



Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: Administrative File (STN 125640/0) and
Yu Do, MS, RPMBI/DRPM/OTAT

From: Natalya Ananyeva, PhD, Review Committee Chair, CMC reviewer, Hemostasis
Branch (HB)/Division of Plasma Protein Therapeutics (DPPT)/Office of Tissues
and Advanced Therapies (OTAT)

Through: Timothy K. Lee, PhD, Acting Chief, HB/DPPT/OTAT
Basil Golding, MD, Division Director, DPPT/OTAT/CBER

Applicant: Instituto Grifols, S.A.

Product: Fibrin Sealant (Human)

Subject: Final Review of the CMC Information in the Original Biologics License
Application and CMC amendments from Instituto Grifols, S.A. for Fibrin Sealant
(Human) under STN 125640/0

TABLE OF CONTENTS

INTRODUCTION	2
BACKGROUND	2
EXECUTIVE SUMMARY FROM COMBINED CMC REVIEW	5
RECOMMENDATION	6
DESCRIPTION AND COMPOSITION OF DRUG PRODUCT (SECTION 3.2.P.1).....	7
PHARMACEUTICAL DEVELOPMENT (SECTION 3.2.P.2)	9
MANUFACTURING PROCESS DESCRIPTION (SECTION 3.2.P.3.3)	16
CONTROL OF CRITICAL STEPS AND INTERMEDIATES (SECTION 3.2.P.3.4)	18
PROCESS VALIDATION AND/OR EVALUATION (SECTION 3.2.P.3.5)	28
SPECIFICATIONS FOR DRUG PRODUCT (SECTION 3.2.P.5.1) AND JUSTIFICATION OF SPECIFICATIONS (SECTION 3.2.P.5.6)	39
ANALYTICAL PROCEDURES (SECTION 3.2.P.5.2) AND VALIDATION OF ANALYTICAL PROCEDURES (SECTION 3.2.P.5.3)	44
BATCH ANALYSES (SECTION 3.2.P.5.4) AND IN-SUPPORT TESTING	44

STABILITY (SECTION 3.2.P.8)	45
COMBINATION PRODUCT: DESIGN HISTORY FILE FOR DEVICE COMPONENTS	46
ADVENTITIOUS AGENTS SAFETY EVALUATION (SECTION 3.2.A.2).....	49
CBER LOT RELEASE.....	51
CONCLUSION.....	52
APPENDIX: HISTORY OF INFORMATION REQUESTS AND RESPONSES	53

INTRODUCTION

Instituto Grifols, S.A. (Grifols) submitted an original biologics license application (BLA) to seek U.S. licensure for Fibrin Sealant (Human). The commercial product is provided as a kit comprised of two pre-filled syringes containing sterile frozen solutions of Human Fibrinogen (component 1) and Human Thrombin with calcium chloride (component 2), which are assembled on a single syringe holder. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biologics. An application cannula (Class I device) is co-packaged with the product for application by dripping. Fibrin Sealant (Human) is available in the 2-mL, 4-mL, 6-mL and 10-mL package sizes. There is no proprietary name for this product.

Fibrin Sealant (Human) is indicated for topical use as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Fibrin Sealant (Human) is effective in heparinized patients.

BACKGROUND

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

Grifols' Fibrin Sealant (Human) is another two-component fibrin sealant in a frozen liquid formulation (company's internal name FS Grifols is used interchangeable with the proper name in this memorandum). FS Grifols meets the definition of a biologics/device combination product (21 CFR Part 3) with the primary mode of action being provided by the biological components, and was reviewed according to the requirements stipulated in the Final Rule, 21 CFR Part 4 (Subpart A). Fibrin Sealant (Human) is not marketed in other countries.

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

- **Study IG1101** "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Peripheral Vascular Surgery".
- **Study IG1102** "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Parenchymous Tissue Open Surgeries"
- **Study IG1103** "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Soft Tissue Open Surgeries"

Regulatory History

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

TABLE 1: Review Milestones

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

This reviewer has been involved in review of this product since the submission of INDs. This memorandum summarizes the review of several aspects of the Chemistry, Manufacturing and Controls (CMC) in the original BLA and amendments under STN 125640/0. The manufacturing process for this combination product is a continuous process with hold times but without a clearly defined Drug Substance stage, and all information was submitted in the Drug Product Module. The Drug Substance Module contains information on control of starting materials only. The scope of my review included the following eCTD sections:

- Pharmaceutical Development [3.2.P.2] (product-related sections) which describes formulation development, manufacturing process development, characterization of structure and function of Human Fibrinogen and Human Thrombin components, and container closure system development.

- Description of the Manufacturing Process and Process Controls [3.2.P.3.3]
- Controls of Critical Steps and Intermediates [3.2.P.3.4]
- Process Validation and/or Evaluation [3.2.P.3.5]
- Specifications of Drug Product [3.2.P.5.1]
- Batch Analyses [3.2.P.5.4]
- Justification of Specification [3.2.P.5.6]
- Stability [3.2.P.8]

The following DPPT reviewers contributed to review of the CMC information for the biological components of Fibrin Sealant (Human):

- Dr. Ze Peng: Evaluation of safety of Fibrin Sealant (Human) with regard to adventitious agents.
- Dr. Svetlana Shestopal: Review of analytical methods to control the quality of intermediates and Drug Product (DP) and their validation; control of materials; excipients; and reference standards.
- Drs. Andrey Sarafanov and Evi Struble: Review of chemistry, identification and quantitation of extractable/leachable substances and their toxicological assessment.

I performed a cursory review of these CMC aspects. Analytical methods were also reviewed by Drs. Grainne Tobin, Hsiaoling Wang, Ritu Agarwal, and Karla Garcia (OCBQ/DBSQ/LACBRP). The suitability of the methods for their intended use as release tests for Drug Product is summarized in their review memoranda.

The following CDRH consult reviewers contributed to review of the information for the device components of Fibrin Sealant (Human):

- Dr. Rong Guo (CDRH/ODE/DAGRID): Engineering and functionality of the delivery device
- Rita Lin (CDRH/ODE/DAGRID): Usability/Human Factors studies for the delivery device

This reviewer participated as a Product Specialist in the Pre-License Inspection (PLI) of the Instituto Grifols, S.A. facility in Barcelona, Spain (March 13-24, 2017) and contributed to the preparation of the Establishment Inspection Report (EIR) and review of responses. The inspection was a combined PLI and cGMP inspection with Team Biologics. A single Form FDA 483 was issued on March 24, 2017, which included a total of 17 observations, three of which were specific to the PLI for FS Grifols (with my contribution to objectionable observation #2):

1. The initiation of documentation of deviations, CAPAs, and change controls are inadequate.
2. The processing times for critical manufacturing steps, including sterile filtration of Thrombin and Fibrinogen bulk, filling of syringes, and their assembly with plungers and syringe holder, preparation for and sterilization with (b) (4), and secondary packaging up to freezing of the final product, are not established or clearly defined.

3. Aseptic techniques were not always optimally applied during aseptic operations that include filling.

The responses to 483 observations were received electronically in Amendment 24, dated April, 12, 2017 and additional information was further provided in Amendment 30, dated May 30, 2017 and Amendment 36, dated August 1, 2017. The responses were reviewed by the DMPQ reviewer and this reviewer and were found adequate. Please refer to the EIR and 483 Response Review memorandum.

EXECUTIVE SUMMARY FROM COMBINED CMC REVIEW

1. The validation strategy for the commercial manufacturing process of Fibrin Sealant (Human) is consistent with ICH Guideline Q11 (*discussed in this memorandum*). The validation studies were performed at Grifols' Barcelona facility, the intended commercial site, under prospective process validation protocols. Per FDA requests, the Applicant performed additional studies and analyses to fully validate the aseptic filling process and establish time limits for critical processing steps. Grifols also developed a Study Protocol for concurrent full-scale validation of the lifetime of the SP-Sepharose chromatographic resin used in the manufacture of Thrombin. All process and quality controls in the validation studies complied with pre-defined acceptance criteria stated in the protocols. All hold times are adequately validated and supported by stability data. Based on the evaluation of the manufacturing and analytical data for clinical and conformance lots, the manufacturing process for Fibrin Sealant (Human) was found to be sufficiently controlled, consistent and adequately validated. The process does not allow any reprocessing steps.
2. The characterization program for Fibrin Sealant (Human) used an extensive panel of analytical methods to evaluate physicochemical, biochemical and functional properties of the Fibrinogen and Thrombin components as well as structural characteristics of the fibrin clot made from Fibrin Sealant (Human) (*discussed in this memorandum*). The uniformity of the results obtained from different lots of Fibrinogen and Thrombin demonstrates that the manufacturing processes are capable of manufacturing consistently high-quality products with integral functional properties, and to effectively remove process- and product-related impurities. The Fibrin Sealant (Human) clot characteristics are comparable to those of other licensed fibrin sealant products.
3. The Specifications for Drug Product were established in accordance with ICH Guideline Q6B and FDA recommendations provided during the BLA review (*discussed in this memorandum*). The parameters were selected from critical quality attributes determined in process development studies and risk assessments. Acceptance ranges/limits are established based on regulatory requirements ((b) (4)), manufacturing experience (analysis of the release and stability data), process capability to remove impurities, analytical variability, and previous experience with other licensed Grifols products. The final Drug Product release specifications are considered adequate to control the identity, quality, purity, potency, and safety of Fibrin Sealant (Human).

4. Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release and stability monitoring. In the course of review, per FDA requests, Grifols performed additional experimentation and analyses to complete validation of a number of assays. An acceptable reference standard qualification and maintenance program has been established. *(Please refer to memoranda of Dr. Svetlana Shestopal and DBSQC reviewers).*
5. The real-time stability data for conformance lots support the proposed shelf-life of 24 months for Fibrin Sealant (Human) final container when stored at a temperature of $\leq -18^{\circ}\text{C}$ *(discussed in this memorandum).*
6. The safety of the product with regard to adventitious viruses is ensured by the inclusion of two orthogonal viral clearance steps in the purification process: Solvent/Detergent treatment for inactivation of enveloped viruses and nanofiltration for removal of enveloped and non-enveloped viruses. The results of validation studies using relevant and model viruses with a wide range of physicochemical characteristics support effectiveness of viral clearance in the commercial manufacture of Fibrin Sealant (Human). *One remaining CMC deficiency will be addressed as a Post-Marketing Commitment as stated in Dr. Peng's memorandum.*
7. The Applicant provided sufficient information to demonstrate the safety and effectiveness of the device constituent parts of this combination product. The functionality of the application systems was studied by assessing essential performance characteristics. Functionality, stability of performance characteristics during product storage, and compatibility of the application device with the biologic components are sufficiently verified. Per FDA request, the Applicant modified and qualified the design of the syringe holder for the 3-mL syringe to ensure its tight fixation. The Applicant committed to conduct a new Human Factors validation study as part of the deferred pediatric clinical trial which is a Post-Marketing Requirement study under PREA. *(Please refer to memoranda of CDRH consult reviewers).*

RECOMMENDATION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA, and has adequately addressed the requests from all CMC reviewers in the course of review. Issues resolved during the review process are discussed in respective sections of this memorandum.

