

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH INTERCENTER CONSULT MEMORANDUM



Device Constituent Part Design Review: CBER BLA 125640 - CDRH ICC1600853

Date: October 19, 2017

To: Yu Do, Regulatory Project Manager
Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)

From: Rong Guo, Lead reviewer
General Hospital Devices Branch (GHDB)
Division of Anesthesiology, General Hospital Respiratory, Infection Control, & Dental Device (DAGRID)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)

Through: Alan Stevens, Branch Chief
CDRH/ODE/DAGRID/GHDB

Re: BLA 125640

Subject: Device Constituent Part Design Review: CBER BLA 125640 - CDRH ICC1600853; CBER review of Fibrin Sealant (FS) Grifols; CDRH review of device constituent part of the combination product (functionality of the syringe)

Recommendation: CDRH recommends **approval** based on review of the device constituent part of the combination product.

I. Recommendation and Summary

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. Review of this information found that there are sufficient design control documentation and verification activities for the device constituent part of the combination product to recommend approval. The design requirements of the device components are acceptable and that essential performance of the final finished device can be assured with a reasonable degree of certainty

SBRA summary:

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). (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. Labeling of the container closure system is performed by Grifols at their facility in Barcelona, Spain.

FS Grifols can be administered by two ways: dripping or spraying.

Dripping: (b) (4) Cannula (b) (4) Cannula (b) (4) is co-packaged with FS Grifols. 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 the 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.

II. Submission Content Reviewed by CDRH/ODE

The CDRH/ODE reviewer performed an evaluation of the design of the device constituent parts of FIBRIN SEALANT (Human) combination product. This evaluation covered the intended design and design control information for the subject device constituent part. Essential performance elements of the device under review by the consultant were considered to be:

- Dose accuracy
- Functionality (break loose force and gliding force)

This review covered materials from the following modules:

- 1.12.11. ANDA Basis for Submission Statement
- 3.2.P.3.2. Pharmaceutical Development
- 3.2.P.3.1. Manufacturer(s)
- 3.2.P.7. Container Closure System
- 3.2.R. Regional Information
- 5.3.5.4. Other Study Reports

This review did not cover the following content

- Human factors study
- Review of drug product
- Review of primary container closure-drug product interaction, sterility, or toxicology
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

III. Review Team

Review Team	
CBER Lead Review Division	OTAT
Submission RPM	Yu Do
Lead Device Reviewer	Rong Guo
The CDRH review is being managed under ICC #:ICC1600853	
(b) (4)	
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1700313 in CTS.	

Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Human factor	Rita Lin		ICC1700313	CON178638

Note: Human factors review is not included in this review memo. There is a separate human factors review memo from the human factors reviewer.

IV. Intended Use

The following intended use was taken from the draft labeling in section 1.14.1.3:

“VeraSeal is a fibrin sealant (human) indicated as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VeraSeal is effective in heparinized patients.”

V. Consult Purpose

The Center for Biologics Evaluation and Research (CBER) requested a consult from CDRH/ODE for review of device constituent part design for the combination product submitted under the BLA125640. CDRH/ODE was consulted to review the device design and performance of two pre-filled syringes assembled on a syringe holder and a single-use sterile applicator tip of the combination product.

VI. Background

Fibrin Sealant is an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

Fibrin Sealant Grifols is supplied as a single-use kit containing one fibrinogen syringe and one thrombin syringe assembled on a syringe holder. A single-use sterile dual cannula applicator tip for dripping application will be co-packaged with the syringes. Additionally, the product may be applied by spraying with a spray applicator.

Dosage and Administration

FS Grifols contains human fibrinogen 80 mg/ml (component 1) and human thrombin 500 IU/ml (component 2). The following is directly taken from the Prescribing Information, 2.1 Dosage:

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.3 to 18.0 ml. For other procedures, larger volumes may be required.

The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. Vera Seal should be applied as a thin layer. The application can be repeated, if necessary.

As an approximate guide, the surface area that can be covered by application of one FS Grifols kit is as follows:

Table 1. Surface area coverage

FS Grifols pack size	Surface area coverage (cm ²) Application by dripping or spray (1 mm thick layer)
2 mL	14-20
4 mL	28-40
6 mL	42-60
10 mL	70-100

Note: Vera Seal is the proposed proprietary name for FS Grifols at the time when this review memo is drafted.

VII. Device Description

FS Grifols will be supplied as a single-use kit consisting of two separate packages:

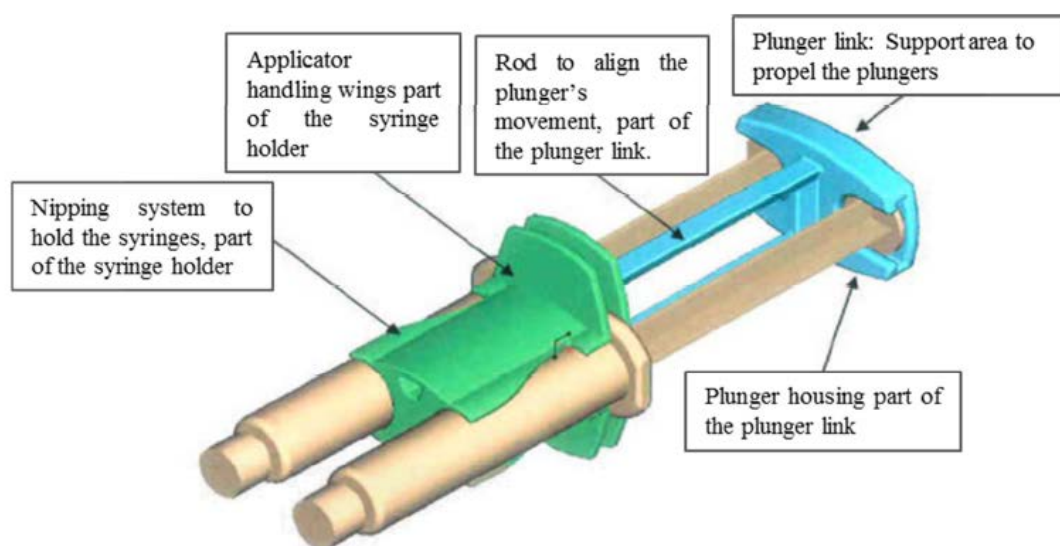
- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions which are assembled on a syringe holder.
- A package containing an application cannula.

