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**To:** Administrative File: STN 125640/0  
Natalya Ananyeva, Committee Chair, CBER/OTAT/DPPT/HB  
Yu Do, RPM, CBER/OTAT/DRPM/RPMBI

**CC:** Review Committee Members

**From:** Christine Harman, Chemist, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/BI

**Through:** Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI

**Through:** John Eltermann, Division Director, CBER/OCBQ/DMPQ

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

**Product:** Fibrin Sealant (Human)

**Indication:** For use as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) [redacted] undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical, additionally, is effective in heparinized patients.

**Subject:** BLA Primary Review: Review of Fibrin Sealant (Human), covering the DMPQ related aspects of the drug manufacturing provided in the BLA submission.

**Due Date:** 04-Nov-2017

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**RECOMMENDATION**

Based on the information provided in the original submission, amendments and the FDA Form 483 response from Instituto Grifols, approval is recommended with the following inspectional considerations for the next biennial inspection. The inspectional consideration is part of the standard scope of inspection. CBER understands that the consideration may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

- (b) (5), (b) (7)(E) [redacted]

(b) (5), (b) (7)(E)

**EXECUTIVE SUMMARY**

Instituto Grifols, S.A. submitted an original BLA (standard 12-month review) that was received by the Agency on November 4, 2016 as an electronic submitted in eCTD format (STN 125640/0, (0000)). This review covers the aspects of the BLA submission that are under the purview of DMPQ as per responsibilities outlined in “SOPP 8401.4: Review Responsibilities for CMC Section of Biologic License Applications and Supplements. The review of other aspects of the submission, which are under the purview of the other offices/divisions as outlined in SOPP 8401.4 are deferred to the appropriate office/divisions. The main sections of the BLA that were reviewed by DMPQ and that are summarized in this review include the following eCTD sections of the BLA:

Module 1: Regional

Module 2: Common Technical Document Summaries

Module 3: Quality

3.2.S Drug Substance

3.2.P Drug Product [Product-Dosage Form-Manufacturer]

3.2.P Drug Substance

3.2.A. Appendices

During the review, there were seven information requests sent from DMPQ reviewer to the firm. The firm responses provided as amendments 3 (eCTD 0005), 10 (eCTD 0011), 13 (eCTD 0014), 30 (eCTD 0031), 46 (eCTD 0047), 57 (eCTD 0058) and 62 (eCTD 0063) were reviewed and found to be adequate. Based on the information provided in the original submission and corresponding amendments, approval is recommended provided there are no outstanding issues from the product office, clinical and other offices/divisions associated with the BLA review.

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BLA Review Narrative

**DESCRIPTION OF PRODUCT AND PROPOSED INDICATION**

The Grifols product is a human plasma derived fibrin sealant supplied as a kit of two syringes containing sterile frozen solutions of human fibrinogen (Component 1) and human thrombin with calcium chloride (Component 2) assembled on a syringe holder that is co-packaged with an applicator cannula. Additionally, the syringe system can be used with a spray applicator that is supplied separately.

The Fibrin Sealant (FS) Grifols product is intended to be used 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. Fibrin Sealant Grifols is effective in heparinized patients.

**COMPOSITION OF DRUG PRODUCT AND DOSAGE FORM**

The product consists of the following:

Human Fibrinogen- Isolated from Source Plasma by fractionation process based on the Cohn Method. Composition of Fibrinogen was indicated as follows:

Name of ingredients	Dosage Form (ml)				Reference
	1	2	3	5	
Human Fibrinogen	80 mg	160 mg	240 mg	400 mg	Not applicable
Sodium citrate, (b) (4)	(b) (4)				
Sodium chloride					
Arginine					

L-isoleucine	(b) (4)				
L-glutamic acid, monosodium					
WFI (q.s.)	1 ml	2 ml	3 ml	5 ml	(b) (4)

Dosage form is frozen with sizes of 1mL, 2 mL, 3mL, and 5 mL volumes.

Human Thrombin- Isolated from Source Plasma by fractionation process based on the Cohn Method. Composition of Thrombin was indicated as follows:

Name of ingredients	Dosage Form (ml)				Function	Reference
	1	2	3	5		
Human Thrombin	500 IU	1000 IU	1500 IU	2500 IU	Active ingredient	Not applicable
CaCl <sub>2</sub> ·2H <sub>2</sub> O	(b) (4)					
Human Albumin						
Sodium chloride						
Glycine						
WFI (q.s.)	1 ml	2 ml	3 ml	5 ml	Solvent	Ph. Eur.

Dosage form is frozen with sizes of 1mL, 2 mL, 3mL, and 5 mL volumes.

#### MANUFACTURING AND FACILITIES OVERVIEW

Drug substance and drug product manufacturing of thrombin and fibrinogen, in addition to filling, labeling, packaging and batch release testing activities are performed at a single facility, Instituto Grifols located in Barcelona, Spain. Below is an overview of the manufacturing processes of fibrinogen and thrombin:

Fibrinogen: Manufactured from Fraction I of frozen plasma fractionation (from source plasma) (refer to APPENDIX Figure 1 for details of production scheme). The process was summarized as follows in eCTD section 2.3.P Human Fibrinogen:

1. (b) (4) Fraction I
2. (b) (4) is treated with solvent detergent (Viral inactivation)
3. Three sequential precipitations with glycine (b) (4)
4. Precipitate, (b) (4) double Nano-filtration through (b) (4) 35 nm and 20 nm filters (viral removal step)
5. (b) (4) formulation by (b) (4)
6. Sterile bulk filtration, aseptic filling into syringes and freezing

Thrombin: Obtained from prothrombin Complex (PTC) captured with ion exchange resin (b) (4) ) from supernatant of Fraction I (Fr I) of fractionation of (b) (4) (refer to APPENDX Figure 2 for details of productions scheme). The process was summarized as follows in eCTD Section 2.3.P Human Thrombin:

1. Fractionation of (b) (4) Fr I supernatant following (b) (4)
2. (b) (4)
3. Solvent/Detergent treatment of eluate using Tri-n-butyl phosphate (TNBP) and polysorbate 80 (viral inactivation)
4. Purification by cation exchange resin column ((b) (4) )
5. (b) (4) double nanofiltration of eluate fraction through two filters (b) (4) (15 nm pore size)
6. (b) (4) , sterile filtration (b) (4) , aseptic filling of syringes and freezing

## **DRUG MANUFACTURING PROCESS AND VALIDATION**

The firm indicated that due to the continuous manufacturing process of both components of the Fibrin Sealant Grifols from fractionation to the final component, there is no distinct drug substance intermediate, thus the information provided in the submission is pre-dominantly found in the Drug Product sections of the BLA.

### ***I. Fraction I and Prothrombin Complex (PTC) Manufacturing Process and Validation***

Fibrinogen and Thrombin are manufactured from Fraction I. Fibrinogen is directly manufactured from Fraction I, whereas Thrombin is manufactured from Prothrombin Complex, which is a further fractionated intermediate obtained from Fraction I (Refer to Figure 2 in APPENDIX). Fraction I is manufactured from (b) (4) plasma per procedures described in IG\_MG\_000026\_INGv7 (see Figure 3 in APPENDIX for manufacturing scheme).

The validation report IG\_VS\_001520 summarizes the manufacturing process performed in the fractionation area in Building (b) (4) to obtain (b) (4) , Fraction I and prothrombin complex (PTC), which are used to manufacture Fibrinogen and Thrombin. The manufacture of Fraction I and PTC as described in IG\_MG-000026 is summarized as follows:

Plasma is stored (b) (4) until the manufacturing process starts as follows:

(b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

(b) (4)

[Redacted text block]

Several process validation reports were provided covering the manufacturing steps prior to the start of fibrinogen and thrombin, to obtain Fraction I and Prothrombin Complex. The process validation report IG\_VS-001520 (“Manufacturing Process Validation (From (b) (4) of Human Plasma to PTC Obtaining)- Building (b) (4)”) summarizes the data of the validation of the fractionation processes performed in the fractionation area in Building (b) (4) to obtain Fraction I and prothrombin complex (PTC) thus includes the additional extraction of PTC from Fraction I. Reports IG\_VS-001527 (“Manufacturing Process Validation (From (b) (4) of Human Plasma to Fraction I)-Building (b) (4) (scale of (b) (4) Plasma”) and IG\_VS-001528 (“Manufacturing Process Validation (From (b) (4) of Human Plasma to Fraction I)-Building (b) (4) (scale of (b) (4) Plasma”) covers the validation of the fractionation process to obtain Fraction I without the additional extraction step to obtain PTC, yielding only Fraction I, which is used for further manufacturing, which is performed in Building (b) (4). Validation report IG\_VS-001520, includes data from (b) (4) processes (historical batches) performed from January 2012 to June 2013, whereas validation report IG\_VS-001527 includes data from the first three fractionation

processes performed at a scale of (b) (4) of plasma performed between October and November 2013 in Building (b) (4) and validation report IG\_VS-001528 includes data from the (b) (4) fractionation process runs same as that performed in report IG\_VS-001527; however at a larger scale of (b) (4) of plasma and also manufactured in Building (b) (4). These runs were also performed between October and November of 2013. The reports are summarized as follows:

The overall manufacturing scheme covered by the validation:

(b) (4)

(b) (4)

(b) (4)



(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

*Reviewer Comments:* Given the storage duration of (b) (4) for Fraction I, a manufacturing intermediate for both Fibrinogen and Thrombin, the firm should have stability data and process data to support this storage duration. This is deferred to the product office for further assessment.

**II. Fibrinogen Manufacturing Process and Validation**

The manufacturing process and controls are described in detail in protocol IG MP-000033\_INGv10 provided in eCTD section 3.2.P.3.3 Description of Manufacturing Process and Controls. The process involves the following:

Fraction I, which is manufactured and stored prior to the manufacturing of Fibrinogen, can be

optionally be stored for up to (b) (4) at temperature of (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted text block containing multiple lines of obscured content]

Several process validation reports were provided for Fibrinogen manufacturing. These reports include the following:

- IG\_VS-001293- Validation Fibrinogen process validation
- IG\_VS-001290- Validation of the solvent detergent (SD) treatment process performed to fibrinogen solution

These reports are summarized as follows:

IG VS-001293- Validation Fibrinogen process validation

The validation report IG\_VS-001293 “Human Fibrinogen Process Validation for Fibrin Sealant Grifols” provides the method validation and results. The validation was designed in three phases that included: Phase I Process Design, Phase II: Qualification of the commercial manufacturing process and Phase II Continued Process verification. Report IG\_VS-001293 covers the activities that are associated with Phase II that includes the following two stages:

- Stage 1: Qualification of facilities and equipment that take part in the commercial manufacturing process (IQ/OQ) and prospective validations studies
- Stage 2: Process Performance Qualification (PPQ)

Stage I activities ensure that the facilities and equipment involved in the manufacturing process are assessed to assure that they have been constructed, installed and operate for their intended use and that prospective validation studies are conducted on the conditions under the manufacturing process will be performed. Once the IQ/OQ demonstrating facilities and equipment are properly operational, the PPQ is performed. Equipment qualification for the fibrinogen manufacturing is covered in the Facilities, Equipment Qualification and Cleaning section of this memo, in addition this information was provided in a response to an IR. Please refer to Information Request section, specifically, IR#3, response submitted as Amendment 13.

The PPQ study included the first three FS (Fibrin Sealant) Grifols product lots manufactured in the facilities of Building (b) (4). The following details were indicated regarding the study:

- The final presentations for FS includes the following:

Presentation	Syringe/Dosage Product
2 mL	(b) (4) 3 mL/1mL/Human Fibrinogen
	(b) (4) 3mL/1 mL/Human Thrombin
4 mL	(b) (4) 3 mL/2mL/Human Fibrinogen
	(b) (4) 3mL/2 mL/Human Thrombin
6 mL	(b) (4) 5 mL/3mL/Human Fibrinogen
	(b) (4) 5mL/3 mL/Human Thrombin
10mL	(b) (4) 5 mL/5mL/Human Fibrinogen
	(b) (4) 5mL/5 mL/Human Thrombin

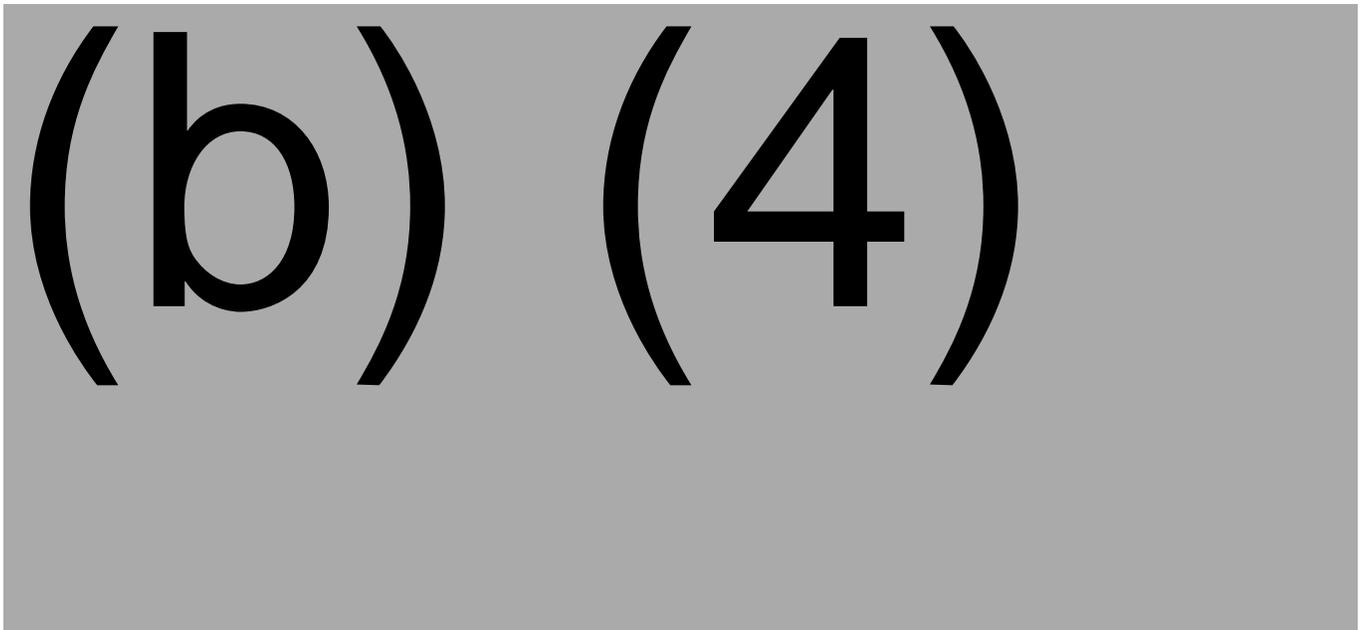
The manufacturing process of all fill sizes are identical until the aseptic filling step. Thus, the first three batches manufactured included dosages of 1 and 2 mL