The manufacturing process for Fibrin Sealant (Human) is considered to be adequately validated at the commercial scale and is sufficiently controlled to ensure consistent manufacture of the commercial product that meets the acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. The information supporting the safety and effectiveness of the device components of this combination product was found sufficient and acceptable. All 483 observations from the PLI have been adequately addressed.

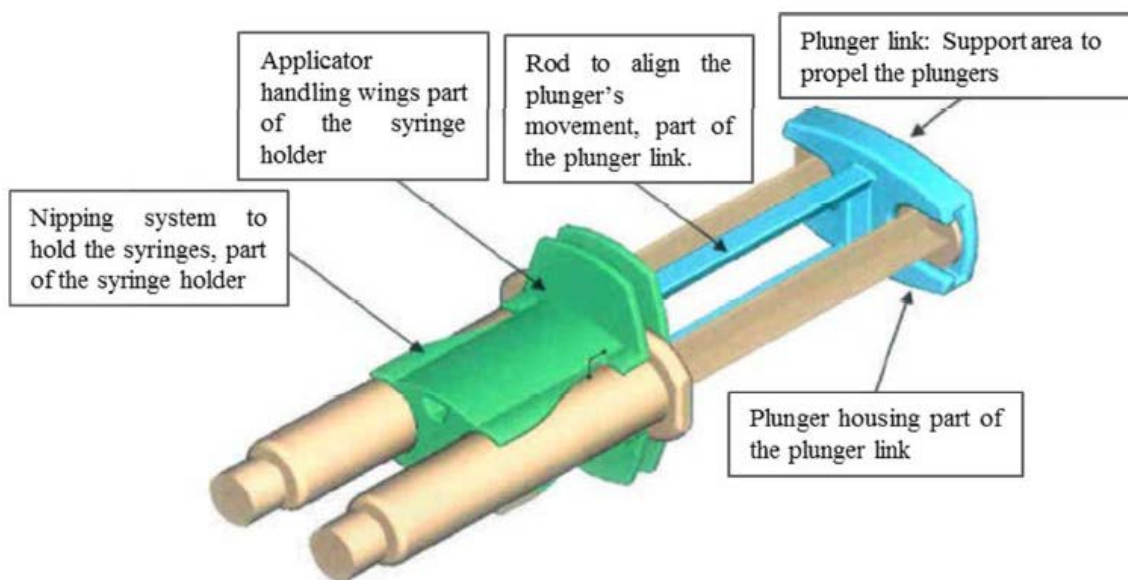
I and other CMC reviewers from the Division of Plasma Protein Therapeutics, OTAT, CBER, and consult reviewers from CDRH recommend **APPROVAL** of the BLA for Fibrin Sealant (Human).

DESCRIPTION AND COMPOSITION OF DRUG PRODUCT (SECTION 3.2.P.1)

According to 21 CFR Part 3, Fibrin Sealant (Human) is defined as a biologics-device combination product, Type 3, with the primary mode of action being provided by the biological components (Human Fibrinogen and Human Thrombin). Fibrin Sealant (Human) is provided as a kit consisting of two separate packages:

- A package containing one syringe each of human fibrinogen 80 mg/mL as an active substance (component 1, pH 6.5 – 8.0) and human thrombin 500 IU/mL as an active substance (component 2, pH 6.0 – 8.0) sterile frozen solutions which are assembled on a syringe holder. The two syringe plungers are connected by a plunger link to ensure simultaneous application of the biological components as depicted in Fig. 1 (reproduced from Report REGD-0019886, *Risk Analysis DG-316*).
- A package containing an application cannula (Class I device) for application by dripping.

FIGURE 1



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

Biological Components

TABLE 2. Composition of the Fibrinogen Component

Name of Ingredient	Concentration	1 mL dosage form	2 mL dosage form	3 mL dosage form	5 mL dosage form
Human	80 mg/mL	80 mg	160 mg	240 mg	400 mg

Fibrinogen					
Sodium citrate, dihydrate	(b) (4)				
Sodium chloride					
Arginine					
L-isoleucine					
L-glutamic acid, monosodium					
WFI (q.s.)	1 mL	1 mL	2 mL	3 mL	5 mL

TABLE 3. Composition of the Thrombin Component

Name of Ingredient	Concentration	1 mL dosage form	2 mL dosage form	3 mL dosage form	5 ml dosage form
Human Thrombin	500 IU/mL	500 IU	1000 IU	1500 IU	2500 IU
CaCl ₂ ·2H ₂ O	(b) (4)				
Human Albumin					
Sodium chloride					
Glycine					
WFI (q.s.)	1 mL	1 mL	2 mL	3 mL	5 mL

Device Components: Container Closure and Application System

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

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

The syringe holder and plunger link are manufactured from polycarbonate by Laboratorios Grifols, S.A. and are used to allow for simultaneous application of equal amounts of fibrinogen and thrombin. Two filled syringes (one with Thrombin and one with Fibrinogen) are assembled on the syringe holder. The syringe assembly is packaged into blister packaging and sterilized using (b) (4).

Fibrin Sealant (Human) can be administered in two ways: dripping or spraying.

Dripping: (b) (4) Cannula (b) (4) length tube) is co-packaged with Fibrin Sealant

(Human). The applicator tip is manufactured by (b) (4). The device was 510(k)-cleared ((b) (4)) under Irrigating Syringe and this category has since been reclassified as a Class I device. (b) (4) dual cannula is designed to facilitate the dispensing and application of FS Grifols by isolating the channeling of the Thrombin and Fibrinogen components until they are mixed at the treatment site. This design ensures the accurate dosing of both components and prevents premature interaction of Fibrinogen and Thrombin as well as clogging of the cannula.

FIGURE 2 shows the pre-filled syringes assembled on the syringe holder with or without the cannula attached. Reproduced from Report REGD-0019886, *Risk Analysis DG-316*.



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

PHARMACEUTICAL DEVELOPMENT (SECTION 3.2.P.2)

Formulation development

The formulation development for the Fibrinogen component is described in Report IG_ITEC 001948_ING, *Fibrinogen for Fibrin Adhesive. Development of the Production Process* (effective date: June 23, 2016). In developing the formulation, the following critical attributes were taken into account:

- High Fibrinogen concentration in the final product ((b) (4)). This feature is known to have an impact on the sealant properties of the product. The concentration of (b) (4) was found optimal during the development of FS Grifols.

- Long-term stability of the product by preserving unaltered physicochemical and biological properties of natural fibrinogen. To achieve this, a formulation was developed based on the (b) (4).
- Easy application product. The product applicability can be enhanced by (b) (4).
- (b) (4).

The formulation development for the Thrombin component is discussed in Report IG_ITEC-002008_ING, *Thrombin for Fibrin Adhesive. Development of the Production Process* (effective date: June 30, 2016). In developing the formulation, the following critical attributes were taken into account:

- Human origin of Thrombin.
- High target Thrombin potency (of approximately 500 IU/mL) in order to trigger a rapid formation of the fibrin clot upon contact with the Fibrinogen component.
- Long-term stability of the product by preserving unaltered physicochemical and biological properties of thrombin. To achieve this, a formulation based on (b) (4).
- Compatibility of the formulation with nanofiltration.

Physicochemical and Biological Properties: Characterization Studies

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

Fibrinogen Component

The biochemical characterization data for the Fibrinogen component are summarized in Report IG_IC-000098_ING, *Fibrinogen (Fibrin Sealant Grifols Component): Characterization Study* (effective date: April 27, 2016). The characterization of the Fibrinogen component included the assessment of product-related parameters, dynamic viscosity of the solution, excipients, functionality, and process- and product-related impurities. Purity was assessed by *Fibrinogen Clottable Protein* and *Total Protein* assays to calculate % Clottable Protein, (b) (4)


by (b) (4). In protein composition and biochemical characteristics, Grifols' Fibrinogen is distinguished by:

(b)
(4)

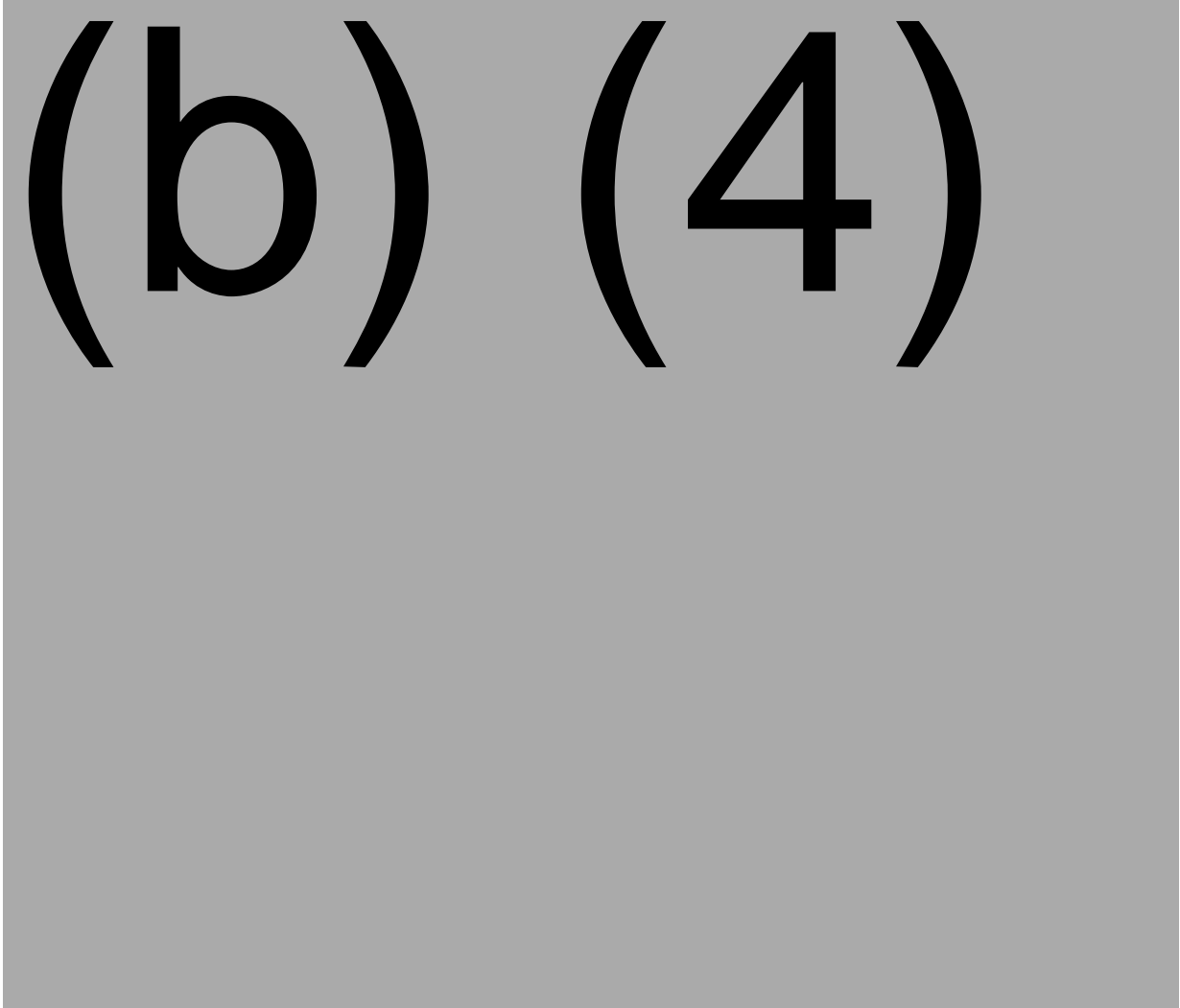
A large rectangular area of the document is redacted with a solid gray fill. To the left of this area, there are two small vertical gray bars, one near the top and one further down.