Device Components

- Pre-filled syringes
- Syringe holder
- (b) (4) Applicator Tip

All engineer drawings are contained in report REGD-0019823 Design Outputs in Module 3.2.P.3.1 (submitted on February 15, 2017). The syringes, tip caps and plunger stoppers ((b) (4)) are purchased from (b) (4). (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. The syringe holder consists of a sliding part and a plunger, both are made of transparent polycarbonate. The plastic syringe holder allows for the simultaneous application of equal amounts of fibrinogen and thrombin.

FIGURE 1



A single-use sterile dual cannula applicator tip for dripping application will be co-packaged with the syringes. The dual cannula applicator allows mixing of both fibrinogen and thrombin components of FS Grifols in a 1:1 fashion the distal end of the applicator tip, preventing premature clotting. The applicator is a double-channel applicator with Luer-lock connections, made of 304 stainless steel, cannula of calibre 20 GA and 5.1 cm length tube of FEP fluoropolymer medical grade, made by (b) (4). The applicator is 510(k) cleared ((b) (4)). (b) (4) dual cannula is designed to facilitate the mixing and application of Fibrin Sealant by isolating thrombin and fibrinogen components until they passively mix at the treatment site. This prevents the cannula to get blocked and the product obtained is always equal, regardless of the cannula length. Optionally, the product may be applied by spraying with a spray applicator, which is not part of the combination product and can be purchased elsewhere.

The design of the Fibrin Sealant applicator device ensures that equal volumes of fibrinogen and thrombin are fed through the cannula as both syringes are pushed at same time.

The following shows the pre-filled syringes assembled in the syringe holder with or without the cannula attached.



The following pack sizes are available: 1 ml or 2 ml of human Fibrinogen or human thrombin is filled into 3 ml (b) (4) glass syringes with bromo-butyl-rubber plunger stopper. Syringes are closed with appropriate sized tip cap made of bromo-butyl-rubber. 3 ml or 5 ml of human Fibrinogen or human thrombin is filled into 5 ml (b) (4) glass syringes with bromo-butyl-rubber plunger stopper. Syringes are closed with appropriate sized tip cap made of bromo-butyl-rubber. The syringes are assembled on a sterile plastic syringe holder designed by Grifols with two different sizes for 3 ml or 5 ml syringes.

Table 2. VeraSeal pack sizes

Pack size (Total volume)	Human fibrinogen	Human thrombin
2 ml	1 ml	1 ml
4 ml	2 ml	2 ml
6 ml	3 ml	3 ml
10 ml	5 ml	5 ml

Instructions for Use:

The following information is taken from the Prescribing Information draft:

The product should only be prepared and administered according to the instructions and with the devices recommended for this product.

•Thawing

Room temperature thawing

VeraSeal should be thawed at room temperature (20 °C - 25 °C, [68 – 77 °F]) for approximately eighty (80) minutes for the 2 ml and the 4 ml presentations and one hundred twenty (120) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are: -Open the cardboard case and take out the inner contents. -Place this packaging on a surface at room temperature. After thawing, it is not necessary to warm the product for its use.

Water bath

In case thawing times need to be shortened, a thermostatic water-bath could be used, but always at a temperature not higher than 37 °C [99 °F]. At 37 °C the times needed are approximately twenty (20) minutes for the 2 ml and the 4 ml presentations and thirty (30) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are: -Open the cardboard case and take out the inner contents. -Place this packaging into water bath. -Ensure this packaging remains submerged throughout thawing.

The temperature must not exceed 37 °C.

•Preparation

After thawing, VeraSeal can be maintained for not more than 48 hours at 2-8°C [36 - 46 °F] or 24 hours at room

temperature (20 °C - 25 °C [68 - 77 °F]) before use if it remains sealed in the original packaging. Once the packaging is opened, VeraSeal should be used immediately. Once thawed, do not refreeze. After thawing the solutions must be clear to slightly opalescent and colorless to pale yellow. Solutions that are cloudy or have deposits should not be used.

Transferring operations include:

- Remove the packaging from the surface at room temperature, from the refrigerator at 2 - 8 °C or from the water bath (and dry the outer pouch) after thawing.
- Open the outer pouch and remove the sterile inner blister.
- Open the inner blister and make the VeraSeal syringe holder available to a second person for transfer to the sterile field. The outside of the blister package should not come in contact with the sterile field.

Connection operations include:

- Hold the VeraSeal syringe holder slightly inclined upwards.-Unscrew and remove the tip cap of both fibrinogen and thrombin syringes.
- To remove air bubbles from syringes, strike gently the side of the syringes one or two times while keeping the syringe holder in an upright position and eject air.
- To attach the applicator tip, screw both syringes consecutively, making a quarter (90 degree) turn each time.

•Administration

VeraSeal must be applied with the syringe holder supplied.

Before administration of VeraSeal, care must be taken that the parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

Prior to applying VeraSeal the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

•Application by dripping

VeraSeal must be applied with the cannula provided with the product, or an equivalent cannula (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. When using the provided cannula, follow the connection instructions in section 2.2 Preparation and Handling. When using other applicator tips, the instructions for use of the tips should be followed.