***Reviewer Comments:** The narrative provided in this report in regards to the fill sizes of the batches manufactured in support of the process validation is not clear. The firm seems to indicate that the 1 and 2 mL configurations were used, but provides no justification for why these fill sizes were used. The firm should clarify the fill sizes used in the validation and provided a justification for why these fill sizes were used. The firm was issued an IR, in addition, there were discussions during the pre-license inspection between the product specialist and the firm in regards to the fill sizes covered in the validation. Please refer to Information Requests section of memo (IR#4, Response as Amendment 30) for details of the firm’s response in regards to the fill sizes covered in the validation, in addition, refer to the EIR for the issues that were discussed.*

- The parameters and testing to support validation included the following:

- **Production consistency parameters:** Human Fibrinogen recovery study was performed to evaluate the reproducibility and consistency of the manufacturing process. The various process variables were studied, in addition to yield, recovery and purification values
- **Routine quality assays:** Assays included the following:  
Product Release testing and Acceptance Criteria

Intermediate Product	Routine Assays	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)
Final Container	Routine Assays	
Final Frozen container	Current quality assays	Current specifications



(b) (4)

[Redacted text block]

-Product Uniformity: Two studies were performed to verify the correct Fibrinogen FS lots uniformity.

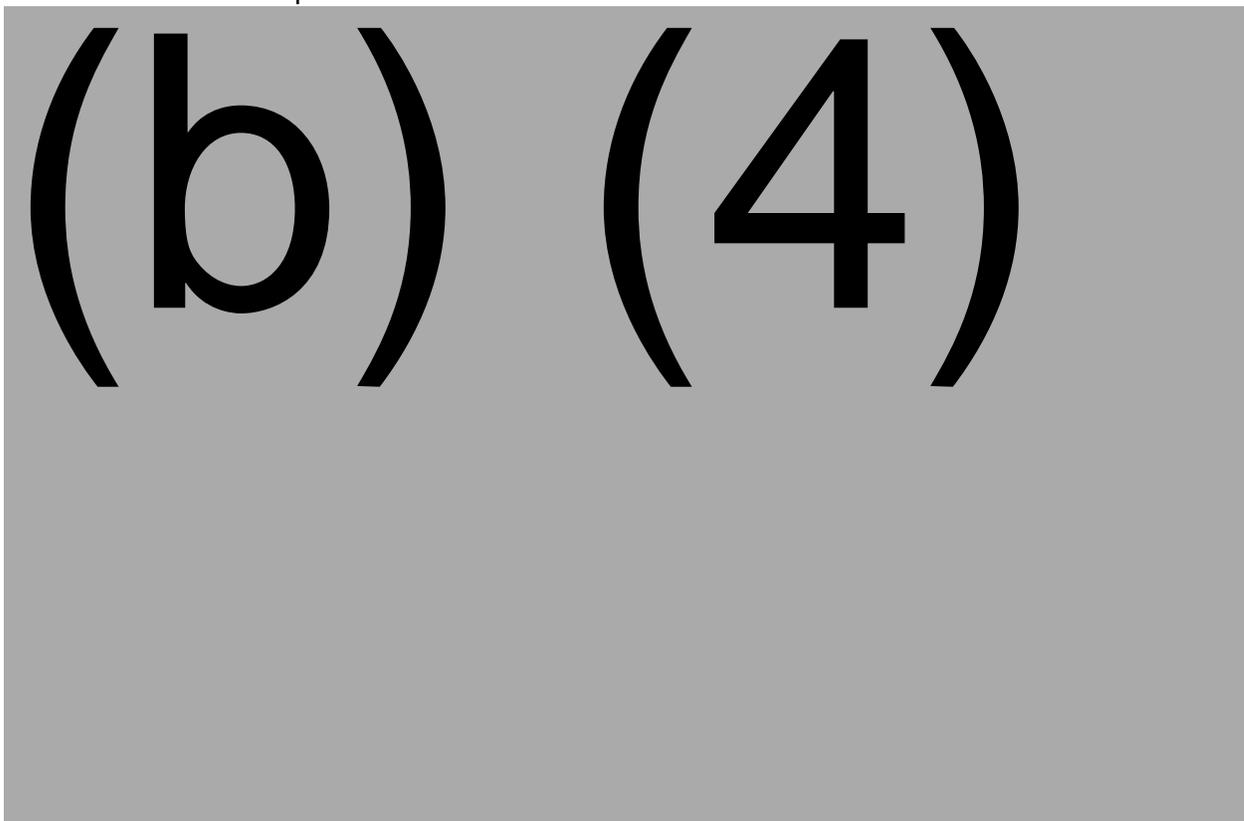
Product Uniformity	Assays	Acceptance Criteria
Study 1: Protein concentration uniformity of the first filled units	Total protein	(b) (4)

Study 2: Uniformity of the quality criteria in the entire filled lot	Endotoxin, Fibrinogen (clottable protein), Chlorides, citrate, endotoxins	Endotoxin: (b) (4) Fibrinogen: (b) (4) Chlorides: (b) (4) Citrate: (b) (4)
----------------------------------------------------------------------	---------------------------------------------------------------------------	-------------------------------------------------------------------------------------

-Final product characterization study: Analytical parameters are not routinely performed on a batch to batch study but are for information only on the suitable purification capacity of the manufacturing process

Final Container	Assay	Acceptance Criteria
Final Frozen Container (Fibrin Sealant)	(b) (4)	(b) (4)

- Results were reported as follows



(b) (4)

[Redacted text block consisting of several lines of greyed-out content]

(b)

(4)

[Redacted]

(b) (4)

(b) (4)

*Reviewer Comments:* Validation study IG\_VS-001292 covering the overall process validation of thrombin did not provide details or results of the filling process or how the aseptic filling process was monitored for consistency (i.e. in-process parameters including (b) (4) etc. and the associated acceptance criteria). The firm was issued two IRs in regards to this issue. Additionally, this issue was discussed with the firm during the pre-license inspection and was included on the FDA Form 483 as observation #2. Please refer to Inspection Follow-ups, Information Requests sections of memo, in addition to EIR for details.

**Inspectional Follow-Up: Review process validation data in regards to the aseptic filling process for Fibrinogen.**

IG VS-001290- Validation of the solvent detergent (SD) treatment process performed to fibrinogen solution

The validation report IG\_VS-001290 “Validation of the solvent detergent (SD) treatment process performed to Fibrinogen Solution (Fibrin Sealant Grifols)” summarizes the data of the solvent detergent treatment process performed to fibrinogen product using heat treatment equipment no. (b) (4). The purpose and validation method, in addition to results were described as follows:

- Purpose: to validate that fibrinogen solution with the mixture of proper proportions of TnBP (Tri-n-butyl phosphate) and TWEEN 80 (Polysorbate 80) is (b) (4)

[Redacted]



- o (b) (4)

Results- For all three runs at the (b) (4) load for the homogenization stage and the SD treatment stage, the acceptance criteria for (b) (4), additionally, the acceptance criteria was met for the validation run at the (b) (4) load for both stages of SD treatment.

### **III. Thrombin Manufacturing Process and Validation**

Thrombin is obtained from the prothrombin complex concentrate (PTC) obtained from Fraction I supernatant of (b) (4), per Instituto Grifols production method IG-MP-000026. The manufacturing process and controls for the manufacturing of thrombin from Fraction I are described in detail in document IG MP-000034\_INGv7 provided in eCTD section 3.2.P.3.3 Description of Manufacturing Process and Controls. The process involves the following:

(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey bars.]



(b) (4)

(b) (4)

Several process validation reports were provided for Thrombin manufacturing. These reports include the following:

- IG\_VS-001292- Human Thrombin process validation for Fibrin Sealant Grifols
- IG\_VS-001435- Validation of the chromatographic process and cleaning of the thrombin purification column
- IG\_VS-001289- Validation of the solvent detergent treatment process performed to thrombin solution

These reports are summarized as follows:

IG\_VS-001292- Human Thrombin process validation for Fibrin Sealant Grifols

The validation report IG\_VS-001292 “Human Thrombin Process Validation for Fibrin Sealant Grifols” provides the overall process validation and results for the manufacturing of Human Thrombin. The validation was designed in three phases that included: Phase I Process Design, Phase II: Qualification of the commercial manufacturing process and Phase II Continued Process verification. As with Report IG\_VS-001293 for Fibrinogen, Report IG\_VS-001292 covers the activities that are associated with Phase II that includes the following two stages: Stage I, Qualification of facilities and equipment that take part in the commercial manufacturing process (IQ/OQ) and prospective validations studies and Stage 2, Process Performance Qualification (PPQ).

The PPQ was performed once the IQ/OQ demonstrating facilities and equipment are properly operational and included the first three FS (Fibrin Sealant) Grifols product lots manufactured in the facilities of Building (b) (4) (reference Facilities and Equipment section of memo for details). The following details of the validation study were described as follows:

- The same final presentations (syringes/dosage) previously reviewed in report IG\_VS-

001293 for Fibrinogen were also covered in this process validation with validation included three batches of dosage of 1 and 2 mL

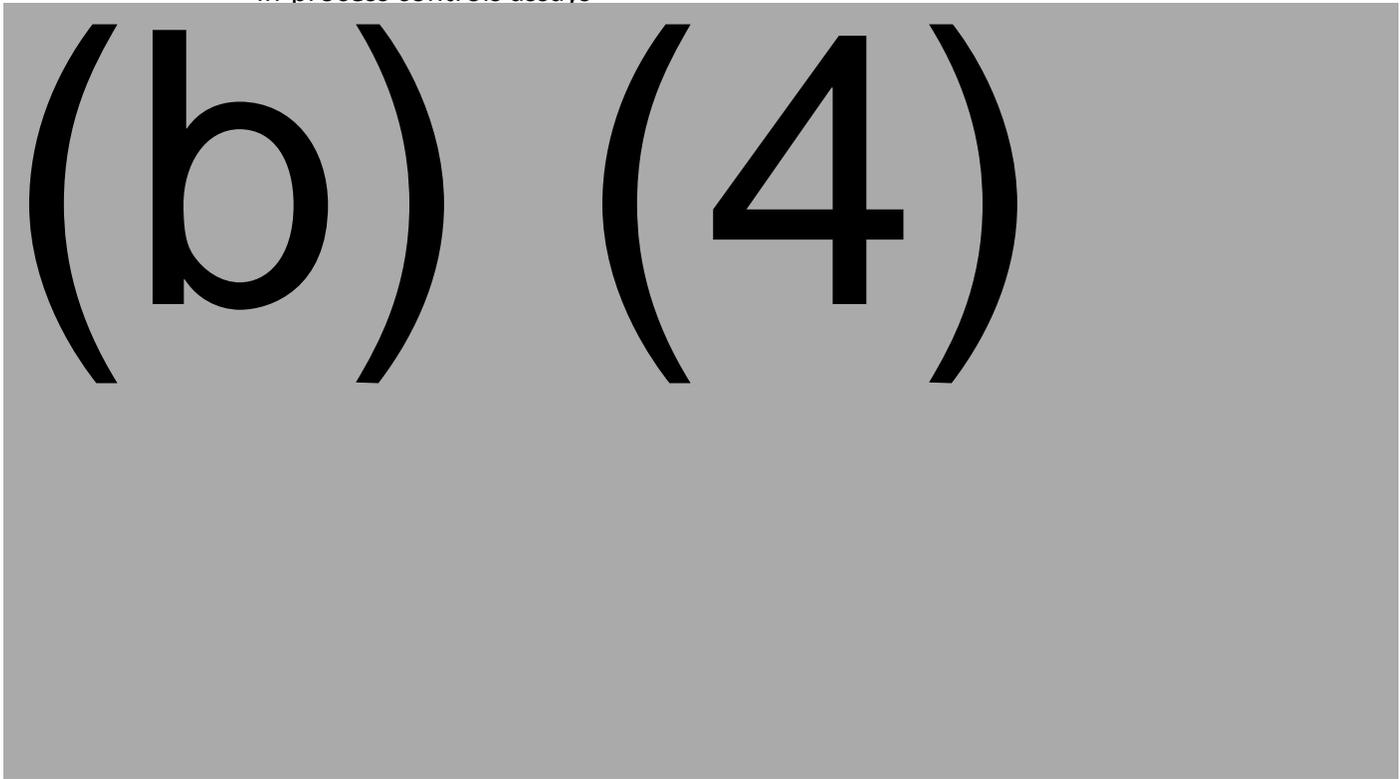
- Parameters in validation consisted of Production consistency parameters, routine quality assays and additional assays. The parameters and acceptance criteria were indicated as follows:
  - Production consistency parameters included monitoring the (b) (4)
  - Routine Quality Assay- Assays included routine quality assays and in-process controls assays

Routine Quality Assays

Product	Routine Assays	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Final Frozen Container (final container)	Current quality assays	Current specifications <sup>(1)</sup>

<sup>(1)</sup>After the study was performed specifications for (b) (4)

In-process controls assays





(b)

(4)

[Redacted text block]

(b) (4)

(b) (4)  
[Redacted text block]

*Reviewer Comments:* Validation study IG\_VS-001292 covering the overall process validation of thrombin did not provide details or results of the aseptic filling process or how the aseptic filling was monitored for consistency (i.e. in-process parameters including (b) (4) etc. and the associated acceptance criteria). The firm was issued two IRs in regards to this issue. Additionally, this issue was discussed with the firm during the pre-license inspection and was included on the FDA Form 483 as observation #2. Please refer to Inspection Follow-ups, Information Requests sections of memo, in addition to EIR for details. The results of the other assays not including sterility, (b) (4) are deferred to the product office for assessment.