The analysis of the molecular integrity of the fibrinogen chains showed their ability to cross-link with each other and form a stable clot in the presence of calcium demonstrating the proper functionality of the fibrinogen molecule.

(b) (4)

A horizontal rectangular area of the document is redacted with a solid gray fill.

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. The text "(b) (4)" is printed in large, bold, black font across the top of this redacted area.

Characterization of process intermediates and impurities during commercial scale manufacture of Fibrinogen lots is summarized in Report IG_ITEC-002242_ING, *Fibrinogen (Fibrin Sealant Grifols Component): Characterization Study of the Manufacturing Process* (effective date: June 15, 2015). The results of this characterization study demonstrated robust removal of process-related impurities by the consecutive glycine precipitation steps until being undetectable ((b) (4)) or detectable at trace levels in the final product. ((b) (4)), which is quantified at low levels in the final product, and TnBP and Polysorbate 80, which are used at the viral inactivation step, are controlled to acceptable limits as DP Specification parameters. The most relevant product-related impurities ((b) (4)) are eliminated by the purification process to undetectable or trace levels in the final product.

Thrombin Component

The biochemical characterization of the Thrombin component is summarized in Report IG_IC-000095_ING, *Thrombin (Fibrin Sealant Grifols Component): Characterization Study* (effective date: September 26, 2016). The characterization study included assessment of product-related parameters, excipients, impurities, functionality, and biological tests (abnormal toxicity, endotoxins and sterility). Purity was assessed by *Thrombin Activity* and *Total Protein* assays, ((b) (4)) by ((b) (4))

The
Functionality test showed consistent clot formation when the two components (Fibrinogen and Thrombin) are mixed.

((b) (4))

((b) (4))

(b) (4)

Analysis of process intermediates and/or the final product during commercial scale manufacture of Thrombin lots is summarized in Report IG_ITEC-002243_ING, *Thrombin (Fibrin Sealant Grifols Component): Characterization Study of the Manufacturing Process* (effective date: February 12, 2016). This analysis confirmed that process-related impurities (TnBP, Polysorbate 80, (b) (4), citrate, (b) (4)) are consistently removed to undetectable or trace levels in the final product. The residual levels of TnBP and Polysorbate 80 in the final product are controlled to acceptable limits as DP Specification parameters. The most relevant product-related impurities (b) (4)

(b) (4) are eliminated by the chromatographic step and are not detectable or present at trace levels in the final product. In addition, the efficacy of the manufacturing process to purify Thrombin was demonstrated by an increase of *Thrombin Specific Activity* at consequent process steps and in the final product.

In conclusion, the uniformity of the results obtained from different lots of Fibrinogen and Thrombin demonstrates that the established manufacturing processes allow for the purification of the Fibrinogen and Thrombin components in a consistent way, achieving a high purity product and maintaining its functional properties.

In vitro Clot Structure Characterization

The specific feature of FS Grifols is that its Fibrinogen component is produced from the Cohn's Fraction I obtained from the (b) (4) Supernatant. Other licensed fibrin sealant products contain fibrinogen which is produced from the (b) (4). During the IND stage and in support of the BLA, the Applicant performed a series of studies per FDA requests with the objective to explore the effect of the starting material on the structural characteristics of the resulting fibrin clot. The results are summarized in Report IG_ITEC-002019_ING, *Fibrin Sealant Grifols: Clot Structure and Characterization* (effective date: June 3, 2014). The FS Grifols clot structure was characterized in a series of *in vitro* assays:

(b) (4)

Clot Structure

(b) (4)

MANUFACTURING PROCESS DESCRIPTION (SECTION 3.2.P.3.3)

FS Grifols is manufactured at the Instituto Grifols S.A. facility located at Can Guasch Street # 2, Parets del Valles, Barcelona, 08150 Spain. The manufacturing procedures are described in the BLA and the process flow was also observed during the Pre-License Inspection.

Both Human Fibrinogen and Human Thrombin (biological components of FS Grifols) are isolated from pooled human Source Plasma obtained from FDA-licensed plasma collection centers in the United States. The modified Cohn's plasma fractionation method is used to obtain Fraction I, which is the starting material for the production of Fibrinogen, and the Prothrombin Complex (PTC) captured from the Supernatant of Fraction I, which is the starting material for the production of Thrombin.

The plasma fractionation process is described in the Production Method IG_MP-000026, *Human Plasma Fractionation* (effective date: December 5, 2015) and is conducted in the Fractionation areas of Building (b) (4) and Building (b) (4) of Instituto Grifols facility. In this (b) (4)

Manufacture of Fibrinogen Component

The manufacturing process for Fibrinogen is described in the Production Method IG_MP-000033_ING, *Fibrinogen for Fibrin Sealant* (v. 11, effective date: May 30, 2017) and is performed in the Purification area of Building (b) (4). Fraction I is (b) (4). The (b) (4) solution undergoes Solvent/Detergent (S/D) treatment with 0.30% (v/v) tri-n-butyl phosphate (TNBP) and 1.0% (v/v) polysorbate-80 (Tween 80) at $27.0 \pm 1.5^\circ\text{C}$ for 6.0 – 6.5 hours validated to inactivate enveloped viruses. Fibrinogen is further purified through three rounds of glycine precipitation at (b) (4), and the third glycine precipitate is (b) (4). After (b) (4) solution undergoes nanofiltration through a series of 35 nm ((b) (4) 35N) and 20 nm ((b) (4) 20N) pore size filters. Nanofiltration is the second virus clearance step validated to remove enveloped and non-enveloped viruses. The formulated (b) (4) Fibrinogen bulk is (b) (4), sterile filtered through a (b) (4), and is used to aseptically fill syringes with 1 mL and 2 mL nominal fill volume for the 3-mL syringes and with 3 mL and 5 mL nominal fill volume for the 5-mL syringes. The filling operations are performed in the Class (b) (4) Aseptic area.

The filled syringes are immediately stoppered in the Aseptic area and are moved outside the Aseptic area to Class (b) (4) area where they are visually inspected and labelled.

The standard production batch size is approximately (b) (4) of Fibrinogen and it is obtained from an equivalent to (b) (4) of plasma. The production batch can be divided to dispense different presentations. The plasma pool used for Fibrinogen production comes from (b) (4). Estimated maximum final product lot size:

(b) (4)

(*) The 1 mL dosage form does not correspond to a whole production lot.

Manufacture of Fibrinogen Component

The manufacturing process for Thrombin is described in the Production Method IG_MP-000034_ING, *Thrombin for Fibrin Sealant* (v. 8, effective date: May 30, 2017). In the Fractionation area, the PTC is obtained from Fraction I Supernatant (b) (4)

Further steps are performed in the Purification area of Building (b) (4). Prothrombin in PTC is (b) (4) into Thrombin by (b) (4). The conditions for (b) (4)

The (b) (4) solution undergoes the S/D treatment with 0.3% (v/v) TnBP and 1.0% (v/v) polysorbate-80, pH 6.5 ± 0.1 , at $25 \pm 1^\circ\text{C}$ for 6.0 – 6.5 hours to inactivate enveloped viruses. Thrombin is further purified by cation exchange chromatography on a SP-Sepharose XL column at (b) (4). The (b) (4) is (b) (4), formulated (b) (4).

(b) (4) subjected to the double nanofiltration at (b) (4) through two 15 nm pore size (b) (4) 15N filters to remove enveloped and non-enveloped viruses. (b) (4)

. The (b) (4) Thrombin bulk solution undergoes the final sterile filtration through (b) (4) and is used for aseptic filling into syringes.

The standard production batch size is approximately (b) (4) of Thrombin and is obtained from an equivalent of (b) (4) of plasma. (b) (4)

The plasma pool used for Thrombin production comes from (b) (4). Estimated maximum batch size of final product:

(b) (4)

(*) The 1 mL dosage form does not correspond to a whole production lot.

The manufacturing areas for Fibrinogen and Thrombin processes in the Purification area of Building (b) (4) are spatially separated, i.e., there is no cross-flow of the two processes until the

formulated bulk solutions are delivered for final sterile filtration. Pre-viral and post-viral areas are physically segregated.

Packaging, Freezing and Storage

The Filling process is performed subsequently with Thrombin and Fibrinogen solutions. After the Filling process is completed and syringes are visually inspected and labeled, the Thrombin and Fibrinogen syringes are then assembled with syringe plungers, the syringe holder and plunger link. Assembled units are sealed into a blister, the blister is bagged in a thermo-sealed plastic packing and sterilized using (b) (4). The sterilized product is moved to the Packaging facilities where it is co-packaged with the applicator tip in the carton box and the kit is frozen and stored at $\leq -20^{\circ}\text{C}$.

CONTROL OF CRITICAL STEPS AND INTERMEDIATES (SECTION 3.2.P.3.4)

Manufacturing process controls - critical process parameters (CPPs) and in-process control (IPC) tests - were established during process development through extensive experimental evaluation to ensure product purity, safety and sterility, to reduce processing times, increase the yield, and optimize conditions taking into consideration the specifics of the Fibrinogen and Thrombin proteins. Critical quality attributes were established based on process understanding through developmental studies and risk assessments. Grifols stated that the operational ranges for the CPP and acceptance criteria for the IPC tests were initially determined for each unit operation in clinical-scale studies, and the consistency of this scale was demonstrated to support the clinical trials. The established process controls were further verified during process validation at the commercial scale as detailed in the comparability reports.

Reviewer Assessment

The original submission did not include description of changes in the manufacturing process, from material used in clinical trials to commercial production lots. Per FDA request, Grifols submitted this information and comparability reports in Amendment 15, dated March 9, 2017. The following changes were implemented:

- Increase in the production scale: Clinical batches were representative of a scale of approximately (b) (4) for Fibrinogen component and approximately (b) (4) for Thrombin component. Conformance (Process Performance Qualification) and commercial batches are manufactured at a scale of approximately (b) (4) for Fibrinogen component and approximately (b) (4) for Thrombin component.
- For each scale, different and dedicated rooms and equipment were used.
- Change in the materials of the double-barrier packaging for the Fibrin Sealant assembly (syringes assembled on a syringe holder) to increase the throughput capacity.

The main characteristics of both Fibrinogen and Thrombin processes of clinical and commercial scales are described in two comparability reports:

- Report IG_ITEC-002225_ING, *Study of the Comparability of Scale of the Fibrinogen Production Process* (effective date: July 1, 2015). In this study, a total of (b) (4) Fibrinogen processes were performed ((b) (4) runs at the clinical scale and (b) (4) runs at the commercial scale), resulting in representative lots of the finished product filled into syringes.
- Report IG_ITEC-002224_ING, *Study of the Comparability of Scale of the Thrombin Production Process* (effective date: July 1, 2015). In this study, a total of (b) (4) Thrombin processes were performed ((b) (4) runs at the clinical scale and (b) (4) runs at the commercial scale), resulting in representative lots of the finished product filled into syringes.