When dripped, the tip of the applicator should be kept as close as possible to the tissue surface, but without touching the tissue during application. Individual drops should be applied to the area to be treated.

To prevent uncontrolled clotting, the drops should be allowed to separate from each other and from the tip of the applicator.

•Application by spraying

VeraSeal must be applied with the spray device supplied separately (Fibrijet Gas assisted applicator), or an equivalent spray device (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. Always refer to the specific instructions provided with the device packages.

When applying VeraSeal using a spray device, it has to be ensured that the pressure is within the recommended range of 15 - 25 psi (1.0 - 1.7 bar). Do not spray closer than the recommended distance of 10 cm (3.9 inches) from the surface of the bleeding tissue.

Connect the short gas tube on the application device to the luer-lock end of the filter tubing. Then connect the luer-lock of the gas tube to a pressure regulator capable of delivering 15 - 25 psi (1.0 - 1.7 bar) of gas pressure.

The product should then be sprayed onto the surface of the tissue in short bursts (0.1 - 0.2 ml) to form a thin, even layer. The spray applicator is to be used with CO₂, nitrogen or medical air. To reduce the risk of potentially life-threatening air or gas embolism VeraSeal is recommended to be sprayed using pressurized CO₂. The pressure regulator should be used in accordance with the manufacturer's instructions

Reviewer comment: The above draft Instructions for Use is not clear. Especially, instructions for use need to be clearly written about how to attach the cannula to the double syringe correctly. Comments were sent to ATL. The device reviewer and the human factor reviewer attended and participated in the labeling meetings held on October 2, 2017. The above IFU has gone through several rounds of revisions. The Sponsor added figures for each step. The final version is not

finalized yet when this review memo is written.

VIII. Combination Product Design Inputs

An IR was sent to the Sponsor on December 15, 2016.

The Sponsor has provided minimal information regarding the design of the device constituent parts of the proposed pre-filled syringe combination products. The following are requested by the device reviewer:

- *A complete description of design control inputs, in the form of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered.*
- *Design output information in the form of test reports and other activities which verify the individual requirements and specifications for the system and validate the system is fit for its intended use within the context of the medication being delivered.*

IG_ITEC-002783_ING in Module 3.2.P.3.1 (submitted on April 11, 2017) provided an overall design plan for FS Grifols kit.

The following table selectively taken from IG_ITEC-002800_ING in Module 3.2.P.3.1 (submitted on September 29, 2017) shows the device related design requirement.

Customer requirement	PRS Description	Verification and validation	Pass/Fail
Device must allow the simultaneous application of fibrinogen and thrombin to form a clot on the application surface	PRS-133: FS Grifols kit shall allow the dispensation of a 1:1 mixture of fibrinogen and thrombin, each one contained in an individual syringe, with the help of a cannula supplied as accessory.	IG_ITEC-002497_ING: Fibrin Sealant: viability of the application device.	Pass
		IG_ITEC-002493_ING: Fibrin Sealant: functionality of the application systems.	Pass
		IG_ITEC-002568_ING: Viability and functionality of the Fibrin Sealant Grifols application device.	Pass
		IG_ITEC-003053_ING: Fibrin Sealant. Evaluation of the functionality and applicability of the application device.	Pass
The volume of FS Grifols to be applied should be sufficient to entirely cover the intended application area	PRS-134: FS Grifols kit shall be available in the following pack sizes: <ul style="list-style-type: none"> • 2 mL (containing 1 mL of human fibrinogen and 1 mL of human thrombin). • 4 mL (containing 2 mL of human fibrinogen and 2 mL of human thrombin). • 6 mL (containing 3 mL of human fibrinogen and 3 mL of human thrombin). • 10 mL (containing 5 mL of human fibrinogen and 5 mL of human thrombin). 	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information.	Pass
		IG_ESP-000320_ING: Specifications of the finished product Fibrin Sealant.	Pass
FS Grifols should be manually applied	PRS-90: FS Grifols kit shall need a force of (b) (4) to be applied.	ITEC-001403: Fibrin Sealant. Application tests depending on the type of cannula. (Note: From this report only the information related to the 20 GA cannula is applicable).	Pass
Needed to help stop bleeding during surgeries	PRS-114: FS Grifols kit shall be administered by a surgeon only.	FS Grifols kit is a Fibrin Sealant (human) indicated as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Vera Seal is effective in heparinized patients (section 1 of the labeltext-fs-22sept2016 v1.docx).	Pass
FS Grifols should be safe to use	PRS-124: The surfaces of FS Grifols kit shall not have cutting edges.	IG_ITEC-002747_ING: Fibrin Sealant. Usability.	Pass

Customer requirement	PRS description	Verification and validation	Pass/Fail
The device materials should have a low risk of causing a physiological reactions	PRS-152: ISO 10993 Biological evaluation of medical devices.	IG_ITEC-002201: Fibrin Sealant (FS) Grifols. Leachables study on syringe with tip cap (b) (4) and plunger stopper (b) (4). IG_ITEC-002265_ING: Fibrin Sealant (FS) Grifols. Leachables study on syringe with tip cap (b) (4) and plunger stopper (b) (4). IG_ITEC-001660: Fibrin Sealant: Compatibility with tip cap (b) (4). IG_ITEC-002416_ING: Fibrin Sealant: Compatibility with tip cap (b) (4). IG_ITEC-002666: Fibrin Sealant (FS) Grifols. Study of potential leachables from (b) (4) applicator dual cannula device. IG_ITEC-001543: Homologation report of the applicator (b) (4) from (b) (4). IG_ITEC-000830: Qualification report of the topical applicator spray kit for the Fibrin Sealant (b) (4) from (b) (4).	Pass
FS Grifols should be safe and effective	Nonclinical studies in animal models support the safety and efficacy of FS Grifols.	IG_ITEC-002063_ING: Fibrin Sealant (FS) Grifols: evaluation of preclinical studies on safety and efficacy. IG_ITEC-000711_ING: Evaluation report of the pre-clinical studies of Fibrin Sealant Grifols compared to other Fibrin Sealants. IG_ITEC-2235_ING: Safety pharmacology aspects of Fibrin Sealant Grifols.	Pass

REGD-0020150 in Module 3.2.P.3.1 (submitted on February 15, 2017) also contains a list of product requirements specification.