**Inspectional Follow-Up: Review process validation data in regards to the filling process for Thrombin.**

IG\_VS-001435- Validation of the chromatographic process and cleaning of the thrombin purification column

The validation report IG\_VS-001435, “Validation of the chromatographic process and cleaning of the thrombin purification column” summarizes the data from the chromatographic process, cleaning and storage of the column, mach. No. (b) (4) used in the Thrombin purification process



(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

*Reviewer Comments: Several deficiencies in validation report in regards to the cleaning and storage of columns resins are noted as follows:*

- 1. The firm did not indicate the number of times the resin can be re-used or will be re-used nor*

indicate a plan to monitor the resin if more used than the number of runs covered in the validation.

2. There were no details in regards to the storage time between uses indicated i.e. what is the maximum storage time between runs. Given these deficiencies, the chromatography column process validation and cleaning was reviewed on inspection, in addition, an IR was issued after inspection. Please refer to the EIR and IR#4 item #3

**Inspectional Follow-up-Review the cleaning validation of the column resin and re-use including reviewing storage conditions and time of storage between re-uses.**

IG VS-001289- Validation of the solvent detergent treatment process performed to thrombin solution

The report IG\_VS-001289- Validation of the solvent detergent treatment process performed to thrombin solution summarizes the data from the validation of the Solvent Detergent (SD) treatment process performed for thrombin product for Fibrin Sealant using heat treatment equipment (b) (4). This validation is performed similarly to the SD treatment for Fibrinogen (Report IG\_VS-001290), which was previously reviewed in this memo. The purpose, validation and results in the report are summarized follows:

- Purpose- To demonstrate that the thrombin solution is mixture is at the proper proportions of TnBP (Tri-n-butyl phosphate) and Tween (polysorbate 80) and is (b) (4).
- Validation consisted of 3 runs at (b) (4) load and one additional run with (b) (4) load with placebo, having same physicochemical characteristics and composition as real product, but containing no protein.
- Parameters controlled in validation runs included:

(b) (4)

[Redacted text block containing multiple lines of information, likely a list of parameters controlled in validation runs.]

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

**IV. Bulk Filtration and Aseptic Filling of Fibrinogen and Thrombin**

The filling of thrombin and fibrinogen syringes are both filled for each lot which is performed (b) (4). The bulk filtration and aseptic filling of Thrombin and Fibrinogen were detailed in the submission as follows:

(b) (4)

[Redacted text block]

(b) (4)

- █ [redacted]
- █ [redacted]
- █ [redacted]
- █ [redacted]

[redacted]

[redacted]

- █ [redacted]
- █ [redacted]
- █ [redacted]
- █ [redacted]
- █ [redacted]
- █ [redacted]

[redacted]

The following validation that supports the aseptic filling process is summarized as follows:

IG\_VS-001533, "Validation of the Aseptic Filling of 3 mL and 5 mL (b) (4) syringes in Machine no. (b) (4)"

The document IG\_VS-001533 provided in eCTD section 3.2.P.3.5 Process Validation summarizes the validation of the aseptic filling of 3 mL and 5 mL (b) (4) syringes used for the filling of Fibrinogen and Thrombin and was provided to support the aseptic filling process.

For the validation, the following was noted:

The variables used to define the 'worst case' scenario of the filling process for 3 and 5 mL (b) (4)



(b) (4)

(b) (4)

(b) (4)

*Reviewer Comments: The firm needs to provide more details in regards to the interventions performed and provide the filling times that were covered in the validation. Additionally, the firm did not indicate if deviations occurred during the media fill runs. The media fill reports should be further assessed on inspection and be included as an inspection follow-up:*

***Inspectional Follow up- Review media fill reports that include all deviations (and investigations) occurring during the media fill re-validation, in addition review the interventions performed during the media fill simulations and review the details of the fill sizes used in the validation.***

Sterile Filter Validation and Integrity testing

**Filters used for Fibrinogen-** In document IG\_MP-000033v10, a listing of the filters used to



(b) (4) [Redacted text block]

**V. Assembly and Sterilization of Fibrinogen and Thrombin Syringes for Fibrin Sealant Drug Product**

The same procedures are described for the assembly of the Fibrinogen and Thrombin Syringes to form the Fibrin Sealant Drug product. These procedures are summarized as follows:

**Assembling the Syringes of Fibrinogen and Thrombin for Fibrin Sealant Grifols-** The labeling and assembly of the syringes with the holder is performed outside the aseptic area. The syringes are labelled with the corresponding identifying label of each Fibrin Sealant Grifols component that includes the lot and expiry date. Once the syringes of the two components are labelled, the plunger is placed in each syringe and is assembled in the applicator holder. The holder with the syringes is put inside a blister pack. The blister pack is closed by heat-sealing (b) (4) [Redacted]. The sealed blister is labeled with the lot number and expiry date. After the blister is labelled, the sealed blisters are placed in inside a heat-sealed bag, which keeps a permeable side to (b) (4) [Redacted]. The bag is identified with the product description, the lot number and expiry date

*Reviewer Comments:* There were no details in regards to the assembly of the syringes and holder and packaging of the assembly specifically. However, the firm provided a validation that covers the sterilization of the Fibrin Sealant kit using (b) (4) [Redacted] after assembly of the

kit. This assembly of the kit into the blisterpak will be review on inspection.

**Inspectional Follow-up- Review the procedures and validations associated with the assembly of the fibrin sealant kit including the blisterpak sealing and visual inspection process.**

**Sterilization of Fibrin Sealant Kit with (b) (4)** - The products inside a heat-sealed bag are (b) (4). The method and validation was described in report IG\_VS-001532 which provides results the sterilization of Fibrin Sealant applicator system and its packaging components using (b) (4). The report is summarized as follows:

- (b) (4) [Redacted]
- [Redacted]

(b) (4)

- (b) (4) [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]



(b) (4)

(b) (4)

(b) (4)

(b) (4)

**VI. Final Packaging and Freezing of Fibrin Sealant Drug Product**

After sterilizing with (b) (4), each unit is packed inside a single unit carton with the leaflet and the cannula application device. The single unit of Fibrin Sealant Grifols product is labelled with lot number and expiry data. Once packed, the single carton units are frozen at  $\leq -20^{\circ}\text{C}$ . The product is stored frozen at  $\leq -20^{\circ}\text{C}$ .

*Reviewer Comments: The firm did not provide any details of the cannula application device that is co-packaged with the drug product specifically in regards to how the device is sterilized and individually packaged. An information request was sent to the firm asking to clarify this*

information. In the response from the firm, the firm indicated that the device is purchased as an off-the-shelf component, which is received sterile and individually packaged. Sterilization is performed by the manufacturer (b) (4). The package for the cannula is sealed with a (b) (4) to enable the sterilization. The firm indicated that there is no manipulation of the cannula at Instituto Grifols, S.A. Please refer to section "Information Requests" IR#1 for additional details of the firm's response in regards this IR.

**VII. Component Sterilization Validation**

The cleaning of equipment is covered under Facilities, Equipment Qualification and Cleaning section of this memo. This section covers the sterilization validation of the components and equipment used in the aseptic filling process of Fibrinogen and Thrombin that includes the following:

(b) (4) syringes and stoppers: Two validation reports IG\_VS-001517, "Validation of the Sterilization of (b) (4) Syringes in (b) (4) of Aseptic Filling Area (b) (4)" and IGVS-001519, "Validation of the Sterilization of (b) (4) syringes in (b) (4) of Aseptic Area (b) (4) were provided. These validations reports cover the sterilization of the (b) (4) syringes used in for the filling of Thrombin and Fibrinogen in (b) (4) and (b) (4). The studies are summarized as follows:

(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

(b) (4)

(b) (4)



(b) (4)

(b) (4)

*Reviewer Comments: The reports provided did not indicate how the syringes are prepared for sterilization nor provided any information for how the syringes and stoppers are depyrogenated or if syringes and stoppers are tested for (b) (4) . The firm was issued an information request February 6, 2017 to provide additional information in regards to how the syringes and stoppers are prepared for sterilization. For details, please refer to Information Requests section of memo, particular IR#3, item 4.*

(b) (4)

[Redacted]

- [Redacted]

- [Redacted]

[Redacted]

- [Redacted]

- [Redacted]



(b) (4)

(b) (4)

(b) (4)

(b) (4)

**VIII. Container Closure and Container Closure Integrity Testing**

The overall container closure system consists of single use kit that contains one pre-filled syringe of fibrinogen and one pre-filled syringe of thrombin assembled on a syringe holder. The kit is then packaged into blisterpak (sealed with (b) (4)) and then packaged into a (b) (4) bag, which is subsequently sterilized by (b) (4).

Primary Container:

The primary container consists of either a 3 mL or 5 mL (b) (4) glass syringe with a bromo-butyl rubber plunger stopper and tip cap made of bromo-butyl-rubber. In the 3 mL syringes the fill volumes include either 1 mL fill or 2 mL fill. In the 5 mL syringes, the fill volumes include either a 3 mL fill or 5 mL fill.

The syringes, tip caps and plunger stoppers ((b) (4) syringes) are purchased from

(b) (4) . (b) (4) established a Biologics Master File (No. BB-MF-(b) (4)) with CBER for the syringes and has authorized Instituto Grifols, S.A. to reference their master file. The authorization letter is provided in Module 1.4.1.

Certificates of analysis were provided for the syringes, tip cap and plunger stoppers. The compatibility of the packaging components is support by stability reports in Module 3.2.P.8.3. The samples used in the stability study are stored in an inverted position to keep the solution in contact with the stoppers as “worst case” storage conditions.

*Reviewer Comments: The referenced Master File BB-MF-(b) (4) for the syringes, tips caps and plunger was not reviewed as part of this BLA. The review of the compatibility of the packaging components and the supporting stability studies is deferred to the product office for assessment.*

The syringes are assembled onto a syringe holder, which was designed and manufactured by Laboratorios Grifols ((b) (4) Spain).

#### Secondary containers and packaging

The syringes (containing Fibrinogen and Thrombin)/syringe holder kit is packaged into blister packaging that is further packaged into (b) (4) bags and subsequently sterilized with (b) (4) . After sterilization, the (b) (4) bags containing the blisterpaks are further packaged into single unit cartons with the package insert and a separately packaged cannula applicator tip.

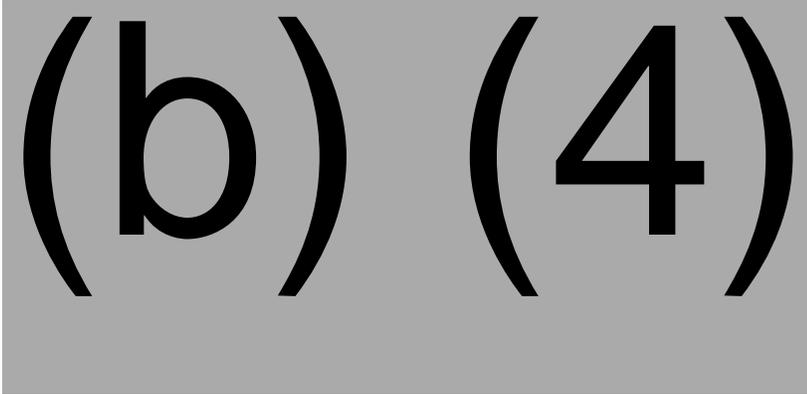
The purpose of sterilizing the blisterpak containing the syringe kit is to sterilize the outer surface of the syringe kit since this kit will be used in an operating room setting; thus, the purpose of the blisterpak is to maintain the sterility of the kit before use.

*Reviewer Comments: Since the syringe kits are placed into blisterpaks and then are subsequently sterilized with (b) (4) , the blisterpak are serving two functions that include protection of the product, in addition to, maintaining the sterility before use in the operating room. Given this, the firm should provide studies that demonstrate packaging integrity and seal strength of the blisterpaks to ensure that the sterility can be maintained until use. These types of studies were not provided in the original submission; thus, the firm was issued an information request to provide these studies. Please refer to Information Requests section of memo, specifically the firm response to IR# 3 (sent February 6, 2017), item#1 for details of the studies provided.*

#### Container Closure Integrity Testing of (b) (4) Syringes

Container closure integrity testing was performed on the pre-filled syringes and is summarized in the report IG\_VS-001295, “Container closure Integrity Validation”. The (b) (4) method

was used to demonstrate the integrity of the container closure system of the Fibrin Sealant product which includes 3 and 5 mL (b) (4) syringes and plunger stopper. The following presentations of the container closure were considered in the validation study:



(b) (4)

[Redacted text block consisting of several lines of greyed-out content]

Quantity of manufactured units: The WFI filling process of the test syringes should be representative of the routine production process. The minimum number of syringes filled per run ((b) (4) units) was established per (b) (4) [Redacted] for a lot size greater than (b) (4) units, significant greater than the usual production lot size.