The design of both studies included comparison of critical process and analytical data from intermediate steps (b) (4), and comparison of analytical data from the final products (filled into syringes and tested after final sterilization). All relevant process and analytical data from process intermediates, as well as analytical data from the final product, demonstrated that the production processes at clinical and commercial scales are equivalent and allow purification of Fibrinogen and Thrombin in a consistent manner. The analytical data for the Fibrinogen and Thrombin components in the final products from the clinical- and commercial-scale processes are compared in Table 4 and 5. These data adequately justify that clinical material is representative of the intended commercial manufacturing process.

TABLE 4. Summary of Analytical Data for the Fibrinogen Component from the Final Product (Mean ± SD)

Parameter	Specification	Clinical Scale	Commercial Scale
pH	6.5 - 8.0	7.3 ± 0.1	7.6 ± 0.1
Stability of the solution (2 h at 20 - 25 °C)	(b) (4)	Correct	Correct
Clottable Fibrinogen (mg/mL)	(b) (4)		
Chlorides (mM)			
Sodium (mM)			
Glycine (mg/mL)			
Arginine (mg/mL)			
L-Isoleucine (mg/mL)			
Glutamic acid (monosodium salt) (mg/mL)			
Citrate (mM)			
(b) (4)			
TNBP (µg/mL)			
Polysorbate 80 (µg/mL)			
(b) (4)			

TABLE 5. Summary of Analytical Data for the Thrombin Component from the Final Product (Mean \pm SD)

Parameter	Specification	Clinical Scale	Commercial Scale
pH	6.0 - 8.0	6.4 \pm 0.1	6.8 \pm 0.1
Thrombin Activity (IU/mL)	(b) (4)		
Albumin (mg/mL)			
Chlorides (mM)			
Sodium (mM)			
Calcium (mM)			
Glycine (mg/mL)			
(b) (4)			
TNBP (μ g/mL)			
Polysorbate 80 (μ g/mL)			

(b) (4)

References:

1. IG_ITEC-001948_ING: Fibrinogen for Fibrin Adhesive: Development of the production process, in Module 3.2.P.2.
2. IG_ITEC-002503_ING: Fibrinogen for Fibrin Adhesive: Process parameters evaluation, in Module 3.2.P.2.
3. IG_MP-000033_ING: Fibrinogen for Fibrin Sealant, in Module 3.2.P.3.3.
4. IG_VS-001532: Sterilization of the Fibrin Sealant Grifols applicator with (b) (4), in Module 3.2.P.3.5.
5. IG_IVMA-000505_ING: S/F-VIII (b) (4) - Plasma Pool. Validation of the (b) (4) method, in Module 3.2.P.3.4.
6. IG_IVMA-000469_ING: (b) (4) Fibrinogen – Fraction I (b) (4). Validation of the (b) (4) method, in Module 3.2.P.3.4.
7. IG_ISVR-000060_ING: Evaluation of the viral elimination capacity of the production process of Fibrinogen for Fibrin Sealant, in Module 3.2.A.2.
8. IG_IVMA-000470_ING: Reconstituted Fibrinogen-Glycine precipitations. Validation of the (b) (4) method, in Module 3.2.P.3.4.
9. IG_IVMA-000462_ING: Fibrinogen (b) (4) - Before sterile filtration. Validation of the (b) (4) method, in Module 3.2.P.3.4.
10. IG_VS-001529: Qualification of (b) (4) filter used for the production of Fibrinogen for Fibrin Sealant, in Module 3.2.P.3.5.

(b) (4)

References:

1. IG_ ITEC-002008_ING: Thrombin for Fibrin Adhesive: Development of the production process, in Module 3.2.P.2.
2. IG_ITEC-002506_ING: Thrombin for Fibrin Adhesive: Process parameters evaluation. Please find this report attached in Module 3.2.P.2.
3. IG_MP-000034: Thrombin for Fibrin Adhesive, in Module 3.2.P.3.3.
4. IG_VS-001532: Sterilization of the Fibrin Sealant Grifols applicator with (b) (4), in Module 3.2.P.3.5.
5. IG_IVMA-000132_ING: PTC (b) (4) - Extraction of Prothrombin Complexe. Validation of the (b) (4) method, in Module 3.2.P.3.4.
6. IG_ISVR-000150_ING: Evaluation of the viral elimination capacity of the production process of Grifols Human Thrombin, in Module 3.2.A.2.
7. IG_IVMA-000435_ING: Thrombin validation of protein determination by (b) (4) method (b) (4) sample, in Module 3.2.P.3.4.
8. IG_IVMA-000468_ING: Adjunt. Thrombin (b) (4) – (b) (4). Validation of the (b) (4) method, in Module 3.2.P.3.4.
9. IG_IVMA-000465_ING:Thrombin bulk (b) (4) (Fibrin Sealant) – Before sterile filtration. Validation of the (b) (4) method, in Module 3.2.P.3.4.
10. IG_VS-001530: Qualification of (b) (4) filter and (b) (4) filter used for the production of Thrombin for Fibrin Sealant, in Module 3.2.P.3.5.

In the original submission, the information on CPPs and IPC tests, although described in the appendices to the Production Methods and validation reports, was not presented in a consolidated format to adequately describe the manufacturing process in the BLA. In response to the FDA request, Grifols submitted, in a tabular format, lists of CPPs with acceptance ranges and lists of IPC tests with acceptance criteria for each step of the Fibrinogen and Thrombin processes (Amendment 49, dated September 27, 2017). Grifols also included references to the respective documents that justify the acceptance ranges/acceptance criteria. To meet the FDA requirements for the eCTD structure, this information was included in section 3.2.P.3.4 and is summarized in Tables 6-9.




Reviewer Assessment

As a result, the identification of critical process parameters and in-process control tests with acceptance criteria has established an adequate strategy for controlling the manufacturing processes of Fibrinogen and Thrombin. The control strategy was also discussed during the PLI, and adherence to this strategy was verified during observation of some manufacturing steps and review of batch records.

Hold Times

The hold times for process intermediates were established during process development in clinical-scale runs based on stability data of intermediate samples taken at the defined process steps, and were validated during production of conformance lots.

(b) (4)



(b) (4)

In conclusion, based on the stability assessment of intermediates and verification of no adverse impact on the quality and stability of the final product, the established hold times for both Fibrinogen and Thrombin processes intermediates are adequately validated.

PROCESS VALIDATION AND/OR EVALUATION (SECTION 3.2.P.3.5)

The validation studies were performed at the Grifols' Barcelona facility, the intended commercial site, under prospective process validation protocols. Validation of the manufacturing process for FS Grifols at the commercial scale was designed as a series of separate studies covering consequent specific manufacturing stages of the Fibrinogen and Thrombin processes and subsequent filling and sterilization of the final product.

Validation of Plasma Fractionation Process

The plasma fractionation in Building (b) (4) is performed at the scale of (b) (4) of plasma. Validation of the fractionation process from (b) (4) of human plasma to Fraction I and PTC obtained in Building (b) (4) is summarized in Report IG-VS-001520 (effective date: June 10, 2016). Grifols performed a retrospective analysis of experimental data for (b) (4), Fraction I and PTC from (b) (4) processes performed in the Fractionation area of Building (b) (4) from January 2012 to June 2013. The following parameters were assessed:

(b) (4)

(b) (4)

fractionation processes in Building (b) (4) and Building (b) (4) to produce PTC and Fraction I of adequate quality, when performed at respective validated scales.

Validation of Solvent/Detergent Treatment Process

Validation studies for the S/D treatment process are summarized in the following reports:

- Report IG_VS-001289, *Validation of the Solvent Detergent (SD) Treatment Process Performed to Thrombin Solution (Fibrin Sealant Grifols)* (effective date: May 07, 2014).
- Report IG_VS-001290, *Validation of the Solvent Detergent (SD) Treatment Process Performed to Fibrinogen Solution (Fibrin Sealant Grifols)* (effective date: May 07, 2014).

Both validation studies used a similar approach: The validation consisted of three S/D treatment runs at the (b) (4) tank load and one run at the (b) (4) load, using placebo solution which had the same physicochemical characteristics and composition as the real product but contained no protein. In every validation run, the following critical process parameters were controlled:

(b) (4)

Reviewer Assessment

The results from the S/D treatment runs of both Fibrinogen and Thrombin processes demonstrated that the proper temperature and concentrations of TnBP and Tween were achieved during the (b) (4) (giving homogeneous solutions) and were maintained within their acceptance ranges throughout the treatment process duration thus supporting adequate performance of this step. However, the acceptance ranges for S/D concentrations appeared too wide ((b) (4) of the target concentrations) and not centered: for TnBP % (v/v): (b) (4) (for Fibrinogen) and (b) (4) (for Thrombin) compared to the target value of 0.3%, and for Tween 80 % (v/v): (b) (4) (for Fibrinogen) and (b) (4) (for Thrombin) compared to the target value of 1%. Per my request, Grifols provided an explanation on how these ranges were established and justified their acceptability (Amendment 30, dated May 30, 2017). Grifols reasoned that the initial addition of TnBP and Tween to their nominal final concentrations in the Fibrinogen and Thrombin solutions is controlled (b) (4). The analysis of both components in the in-process samples at the end of the treatment is performed as a verification to confirm consistency of the process. For both TnBP and Tween 80, the acceptance ranges were established based on experimental data

accumulated during development as mean (b) (4). Grifols further stated that the current ranges are justified by the results from viral clearance validation studies where the S/D concentrations at (b) (4) of the nominal level were effective in inactivating the most resistant parvovirus (PRV). Regarding tightening ranges, which I recommended, Grifols considers that an increased population of historical data at commercial scale is needed to perform a more accurate evaluation of the statistics of the population. I found the provided justification acceptable.

Validation of Fibrinogen and Thrombin Processes

Validation of the commercial manufacturing processes for Fibrinogen and Thrombin components is summarized in Report IG_VS-001293 (effective date: June 30, 2016) and Report IG_VS-001292 (effective date: June 30, 2016), respectively. The validation for both components was performed by manufacturing first three batches of Fibrinogen and Thrombin at commercial scale that were filled into 3 mL syringe with 1 mL and 2 mL fill volumes (batches (b) (4)). The validation design was similar for Fibrinogen and Thrombin and included assessment of the following:

- Production consistency parameters such as (b) (4)
- Routine quality assays including in-process control testing (please refer to Tables 7 and 9) and release testing according to Specifications (please refer to Tables 16-18)
- Additional, validation-specific assays, which are not routinely performed, included assessment of:

(b) (4)

[REDACTED]

The results of routine testing met respective acceptance criteria and were within specification ranges. In assessing uniformity of quality parameters within the whole batch, the results for key parameters were compared to specification ranges and were within these ranges for all samples tested.