Design change

The reviewer discovered that the holder for the 3 ml syringes is too loose to securely hold the syringes in place. During inspection, the CBER reviewers discovered the same issue. Per the 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. Report IG_ITEC-003057_ING submitted on September 29, 2017 provided verification of the new mold used in the holder manufacturing meeting specification.

IX. Combination Product Verification and Validation Activities

Summary of Design V&V Attributes

Discipline Specific Design Verification / Validation*						
	Consult Needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		x			x	
Biocompatibility		x			x	
Sterility			x			
Software / Cybersecurity			x			
Electrical Safety / EMC			x			
Human Factors	x			Rita Lin		x

Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results	
		PASS	FAIL
Break loose Force	(b) (4)	x	
Glide Force		x	
Fill Volume		x	
Expelled Volume		x	
Tip Cap Removal		x	

Sharps Injury Protection	n/a	X	
Biocompatibility per ISO 10993		X	
Stability adequately verifies device will meet essential performance requirements at expiry		X	
Sterility	n/a		

Report REGD-0019822 in Module 3.2.P.3.1 (submitted on February 15, 2017) provided verification procedures for all sections of the Product Requirements Specification of FS Grifols Kit.

ID PRS	PRS	Verifications	Pass/ Fail
PRS-133	FS Grifols Kit shall allow the dispensation of a 1:1 mixture of fibrinogen and thrombin, each one contained in an individual syringe, with the help of a cannula supplied as accessory.	ITEC-002568_ING VIABILITY AND FUNCTIONALITY OF THE FIBRIN SEALANT GRIFOLS APPLICATION DEVICE IG_ITEC-002497_ING: Fibrin Sealant: viability of the application device IG_ITEC-002493_ING Fibrin Sealant: functionality of the application systems	Pass
PRS-134	FS Grifols Kit shall be available in the following pack sizes: 2ml (containing 1 ml of human fibrinogen and 1 ml of human thrombin) 4ml (containing 2 ml of human fibrinogen and 2 ml of human thrombin) 6ml (containing 3 ml of human fibrinogen and 3 ml of human thrombin) 10ml (containing 5 ml of human fibrinogen and 5 ml of human thrombin)	IG_DHF-000004_ING: Prescribing information IG_ESP-000304_ING: Specifications of the finished product -Fibrin Sealant	Pass
PRS-114	FS Grifols Kit shall be administered by a surgeon only.	FS Grifols Kit is a fibrin sealant (human) indicated as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VeraSeal is effective in heparinized patients. (section 1 of the labeltext-fs-22sept2016 v1.docx)	Pass

ID PRS	PRS	Verifications	Pass/ Fail
PRS-80	The shelf-life of FS Grifols Kit shall be 2 years stored at ≤-18°C.	IG_IE-000217_ING: FIBRIN SEALANT GRIFOLS: STABILITY STUDY IG_DHF-000003_ING: Fibrin Sealant (FS) Grifols: labeling	Pass
PRS-128	After thawing, the shelf life of FS Grifols Kit (in its original packaging) shall be 48 hours at 2°C - 8°C or 24 hours at room temperature (20°C - 25°C). Once the packaging is opened, FS Grifols Kit shall be used immediately.	IG_IE-000222_ING: FIBRIN SEALANT (FS) GRIFOLS. STABILITY STUDY AFTER PRODUCT THAWING	Pass
PRS-144	The PI shall include an statement about to use FS Grifols Kit with the syringe holder supplied.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-145	The PI shall include the recommended distance when apply FS Grifols Kit by spraying.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-146	The PI shall include the recommended pressure when apply FS Grifols Kit by spraying.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-95	The PI shall include the storage conditions of the product.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-100	The PI shall include the operating conditions of the product.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-148	The PI shall include transferring operations to transfer the FS Grifols Kit correctly to the sterile field.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass

ID PRS	PRS	Verifications	Pass/ Fail
PRS-149	The PI shall include connections operations to connect the cannula correctly.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-111	The PI shall include the verifications to follow prior to the use of the product.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-116	The PI shall include an statement about not to apply the product intravascularly.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-140	The PI shall include an statement about not to use the product in patients known to have anaphylactic severe systemic hypersensitivity reactions to the administration of blood products.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-97	The PI shall include the most appropriate thawing methods.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-117	The PI shall include the time for each complete thawing process.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-99	The PI shall include an statement about not to exceed the 37°C while the thawing process takes place.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-147	The PI shall include instructions which indicate that the outer pouch shall be opened after thawing.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-119	The PI shall include an statement about not to refreeze the product once thawed.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-121	The PI shall include a complete list of warnings and precautions of FS Grifols Kit.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
ID PRS	PRS	Verifications	Pass/ Fail
PRS-150	The PI shall include an statement about the higher risk of air or gas embolism when FS Grifols Kit is sprayed with air as compared to CO ₂ .	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-127	The PI shall include an statement about the administration of FS Grifols Kit only with the accessories recommended.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-109	The PI shall be written in a clear and understandable way.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-158	The PI shall include an statement about to discard the product if the packaging is damaged.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-153	The PI shall include an statement about to discard the unused contents.	IG_DHF-000004_ING: Fibrin Sealant (FS) Grifols: Prescribing information	Pass
PRS-135	FS Grifols Kit shall be supplied in a double-barrier sterile packaging.	IG_VS-001532: STERILIZATION OF THE FIBRIN SEALANT GRIFOLS APPLICATOR SYSTEM WITH (b) (4)	Pass
PRS-141	The packaging shall include all the relevant information (expiry date, lot, single use, sterile...)	IG_DHF-000003_ING: Fibrin Sealant (FS) Grifols: labeling	Pass
PRS-90	FS Grifols Kit shall need a force of (b) (4) to be applied.	ITEC-001403_ING_FIBRIN SEALANT. APPLICATION TESTS DEPENDING ON THE TYPE OF CANNULA. May 2012. (Note: From this report only the information related to the 20GA cannula is applicable)	Pass
ID PRS	PRS	Verifications	Pass/ Fail
PRS-124	The surfaces of FS Grifols Kit shall not have cutting edges.	IG_ITEC-002747: FIBRIN SEALANT. USABILITY	Pass
PRS-126	(b) (4)	IG_ESP-000304_ING SPECIFICATIONS OF THE FINISHED PRODUCT - FIBRIN SEALANT IG_ITEC-002588_ING: FIBRIN SEALANT: SPECIFICATIONS RATIONALE	Pass
PRS-137	EN 1041:2008+A1:2013 Information supplied by the manufacturer of medical devices.	IG_DHF-000002_ING Fibrin Sealant (FS) Grifols. Cannula (b) (4): label and instructions of use	Pass
		IG_ITEC-001543: Report Homologation cannula (b) (4)	
		IG_ITEC-000830: Homologation report spray applicator SA-6205	
		Note: The syringe holder and plunger link are not medical devices, but they are defined as device components of the combination product.	

The Sponsor complied to the following standards:

ID PRS	PRS	Verifications	Pass/ Fail
		The syringe holder and plunger link are not medical devices, but they are defined as device components of the combination product.	
PRS-139	ISO 11040-4:2015 Prefilled syringes - Part 4: Glass barrels for injectables and sterilized syringes subassembled syringes ready for filling.	IG_APPLUS-FS-ITEC_16-31702709_ING_2 3020103 (b) (4) 3ml (b) (4) Certificado análisis 21.02.12.pdf 3026441 (b) (4) 5ml (b) (4) Certificado 31.03.16.pdf	Pass
PRS-107	ISO 11607-1:2006 Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems.	IG ITEC-002748: EVALUATION OF THE CORRECT INSTALLATION AND OPERATION OF (b) (4) (b) (4) AND (b) (4) (b) (4) MACHINES USED FOR THE FIBRIN SEALANT GRIFOLS PACKAGING	Pass
PRS-108	ISO 11607-2:2006 Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes.	IG ITEC-002748: EVALUATION OF THE CORRECT INSTALLATION AND OPERATION OF (b) (4) (b) (4) AND (b) (4) (b) (4) MACHINES USED FOR THE FIBRIN SEALANT GRIFOLS PACKAGING	Pass
PRS-152	ISO 10993 Biological evaluation of medical devices.	IG ITEC-002201_ING FIBRIN SEALANT (FS) GRIFOLS. LEACHABLES STUDY ON SIRYNGE WITH TIP CAP (b) (4) AND PLUNGER STOPPER (b) (4)	Pass
PRS-160	ASTM F88/F88M-15: Standard test method for seal strength of flexible barrier materials.	IG ITEC-002798 Seal integrity test of the Fibrin Sealant Grifols blister	Pass
PRS-161	ASTM F1140/F1140M-13: Standard test methods for internal pressurization failure resistance of unrestrained packages.	IG ITEC-002798 Seal integrity test of the Fibrin Sealant Grifols blister	Pass
PRS-162	ASTM F1929-98: Standard test method for detecting seal leaks in porous medical packaging by (b) (4)	IG ITEC-002798 Seal integrity test of the Fibrin Sealant Grifols blister	Pass
PRS-164	ASTM D4169-14: Standard practice for performance testing of shipping containers and systems.	IG ITEC-002797 Package testing of Fibrin Sealant Grifols. Mechanical test of shipping containers	Pass

Dose Accuracy

An IR was sent to the Sponsor on March 20, 2017:

“In 3.2.P.5.1, you provided the specifications for the filled volume of the drug products. In order to show the dose delivery efficiency/accuracy of the delivered volume, please provide container content (delivered volume) study for both drug products (fibrinogen and thrombin).”

The Sponsor stated that in order to assure the requirements for delivered volume, the filling volume must be greater than the nominal volume, due to product characteristics. The overfill volume is defined as the retained volume once the syringe is emptied. The control of fill volume was established according to the studies IG ITEC-001698_ING in Module 3.2.P.2 (submitted on April 11, 2017) and IG ITEC-002020_ING in Module 3.2.P.2 (submitted on November 4, 2016). The objective of the two studies are to determine the residual volumes of fibrinogen and thrombin for 3-ml and 5-ml syringes filled with Fibrin Sealant, with the aim of establishing the corresponding overfill volumes, and to establish the specifications for control of fill volume in each manufactured lot of Fibrin Sealant.