Method:

(b) (4) [Redacted text block consisting of several lines of greyed-out content]



(b) (4)

*Reviewer Comments: The firm was issued an IR recommending that the firm incorporate CCIT testing at expiry into the stability testing protocol and the firm agreed to perform this testing as part of the stability testing protocol. For details, please firm response to IR#4, item 9.*

## FACILITIES, EQUIPMENT, QUALIFICATION AND CLEANING

### I. Description of facilities

The manufacturing of Fibrin Sealant Grifols is performed at the facilities located in Barcelona, Spain. The facility is composed of several buildings where buildings (b) (4) and (b) (4) are used for manufacturing activities, Building (b) (4) is used for Quality Control activities, building (b) (4) is used for warehousing of non-plasmatic raw materials and Building (b) (4) (Building (b) (4)) houses plasma storage (b) (4) and storage chamber of final product.

The following facility details were indicated in regards to Fibrin Sealant manufacturing steps:

- Fractionation process to obtain Fraction 1 and prothrombin complex (PTC) eluate is performed in the currently licensed fractionation areas that include Building (b) (4) and Building (b) (4)
- Purification, viral inactivation and final adjustment processes take place in facilities dedicated to Fibrinogen and Thrombin

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey bars.]

**II. Manufacturing Flow**

The manufacturing flows of the materials, products, personnel and waste were described and flow diagrams of the manufacturing processes (process/ production of plasma fractionation, fibrinogen and thrombin manufacturing, aseptic filling, packaging and sterilization), materials, products and personnel were provided in Appendices section 3.2.A.1 of the submission. The flows are summarized as follows:

**Process Flow-** A description of the process flow in the facility for the fibrinogen and thrombin manufacturing is provided as follows:

Fibrinogen purification and aseptic filling process (Building (b) (4) )

(b) (4)

[Redacted text block containing multiple lines of information for the Fibrinogen purification and aseptic filling process.]

Thrombin purification and aseptic filling process (Building (b) (4) )

(b) (4)

[Redacted text block containing multiple lines of information for the Thrombin purification and aseptic filling process.]

Packaging, freezing and storage (Building (b) (4) , Building (b) (4) , Building (b) (4) )

(b) (4)

[Redacted text block containing multiple lines of information for the Packaging, freezing and storage process.]

**Raw Materials and Waste Flow-** The following was indicated for raw materials and waste



(b) (4)

### III. *Equipment*

A listing of the main equipment used in the manufacture of Fibrin Sealant was provided in Section 3.2.A.1. The list divided into three tables includes the name of equipment, a description of the use and the number of the room where the equipment is located for equipment used in the fractionation process in Buildings <sup>(b) (4)</sup> and <sup>(b) (4)</sup>, in the Fibrinogen purification process, in the Thrombin purification process and in the aseptic filling and packaging of pre-filled syringes. These lists provided were comprehensive including production equipment and <sup>(b) (4)</sup> equipment such as (b) (4). The types of equipment listed for the various manufacturing processes are condensed as follows:

(b) (4)

#### **Fibrinogen Process Equipment**



(b) (4)

The firm indicated that all equipment is included in preventive maintenance and calibration program which details the methods and frequencies of these operations. Cleaning Validation for equipment is described and reviewed in following Section IV: Cross-Contamination and Cleaning Validation.

*Reviewer Comments:* Although the firm indicated that qualification of facilities and equipment were performed as part of Stage I Validation, there were no qualification summaries (OQ) of the equipment provided in the submission. To address this deficiency, an IR was sent to the firm asking to indicate the IQ status and to provide the OQ/PQ of select equipment, mainly critical equipment such as centrifuges, chromatography column and skids, (b) (4) units and filling and packaging equipment. Please refer to Section "Information Requests" IR#3 of this memo for details of the qualification summaries for critical equipment. Please note that the overall qualification of all equipment used in the manufacturing process were reviewed and verified on the pre-license inspection. Please refer to EIR for details of equipment that was reviewed on inspection.

#### **IV. Cross Contamination and Cleaning Validation**

A brief description of the overall activities and procedures that are implemented to prevent cross contamination and cleaning procedures was provided and is summarized as follows:

##### **Containment Features**

The following was indicated to prevent contamination and/or cross contamination:

##### Facility

(b) (4)

[Redacted facility details]



(b) (4)

[Redacted text block]

### Equipment and cleaning procedures/validation

The cleaning of equipment is either performed using Clean in place processes or by manual cleaning. Cleaning of main equipment such as (b) (4) using Clean in place units, which are controlled by a validated computer program. Written procedures specify the cleaning procedure and frequency of external and internal parts of the (b) (4). Equipment for which is not possible to use automatic CIP procedure are manual cleaned. In general, the manual process consists of cleaning with (b) (4). Cleaning is always performed between lots after each process. A description of the cleaning procedures and cleaning agents used for main equipment was provided in Section 3.2.A.1 and is summarized as follows:

(b) (4)

- [Redacted list item]



(b) (4)

(b) (4)

*Reviewer Comments: The firm did not indicate how the manual cleaning process is monitored, thus the firm was issued an IR asking to indicate if there is a routine monitoring program and how frequent monitoring is performed in regards to their manual cleaning processes. For details of firm response, please refer to IR#6, item 3.*

(b) (4)

(b) (4)

(b) (4)



(b) (4)

Results: The results reported in both validation reports for Fibrinogen and Thrombin met the acceptance criteria. No deviations in the acceptance criteria were indicated.

*Reviewer Comments:* In regards to the overall prevention of cross contamination and cleaning there were no specific details in regards to which equipment is shared or dedicated or which equipment is product contact. Additionally, more clarification is needed in regards to which equipment are cleaned CIP vs manual. To address this item, an IR was issued to the firm. Please refer to Section "Information Requests" of this memo, specifically IR#2, firm response submitted as Amendment 10 for details. In regards to the (b) (4) membranes, the firm did not provide sufficient details in regards to storage time and conditions of membrane between uses, in addition to monitoring of (b) (4) testing). The firm was issued an IR to provide these details. Please refer to IR#6, item 2 for details of firm response.

## V. Water Systems

Water for Injection (WFI) and purified water are used in the manufacturing process. Purified water is used only for the cleaning process of equipment and materials, with exception for final rinsing after cleaning. WFI is used for final rinsing of after cleaning, in addition, only WFI is used washing of final product containers. A general description of the water systems including the purification, sanitization and control was provided as follows:

Water system including WFI and Purified Loops that supply water to different Fibrin Sealant consist of:

- Purified Water Loop No. (b) (4)
- Cold WFI Loop No. (b) (4)
- Cold WFI Loop No. (b) (4)
- Hot WFI Loop NO. (b) (4)

A schematic of the loops, in addition to a flow chart of the water purification and distribution

systems were provided in the submission in Module Section 3.2.A.1. The flow chart of the distribution systems and description of the water system was provided and is summarized as follows:

(b) (4)

[Redacted text block]

- (b) (4)
  - [Redacted text]
  - [Redacted text]
  - [Redacted text]
  - [Redacted text]
- [Redacted text]
  - [Redacted text]
  - [Redacted text]
  - [Redacted text]
  - [Redacted text]
- [Redacted text]
  - [Redacted text]
  - [Redacted text]
  - [Redacted text]

(b) (4)

[Redacted text block]

[Redacted text block]







(b) (4)

**VII. HVAC**

A description of the air handling systems was provided and is summarized as follows:

There are (b) (4) air handling units that supply air to the different rooms involved in the product manufacture. In each unit, (b) (4)

[Redacted]

Manufacturing rooms have been classified depending on their use and according to the following guidelines indicated as follows:

- (b) (4) [Redacted]
- [Redacted]

There are (b) (4) laminar flow cabinets that are involved in the manufacturing of Fibrin Sealant. The laminar flow cabinets consist of the following:

- (b) (4) [Redacted]
- [Redacted]



(b) (4) [Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

**QUALITY SYSTEM FOR COMBINATION PRODUCT**

The Fibrin Sealant kit which consists of two syringes containing sterile frozen solutions of human fibrinogen (Component 1) and human thrombin with calcium chloride (Component 2) assembled on a syringe holder that is co-packaged with an applicator cannula, in addition, the syringe system can be used with a spray applicator that is supplied separately. According to 21 CFR Part 3 this product meets the definition of a single-entity, co-packaged and cross-labelled combination product in that this is a product that is composed of a biologic that includes the sterile solutions of fibrinogen and thrombin and a device that includes the pre-filled syringe with syringe holder and that is co-packaged with a separate unit device the cannula, in addition to separate device that can be used with product but is packaged separately. The cGMP requirements for combination products are defined in 21 CFR Part 4 and include two approaches in demonstrating compliance with all cGMP requirements applicable to all constituent parts that include the drug component and the device component (i.e. for drugs the 21 CFR 211 and for devices 21 CFR 820). In regards to the Fibrin Sealant product, the firm is following the streamlined approach, demonstrating compliance with

specified provisions from the cGMPs for drugs (21 CFR Part 211) and for devices (21 CFR Part 820). With this approach, the firm should demonstrate compliance with the following regulations for the devices component of the Fibrin Sealant product:

- 21 CFR 820.20 Management responsibility
- 21 CFR 820.30 Design Controls
- 21 CFR 820.50 Purchasing controls
- 21 CFR 820.100 Corrective and preventive action

The documentation to support compliance with the device component of the combination product was not entirely provided in the BLA submission, thus an information request was sent to the firm Nov 22, 2016. The firm provided the requested information as Amendment 3 (eCTD 0004, STN 125640/0). The documentation provided in Amendment 3 that is under the purview of DMPQ, which includes purchasing controls and CAPA is summarized as follows:

### **Management Responsibility**

This information which was not provided in the original submission nor was the information provided in Amendment 3.

*Reviewer Comments: This information which was not provided in the BLA submission, but was intended to be reviewed on inspection; however, time did not permit and this area was not covered on inspection. An IR was sent to the firm asking to provide documentation that supports compliance with the Quality System Requirement in regards to Management Responsibility. Please refer to IR#5 for details of the firm's response.*

### **Purchasing Controls:**

The following is a listing of the different device constituents included in or used with the Fibrin Sealant kit:

- Pre-filled syringes- includes the syringes, tip caps and plunger stoppers (b) (4) syringes which are purchased from (b) (4)
- Syringe holder and plunger link- designed by Diagnostic Grifols and manufactured by Laboratorios Grifols, S.A. Calle Can Guasch, 2 08150 Paret del Valles Barcelona, Spain (Establishment Registration No. 3002807257)
- Application tip (cannula)- Manufactured by (b) (4)
- Spray Applicator- FibriJet® Gas-assisted spray applicator- Tis applicator is manufactured

by Micromedics Inc., Eagan Minnesota, USA 55121 and is an optional accessory and provided separately.

The firm provided the documents IG\_MSP-000583\_ING and IG\_MSP-001549\_ING in support of the purchasing controls for the device components. These are general procedures that apply for all raw materials and are summarized as follows:

The SOP IG\_MSP-000583 describes the qualification levels of raw materials based on risk that is used as part of the qualification process of a supplier of raw materials. There are two qualification levels established and include level A for materials of medium and high risk and level B for materials of low risk. For level A materials, there are more stringent requirements needed in qualifying a supplier as compared to the requirements for suppliers of level B materials. SOP IG\_MSP-000583 defines these requirements for the qualification of suppliers of level A and level B materials.

The SOP IG\_MSP-001549\_ING describes the approval process and monitoring of suppliers of raw materials based on the risk assessment. All new materials or existing materials to be supplied by a new manufacturer require a proposal of change. This is performed by means of a change control which initiates an evaluation of the risk of material using a risk assessment approach and incorporates the qualification levels described in SOP IG\_MSP-000583. Materials of all risks, low, medium or high that are approved for use are subjected to monitoring, which includes the following:

- Assignment of an inspection plan in the reception of a material before its use according to nature of material defined in MSP-001026
- Follow-up of the quality based on possible incidence that could be detected during the control and during its use. A frequent number of incidences could be cause of revision and reevaluation of the raw material provided by the supplier (requirement of a change control)
- Periodic revision of the supplier dossier. For materials of High risk, supplier evaluation would be every (b) (4) and materials of medium risk would be (b) (4) .

If there are any changes in the parameters in the materials provided by a supplier which could involve a risk in the product quality, there must be an evaluation before acceptance. Change to the material could be either through notification by the supplier and/or changes detected during the monitoring. Included in the SOP IG\_MSP-001549 are the necessary requirements for an approval of a change in a raw material according to an associated risk, in addition to examples of materials with different levels of criticality and examples of changes in facilities, scale (lots size), equipment, manufacturing process and materials and their associated risks

classified as low, medium and high.