Reviewer Assessment

The validation of both processes was performed by manufacturing first three batches of Fibrinogen and Thrombin at commercial scale that were filled into 3 mL syringes with 1 mL and

2 mL fill volumes, whereas the 5-mL syringes were not used. Grifols reasoned that the dispense dose (fill volume) is not critical for this validation considering that the manufacturing processes for Drug Substances are identical for all fill sizes. However, the lack of data for a higher fill volume was identified as one of deficiencies in the validation of the Aseptic Filling process as discussed below.

In both validation studies, all process parameters as well as results of routine in-process and release testing and additional, validation-specific characterization testing met pre-defined acceptance criteria thus supporting consistency of the commercial processes to manufacture Fibrinogen and Thrombin of adequate quality. However, the uniformity of quality parameters within the whole batch was assessed qualitatively, i.e., only by conformance of the results to specification ranges but did not include statistical analysis of the data that would provide a quantitative criterion for process capability to produce product meeting the specifications. The lack of statistical analysis was identified as one of deficiencies in the validation of the Aseptic Filling process as discussed below.

In the reports, specifications for (b) (4), respectively (specifications in place for clinical material), with annotation that the specifications were later revised to (b) (4). Revision of specification for (b) (4) was made on request of European Medicines Agency; specification for (b) (4) was revised based on Grifols's manufacturing experience. As actual results for these parameters in both studies met the revised (commercial) specifications, I concluded that the conformance runs remain valid.

Validation of Chromatographic Process for Thrombin and Life Time of SP-Sepharose Resin

The purification process for Thrombin includes a chromatographic step using SP-Sepharose XL cation exchange resin. The Protocol IG_VSP-000964_ING (effective date: March 13, 2014) defined three Phases in the validation of chromatographic performance, cleaning and storage of SP-Sepharose column in commercial-scale Thrombin purification:

- Phase I (initial study) to demonstrate the effectiveness and validity of the process at the beginning of the use of the packed column
- Phase II (concurrent process monitoring) to ensure adequate column performance in the course of repetitive use
- Phase III (final study) to demonstrate the effectiveness and validity of the process at the end of the intended resin lifetime.

The submitted Report IG_VS-001435, *Validation of the Chromatographic Process and Cleaning of the Thrombin Purification Column* (effective date: June 25, 2015) (linked Report IG_IVSP-001620) demonstrated satisfactory column performance during (b) (4) purification runs at full-scale.

Reviewer Assessment

The proposed lifetime for SP-Sepharose resin was not stated in the BLA. During the PLI, Grifols stated that they plan to apply up to (b) (4) runs for the SP-Sepharose resin in the

purification of Thrombin, based on their experience with purification of another licensed product, (b) (4). However, at the time of the BLA submission, the available data did not support the proposed number of resin re-uses: The Phase I validation of this step was performed in (b) (4) initial full-scale purification runs, and assessment of resin lifetime in small-scale studies was not performed. This deficiency was identified during the review of the BLA and was discussed with Grifols during the PLI. We explained that the maximum number of resin uses (lifetime), that can be approved by FDA, is based on either the results from preliminary assessment in small-scale studies (which is a general approach), or the total number of industrial-scale runs performed during process validation (i.e., currently, (b) (4) runs).

In Amendment 30, dated May 30, 2017, Grifols submitted an updated Report IG_VS-001435 which demonstrated satisfactory resin performance for (b) (4) commercial-scale purification runs. The response was found inadequate because: (i) the accomplished number of runs was significantly lower than the newly proposed maximum number of uses for commercial production ((b) (4)) for which Grifols sought FDA approval as part of the BLA review, and (ii) no Study Protocol was submitted for FDA review. This deficiency was discussed at the Late-Cycle Meeting on August 31, 2017.

Per subsequent FDA request, Grifols developed a Study Protocol IG_VSP-000964_ING, *Validation of the Chromatographic, Cleaning and Storage Process of the Thrombin Purification* (effective date: September 18, 2017) for the Phase II concurrent full-scale validation of resin lifetime (up to (b) (4) runs) and submitted it in Amendment 49, dated September 27, 2017.

The Protocol aimed to study up to (b) (4) commercial-scale purification runs and described controls over (b) (4) parameters that will be monitored during the validation, and assessment of the data against pre-defined acceptance criteria. These controls are summarized in Tables 10-14, and include routine IPC and additional validation-related tests: routine IPC tests are performed every run; additional tests will be performed with a frequency of 1 control every (b) (4) runs.

(b) (4)

(b) (4)

The proposed studies will establish:

- The maximum number of uses for the resin supported by the control over the cleaning process efficiency and column performance in the course of using and at the end of its lifetime
- The maximum acceptable time from the beginning of resin packing until the last use

Any anomalous result will be investigated, corrected and documented. If the investigation concludes that the quality of the product was compromised, the resins will be replaced and the maximum number of uses will be established to the last run in which correct results for all parameters were obtained.

Grifols will submit information on the number of runs and results of column performance / cleaning efficiency in annual reports until run (b) (4) is reached.

Grifols also submitted the updated Report IG_VS-001435 that contains data demonstrating satisfactory column performance and cleaning efficiency for (b) (4) commercial-scale runs (Amendment 51, dated September 29, 2017). Grifols committed to using this Study Protocol in the purification of subsequent Thrombin lots. As the validity of the Study Protocol IG_VSP-000964_ING is supported by the currently accumulated data, FDA considers it as an acceptable basis for release of subsequent commercial lots of FS Grifols by CBER.

Grifols agreed that small-scale studies may be warranted in the future if Grifols plans a further extension of the maximal number of resin uses, beyond (b) (4), for commercial production.

(b) (4)

In conclusion, this deficiency was adequately resolved and the mechanism for routine release by CBER of subsequent commercial lots of FS Grifols with annual reporting has been established.

Validation of the Aseptic Filling Process with Production Batches

The results of the validation of the Aseptic Filling process with production batches of Thrombin and Fibrinogen are summarized in Document IG_VS-001647, *Validation of the Filling Process with Production Batches* (Mach. Num. (b) (4)) (effective date: February 27, 2017) (linked report IG_IVSP-001658) which was included in the original submission. Three validation batches of Fibrinogen and Thrombin were manufactured and filled into 3-mL syringes with 1 mL and 2 mL fill volumes resulting in three filled batches of Drug Product in 2-mL fill size and three batches – in 4-mL fill size. The validation approach included assessment of the following aspects against pre-defined acceptance criteria:

- Results of aseptic process monitoring (sterility control, environmental control, and personnel monitoring)
- Results of routine IPC testing (please refer to Tables 7 and 9) and routine release testing of final containers against Specifications (please refer to Tables 16-18)
- Assessment of filled batch uniformity by (b) (4) and critical quality parameters by compliance to Specifications, similarly to the approach used in the validation of the production processes for Fibrinogen and Thrombin (Report IG_VS-001293 and Report IG_VS-001292)
- Recording of filling duration times

The results for all parameters for both fill sizes were within the respective acceptance criteria and Grifols concluded that the obtained data support consistent operation of the Aseptic Filling process in the production conditions.

Reviewer Assessment

Although the study results were satisfactory, the scope of the validation studies was found incomplete due to the following:

- a) There were no clear definitions of the start and end points and established time limits for each phase of aseptic processing, such as limits for sterile filtration processes for each Drug Substance, time limits for product exposure on the filling line, and an overall time limit for the aseptic processing of Thrombin and Fibrinogen.
- b) The validation data were presented only for the minimal fill sizes (1 + 1 mL and 2 + 2 mL) in the 3-mL syringes but did not include any data for the fill sizes in the 5-mL syringes, while higher filling volumes may potentially affect the filling times.
- c) Homogeneity (Consistency) of critical quality parameters within the filled batch was assessed only by compliance to the specification ranges but did not include statistical analysis of the data with pre-defined acceptance criteria to allow a more accurate assessment of homogeneity by monitoring for any trends within the specification ranges.
- d) The processing times for the steps following the Aseptic Filling process (assembly, packaging, and sterilization), or *the overall processing time* from the start of sterile filtration to the point when the final product is frozen, was not established. Establishing the overall processing time is critical considering that both biologics, from the sterile filtration step to the freezing step, are processed at (b) (4).

The deficiencies (a) and (d) were classified as a 483 objectionable observation #2 during the PLI:

“The processing times for critical manufacturing steps, including sterile filtration of Thrombin and Fibrinogen bulk, filling of syringes, and their assembly with plungers and syringe holder, preparation for and sterilization with (b) (4), and secondary packaging up to freezing of the final product, are not established or clearly defined.”

All four deficiencies regarding the time limits, scope of the validation, and data assessment were also categorized as review-related issues to be followed via information requests during the BLA life-cycle.

Grifols submitted response to 483 item #2 in Amendment 24, dated April 12, 2017. The response was reviewed by the DMPQ Lead Inspector and this reviewer and was found incomplete. Subsequent IR, stating the above deficiencies, was sent to Grifols on April 26, 2017. Per FDA's request, Grifols performed additional studies and analyses to more fully validate the Aseptic Filling process. In Amendment 30, dated May 30, 2017, Grifols submitted an updated Validation Report IG_VS-001647 (effective date: May 30, 2017) which summarizes the following:

- a) The scope of the validation data was expanded to represent 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. The list of conformance batches is presented in Table 15. Batches (b) (4) were filled at the time of the PLI.
- b) Statistical analysis of analytical data of all syringes in each batch was performed, and the results confirm process capability to ensure proper homogeneity of key quality parameters of Fibrinogen and Thrombin in all units within the batch: Cp for *Fibrinogen (Clottable Protein)* was in the range of (b) (4) and for *Thrombin Activity* – in the range of (b) (4) and met the acceptance criterion (Cp^{(b) (4)}).
- c) The definitions and time limits for the critical steps of aseptic processing and total processing time were established based on actual processing times and support process capability:
 - The Sterile Filtration time is defined as the time from the start until the end of sterile filtration of each bulk component (Fibrinogen and Thrombin), with the time limit of (b) (4).
 - The Aseptic Filling time for each component is defined as the time from the first to the last syringe aseptically filled, with the time limit of (b) (4).
 - The total time of the Filling step (Sterile Filtration and Aseptic Filling of both components) is defined as the time from the start of sterile filtration of Thrombin bulk solution until the last Fibrinogen syringe is filled, with the time limit of (b) (4). This time includes the change-over interruption of the filling process, i.e., filling time for Thrombin, time for filling line cleaning, and filling time for Fibrinogen.
 - The Total Processing Time (Filling, Packaging and Sterilization) is defined as the time from the start of sterile filtration of Thrombin bulk solution until the last Fibrin Sealant kit is frozen. The Total Processing Time limit of (b) (4) was established based on actual times and is supported by stability data for Thrombin and Fibrinogen.

In support of Total Processing Time, Grifols provided a feasibility study Report IG_ITEC-001737_ING, *Fibrin Sealant: Stability of the Filtered Bulk Solution of Thrombin and Fibrinogen* (effective date: April 03, 2013) which demonstrated acceptable recoveries of both filtered bulk Drug Substances (b) (4).