The density of Fibrinogen is 1.044 g/ml, and the density of Thrombin is 1.009 g/ml. From Study IG ITEC-001698, the residual volumes retained in the body of the syringe are shown in the following table:

Product	Fill volume (ml)	Retained volume (ml)
Fibrinogen	1	(b) (4)
	2	
	3	
	5	
Thrombin	1	(b) (4)
	2	
	3	
	5	

To calculate the upper fill limit, ^{(b) (4)} excess volume over the minimum volume were added, according to the recommendations provided in (b) (4)

Product	Density (g/ml)	Fill volume (ml)	Total retained volume (syringe+cannula)	Lower fill limit		Upper fill limit	
				Weight (g)	Vol. (ml)	Weight (g)	Vol. (ml)
Fibrinogen	1.044	1 ml	(b) (4)	(b) (4)	(4)	(b) (4)	(b) (4)
		2 ml					
		3 ml					
		5 ml					

Product	Density (g/ml)	Fill volume (ml)	Total retained volume (syringe+cannula)	Lower fill limit		Upper fill limit	
				Weight (g)	Vol. (ml)	Weight (g)	Vol. (ml)
Thrombin	1.009	1 ml	(b) (4)	(b) (4)	(4)	(b) (4)	(b) (4)
		2 ml					
		3 ml					
		5 ml					

In addition, homogeneity in the delivery of Fibrin Sealant was verified in Study IG ITEC-002568_ING in Module 3.2.P.7 (submitted on December 1, 2016). The mixture of Fibrinogen and Thrombin components evaluated by visual examination comparing with a color scale and by the absorbance profile, when the dual cannula tip applicator or the spray applicator are used, indicates that the FS components are mixed in a proportion of 1 to 1 forming an homogeneous clot or layer, respectively.

Reviewer Comment: For Fibrin Sealant, being able to deliver the equal ratio of Fibrinogen and Thrombin is more important than dose accuracy requirement for individual component. Study IG ITEC-002568_ING in Module 3.2.P.7 showed that the FS components are mixed in a proportion of 1 to 1 forming a homogeneous clot or layer. In addition, the Sponsor established the specifications for the volume control of each of the filled products based on these overfill volumes per the reviewer's suggestion. The provided dose accuracy for filled volume verification is acceptable.

Break Loose Force and Gliding Force

An IR was sent to the Sponsor on March 20, 2017:

“You stated that “The surgeon must push the plunger link with a maximum force of (b) (4) to allow the solutions flow and form the fibrin clot in situ”, while you did not specify the Initiating (break loose) and Sustaining (gliding) Force requirement. Please provide Initiating and Sustaining Force specification and verification.”

The Sponsor stated that as the product has to be applied manually by the surgeon, (b) (4) is considered the maximum force (including initiating and sustaining forces) acceptable to apply the product. The result was based in a human anthropometric study, detailed four different hand strengths for both right and left handed males and females of different age groups. One of these strengths was the “Palmer Pinch”, described as the pinch between the thumb pad and the pads of index and middle fingers, which mimics the action performed when a person expels product from a syringe. The forces measured in the study are likely to be comparable to the force a person can apply to a syringe to expel product.

The force required by the surgeon to push the central part of the plunger connecting the two plungers of the syringes held in the holder of the device and connected to a cannula are shown below:

Lot	Presentation	Newton (N)	
		Breaking loose force	Sustaining force
(b) (4)	4 mL	(b) (4)	
	4 mL		
	6 mL		
	6 mL		
	10 mL		
	10 mL		

Reviewer Comment: the provided break loose force and gliding force verification study is acceptable.

Compatibility of the system

FS Grifols can be administered by two ways: dripping or spraying.

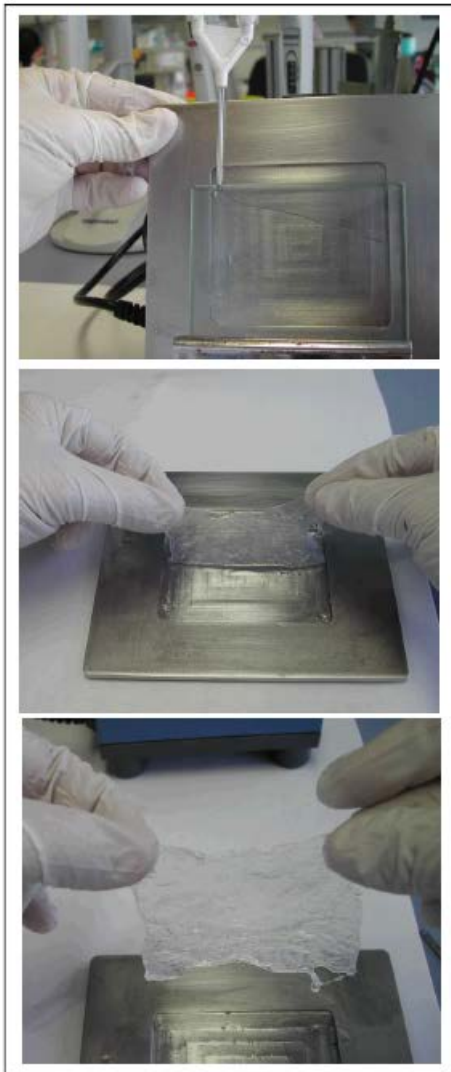
Application by dripping

FS Grifols should be applied with the cannula provided with the product, or an equivalent cannula (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. The applicator tip co-packaged with the product is (b) (4), which is a dual cannula application with two adjacent needles 5.7 cm in length and inner diameter of 20 ga, reference (b) (4), cleared by the Agency in (b) (4) with the 510(k) submission (b) (4). The tip consists of two blunt hypodermic needles fastened together.