*Reviewer Comments: During the Pre-license inspection, purchasing controls in regards to the details relating to (b) (4) syringes such as incoming testing that is performed was further reviewed and discussed with the firm. For additional details in regards to specific purchasing controls for the device components, please refer to the EIR.*

## **CAPA**

In regards to compliance with 21 CFR 820.100 Corrective and preventive action section of the device regulations, the firm provided the SOP IG\_MSP-001134, "Corrective and/or Preventative Actions Follow-Up, which describes the system for the identification, management and follow up of the implementation of the corrective and/or preventative actions and their evaluation, approval and closure. The Technical Director, Division of Quality Assurance, Audits Department and Regulatory Affairs are responsible for managing and coordinating the activities in addition to recording corrective actions and preventative action. The managers of departments that include Research and Development, Production Control and product distribution are responsible for the implementation of the application of the CAPA system. This general CAPA procedure indicates the initiation of CAPA resulting from the following:

- Observations of internal audits, inspections conducted by regulatory and competent authorities, external audits (e.g. customers) and observations detected in audits to suppliers or subcontractors
- Investigation of deviations related to the receipt and use of raw materials or in the processes of production of intermediates or final product in addition to monitoring of equipment, systems and facilities
- Investigation of deviations related to incidents in storage and distribution of released finished product
- Investigation of related deviation with validation, calibration and qualification of facilities and equipment, related to products or processes authorized by the competent authorities
- Investigation of deviations associated with stability studies of products in development stage, trial phase and approved by the competent authorities
- Complaints or customers' notifications
- Other corrective and/or preventative action that may arise as a result of the detection of an anomaly, trend or need of improvement

There are risk levels associated with CAPAs that include levels of low, medium or high risk. The risk level priorities of the follow-up actions with higher risk take more priority. Additionally, the CAPA type is defined per the following:

1. Training
2. Documentary
3. Process
4. Equipment & Facilities
5. Cleaning, Maintenance and Calibration
6. Materials (suppliers, raw materials and packaging materials, etc.) and Services
7. Others

A CAPA is generated by a “Responsible” who makes a CAPA proposal and sends to the appropriate CAPA manager who will be responsible for monitoring the implementation of the action within the prescribed period and to assess where appropriate that such action has been effective. The CAPA manager is usually personnel belonging to the Quality Unit or other departments deemed necessary. The approver of the CAPA, who is responsible for approving the proposed actions and deadlines for implementation is the Directors of the affected area and the Technical Director of IG.

The CAPAs are monitored independently from their origin and are managed through the “Database corrective and/or preventative actions” which requires the printing of relevant records as appropriate.

The SOP further describes the procedures for approving, evaluating the effectiveness and the closing of CAPAs. Quarterly, the Audit Department will generate a written report or e-mail, which includes all new CAPAs generated in that period and the status of pending CAPAs. After a CAPA is closed it is no longer included in report. Additionally, at least quarterly, each CAPA manager may send a summary of the activities to be performed to each CAPA responsible for the different areas of Quality Control, Production, Validation and Research & Development activities. All documentation issued in opening, completion, follow up and evaluation of the CAPA will be kept in the Audits Department.

***Reviewer Comments:** The CAPA procedure and how this applies to the device components was also discussed with the firm on during the pre-license inspection. For additional details of the discussions, please refer to the EIR.*

## Design Controls

The Fibrin Sealant kit was specifically described as consisting of two polycarbonate pieces (syringe holder and plunger) produced through injection molding. The syringe holder is clipped onto the two (b) (4) Syringes filled with fibrinogen (syringe 1) and thrombin/calcium chloride (syringe 2) and it is intended to hold the syringes during transport, storage and application. The plunger link is connected to the syringe holder. It ensures that the plungers of the syringes are connected and move at the same rate during the application of the fibrinogen and thrombin with calcium chloride, resulting in a simultaneous application. The firm indicated in their response provided in Amendment 3 that the design of the combination product was not developed under the design control requirements as the development of this product occurred before the issuance of 21 CFR Part 4. Instituto Grifols has classified Fibrin Sealant product as a Legacy Product and is working with leveraging existing data to apply to regulatory requirements.

Documents IG\_ITEC-002493, "Fibrin Sealant: Functionality of the Application Systems" and IG\_ITEC-00297, "Fibrin Sealant: Viability of the Application Device" were provided in the original submission and both summarize the functionality of the Fibrin Sealant application system. Document IG\_ITEC-002493 evaluates the functionality (verify mixture of both components forms a clot) of the Fibrin Sealant application system, in addition to the testing of the homogeneity (ensure product is delivered homogeneously), consistency (ensure the correct volume is administered) and compatibility of the application tip and spray application

Document IG\_ITEC-002497 summarizes the analysis of the viability and functionality of the Fibrin Sealant Grifols application device over stability when product is subjected to stress conditions ((b) (4) ) and at long-term studies for a total of 24 months at temperatures of -21.4°C and -75±5°C. The syringe holder and the plunger are checked at different time points to ensure correct attachment and that the product can be easily administered through the tip applicator. Additionally, the proper mixing and generation of a fibrin clot was also evaluated. For viability of the application device, the application tip was analyzed in preclinical studies in vascular and cardiac surgery in pig and vascular surgery in rabbits. Viability of the application device using the spray application was analyzed in preclinical study in liver surgery in pigs.

*Reviewer Comments: Given that this combination product is considered a Tier 2 product according to the Intercenter Consult process as per the Intercenter Consult (ICCR) form, a CDRH*

consult reviewer was assigned. Therefore, the review and assessment of the results of functionality studies, in addition to other studies and documents (included in amendment 3, eCTD 0004 under STN125640/0) provided to support compliance with design controls are deferred to the CDRH consult assigned to this BLA.

**ENVIRONMENTAL ASSESSMENT**

In section 1.12.14 of the BLA, the firm requested a categorical exclusions from preparation of an Environmental Assessment in accordance with 21 CFR § 25.25 (d) and based on 21 CFR § 25.31 (c) stating that any action on an NDA, abbreviated application, application for marketing approval of a biologic product or a supplement to such application or action on an OTC monograph is categorically excluded and ordinarily does not require the preparation of an EA for substance that occur naturally in the environment when the actions does not alter significantly the concentration or distribution of the substance, its metabolites or degradation products in the environment and that to Instituto Grifols ‘s knowledge, no extraordinary circumstances exist.

*Reviewer Comments:* Based on the information provided, the firm’s request for categorical exclusion from preparation of an Environmental Assessment as per 21 CFR § 25.31 (c) is justified.

**FACILITY INSPECTIONS AND FOLLOW-UPS**

All manufacturing, testing, and packaging activities will be performed at a single facility. The following facility required an inspection and is included in the compliance check:

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
Instituto Grifols, S.A, 2 Can Guasch St, Poligono Levante, Parets del Valles, Barcelona, Spain 08150 FEI# 3002807257				
Drug Substance and Drug Product Manufacturing	Inspection	Yes	Yes	Performed 13-24 March 2017
All testing including drug product release testing	Inspection	Yes	Yes	Performed 13-24 March 2017
Labeling and packaging	Inspection	Yes	Yes	Performed 13-24 March 2017

**Listing of Inspectional Follow-up for Pre-License Inspection**

Below is a comprehensive listing of Inspectional follow-ups identified and that were further

reviewed on the Pre-License Inspection.

**1. Review process validation data in regards to the aseptic filling process for Fibrinogen and Thrombin.**

*Reviewer Follow up Comments:* This was reviewed on inspection and found to have inadequacies related to the process time limits. The process time limits were not clearly defined for each of the phases of aseptic processing, specifically, a process time for sterile filtration and a process time for filling. Additionally, there were issues with process time limits for post-aseptic processes including the assembly of the syringes to holder to the end of production with the storage of the packaged kits in the freezer. This issue in regards to process time limits was included on the 483 as observation 2 and is discussed in the EIR.

**2. Review the cleaning validation of column resins and reuse including storage conditions and time between storage.**

*Reviewer Follow up Comments:* The column performance and cleaning validation was reviewed on inspection and found to be adequate; however, there was discussion with the firm in regards to the number of reuses of the resin as the firm did not specify in the BLA submission, and the validation provided indicated (b) (4) re-uses had been performed. The firm was advised that the number of intended uses must be specified in the BLA and that this number of used must be validated. This issue is considered a review issue and thus was further discussed through the BLA review as information requests. Please refer to IR#4 and IR#5 for details in regards to column re-use and validation.

**3. Review media fill reports that include all deviations (and investigations) occurring during media fill re-validation, in addition to review the interventions performed during media fill simulations and review the details of the fill sizes used in validation.**

*Reviewer Follow up Comments:* This was reviewed on inspection and no issues were found; however, in discussions with the firm in regards to the aseptic filling process time limits, the firm indicated that the media fill runs that were provided in the original BLA submission did not include the thrombin to fibrinogen changeover. However, since the time of the BLA submission, the firm had performed (b) (4) media fill runs that included the thrombin to fibrinogen filling change over, which were reviewed on the pre-license inspection. There were no issues found with the results and deviations. The firm was advised to submit these recent media fills reports that included the intervention of the change-over to the BLA to be part of the BLA review. Please refer to EIR for details of what was discussed with the firm and IR#4 for details of the review of the media fill reports that were provided.

**4. Review the procedures and discuss with the firm the issue of reprocessing in regards to sterile filtration of product when filter integrity test does not pass after use.**

*Reviewer Follow up Comments: This was reviewed on inspection and not only included discussion relating to sterile filtration, but also included nanofiltration and visual inspection after labelling. The discussion with the firm did not result in an observation as the firm indicated that they had not re-performed sterile filtration. The firm was advised that re-filtration is considered re-processing and would require the firm to submit a supplement for the affected lot, if there was not validation data to support the re-processing. In regards to nanofiltration, the firm indicated that repeating nanofiltration is prohibited; however there was no documenting stating this. This issue was addressed as a review issue and the firm was issued an information request asking to provide a procedure that clearly indicated that no re-working or re-processing in regards to nanofiltration and sterile filtration will be performed. The discussion of reworking/reprocessing was expanded to visual inspection as a result of the Team Bio inspector observing the visual inspection and labeling process for the licensed products, which is a similar process used for the fibrin sealant syringes, in which the syringes are labeled before the AQL is completed. Thus, if the AQL fails, the firm would have to de-label the vials/syringes in order to perform a re-inspection. Although the firm had not encountered a failed AQL, the firm was cited by the Team Bio inspector during the joint PLI and cGMP inspection for the licensed product, IGIV. In regards to the fibrin sealant product, the firm was informed that this activity of de-labeling would be considered reworking and reprocessing. The firm was issued an information request to clarify their activities if the AQL of the inspection should fail. Please refer to EIR for details and refer to IR#4, items 5 and 6 and IR#5, item 5 for the firm's response to reworking/reprocessing in regards to nanofiltration, sterile filtration and labeling of the Fibrin Sealant product.*

**5. Review procedures and validations associated with the assembly of Fibrin Sealant kit including blisterpak sealing and visual inspection of the process.**

*Reviewer Follow up Comments: The overall process of the assembly of the kit from beginning to when the kits are fully packaged and frozen was observed and is discussed in the EIR. There were discussions with the firm in regards to the overall process time for kit assembly, (b) (4) sterilization, packaging and freezing given that the thrombin and fibrinogen are exposed to room temperature during these activities; therefore, there were questions in relation to the stability of thrombin and fibrinogen. The visual inspection process was discussed with the firm and found to be adequate in that there are several visual inspections performed during the process including after assembly of the syringes and after blisterpak sealing with AQLs associated with these checks that are documented and are associated with the batch record. During the review of the*

equipment qualification there was an issue found in regards to the qualification of the automatic thermoforming machine (blisterpak) in that the machine was not qualified before the manufacturing of the conformance lots. This issue was discussed with the firm and was included as observation on the 483 (observation 1b).

## INFORMATION REQUESTS

Over the course of the review, there were five information requests sent to the firm by DMPQ. Below are the IRs sent with the corresponding responses from the firm.

IR#1: Sent December 6, 2016 and firm response received Dec 7, 2016 as Amendment 4 (eCTD 0005, BLA STN125640)

1. **Please indicate if the cannula, which is purchased as an off-the-shelf component from (b) (4) is received as a sterile component. If yes, please indicate how the cannula is sterilized and individually packaged.**

**Firm Response:** The firm confirmed that the (b) (4) cannula is received sterile and individually packaged and that the sterilization is performed by the manufacturer using (b) (4). The package is sealed with a spunbonded olefin sheet material (b) (4) ) to enable sterilization. The firm further clarified that there is no manipulation of the cannula at Instituto Grifols, S.A.

**Reviewer Comments:** *The firm has adequately addressed this IR item. No further action needed.*

IR#2: Sent January 10, 2017 and firm response for items 1 and 2 were received Feb 3, 2017 as Amendment 10 (eCTD 0011, BLA STN125640/0). The response to item 3 was received Feb 23, 2017 as Amendment 12 (eCTD 0013)

1. **Please provide a comprehensive listing of all products, including those that are also manufactured or manipulated in the same manufacturing areas as fibrinogen and thrombin.**

**Firm Response:** The firm provided the requested information. Please see table below for details:

Product	Manufactured or Manipulated in Fibrin Sealant Manufacturing Areas
Albumin (Human) Grifols	No
Coagulation Factor IX (Human) Grifols	No
Coagulation Factor FVIII and Von Willebrand factor (Human) [Fanhdi®]	No
Anithrombin (Human) [Anbinex]	No

Normal Intravenous Immunoglobulin (Human) [Flebogamma DIF®]	No
Anti-HB Intravenous Immunoglobulin (Human) [Niuliva®]	No
Hight Titre Intramasuclar Immunoglobulin (Human) Products [Anti-T; Anti-HB; Anti-D; Polyvalent]	No
Alpha1-antitrypsin (Human) [Prolastin®]	No

The firm did indicate the following exceptions and clarifications not noted in the table:

(b) (4)

[Redacted text]

2. Please identify all process steps as either open or closed systems and indicate in a table format the room classification of the areas for which process steps occur.

