs as possibly treatment-related in the context of fibrin sealant use, which is known to be thrombogenic.⁶ Given that the controls used were not fibrin sealants products and thus carry an inherently lower risk of TEEs, the small imbalance is expected.

Finally, TEAEs included 13/500 (2.6%) deaths in FS Grifols and 4/320 (1.3%) deaths in the Surgicel group. The Sponsor has assessed the deaths reported to be not related to the product. The variety of causes and the timing of the reported deaths casts some doubt on the degree to which the product is attributable. However, this reviewer believes that deaths involving myocardial infarction and/or vena cava thrombosis are possibly related given the documented relationship between fibrin sealant products and thromboses.

6.0 Post-licensure Safety Data

There are no post-licensure materials for review, as the product has not been marketed in any country.

7.0 LITERATURE REVIEW

Literature search of PubMed for “fibrin sealant Grifols,” “FS Grifols,” “fibrin sealant” and “Grifols” yielded no literature articles. There is no published clinical data for FS Grifols or for the previously proposed proprietary name “VeraSeal.”

8.0 PHARMACOVIGILANCE PLAN REVIEW

The Pharmacovigilance Plan submitted provides details of the pharmacovigilance activities to be

⁶ Clotting factor product administration and same-day occurrence of thrombotic events, as recorded in large healthcare database during 2008-2013. Ekezue BF et al. J Thromb Haemost. 2015 Dec;13(12):2168-79.

applied to the medicinal products by reviewing each safety concern of the product. The pharmacovigilance (PV) system implemented at Grifols provides a mechanism to report, collect and assess suspected adverse event reports with Grifols products licensed worldwide. It allows assessment of adverse events for expedited and timely evaluation and provides information on the safety profile of the products.

Safety concerns and overview of planned pharmacovigilance actions⁷

The important identified risks, important potential risks, unassessed risks, and associated planned pharmacovigilance activities are presented below.

Safety Concern	Comment
Important identified risk Lack of Efficacy resulting in re-bleeding	Routine pharmacovigilance
Important potential risk Transmission of infectious agents	Measures to prevent infections include selection of donors, screening of individual donations and plasma pools, inclusion of effective manufacturing steps for inactivation/removal of viruses. Additionally, only non-ruminant sources are used. This risk is addressed by routine pharmacovigilance.
Important potential risk Hypersensitivity and/or anaphylaxis	This risk is addressed by routine pharmacovigilance.
Important potential risk Tissue Adhesion	Tissue adhesion and the associated complications are a known risk of fibrin sealant products. Care is to be taken that body parts outside of the desired application area <i>are</i> sufficiently protected to prevent tissue adhesion at undesired sites. Application errors or uncontrolled application to other surgical sites may lead to undesired gluing of other organs/locations. This risk is addressed by labeling and routine

⁷ 1.16.1 Risk Management Plan_Sep 2016

	pharmacovigilance.
Important potential risk Air or Gas embolism	Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulators. This event appears to be related to use of the spray device at higher than recommended pressures, or close proximity to the tissue surface. Any product delivered by a spray device can carry the risk of air embolism. This risk is addressed by adequate labeling and routine pharmacovigilance. Assessment of the adequacy of this risk mitigation strategy is being completed within CDRH.
Important potential risk Thromboembolic events	Life threatening thromboembolic complications may occur if FS Grifols is unintentionally administered intravascularly. This is expected to carry the same risk as any other fibrin sealant product. This risk is addressed by labeling and routine pharmacovigilance.
Important missing information Use in pediatric populations	IG1405: A Prospective, Controlled, Randomized, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols as an adjunct to Haemostasis during Surgery in Pediatric Subjects.
Important missing information Use in pregnant or lactating women	Routine pharmacovigilance

The sponsor proposes routine pharmacovigilance for post-market safety monitoring, should the product be approved. Routine pharmacovigilance monitoring will be “completed according to regulation” (PVP, p.5). This would include the submission of all serious, unexpected (unlabeled) AE reports to FDA within 15 days (expedited reporting) and the quarterly submission of Periodic Adverse Experience Reports (PAERs) for the first 3 years after licensure. Routine pharmacovigilance also includes continuous monitoring of the safety profile including signal detection, issue evaluation, updating labeling as necessary, and liaison with regulatory authorities.

Additionally, a clinical trial is currently being planned to assess the efficacy and safety of FS Grifols as an adjunct to hemostasis during surgery in pediatric subjects (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. The protocol was submitted on February 6, 2017. The study is summarized below.

Study IG1405: A Prospective, Controlled, Randomized, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols as an adjunct to Haemostasis during Surgery in Pediatric Subjects.

Study Start: January 2018

Study finish: June 2023

IG1405 is a multicenter clinical trial to be carried out in European countries. As of this writing, the investigational sites participating are not yet determined. The primary efficacy objective is to evaluate if FS Grifols 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 FS Grifols group and 86 in the EVICEL® comparator group, with a 1:1 assignment ratio). Safety will be monitored for FS Grifols and EVICEL®.

9. CONCLUSION

Fibrin sealants have been available and in use for many years⁸, and are generally considered to be a safe adjunct to hemostasis in surgical procedures. Safety data for FS Grifols 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. However, the submitted data do not provide evidence of safety of FS Grifols as compared to any other available fibrin sealant product. Study IG1405, comparing safety and efficacy of FS Grifols with Evicel®, will fulfill PREA requirements, as well as provide additional post-marketing study data of use with a fibrin sealant as a comparator.

10. RECOMMENDATIONS

DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP with adverse event reporting as required under 21 CFR 600.80. The submitted pharmacovigilance plan is acceptable.

⁸ Tisseel STN 103980 approved 1998, Evicel STN 125010 approved 2007