IG_ITEC-002493_ING in Module 3.2.P.7 (submitted on November 4, 2016), FIBRIN SEALANT: FUNCTIONALITY OF THE APPLICATION SYSTEMS, evaluated the functionality of the application systems of FS Grifols (application tip and spray application). The FS kits were thawed in a thermostatic bath at 37 °C. After thawing, the application tip was assembled, and homogeneity, consistency and compatibility tests were performed. The results confirmed that the Fibrin Sealant (FS) Grifols delivery using both, the application tip and spray application is consistent and homogenous along its administration. A representative result is shown here for reference:


FIGURE 2

Tip application. Consistency of fibrin layer



IG_ITEC-002497_ING in Module 3.2.P.7 (submitted on November 4, 2016), IG_ITEC-002568_ING in Module 3.2.P.7 (submitted on December 1, 2016), and IG_ITEC-003053_ING in Module 3.2.P.7 (submitted on September 29, 2017) provided more verifications of viability, functionality and compatibility of the application device.

(b) (4)

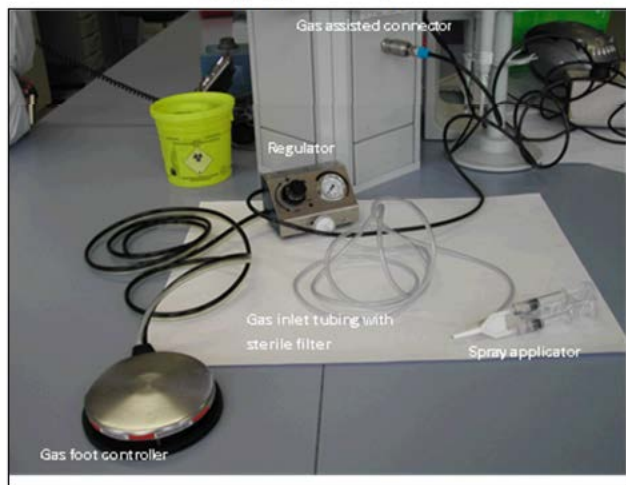


Application by spraying

FS Grifols can also be applied with the spray device. Since the spray device is not provided by the Sponsor in the package, FS Grifols must be applied with the spray device supplied elsewhere. Fibrijet Gas assisted applicator (with FDA clearance K012868), or an equivalent spray device (including open surgery and laparoscopic or endoscopic use devices)

cleared by FDA for this use is recommended by the Sponsor. Always refer to the specific instructions provided with the device packages. When applying FS Grifols using a spray device, it has to be ensured that the pressure is within the recommended range of 15 - 25 psi (1.0 - 1.7 bar). Do not spray closer than the recommended distance of 10 cm (3.9 inches) from the surface of the bleeding tissue.

FIGURE 4
Spray application system



The above picture shows the spray device supplied separately

Study IG ITEC-002568_ING in Module 3.2.P.7 (submitted on December 1, 2016) showed that the mixture of Fibrinogen and Thrombin components evaluated by visual examination comparing with a color scale and by the absorbance profile, when the dual cannula tip applicator or the spray applicator are used, indicates that the FS components are mixed in a proportion of 1 to 1 forming an homogeneous clot or layer, respectively. The Fibrin Sealant Grifols application device is viable and functional in combination with the applicator systems. The Fibrin Sealant Grifols delivery using both, the applicator tip and spray applicator is consistent and homogenous along its administration.

IG ITEC-002493_ING in Module 3.2.P.7 also confirmed the compatibility of the spray applicator (Micromedics spray, applicator kit reference SA-6205 and (b) (4) compressed air regulator reference (b) (4)) with FS Grifols.

IG ITEC-000830_ING in Module 3.2.P.3.1 (Submitted on March 21, 2017) contains verifications that recommended spray applicator SA-6205 (K012868) from the manufacturer Micromedics Inc to the specifications and requirements for its use to deliver FS Grifols

The reviewer checked a few FDA cleared spray device, all are intended to apply two nonhomogeneous fluids to a treatment site. All these devices are able to spray with the sterile gas pressure regulated between 15 psi and 25 psi.

- Micromedics FibriJet Aerosol Applicator (K012868), intended for use in applying two nonhomogeneous fluids to a treatment site.
- Micromedics FibriJet Air Assisted Endoscopic Applicator (K042834), intended to be used for the application of two nonhomogeneous fluids to a treatment site.
- Laparoscopic Spray Applicator with Spinning Luers (K162077), intended for the application of two nonhomogeneous liquids.
- 360° Gas Assisted Endoscopic Applicator (K122526), intended for the application of two nonhomogeneous liquids.

Reviewer Comment: the provided compatibility of the device with the cannula tip applicator or the spray applicator is acceptable.

Biocompatibility

Assessment of the syringe barrels is the scope of the CMC discipline and is not covered in this review memo as the

syringe barrel is the primary container system. While the plastic syringe holder is not the drug fluid path, it has brief contact with the HCP during the delivery of the medication.

An IR was sent to the Sponsor on March 20, 2017:

“In your response to the IR sent on Mar 7, 2017, you stated that biocompatibility aspects of the combination product have been covered in PRS-152 in agreement with ISO 10993. Please provide a full biocompatibility report for the plastic syringe holder, or provide the exact location if it is included in the dossier.”