In addition, Grifols submitted Report IG_ITEC-002873_ING (effective date: May 30, 2017) which describes another stability study where one batch of Fibrinogen and one of Thrombin, after being aseptically filled in syringes, were stored at (b) (4) before freezing and then put on long-term stability testing ($\leq -20^{\circ}\text{C}$ up to (b) (4)). Analytical results for (b) (4) demonstrated stability of these quality parameters under all conditions. This further validates the established Total Processing Time.

TABLE 15. List of Fibrin Sealant (Human) Conformance Batches

Number	Batch Code	Manufacturing Date (Fibrinogen and Thrombin)	Fill Size (mL)
1	(b) (4)	(b) (4)	2
	(b) (4)	(b) (4)	4
2	(b) (4)	(b) (4)	2
	(b) (4)	(b) (4)	4
3	(b) (4)	(b) (4)	2
	(b) (4)	(b) (4)	4
4	(b) (4)	(b) (4)	6
	(b) (4)	(b) (4)	10
5	(b) (4)	(b) (4)	10
6	(b) (4)	(b) (4)	6
7	(b) (4)	(b) (4)	4
8	(b) (4)	(b) (4)	6
9	(b) (4)	(b) (4)	4

Grifols updated Production Procedures IG_MP-000033, *Fibrinogen for Fibrin Sealant* and IG_MP-000034, *Thrombin for Fibrin Sealant* with the validated processing times and submitted the revised documents to the BLA file. In conclusion, all identified deficiencies have been fully addressed by the Applicant and the Aseptic Filling process can be considered adequately validated.

The validation of the sterilization process for blisterpacks was reviewed by the DMPQ reviewer (Dr. Christine Harman) and was found adequate as reflected in her memorandum.

In conclusion, all process and quality controls in the series of validation studies complied with pre-defined acceptance criteria stated in validation protocols, and the results of release testing were within specifications; thereby, fulfilling the requirements for successful process validation. Based on the evaluation of the manufacturing and testing data for clinical and conformance lots, the manufacturing process for FS Grifols was found to be sufficiently controlled, consistent and adequately validated. The deviations that occurred during process validation were reviewed during the PLI and were found to be addressed adequately and not affecting the validity of the results. Please refer to the Establishment Inspection Report.

Reprocessing

Each of the nanofilters that is used in the manufacturing processes ((b) (4) 35N, (b) (4) 20N and (b) (4) 15N) undergoes an individual integrity test pre-use ((b) (4)) and post-use ((b) (4)) as recommended by the manufacturer. If post-operation filter integrity test fails, re-processing at this step is not performed but the Production Procedures did not specify this. Per my request, Grifols submitted their revised general SOP IG_MSP-001940, *Procedure for Reprocessing/Reworking of Instituto Grifols' Products* (effective date: May 22, 2017) to include the restriction statement of no-refiltration at the

nanofiltration step specifically for Fibrin Sealant (Human) product (Amendment 30, dated May 30, 2017).

The manufacturing procedures for Thrombin and Fibrinogen in the original versions have allowed for re-processing at the sterile filtration step if the filter integrity test fails. Grifols was asked to submit data that evaluate the impact of repeated sterile filtration on the quality and stability of Fibrinogen and Thrombin at small and full scales. As no industrial scale lots that underwent re-processing were manufactured, such supporting data are not available (stated in Amendment 30), and re-processing will not be allowed. Thus, this approval does not include any reprocessing steps.

SPECIFICATIONS FOR DRUG PRODUCT (SECTION 3.2.P.5.1) AND JUSTIFICATION OF SPECIFICATIONS (SECTION 3.2.P.5.6)

The originally-proposed Specifications for Drug Product are summarized in Document IG_ESP-000304_ING, *Specifications of the Finished Product - Fibrin Sealant*. Justification of Specifications is provided in Document IG_ITEC-002588_ING, *Fibrin Sealant: Specifications Rationale*. The Specifications were established in accordance with ICH Guideline Q6B. The parameters were selected from critical quality attributes determined in process development studies and risk assessments. Acceptance ranges/limits are established based on regulatory requirements ((b) (4)), manufacturing experience (analysis of the release and stability data for clinical and conformance lots), process capability to remove impurities, analytical variability, and previous experience with other licensed Grifols products (IGIV, Intravenous Immunoglobulin).

Reviewer assessment

In the course of review, IRs regarding Specification parameters and justification of specification ranges were sent to Grifols on June 15, 2017 and September 08, 2017. The responses were submitted in Amendment 33, dated July 05, 2017 and Amendment 48, dated September 25, 2017. The following modifications were made to the DP specification:

Total Protein for Fibrinogen

The parameter “Total Protein” was added in the final specifications for Fibrinogen to provide a tool (% Clottable Protein) for process consistency control and early detection of any trends during commercial manufacture. Grifols had been measuring both *Total Protein* and *Fibrinogen (Clottable Protein)* throughout development and in characterization studies. Their data indicate a high purity of Fibrinogen ((b) (4)), and the stability data assured the stability of this purity level through the proposed product dating period (shelf-life). Therefore, the specification range for *Total Protein* is ((b) (4)), which is equivalent to the specification for *Fibrinogen (Clottable Protein)*.

For Thrombin, measuring *Total Protein* in the final product is not informative due to the presence of albumin in the formulation. However, Grifols has in-process tests at the end of the

(b) (4) are monitored. These IPC tests are sufficient to control process consistency for Thrombin.

Volume

The acceptance criterion for the parameter “Volume” was revised from the limit (e.g., (b) (4)) to the range (e.g., 1.0 (b) (4) mL; 5.0 (b) (4) mL [(b) (4)]) based on the overfill studies summarized in Report IG_ITEC-002020_ING, *Determination of Specifications for Fibrin Sealant Dose Control* (effective date: August 1, 2014). The rationale for this revision is to ensure that equivalent doses of Fibrinogen and Thrombin are filled into syringes. This revision was proposed by this reviewer and CDRH consult reviewers.

Appearance of Solution

The acceptance criterion for the parameter “*Appearance of the solution (after thawing)*” was edited to use the USP language as underlined: “*Colourless or pale yellow solution, essentially free of visible particulates*”. This revision is related to discussions during the course of review on the classification of Fibrin Sealant (Human) as a parenteral or non-parenteral product. The definition of the route of administration “For Topical Use Only” has been historically used for all fibrin sealants. The specific feature of these products, compared to other products for topical use, is that they are applied onto the surface of organs *inside the body* and in this way appear to be closer to parenteral products. However, the risks associated with the use of fibrin sealants appear to be lower, compared to parenteral products that are intravenously injected. FS Grifols is not intended for systematic administration; it is intended to be used locally, once per surgery and in small volumes, and will instantly form a gel upon application onto the wound site. Thus, by the level of risk they are closer to non-parenteral products. The outcomes of these discussions are as follows:

- Grifols agreed to use the USP language for parenteral products as an acceptance criterion for the parameter “*Appearance of the solution*” which is also consistent with the method used for release testing (visual inspection).
- In the Prescribing Information, based on discussions during the labeling review, the route of administration will be stated “For Topical Use Only”, which is consistent with the term established by FDA for this class of products.
- For visual inspection of the filled syringes during the manufacture, FDA allowed Grifols to continue following the requirements for particulates for non-parenteral products (Acceptance Quality Limit of (b) (4) is currently used by Grifols) but this limit may be re-evaluated as more information regarding risks of particulates with Fibrin Sealant products becomes available (as discussed in detail in the DMPQ memorandum and EIR).

General Safety Test

Grifols submitted a request to remove the General Safety Test (GST) from DP Specifications and Stability Program. To justify this request, Grifols submitted Technical Report IG_ITEC-002990_ING, *Evaluation of the Exemption from the General Safety Test for Fibrinogen and*

Thrombin Components of Fibrin Sealant Grifols (effective date: July 4, 2017) which demonstrates GST compliance on representative manufactured batches, the implementation of an adequate safety control program and analytical techniques in place ensuring product safety. Based on the FDA Final Rule (Federal Register /Vol. 80, No. 127, July 2, 2015, page 37971 to 37974), we approved Grifols' request to remove the GST from the DP Specifications and Stability Program.

Potency

The proposed acceptance criteria for *Fibrinogen (Clottable Protein)* and *Thrombin Activity* set as (b) (4) and (b) (4) of the target values, respectively, present wide ranges and therefore were discussed with Grifols.

In their response (Amendment 33, dated July 5, 2017), Grifols reasoned that, according to the Fibrin Sealant monograph (b) (4)

(b) (4), therefore for the Fibrinogen component of FS Grifols (nominal value of 80 mg/mL), Grifols established the range of (b) (4). Similarly, for the Thrombin component, the (b) (4)

(b) (4). Therefore, for the Thrombin component of FS Grifols (nominal value of 500 IU/mL), Grifols established the range of (b) (4). Grifols stated that the currently available population of historical data from commercial scale batches is not sufficient to perform an accurate evaluation of the statistics of the population. Based on the statistical analysis of the data for (b) (4) commercial-scale lots of Fibrin Sealant (Human), the proposed ranges are close to ranges determined as Mean (b) (4) for *Clottable Fibrinogen* and (b) (4) for *Thrombin Activity*. Grifols will explore the possibility of tightening the current ranges when the population of historical data at commercial scale becomes sufficient. I find the response satisfactory. The proposed ranges for potency of both components are comparable to respective ranges of other licensed fibrin sealant products.

Polysorbate

I also requested justification of the specification for Polysorbate 80 ((b) (4)), which was significantly higher than that for TnBP ((b) (4)). Grifols explained that this difference is related to the specifics and capability of the assays. The assay for Polysorbate 80 involves extraction of Polysorbate by means of a (b) (4) technique and further determination by a (b) (4) assay which requires (b) (4). The working standard curve has a concentration range of (b) (4). Considering a (b) (4) dilution of the sample during the assay, those samples which have responses lower than or equal to the most diluted standard point (i.e., (b) (4)), are reported as (b) (4). In the case of TnBP, quantification is performed by means of (b) (4) which allows a higher sensitivity of the method (a working standard linear range of (b) (4)). Grifols provided references to numerous published toxicological assessments and animal studies. Based on these reports, the toxicity of polysorbates is considered low. In the evaluation of the U.S. FDA, the Acceptable Daily Intake (ADI) of polysorbates was set at 1.500 mg/person/day (0 – 25 mg/kg body weight/day). Thus, the proposed limit ((b) (4)) is sufficient to ensure a wide safety margin with the use of Fibrin

Sealant (Human). In my review of the batch analyses results, the levels of Polysorbate 80 and TnBP were below (b) (4), respectively, for all batches manufactured thus far. These results confirm process capability to effectively remove these process-related impurities.

Stability of Solution for Fibrinogen

The specification for this parameter is set for (b) (4) at 20 – 25°C based on the (b) (4). In addition, Grifols tested quality parameters of the Fibrinogen component in in-use stability studies for a longer time intervals as discussed in Stability section.

The final DP Release Specifications are summarized in Document IG_ESP-000320_ING, *Specifications of the Finished Product - Fibrin Sealant* (effective date: September 22, 2017) submitted in Amendment 48, dated September 25, 2017 and are reproduced in Tables 16-18. The final Specifications reflect revisions made per the FDA requests and are considered adequate to control the identity, quality, purity, potency, and safety of Fibrin Sealant (Human).