Firm Response: The firm provided the requested information and is shown below:

(b) (4)

(b) (4)

*Reviewer Comments:* The firm provided the requested information and has adequately addressed this IR item. The majority of the manufacturing steps are indicated as open (considered (b) (4) ) and are performed in a Class <sup>(b) (4)</sup> area, with exception to aseptic processing steps which are considered occur in a class <sup>(b) (4)</sup> area. The manufacturing processes will be further reviewed and observed on inspection.

**3. Please provide the following information on all computer systems that control critical manufacturing processes:**

- a. List of manufacturing steps which are computer-controlled and computer systems used to control these steps.**
- b. Validation summary of the computer systems that includes a description of the validation process with acceptance criteria, certification that IQ/OQ was completed, an explanation of the parameters monitored and tests performed along with summary of the data, an explanation of all excursions and/or failures and deviation reports and results of investigations of all excursions or failures.**

**Firm Response:** The firm provided the requested information. The following equipment was indicated to be controlled by Programmable Logic Controller-Human Machine Interface (PLC-HMI) systems:

(b) (4)

The IQ/OQ testing for most the computer systems using PLC-HMI included the following:

IQ- Documentation (installation design, component list, certificates, handbooks, Hardware and Software and operating procedures), Calibration and Maintenance and Installation (Utilities, components and analogical and digital inputs and outputs)

OQ- Components performance, and computerized system (turn on and shutdown, connection/disconnection, user interface, parameters management, access levels, system functionalities, and warnings, alarms and interlocks)

Other equipment listed included the control and monitoring system for buildings (b) (4) and (b) (4) and the (b) (4) all of which are controlled by different computer systems that included (b) (4) for the control and monitoring systems in Building (b) (4) and (b) (4) for the (b) (4).

The IQ/OQ/PQ testing for the (b) (4) computer system used for the monitoring control systems included the following:

IQ- General (components list, handbooks, operating procedures, maintenance, and documentation control), Engineering and structural (drawings), and Hardware and



(b) (4)

(b) (4)

*Reviewer Comments: The firm adequately responded to this IR item. No further regulatory action needed.*

IR#3: Sent February 6, 2017 and firm response received March 27, 17, 2017 as Amendment 13 (eCTD 0014, BLA STN125640)

- 1. Please provide qualification data to support package integrity and seal strength of the blisterpak packaging. Please note that this testing should be performed on the blisterpak after all final packaging activities which includes after freezing of the final packaged product.**

Firm Response: The firm provided the report IG\_ITEC-002798: Integrity test of the Fibrin Sealant Grifols sealing” which covers the qualification data regarding the package integrity and seal strength of the blister packaging. The firm confirms that the testing was performed with blisterpak units that were sampled after all the final packaging activities and after freezing of the final packaged product. The report is summarized as follows:

**Scope:** The study includes the system integrity of the blister performed by a (b) (4) process in the automatic thermoforming machine (b) (4). After blistering, the kits are processed by (b) (4) sterilization and freezing process at temperature of  $\leq -20^{\circ}\text{C}$ .

The main operating parameters of the machine are sealing temperature and sealing time. The testing performed included testing the Seal Strength and the Packaging integrity. The test methods and results were described as follows:



(b) (4)  
[Redacted]

[Redacted]

[Redacted]

[Redacted]

*Reviewer Comments: The firm has adequately addressed this IR item. No further regulatory action required. Please note however, that the testing of the blisterpak package integrity and sealing, in addition to, the qualification of the thermoforming machine were performed after the conformation lots were manufactured. Please refer to EIR for additional information in discussion with the firm in regards to the issue relating to qualification of the thermoforming machine.*

- Please provide (or indicate location in submission) details and results of the filling process for fibrinogen and thrombin manufacturing. These details should include a listing of the critical process parameters that are monitored during filling (i.e. (b) (4) [Redacted]), and the acceptance criteria, that ensure consistency in the filling process.**

Firm Response: The firm provided the validation summary IG\_VS-001647, "Validation of the Filling Process with Production Batches (Mach. Num. (b) (4)) which provides the details and results of the filling process for Fibrinogen and Thrombin including critical process parameters that are monitored. The validation is summarized as follows:

This report covers the aseptic filling process of Fibrin Sealant using the filling machine no. (b) (4) located in room no. (b) (4) of Building (b) (4) at Instituto Grifols. Three validation batches were manufactured to validate the aseptic filling process under production conditions. The



Reviewer Comments: The results of the quality controls on the final container that include the product specifications for the quality attributes were provided in the report, but are not reviewed as this data is under purview of the product office and is covered in the process validation. In regards to the filling duration data provided, there are several deficiencies and include the following:

- The firm did not adequately define the various phases of the aseptic filling process such as the time and end of sterile filtration, and start and end of filling. Additionally, there were not process time limits or acceptance criteria defined for these phases
- The firm indicated overall filling duration of (b) (4) . However, it is not clear which phases of aseptic filling that are included within the (b) (4) time limit such as sterile filtration nor is it clear if this includes only thrombin filling or fibrinogen filling as the fill times for thrombin and fibrinogen are indicated separately.
- In comparing the max time of fill of either thrombin and/or fibrinogen to the acceptance criteria limit of (b) (4), the duration limit of (b) (4) is excessive and no justification is provided nor is data provide at the maximum fill time to support this process limit. The firm should indicate how the (b) (4) process limit was determined and is supported.

The issue in regards to process time limits was discussed with the firm during the pre-license inspection and was included on the FDA Form 483 as Observation #2. An IR was issued to the firm as a follow-up to the inspection for two reasons which include 1) this information needed to be provided to the BLA for the review, in addition, the 483 response the firm provided in regards to this issue was also found to be inadequate. For details of the discussions with the firm and the firm response to the IR, please refer to the EIR, the 483 response memo, in addition to the Information Request section specifically, the firm response to IR#4 issued April 26, 2017) item #1.

- 3. Please provide a listing of all product contact equipment used in the Fibrin Sealant manufacturing process and indicate if the equipment is shared vs. dedicated and/or disposable. For shared and/or dedicated equipment please indicate the cleaning method and or sterilization method used if applicable.**

Firm Response: The firm provided a comprehensive table of all equipment from the fibrinogen and thrombin manufacturing (including fractionation, purification and aseptic filling) detailing the equipment number, location (room no.), name of equipment, function of equipment, indicating if equipment is dedicated (and noted as product contact) and how the equipment is cleaned (manual, CIP etc.). The equipment on the comprehensive list

(b) (4)

[Redacted text block]

*Reviewer Comments:* The firm provided the information requested. No further regulatory action needed.

4. **Please provide details in regards to the preparation of the glass syringes and stoppers prior to (b) (4) sterilization. Additionally, please indicate how the glass syringes are depyrogenated and if endotoxin testing is performed on the glass syringes and stoppers.**

*Firm Response:* The firm indicated that the syringes and stoppers are received at Instituto Grifols packed in (b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

*Reviewer Comments:* The firm provided the information requested; however, the firm needs to provide additional information in regards to the following:

- Provide details in regards to a tip cap and how the tip cap is sterilized and

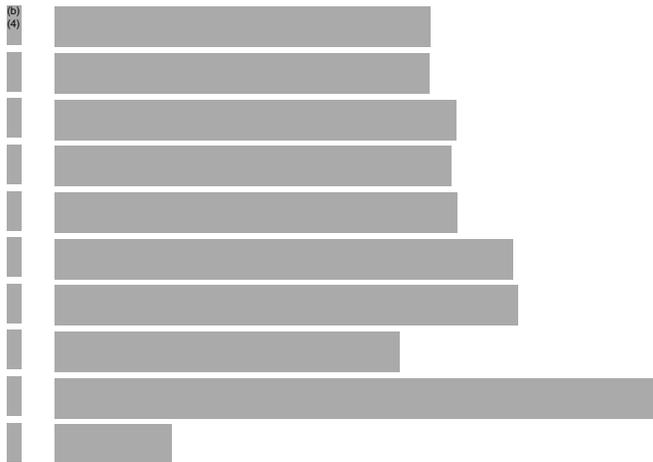
*incorporated in the container closure system*

- *Indicate if there are any detrimental effects on the syringes, stoppers and components when undergoing sterilization (b) (4) (i.e. effects on (b) (4) and functionality of the container closure system).*

The firm was issued two IRs, one of which to address above deficiencies (for details of firm response, refer IR#5, item 1 and 2) and another IR sent Oct 13, 2017 (IR #6) to asking the firm to indicate the frequency of endotoxin testing and the sample size that is used for testing (for details of firm response, refer to IR#6, item 1)

**5. Please indicate the IQ status and provide (in English) the summaries of the OQ/PQ of the following equipment.**

(b) (4)

A large block of text is redacted with grey bars. To the left of the redaction, there is a vertical column of small grey boxes, each containing the text "(b) (4)".

Firm Response: The firm indicated the IQ status and provided the OQ/PQ summaries for the equipment are listed as follows:

(b) (4)



(b) (4) [Redacted]

[Redacted]

IR#4: Sent April 26, 2017 as a joint IR with the product office covering a request for follow-up to information from the pre-license inspection and to supplement the BLA review. The firm's response was received May 30, 2017 as Amendment 30 (eCTD 0031, BLA STN125640). The IR items included in this IR that are relevant to DMPQ are listed as follows:

- 1. The validation of the aseptic Filling process for Thrombin and Fibrinogen in the manufacture of Fibrin Sealant (Human), as presented in the document IG\_VS-001647 (linked report IG\_IVSP-001658), was found to be incomplete. Please submit an updated Validation Report which should include all conformance and post-conformance batches manufactured to date and additional data to address the identified deficiencies. Specifically, please:**

- a. Provide the time limits for each phase of aseptic processing, including limits for sterile filtration processes and product exposure on the filling line (time of fill). Please note that the time limits for each phase of aseptic processing should be established and supported by data that include process validation data, in addition to other types of data. Regarding sterile filtration, please note that the total time of product filtration should be limited to an established maximum and supported by the process capability. Please provide an updated version of the validation report IG\_VS-001647 to include the process time limits and results of the process times for each phase of aseptic processing (sterile filtration and filling) for the conformance lots provided to support the BLA submission, in addition to providing an overall process limit for aseptic processing of Thrombin and Fibrinogen.

Firm Response: The firm provided an updated version of validation report IG\_VS-001647, "Validation of the Filling Process with Production Batches (Mach number (b) (4))" which includes the results of the process times for the manufacturing Fibrin Sealant batches and covers that validation of the filling line used for Fibrin Sealant including filling machine (b) (4) and its related installations (filling system, rooms and laminar air-flows). The results of three validation batches, in addition to data from all industrial scale manufactured batches of the current Fibrin Sealant facilities were included in report IG\_VS-001647. The process times (filling and packaging times) are summarized additionally to establish the time criteria for the sterile filtration, filling and packaging times. The studies batches included the following:

(b) (4)



- Results of Quality Controls on final Container: The report included results of the testing of the final container and routine testing and all acceptance criteria were met including criteria for endotoxin and sterility for all lots included in the study.

*Reviewer Comments: The firm has adequately addressed the IR item relating to the process limits. The process limits indicated for the sterile filtration and filling are reasonable and comparative to their process limit. Additionally, the overall aseptic processing limit of (b) (4) is reasonable given the process capability indicated from the data from all manufactured batches, in addition, the filling times are supported by the media fill studies that were performed that includes the change-over of the thrombin filling to Fibrinogen filling within the (b) (4) process limit (See IR item #2 below); however, the firm needs to clarify if the media fill does include the maximum fill time of (b) (4) as this information was not readily provided in the media fill study reports. In regards to the process limit of the assembly, packaging, sterilization and freezing after aseptic processing is completed, the review of the (b) (4) process limit is deferred to the product office for assessment as support for this process limit is related to stability of the product at room temperature given that these activities are performed at (b) (4). These issues were discussed with the firm on inspection and are included in a follow IR send by product office (see sub-item d below). No further regulatory action needed.*

- b. Provide validation data representative of all fill sizes, including the minimal (1 + 1 mL) and maximal (2 + 2 mL) fill sizes in the 3-mL syringe, and the minimal (3 + 3 mL) and maximal (5+5 mL) fill sizes in the 5-mL syringe. During the PLI, you explained that these data are available. The validation data should include, but not be limited to, in-process controls (IPC) and results of IPC testing, release testing of final containers, assessment of filled batch uniformity by weight and quality parameters, aseptic process monitoring, and actual processing times, as specified in comments 1a and 1d.**

Firm Response: The firm indicated that this information in regards to the filling sizes was included in the filling validation IG\_VS-001647, which was updated to include the processing times. This validation report included a study of all batches Fibrin Sealant manufactured to date and was indicated in the following table from report IG\_VS-001647:

\_\_\_\_ (b) (4)

(b) (4)

Therefore, this filling validation report previously reviewed in sub-item covers all presentation sizes.

*Reviewer Comments:* The firm has adequately addressed this IR sub-item. No further regulatory action needed.

- d. **Establish the processing times for the following filling process (assembly, packing and sterilization) or the overall processing time from the start of sterile filtration to the point at which the final product is frozen. Please support the proposed time limits by providing actual processing times for all conformance and post-conformance lots in the report IG\_VS-001647, to demonstrate process capability.**

Firm Response: The firm provided the filling validation report IG\_VS-001647 that additionally addresses this IR item.