The plastic holder is made of polycarbonate (b) (4) that meets the below listed biocompatibility tests performed by the supplier according to ISO 10993 and USP plastics Class VI at the time of testing:

- Cytotoxicity
- Skin sensitization
- Intracutaneous reactivity (intra dermal irritation)
- Acute systemic toxicity
- Gene mutation in bacteria
- Local effects after intramuscular implantation
- Hemocompatibility (selected tests)
- Pyrogenicity

Reviewer Comment: *The provided biocompatibility information is not sufficient. Manufacturing process is not considered, along with any additives or processing agents. Manufacturing process might impact the raw materials, or impact the interaction of the raw material with other materials, and generate new extractables and leachables. However, based on the nature of the materials (polycarbonate), the likelihood of generating new leachables by the manufacturing process is small. Most importantly, this drug will be administered by professional HCPs or surgeons who would wear gloves when performing the application. Based on these scenarios, the provided raw material biocompatibility assessment is acceptable.*

Stability and Shelf Life

An IR was sent to the Sponsor on August 31, 2017:

“In FDA Guidance for Industry [Q1A\(R2\) Stability Testing of New Drug Substances and Products](#), Section Specification (2.2.5), stability studies should cover testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy, which include functionality tests for a dose delivery system. The proposed combination product will go through dramatic temperature change (being stored lower than -18C and thawed to use), which will likely affect the essential performance requirements of the syringe. However, your stability testing did not include the essential performance requirements of the syringe such as dose accuracy and functionality of the syringe including break loose force and gliding force. Please provide a justification for how you have demonstrated, or plan to demonstrate, that the device still meets the essential performance requirements after its intended shelf-life and use-life. Please include “volume” as a parameter in your stability protocol to ensure intended delivery amount at expiry.”

The Sponsor stated that a functionality test is conducted at each time point in the stability study report IG_IE- 000239_ING. FIBRIN SEALANT GRIFOLS: STABILITY STUDY. FINAL REPORT in Module 3.2.P.8.3). The functionality test, described in method IG_MA-000664_ING FIBRIN SEALANT IDENTIFICATION AND VERIFICATION OF FUNCTIONALITY in Module 3.2.P.5.2), allows to evaluate the functionality and delivery of the product, measuring clotting time of the resulting fibrinogen and thrombin mixture, and to identify the product. The identification of the product evaluates the whole device as a combination product including the proper manually application of the product and therefore that the essential performance of the device (syringes, holder and application cannula) is suitable. This correct performance of the whole combination product results in the properly formation of the clot along the shelf-life of the product, meeting the specifications in all filling sizes and showing that the device still meets identification and functionality.

In addition, FS Grifols, as a combination product, has been studied at the end of its shelf life as a worst case scenario. Report IG_IE-000222_ING in Module 3.2.P.8.3 provided information of the Fibrin Sealant identification and verification of functionality test and established that FS Grifols can be maintained for not more than 48 hours at 2 °C - 8°C or 24 hours

at room temperature (20 °C – 25 °C) after thawing. During this period the device meets identification and functionality specifications.

The breaking loose and gliding force was evaluated in (b) (4) batches of Fibrin Sealant (FS) Grifols at the end of their shelf-life (24 months at $-21 \pm 4^{\circ}\text{C}$) and all meet spec. The maximum force applied at the end of the shelf-life was (b) (4), which is equivalent to the maximum force (which include breaking loose and sustaining forces) needed to empty the kit, (b) (4) from report IG_ITEC-001403_ING in Module 3.2.P.3.1. Thus, there is no increase in force to be applied during the whole life of the product. Regarding to dose accuracy, volume determination will be included in the updated version of the stability protocol in order to meet the requirements.

FS Grifols Kit has a shelf-life of 2 years (stored at -18°C).

Reviewer Comment: *The provided stability study is acceptable. In addition, the Sponsor is adding “volume” as a parameter in their stability study per the reviewer’s suggestion. Tests in all of the study reports referenced in this review memo were performed using frozen and thawed products, which indicate that the application device meets its intended use after various length of storage at -18°C .*

Human Factor Validation

Rita Lin is the human factors reviewer. Her review memo is submitted separately.

Risk Analysis

Risk analysis REGD-0019886 version 4 in Module 5.3.5.4 (submitted on February 15, 2017) provided assessment of the risks related to the patient use of the device part of the product, including characteristics that could impact on safety, categorization of probability and severity levels, acceptance criteria of each probable risk, risk analysis, assessment and control, residual risk evaluation and risk/benefit analysis.

Reviewer comment: *The FS Grifols device risks have been managed to the point where it is appropriate for moving forward into commercial supply. The sponsor has identified tolerable residual risks after mitigation steps. The reviewer agrees that the combination product is acceptable for the patient use from the device point of view.*

Design Transfer Activities – Release Specification

Certificates of analysis of the syringes, tip cap and plunger stoppers are provided in the submission (Certificates container closure system in Module 3.2.P.7), including

- 3 ml syringe (b) (4) (includes Tip cap)
- 5 ml syringe (b) (4) (includes Tip cap)
- 3 ml plunger rod (b) (4)
- 5 ml plunger rod (b) (4)
- 1-3 ml plunger stopper (b) (4)
- 5 ml plunger stopper (b) (4)

IG_ITEC-001543_ING in Module 3.2.P.3.1 (submitted on March 21, 2017) provided verifications that the co-packaged applicator (b) (4) conforms to the specifications and requirements for its use to deliver Fibrin sealant Grifols.

Reviewer Comment: *There is no direct device related specification in Module 3.2.P.5. Functionality (clot formation time) is an indirect indicator that the device can deliver equal ratios of both components and form Fibrin Sealant. In addition, per the reviewer’s suggestion, the Sponsor is changing the specification of volume from “(b) (4)” to “1.0 mL (b) (4)”.* *The provided device components specifications are acceptable.*

X. Review History

Four IRs were communicated with ATL and sent out to the Sponsor.

The sponsor has responded to all the sent IR. All deficiencies have been resolved.

The reviewer attended the filing meeting on November 14, 2016, internal CMC meeting on April 6, 2017, mid-cycle meeting on April 13, external late -cycle meeting with the Sponsor on August 31, labeling meeting on October 2, 2017.

XI. Concurrence Table

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Sign-Off	