TABLE 16: SPECIFICATION FOR DRUG PRODUCT: FIBRINOGEN COMPONENT

Attribute	Parameter	Method	Specification
IMMUNO-CHEMICAL CONTROL	IDENTIFICATION	(b) (4) determination by (b) (4)	It complies with the limits of the assay for fibrinogen
	FIBRINOGEN (clottable protein)	(b) (4) determination by (b) (4)	(b) (4)
	TOTAL PROTEIN	Bradford method	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
PHYSICO-CHEMICAL CONTROL	APPEARANCE OF FROZEN PRODUCT	Visual inspection	Colorless or pale yellow, opaque solid
	APPEARANCE OF SOLUTION (AFTER THAWING)	Visual inspection	Colorless or pale yellow solution, essentially free of visible particulates
	pH	pH meter	6.5 – 8.0
	STABILITY OF SOLUTION (2 hours at 20-25°C)	Visual stability	(b) (4)
	ARGININE	(b) (4)	(b) (4)
	L-ISOLEUCINE	(b) (4)	(b) (4)
	GLUTAMIC ACID (monosodium salt)	(b) (4)	(b) (4)
	CHLORIDE	(b) (4)	(b) (4)
	SODIUM	(b) (4)	(b) (4)
	CITRATE	(b) (4) method	(b) (4)
	GLYCINE	(b) (4)	(b) (4)
	TNBP	(b) (4)	(b) (4)
	POLYSORBATE 80	(b) (4) assay	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	VOLUME	Measurement	1.0 mL (b) (4) 2.0 mL (b) (4)

Attribute	Parameter	Method	Specification
			3.0 mL (b) (4) 5.0 mL (b) (4)
MICROBIOLOGICAL CONTROL	STERILITY	(b) (4)	No microbiological growth
BIOLOGICAL CONTROL	(b) (4)	(b) (4)	(b) (4)

TABLE 17: SPECIFICATION FOR DRUG PRODUCT: THROMBIN COMPONENT

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

TABLE 18: SPECIFICATION FOR DRUG PRODUCT: FIBRIN SEALANT COMBINATION PRODUCT

Attribute	Parameter	Method	Specification
IMMUNOCHEMICAL CONTROL	IDENTIFICATION	Coagulation method	Clot formation
	FUNCTIONALITY (Clot formation (b) (4))	Coagulation method	(b) (4)

ANALYTICAL PROCEDURES (SECTION 3.2.P.5.2) AND VALIDATION OF ANALYTICAL PROCEDURES (SECTION 3.2.P.5.3)

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

Please refer to the memorandum of Dr. Svetlana Shestopal for further details.

BATCH ANALYSES (SECTION 3.2.P.5.4) AND IN-SUPPORT TESTING

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

During the PLI, I reviewed a list of all drug product lots that were manufactured at the facility until that point including those aborted or failed with dates of manufacture, scale and purpose of use. From (b) (4) lots of Fibrin Sealant (Human) manufactured during (b) (4) lots (around 85%) were CORRECT (meeting release specification) or RELEASED (for use in clinical trials). There were six (6) lots that failed (status: FAILED) and one (1) lot that was aborted (status: ABORTED). The failed lots were from the development stage (manufactured in 2007, 2008, 2009, 2010, and 2013) and had problems with (b) (4), Fibrinogen Clottable Proteins values or incorrect procedures in the Fibrinogen manufacturing process. Relevant adjustments in the manufacturing and analytical procedures were subsequently implemented. All conformance lots received status CORRECT.

The Laboratories of the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality (OCBQ), CBER, FDA, performed in-support testing of three Fibrin Sealant (Human) conformance lots of various fill sizes. The results met the acceptance criteria for the assay performance characteristics. In addition, the DBSQC test results for Fibrin Sealant (Human) samples were within the proposed DP specifications and comparable

to the results reported by Grifols. The in-support testing confirmed the suitability of critical test methods for their intended use as release specification tests.

STABILITY (SECTION 3.2.P.8)

The stability program for Fibrin Sealant (Human) included studies under long-term storage (-21 (b) (4) for (b) (4) in temperature-controlled freezers) and accelerated (b) (4) conditions. The studies were performed on the conformance DP lots representative of the commercial manufacturing process and encompassed all fill sizes – three lots of each 2-mL, 4-mL, 6-mL and 10-mL presentation in the long-term study, and (b) (4) of each size in the accelerated study. Stability samples were tested at defined time intervals for all specification parameters. In Amendment 30, Grifols submitted up-to-date stability data in Report IG_IE-000239_ING, *Fibrin Sealant Grifols: Stability Study. Final Report* (effective date: February 10, 2017). The studies are now completed, with data meeting specifications for all parameters and all fill sizes throughout storage periods. Recoveries of Fibrinogen and Thrombin after 24-month storage under long-term conditions were 104% and 93%, respectively, and after (b) (4) under accelerated conditions – 106% and 94%, respectively.

The proposed storage conditions are described in the Prescribing Information as follows: “Store the kit with the frozen package of FIBRIN SEALANT (Human) in a freezer (at -18 °C [0 °F] or colder) for up to 2 years. The cold storage condition must not be interrupted until use.” In Amendment 48, dated September 25, 2017, Grifols clarified that the proposed storage temperature $\leq -18^{\circ}\text{C}$ is within the temperature interval tested in stability studies. In addition, Grifols took into account the capability of common equipment (freezers) with potential temperature excursions. The proposed temperature ensures that it will be maintained reliably in common-use freezers at the end-user locations, and guarantees product’s stability within the shelf-life. Based on the satisfactory data, the proposed shelf-life of 24 months at a temperature of $\leq -18^{\circ}\text{C}$ can be granted.

The in-use (post-thawing) stability study was performed for (b) (4) lots of FS Grifols at the end of shelf-life which covered all dosage forms. The results are summarized in Report IG_IE-000222_ING, *Fibrin Sealant (FS) Grifols. Stability Study after Product Thawing* (effective date: July 22, 2016). The in-use stability data support unchanged product quality for up to 48 hours when the product is kept at $5 \pm 3^{\circ}\text{C}$ and up to 24 hours when kept at $25 \pm 2^{\circ}\text{C}$. The storage conditions and handling of FS Grifols after thawing are accurately described in the labeling and specify that the product should remain sealed in the original packaging to maintain sterility:

“After thawing, FIBRIN SEALANT (Human) can be stored before use for not more than 48 hours at $2 - 8^{\circ}\text{C}$ [36 - 46 °F] or 24 hours at room temperature ($20 - 25^{\circ}\text{C}$ [68 - 77 °F]) if it remains sealed in the original packaging. Once the package is opened, use FIBRIN SEALANT (Human) immediately during the surgery and discard any unused contents.”

The established Stability Protocol for post-approval testing was revised according to revisions in DP Specifications and includes FDA recommendation to ensure that the annual testing of the product in the 3-mL and 5-mL syringes is performed in an alternating manner. The final version

of the Protocol IG_PE-000128_ING (effective date: September 22, 2017) submitted in Amendment 48, dated September 25, 2017, is adequate to control DP stability post-approval.

COMBINATION PRODUCT: DESIGN HISTORY FILE FOR DEVICE COMPONENTS

The development of FS Grifols started in early 2000's, i.e., prior to issuance of the final rule codified in 21 CFR Part 4 for combination products. With introduction of 21 CFR Part 4.4(b), Grifols has chosen to establish a cGMP operating system using the biological cGMP-based streamlining approach (i.e., compliance with Parts 600-680 and 211 of the CFR) and started working to leverage existing data for developing the applicable contents to comply with the additional provisions of Part 820 Quality System regulations for medical devices in accordance with 21 CFR 4.4. (b) (1). This device information was not included in the original submission and was requested by the FDA at the BLA filing stage (in the Filing Letter).

In Amendment 11, dated February 15, 2017 and Amendment 23, dated April 4, 2017, Grifols submitted a set of activity reports to address the following requirements of 21 CFR 820:

820.30(b) Design and Development planning

820.30(c) Design Inputs

820.30(d) Design Outputs

820.30(e) Design Review

820.30 (f) Design Verification

820.30(g) Design Validation

820.30(h) Design Transfer

820.30(i) Design Changes

820.30(j) Design History File

820.50 Purchasing Controls

820.100 Corrective and preventive actions

The information on the device components of FS Grifols was reviewed in detail by the DMPQ reviewers from CBER and consult reviewers from CDRH as summarized in their memoranda. I reviewed selected documents during the PLI and provide my assessment below:

Document IG_ITEC-002783_ING, *Fibrin Sealant Grifols Kit: Overall Design Plan* (effective date: February 06, 2017) represents a design plan with established phases for design development activities: Planning and Initiation, Feasibility Assessment, Design Verification, Design Validation, and Product Launch/Commercialization.

Document IG_MSP-002046_ING, *Medical Device Design History File* (effective date: February 07, 2017) established a system, described procedures and assigned responsibilities for constructing the Design History File (DHF) for medical device projects at Grifols.

Document IG_ITEC-002792_ING, *Fibrin Sealant Grifols: Design History File: Table of Contents* (effective date: February 10, 2017) represents a detailed index of records for activities which were accomplished during all phases of design development and are classified according

to respective 21 CFR 820.30(b-g) requirements: Design Inputs, Design Outputs, Design Review, Design Changes, Design Verification, Design Validation, and Design Transfer. The references in the DHF are linked to the records which contain evidence demonstrating that the design was developed in accordance with the approved design plan and the requirements of this part.

Document IG_ITEC-002800_ING, *Fibrin Sealant Grifols: Traceability Matrix* (effective date: February 10, 2017) lists different product requirement specifications, set based on customer requirements, and provides links to respective verification and validation reports which contain objective evidence that the requirement is met. Among product requirements, the following essential performance requirements were assessed: break loose force, gliding force, fill volume, expelled volume, and tip cap removal.

Report IG_ITEC-002568_ING, *Viability and Functionality of the Fibrin Sealant Grifols Application Device* (effective date: October 03, 2016) provides results of assessment of the functionality of the application systems (with drip and spray applicators) by evaluating essential performance characteristics:

- Mixing efficiency (using color scale for visual examination and (b) (4)) to demonstrate delivery of equal doses of Fibrinogen and Thrombin (1:1 mixing).
- Consistency of the fibrin layer by measuring the areas covered by defined volumes of FS Grifols. This experiment determined the ranges for covered areas of (b) (4) for drip application and (b) (4) for spray application.
- Homogeneity in product delivery by measuring clotting times and drop weights at the beginning, middle and the end of the product application.
- Stability behavior (functionality and viability) by measuring clotting times for product after (b) (4), or 24-month storage at long-term storage conditions (-21 (b) (4) C), or 24-month storage at lower temperatures (b) (4).
- Compatibility of biologics with the application device by comparing critical specification parameters of Fibrinogen and Thrombin components before and after contact with the application device.

In summary, the scope of provided documentation appears sufficient and consistent with the requirements of 21 CFR 820.30. The experimental results demonstrate adequate functionality (performance characteristics) and stability behavior of the application system and its compatibility with biologics.