*Reviewer Comments:* The firm adequately addressed this IR sub-item. This report was previously reviewed in sub-item (a) and covers this issue noted in sub-item(d). No further regulatory action needed.

2. **Please provide the three most recent media fill study report summaries that include the intervention of the change-over from Thrombin filling to Fibrinogen filling.**

Firm Response: The firm provided the updated report IG\_VS-001533, "Validation of the Aseptic Filling of 3 and 5 mL (b) (4) syringes in Mach No. (b) (4)", which summarizes the results of the three most recent media fills for the validation of the aseptic filling of 3 mL and 5 mL (b) (4) syringes using filling line mach. No. (b) (4) and includes the intervention of the change-over from Thrombin filling to Fibrinogen filling. Report IG\_VS-001533 is summarized as follows:



(b) (4)

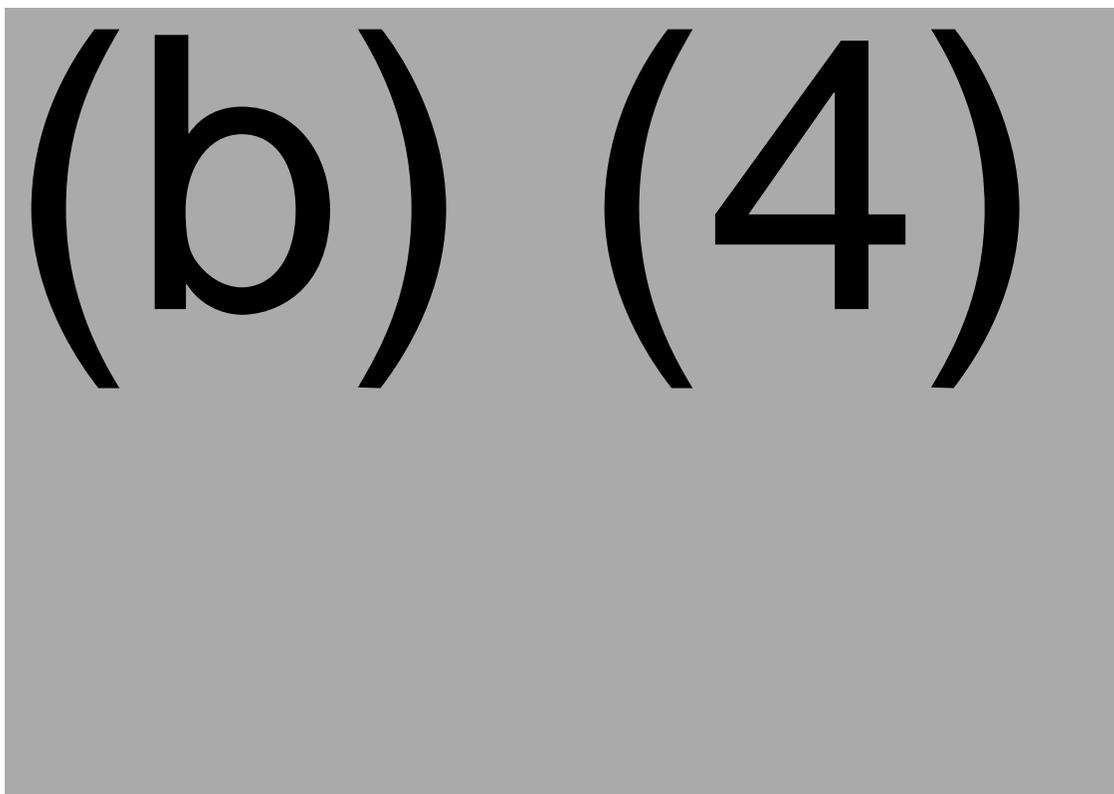
*Reviewer Comments: The firm has adequately addressed this IR item. The firm indicated from the data that the last (b) (4) media fills runs performed April 2016-Feb 2017 were performed including the change over from Thrombin to Fibrinogen as this is the process that is performed in normal production. This was an issue that was discussed on the PLI as the original media fills data provided in the BLA submission did not include this change over process. The overall aseptic processing time limit noted in the filling validation was indicated as (b) (4) and includes the change-over of the thrombin filling and fibrinogen filling; however, the filling times for the media fill were not included in the report. The firm was issued an information request to confirm if the media fills were performed at maximum filling limit of (b) (4) . Please refer to response to IR#5 item 5 for details.*

- 3. There was no proposed number of uses indicated in the BLA for Sepharose XL resin used for Thrombin purification. Please note that with the approval of the BLA, you would only be approved for the number of uses supported by the number of runs performed in the process validation. Report IG\_VS-001435 (linked report IG\_IVSP-001620) provided during the PLI, supported five runs at full-scale only, whereas the assessment of the number of resin uses in small-scale studies was not performed. With regard to the number of uses for the Sepharose XL, please address and note the following:**
  - a. Please indicate the number of uses for Sepharose XL resin that will be intended for future manufacturing**
  - b. If you plan to extend the number of uses as part of the BLA review, please submit an updated report including all subsequent purification runs at full scale that compare column performance parameters against pre-defined acceptance criteria and also include the data relating to the cleaning efficiency, such as monitoring of (b) (4) performed after multiple**

runs.

- c. **If you intend to extend the number of uses beyond the data provided in the BLA (including the supporting data from subsequent purifications performed at full scale), please note the following: You may submit a Comparability Protocol (CP) as a Prior Approval Supplement, post-approval of the BLA, which provides a protocol for performing small-scale (laboratory scale) studies covering the proposed, intended lifetime use of the resin for FDA review. The results from small-scale studies can support extension of the lifetime use of the resin before commercial-scale confirmatory studies are to be completed. Submitting a CP will allow a downgraded reporting category to submit the study results as a CBE-30 supplement, provided that the protocol is executed as initially proposed to, and reviewed by the FDA.**

Firm Response: The firm indicated that the supported number of uses of the resin SP-Sepharose XL to be covered under the BLA is 21 and the updated report IG\_VS-001435, Validation of the Chromatographic Process and Cleaning of the Thrombin Purification Column supports up to (b) (4) reuses. However, the firm indicated that their intention as part of the BLA review is to extend the number of uses for SP-Sepharose XL resin in manufacture of Thrombin (b) (4) repeated uses as lifetime at commercial scale and proposed the following validation study:





(b) (4)

(b) (4)

*Reviewer Comments: The firm provided the storage times between uses but, did not include details of the cleaning process and storage conditions in this validation report; however, details of the cleaning process and storage conditions were included in the production procedure*

IG\_MP-000034\_ING, "Thrombin For Fibrin Sealant" which was provided in the same IR responses (IR #4), specifically, for item 1f requested by the product office, and which is why was not included in this memo. In the production procedure IG\_MP-000034 under section 2.4 the following is indicated for the cleaning and storage of SP-Sepharose XL column:

- (b) (4)
- 

Therefore, the firm has addressed the storage conditions and time between storage and is adequately monitoring the (b) (4) between uses based on their validation and protocol.

Additional results included providing results from routine control parameters testing of (b) (4) prior to set up for sequential batches from (b) (4). Results were provided in table as follows:

#### Routine Control Parameters

(b) (4)

Reviewer Comments: The firm provided cleaning results that supports up to (b) (4) reuses of the SP-Sepharose XP resin; however, the firm's proposal to (b) (4) the number of uses (b) (4) during the BLA review is not feasible. There are two major issues with this approach:

- The firm would be providing this information late in the review cycle and it is not clear if this data at production scale could be provided and reviewed before the Action Due Date
- If the firm can provide data to support the (b) (4) uses during the BLA review and plans to continue studies at production scale to support (b) (4) uses, the firm would not be able to release lots past the approved number of uses. In addition, the firm would not be able to release lots if with only approval for (b) (4) uses. The firm did not perform small studies well beyond (b) (4) uses nor did they propose performing small scale studies at all, thus it is not clear how the firm will achieve extending past (b) (4) uses after BLA approval unless the firm uses new resin for manufacturing.

These issues were discussed with the firm during the late cycle meeting to determine a path forward. The review and discussion of these issues are deferred to the product office.

5. **The production processes for Thrombin and Fibrinogen include a nanofiltration step. According to your explanation during the PLI, if post-operation filter integrity test fails, re-processing at this step is not possible and not allowed. Please submit the respective SOP where this restriction (no re-filtration) is stated.**

Firm Response: The firm provided the SOP IG\_MSP-001940, "Procedure for reprocessing/reworking of Instituto Grifols' products" and indicated that in this procedure it states in section 4.3 Product Qualification of the procedure "Fibrin Sealant: no reprocessing is allowed at the nanofiltration step neither other step of the process". Additionally, the SOP further states that "in cases of reprocessing/reworking were performed, a prior approval submission will be done as a procedure exception change under 21 CFR 640.120 "Alternative Procedure", in order to release the affect lots"

Reviewer Comments: The firm has addressed this IR; however, product office should also include their assessment since this IR item was originally requested by the product office. An additional comment in regards to reprocessing/reworking, on the PLI the firm was cited for a potential issue in which the firm would need to de-label vials in order to repeat a visual inspection since the firm labels vials before the AQL of the visual inspection is completed. In order to re-perform the visual inspection, labels would have to be removed and thus would require re-labeling. Although this issue was discussed in regards to the licensed IGIV product, the concern also would apply to the Fibrin Sealant since the same labeling process is used in which the syringes are labeled before the AQL

for the visual inspection is completed. This was discussed with the firm in regards to the Fibrin Sealant during the inspection and this discussion is documented in the EIR. The SOP IG\_MSP-001940 provided in regards to the reworking/reprocessing of filtration indicated that the scope of this procedure does not cover description of repackaging/relabeling processes, and that these activities are described in a specific procedure IG\_MSP-001941. To address any potential issues in regards to the reworking/reprocessing associated with relabeling etc., the firm was issued an IR to provide this procedure and to indicate what will be done if the AQL for visual inspection fails and if reworking/reprocessing will be allowed in regards to labeling.

6. **According to your explanation during the PLI, the manufacturing procedures for Thrombin and Fibrinogen allow for re-processing at the sterile filtration step if the filter integrity test fails. Please submit supporting data (release and stability) that evaluated the impact of repeated sterile filtration on the quality and stability of Fibrinogen and Thrombin.**

Firm Response: The firm indicated that if post-operation filter integrity test fails, re-processing at this step is not possible and not allowed (reference response to IR item 5). Additionally, the firm indicated that the no industrial scale lots have undergone reprocessing of the sterile filtration step, thus there is no release and stability data to evaluate the impact on repeated sterile filtration. The firm provided SOP IG\_MSP-001940 to indicate that re-processing the sterile filtration in the event the filter integrity fails is not allowed.

Reviewer Comments: *The firm has adequately addressed this IR item; however, the product office should assess whether this response is acceptable as this IR item was requested by the product office.*

9. **Please consider performing Container Closure Integrity Testing (CCIT), as part of the Stability Testing Protocol on stability samples at the end of expiry, in addition to Sterility testing.**

Firm Response: The firm indicated that Grifols will evaluate a methodology suitable to determine Container Closure Integrity Testing as suggested. The methodology for the CCIT will be properly validated. The firm indicated that sterility is currently included in the stability protocol and will not be replaced indicated that the CCIT will be an addition and not a replacement to the stability protocol.

Reviewer Comments: *The firm has adequately addressed this IR sub-item. No further regulatory action needed.*

IR#5: The following IR was sent Aug 18, 2017 as a combined IR with the product office. The firm's response was received Sept 18, 2017 as Amendment 46 (eCTD 0047, BLA STN125640).

The IR items relating to DMPQ and the firm's response is included as follows:

- 1. Please clarify if the tip cap is assembled with the syringe at Instituto Grifols or are syringe received with tip cap in place, in addition, please provide details for how the tip cap is sterilized.**

Firm Response: The firm indicated that the syringe barrel is received from the manufacturer (b) (4) with the tip cap in place and (b) (4). The firm referenced the (b) (4) Syringe System BB-MF-(b) (4) for additional information.

Reviewer Comments: *The firm adequately addressed this IR item.*

- 2. For syringes and stoppers which are received (b) (4), you perform a (b) (4) step. Please indicate why you perform a (b) (4) and if there are any detrimental effects on the syringes, stoppers and components when undergoing (b) (4) (i.e. effects on (b) (4) of the container closure system). What testing is performed to ensure there are no detrimental effects on the container closure components due to the (b) (4) step?**

Firm Response: The firm indicated that a (b) (4) step is performed on all primary container closure components used in the manufacture of Grifols sterile medicinal product as per current procedure. In regards to the syringes and stoppers received (b) (4), these components are removed from its original packaging in a non-aseptic area and are sterilized to be used in the production area. The impact of the (b) (4) on leachable and functionality of the container closure system are covered in study reports IG\_ITEC-002201 and IG\_ITEC-002265 (for leachables) and IG\_ITEC-002568\_ING (for functionality) in which these studies considers (b) (4) as worst case scenario given that this is the current (b) (4) procedure used for the syringes and stoppers. The result of these studies demonstrate that a (b) (4) does not affect the quality, safety and functionality of the final product. Additionally, the firm indicated that the container closure integrity testing also considers the (b) (4) and demonstrates there are no detrimental effects on the primary container.

Reviewer Comments: *Report IG\_ITEC-002568 was reviewed and found to support functionality of the syringe kit that is manufactured as described that includes the (b) (4). The firm has adequately address this IR.*

- 3. In regards to the applicator cannula, please indicate what incoming testing and the frequency of testing that is performed. In addition, please confirm that the supplier of**

the applicator cannula, (b) (4), is audited every (b) (4) as per SOP IG\_MSP-001549\_ING, "Management of Raw Materials Suppliers.

Firm Response: The firm indicated that the following incoming checking and testing is performed on the applicator cannula:

(b) (4)

[Redacted]

Reviewer Comments: The firm was issued an IR asking if sterility testing is performed on the purchased cannula applicator. Refer to IR#6, item 4 for details on firm response.

4. You indicated in your response to IR sent Feb 6, 2017 specifically in regards to the IQ/OQ status of equipment that the (b) (4) will be replaced with (b) (4) and this new equipment is an (b) (4). Is this machine intended to perform a different function other than (b) (4)? Please clarify the function of the new equipment to replace the (b) (4).

Firm Response: The firm indicated that the replacement of the (b) (4) is being considered as part of the process improvement process proposal. The new equipment would be an (b) (4) machine and would be intended to perform the same function as the existing machine but would increase process consistency. This new equipment would undergo qualification activities (IQ/OQ) to verify correct installation and operation. In addition, performance qualification studies will be performed to ensure (b) (4) before implementing it.

Reviewer Comments: Given that the (b) (4) to replace to the (b) (4) appears to have additional function, the firm was advised that supplement is required to be submitted for review, regarding the (b) (4) after pending BLA approval. For details of firm response, please refer to IR#6, item 5.

5. During the Pre-License Inspection, we discussed your labeling process in which the syringes are labeled before the AQL for the visual inspection was completed and the

potential issue this presents should the AQL fail as a re-inspection would require de-labeling. Please note and acknowledge that the process of de-labeling and re-labeling syringes is considered as re-working/re-processing. In your response to item #5 in IR sent April 26, 2017 in regards to reworking and reprocessing for nanofiltration, you provided SOP IG\_MSP-001940, "Procedure for reprocessing/reworking of Instituto Grifols products" for describing reworking/reprocessing for all manufacturing steps for all products. In this SOP, an additional SOP IG\_MSP-001941 was referenced for describing procedures for repackaging/relabeling processes. Please provide SOP IG\_MSP-001941, additionally please confirm that you are not seeking approval with this BLA to rework/reprocess in regards to labeling. Please note that if you plan to rework/reprocess in regards to labeling, you will need to submit a Prior Approval Supplement to release the affected lot.

Firm Response: The firm provide requested SOP and indicated that if the AQL fails, an additional visual inspection will be carried out with the label in place since the labels. The firm indicated that the labels are transparent and that the size of the labels are so that they do not cover the entire surface of the syringe both horizontally and vertically, in addition, the ink on the marked label does not in any way preclude visualization, thus a proper visual inspection can be performed. The firm confirmed that no rework/reprocess in regards to labeling is submitted for approval for Fibrin Sealant destined for U.S. market and in the case if a rework/reprocess to labeling is performed, a Prior Approval Supplement (i.e. as One-Time Exception) for the affected lot will be submitted to FDA prior to release of lot.

The SOP IG\_MSP-001941\_ING which describes the repackaging procedure of products manufactured and packaged at Instituto Grifols includes a statement in section 4.4.1 Unpacking that "In case of Fibrin Sealant, repackaging/relabeling is not permitted".

Reviewer Comments: *The firm has adequately addressed this IR; however, the firm should provide additional clarification in regards to the performing a visual inspection on labeled syringes should the AQL fail. This option to re-perform the visual inspection with labeled syringes should the AQL fail was discussed with the firm; however, the firm was informed that should this option be implemented when the AQL failed, they would have to demonstrate that operators would be able to detect defects as effectively in labeled syringes as with syringes without the labeling. The firm indicated that this could be incorporated into their visual inspection training program. However, the firm did not indicate this in their response. This discrepancy can be addressed as an inspectional follow-up given that this option to re-perform inspection with the labels on should the AQL fail was discussed with the firm on the PLI (refer to the EIR), additionally, this was*

included as a discussion item with the firm included in the EIR.

6. In regards to process limit of (b) (4) for the filling of Thrombin and Fibrinogen and the media fill data provided that includes the intervention of the change-over of thrombin and fibrinogen, please provide the time of fill that was simulated in the last five media fills that support the (b) (4) process limit.

Firm Response: The firm provided the filling times for the media fill validation cycles reported in IG\_VS-001533 as follows:

(b) (4)

The firm noted that these five media fills include the intervention of the change-over of thrombin to fibrinogen filling and that three of these media fills support the process limit of (b) (4) .

Reviewer Comments: The firm has adequately addressed this IR item.

7. Please provide the SOP or documentation that demonstrates compliance with the following Quality System device regulation 21 CFR 820.20 Management Responsibility.

Firm Response: To support compliance in regards to Management Responsibility, the firm provided the following documents:

- IG\_MC-000001\_ING, “Instituto Grifols, S.A. Quality Manual
- IG\_MSP-002061\_ING, “Strategic Planning”

The document IG\_MC-000001\_ING that describes the Quality Management System of Instituto Grifols in accordance applicable requirements of cGMP and ICHQ10 in general terms. The document provides details of the Management Organization and roles of management in the Quality Management System. The main responsibilities of the key responsible individuals of the Quality Management System are described as follows:

- General Management- Assures the accomplishment by all personnel of the established requirements of the Quality Management System. Commitments include the following:
- Technical Direction- The Technical Director is qualified person for releasing the product and responsibilities include overseeing the divisions of quality control, quality assurance, product release, regulatory affairs, and the audits and quality

systems department

- Manufacturing Manager- Responsible for all manufacturing operations of the company including production control area and divisions of final processes, manufacturing and validations
- Quality Control Responsible- Responsible for all Quality Control activities and is under the responsibility of department managers of the different Quality Control Laboratories
- Quality Committee- The Quality Committee is composed of the General Manager, Technical Director, Manufacturing Director, Responsible for Quality Control, R&D Director, Responsible for Quality Assurance and Audits and Quality Systems Manager. The Quality Committee is responsible for the following:
  - Defining the Quality Objectives
  - Makes analysis of all Quality System data such as complaints, non-conformities, audits results, follow-up objectives, follow-up of Key Performance Indicators evolution, Preventive and Corrective Actions, etc.
  - Defines improvements because of analysis of the data generated in the company
  - Collaborates with General Management in the Quality System Review

Quality Department meetings may be attended by all departmental and section managers for multifunctional approach to monitor objectives and study causes of identified quality problems. General management meets biweekly to discuss the monitoring of quality indicators per a predefined periodicity.

In regards to Management Review described in section 5.5 of document IG\_MC-000001\_ING, IG's General Management performs (b) (4) review of the Quality Management system to verify alignment with the ICH Q10 Guidance and GMP requirements and objectives and Quality Policy. The following information is considered in this review:

- Functioning of processes
- Situation of corrective and preventative actions
- Customer information (Claims, product recalls...)
- Results of internal and external audits
- Status of actions initiated from previous reviews
- Changes that affect the quality management system
- Improvement actions aimed at increasing the efficiency of the Quality System Management and its processes

- Training effectiveness
- Evaluation of the adequacy of the Quality Policy
- Update of legal/regulatory requirements

Document IG\_MSP-002061, "Strategic Planning" describes the strategic planning of the organization by which the General Management of Instituto Grifols guarantees the correct performance of the Quality Management System. The document describes who serves on the General Management committee and indicates that the Quality committee meets (b) (4) to discuss quality planning, analysis of the accomplishments of objectives set in (b) (4), defining new (b) (4) Quality Objectives and discuss analysis of review report of the Quality System. Additionally, the committee meets at (b) (4) to discuss the following:

- Monitoring Quality Objectives
- Identification of areas of improvement in organization
- Monitoring the implementation and verification of the effectiveness of adopted actions
- Customer complaints
- Non-conformities (deviations)

This document provides details and overlaps with what is described in document IG\_MC-00001\_ING.

*Reviewer Comments: The firm's overall quality policy and strategic planning documentation covers the areas relating to management responsibility defined in the Quality System regulations for devices. The firm has adequately addressed this IR item.*

IR#6: The following IR was sent Oct 13, 2017. The firm's response was received Oct 18, 2017 as Amendment 57 (eCTD 0058, BLA STN125640). The IR items and firm response is summarized as follows:

- 1. In your response to Information Request dated February 6, 2017, regarding the preparation of glass syringes and stoppers, you indicated that IG performs (b) (4) testing on the syringes and stoppers purchased from (b) (4). Please indicate the frequency of testing (i.e., every lot or every specified number of lots) and the sample size tested.**

Firm Response: The firm indicated that (b) (4) testing is performed on (b) (4) as part of the quality control release testing. The (b) (4) testing on samples is performed as

follows:

(b) (4)  
[Redacted]

*Reviewer Comments:* The firm has adequately addressed this IR item. No further action needed.

2. In regard to your (b) (4), please specify the maximum time frame within which the (b) (4) may be held (stored) prior to recleaning. Information provided should include time and temperature and summary of qualification data to support. Please note that if you are using manufacturer’s recommendations for storage conditions, qualification is not required. Additionally, please indicate if you are performing (b) (4) testing to detect (b) (4); if not, please implement a plan to perform (b) (4) testing or provide a justification for not performing.

*Firm Response:* The firm indicated that the (b) (4) are stored in (b) (4) and provided the following table that summarizes the maximum validated time frame within which the (b) (4) may be stored prior to recleaning:

(b) (4)

The firm provided reports IG\_VS-001666 and IG\_VS-001436 and indicated as per manufacturer’s recommendations the (b) (4) can be stored for (b) (4). The reports were updated to include section 3.4 for monitoring (b) (4) test and (b) (4) test are performed routinely to ensure the correct state of (b) (4).

In regards to the (b) (4) test, the firm indicated that the (b) (4) are not currently under productions; however, once the (b) (4) are under routine production, the (b) (4) test will be performed with water following manufacturer’s recommendations before each use.

Reviewer Comments: *The firm has addressed this IR item. No further action needed.*

3. In regards to your manual cleaning of product contact equipment, please indicate your routine monitoring program. If you do not perform routine monitoring, revalidation every (b) (4) is not sufficient. Please provide an updated requalification schedule or implementation plan for routine monitoring.

Firm Response: The firm provided details of the routine monitoring plan that is applied to product contact equipment with manual cleaning process indicated as follows. For product contact equipment for which there is no routine monitoring plan, an updated cleaning revalidation schedule was also described.

(b) (4)

4 pages have been determined to be not releasable: (b)(4)

Additionally, the firm indicated that an error was detected in regards to mis-identifying equipment (b) (4) as being manually cleaned in a response provided in Information Request dated February 6, 2017. These (b) (4) are cleaned automatically by CIP and not manually as previously indicated.

*Reviewer Comments: The firm has adequately addressed this IR item. No further action is needed.*

**4. In regard to the cannula applicator, please indicate if you are performing any incoming testing to verify sterility. If not, please provide justification.**

Firm Response: The firm indicated that the cannula applicator is a sterile device approved under 510(k) (b) (4) and CE Marked (IIa Class Sterile), thus Instituto Grifols S.A. does not perform incoming testing to verify sterility. IG as previously indicated performs a visual inspection of the units ((b) (4) for reduced inspection) to verify that a proper material is received including inspection of the sealing of the cannula applicator for each incoming batch, in addition to reviewing the supplier certificate of conformity.

*Reviewer Comments: The firm was issued an information request recommending that sterility testing be implemented. Please see IR#7 for firm response.*

**5. Please note that a supplement is required to be submitted for review, regarding the (b) (4) and (b) (4) machine after pending BLA approval.**

Firm Response: The firm agrees to submit a supplement for the new (b) (4) and (b) (4) machine.

*Reviewer Comments: The firm has adequately addressed this IR item. No further action is needed.*

IR#7: The following IR was sent Oct 20, 2017. The firm's response was received Oct 27, 2017 as Amendment 62 (eCTD 0063, BLA STN125640). The IR items and firm response is summarized as follows:

- 1. Please describe in more detail all the testing that Grifols routinely performs on the incoming (b) (4) syringes, including the functionality test. Please specify the parameters assessed in the functionality test and indicate the number of syringes used in this testing and the frequency of testing of incoming lots.**

Firm Response: The firm provided the document, IG\_TA-00160\_ING, which was reviewed on

inspection and discussed in the EIR. This document describes the incoming testing that is performed on the syringe system, which consists of the syringe barrel, stoppers, tip cap and plunger, in addition to the sampling plans used for various incoming testing i.e. number of units tested per incoming batch. The details of this document are summarized as follows:

(b) (4)

[Redacted text block]

[Redacted text block]

(b) (4)

(b) (4)



(b) (4)

(b) (4)

*Reviewer Comment:* The firm has adequately address this IR item. No further action is needed.

2. In regards to the application cannula, please describe the functional testing that is routinely performed on the incoming cannulas and indicate the number of samples taken to perform testing. Additionally, you indicated that you do not perform sterility testing on the incoming cannulas. Please note that sterility of the cannula is considered a critical attribute; thus, as per 21 CFR 820.50, we recommend that you implement testing of the incoming cannula to verify sterility as stated on Certificate of Analysis. Please comment.

*Firm Response:* The firm indicated that the functional testing performed on the cannula included checking the correct fitting of the applicator cannula with the holder-syringe assembly and then simulating administration by pushing the plunger while verifying that it covers its distance to the end of its course without difficulty. The functionality testing is performed on (b) (4) . A number of (b) (4) . In regards to sterility testing, the firm indicated that sterility testing as per (b) (4) STERILITY TESTS will be implemented as part of the Quality Control testing on each incoming batch.

*Reviewer Comment:* The firm has adequately addressed this IR item. No further action needed. (b) (4)