Usability

The original BLA included Report REGD-0019886, *Risk Analysis DG-316* (effective date of the updated report: February 08, 2017) which assessed the risk to the patient, after applying risk control measures and risk/benefit ratio, as tolerable. No other Usability/Human Factors studies were provided based on the similarity of the application system for FS Grifols to that for analogous approved combination products (e.g., EVICEL, TISSEEL). Despite this similarity, the application system for FS Grifols is more complex as it includes several components which need to be assembled for application. FDA found that usability studies were warranted to optimize the assembly and ensure coordinated actions of the device constituents during product

application to the wound site. In December 2016 - January 2017, Grifols performed Usability studies (Report IG_ITEC-002747_ING and IG_ITEC-002779_ING) where five vascular surgeons from three independent sites were asked to follow *Instructions for Use* and test the product in an animal model surgery to give their medical opinion. Although the current design of the application system was considered acceptable for use by end-user surgeons, these reports identified that the assembly of the syringe with the applicator tip represents a challenge.

The instructions for use were extensively discussed during the labeling review with several rounds of revisions. As an outcome, the *Preparation and Handling* and *Administration* sections of the Prescribing Information were substantially revised with detailed instructions and inclusion of explanatory figures.

Both the CDRH reviewers and I (during demonstration of the assembled syringes at the time of the PLI) noted a design issue with the 3-mL syringe holder where syringes were loose in the holder hook. Per FDA request, Grifols has modified the design of the syringe holder for the 3-mL syringe to ensure its tight fixation, and qualified it in an additional functionality study. Investigational Report IG_ITEC-003057_ING, *Qualification Report on the Change of Mold Used in the Manufacturing of the Holder of Fibrin Sealant 3mL from the Supplier Laboratorios Grifols* (effective date: September 29, 2017) and Functionality Report IG_ITEC-003053_ING, *Fibrin Sealant. Evaluation of the Functionality and Applicability of the Application Device* (effective date: September 26, 2017) were submitted in Amendment 51, dated September 29, 2017.

The CDRH reviewers identified a number of deficiencies with Human Factors validation study: the protocol was not clear about critical tasks, use environment, and the approach to analyzing the performance data. In addition, the number of participants was not sufficient. The Applicant committed to conduct a new Human Factors validation study, and incorporate it into the upcoming pediatric clinical trial, which is a Post-Marketing Requirement (PMR) study under PREA. The timelines for submission of the Final Protocol, study completion, and submission of the Final Report for FDA review have been agreed upon. Please refer to the memorandum of the CDRH Human Factors consult reviewer.

Leachables/Extractables

Leachables from long-term product-contacting surfaces of container closure system (syringes, stoppers and application cannula) were adequately assessed for both Fibrinogen and Thrombin, using samples from stability studies. The analyzed compounds were those listed by the manufacturers as extractables, representing the worst-case scenario. Toxicological analysis of the data indicated that the levels of the leachable compounds present in the drug product do not pose a safety concern. In addition, (b) (4) syringes and (b) (4) stoppers are not new materials; they have a long history of use in the pharmacological industry.

For materials used in the manufacturing process (chromatography resins, nanofilters, bags, membranes, hoses), Grifols performed risk assessments based on Extractables reports from manufacturers and Grifols procedures during the manufacture, and qualified these materials as non-risk. Although separate studies of leachables were not performed with these materials, they

are short-term product-contacting surfaces and are used in the same manner in the manufacture of other licensed products at Grifols (IV immunoglobulin and Albumin).

In addition, the potential risk of leachables is low considering product specifics: FS Grifols is not intended for systematic administration, it is used locally, generally once per surgery and in small volumes. Please refer to Dr. Sarafanov's memorandum for detailed analysis.

ADVENTITIOUS AGENTS SAFETY EVALUATION (SECTION 3.2.A.2)

Please refer to the memoranda of Drs. Ze Peng and Svetlana Shestopal for detailed analysis of the information and experimental data. The summary of this assessment is presented below.

Viral Safety

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

The starting material for Fibrinogen and Thrombin is pooled human Source Plasma (21 CFR 640.60) obtained from FDA-licensed plasma collection centers in the United States. All individual plasma donations are tested to be negative for viral serological markers in compliance with the U.S. regulatory requirements stipulated in CFR Subchapter F, Title 21, Part 640, subpart G: Hepatitis B surface Antigen (HBsAg), antibodies against Human Immunodeficiency Virus (HIV)-1/2 and Hepatitis C Virus (HCV). Plasma mini-pools are tested with FDA-licensed nucleic acid test (NAT) for Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), HCV, HIV-1, and human parvovirus B19 (B19V). All the tests must be non-reactive (negative) and the limit for B19V in each mini-pool must be such to ensure that plasma manufacturing pools do not exceed a titer of 10^4 IU/mL. The manufacturing plasma pool is also tested for Anti-HIV 1/2, Anti-HCV antibodies, HBsAg, and for HBV, HCV and HIV with NAT, and all the tests must be non-reactive (negative).

The potential of viral contamination is further mitigated by inclusion in the manufacturing processes for Fibrinogen and Thrombin of two discrete steps which have viral clearance capacity. The manufacturing processes for both components include Solvent/Detergent treatment (0.3% TnBP (v/v) and 1.0% Polysorbate 80 (v/v)) validated to inactivate enveloped viruses, and double ((b) (4)) nanofiltration validated to remove non-enveloped and enveloped viruses (35-nm and 20-nm filters for Fibrinogen and two 15-nm filters for Thrombin). Additionally, the glycine precipitation steps contribute to the overall safety of the product in the purification process of Fibrinogen. The Fraction I precipitation and SP-Sepharose XL ion-exchange chromatography steps contribute to the overall safety of the product in the purification process of Thrombin.

The viral clearance capacity of these virus inactivation/removal procedures has been validated in small-scale *in vitro* studies using relevant and model enveloped and non-enveloped viruses with a wide range of physicochemical characteristics. The results of these validation studies are

summarized in Tables 19 and 20 and are sufficient to support effectiveness of viral clearance in the commercial manufacture of FS Grifols:

TABLE 19. Virus Reduction Factors (Log₁₀) For Human Fibrinogen

Manufacturing Step	Virus reduction factor (log ₁₀)*					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
S/D treatment	≥ 5.33	≥ 6.80	≥ 5.20	≥ 5.60	n.a.	n.a.
Glycine precipitations	n.d.	n.d.	n.d.	n.d.	5.21	2.09
Nanofiltration 35 nm and 20 nm	≥ 5.57	≥ 6.09	≥ 4.51	≥ 4.53	5.22	4.37
Cumulative virus reduction factor (log₁₀)	≥ 10.90	≥ 12.89	≥ 9.71	≥ 10.13	10.43	6.46

TABLE 20. Virus Reduction Factors (Log₁₀) For Human Thrombin

Manufacturing Step	Virus reduction factor (log ₁₀)*					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
Fraction I precipitation	< 1.0	2.13	2.78	1.34	1.18	< 1.0
S/D treatment	≥ 5.52	≥ 5.85	≥ 5.94	≥ 5.09	n.a.	n.a.
SP-Sepharose XL chromatography	n.d.	n.d.	n.d.	n.d.	4.61	3.97
Double nanofiltration 15 nm	≥ 4.03	≥ 5.95	≥ 5.42	≥ 4.93	6.56	6.14
Cumulative virus reduction factor (log₁₀)	≥ 9.55	≥ 13.93	≥ 14.14	≥ 11.36	12.35	10.11

*: Reduction factor below 1 log₁₀ is not considered in calculating the global virus reduction;

n.d.: Not done; n.a.: Not applicable;

HIV: human immunodeficiency virus

BVDV: bovine viral diarrhea virus, model for enveloped RNA viruses including HCV;

WNV: West Nile virus, model for enveloped RNA virus;

PRV: pseudorabies virus, model for large enveloped DNA viruses including HBV;

HAV: Hepatitis A virus;

PPV: porcine parvovirus, model for human B19V.

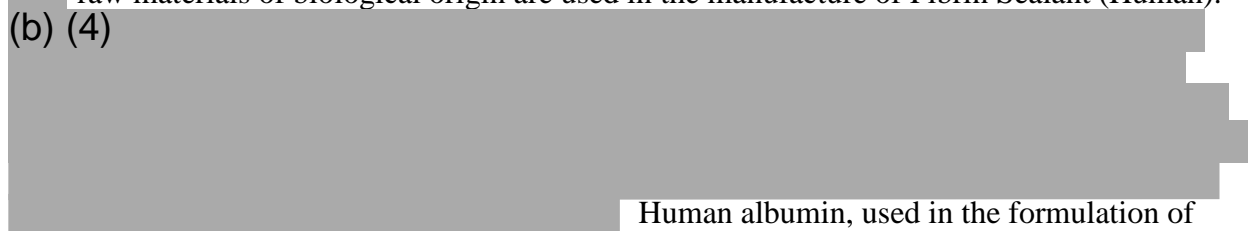
In addition, to avoid carry-over of impurities from one manufacturing step to the next one, strict process segregation has been implemented at Grifols facility by separating plasma fractionation area from purification areas, separating purification areas for Fibrinogen and Thrombin, and separating pre- and post-viral inactivation and nanofiltration areas. This segregation strategy was confirmed during the PLI.

Non-Viral Pathogen Safety

This information is presented in section 3.2.S.2.3, Control of Materials, but is discussed here for the logistics of the review flow. The safety with regard to non-viral adventitious agents such as bacteria, fungi, and mycoplasma is ensured through the control of bioburden in source materials, adherence to current good manufacturing practice, validated cleaning/sanitization procedures, in-process control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for Sterility and Endotoxin. The risk of transmissible spongiform encephalopathy (TSE) agents is minimized by excluding donors who are potentially at risk from plasma donation as specified in the current FDA guidance regarding donations collected in the U.S.

(b) (4) raw materials of biological origin are used in the manufacture of Fibrin Sealant (Human).

(b) (4)



Human albumin, used in the formulation of Human Thrombin, is manufactured by Grifols and licensed in the U.S. for intravenous injections for multiple indications (U.S. License No. 1181).

Other Raw Materials

This information is presented in section 3.2.S.2.3, Control of Materials, but is discussed here for the logistics of the review flow. Grifols has established a defined approval and monitoring process for control of raw materials depending on their risk assessment (impact on the production process and product quality). All materials which are in direct contact with the product during manufacture, storage or application (e.g., excipients, primary packaging and other device components) are considered as high risk. Materials with high risk require qualification of both the supplier (collection of documental and historical data, results of latest audits) and material (in-house analysis of product samples). The approved suppliers are monitored by periodic revision of the supplier dossier and audits. In addition to Certificates of Analyses from the manufacturer, Grifols performs in-house all critical tests for each lot of all high-risk materials according to the requirements of USP or/and Ph. Eur in order to release the material for use. For microbiological control, Grifols also performs tests for Endotoxin and Bioburden.

CBER LOT RELEASE

As a plasma-derived product, Fibrin Sealant (Human) is subject to routine lot-by-lot release by CBER. The Lot Release Protocol template was submitted to CBER for review and found to be acceptable after revisions (Amendment 50, dated September 28, 2017). A Lot Release Testing Plan was developed by CBER and will be used for routine lot release.

CONCLUSION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA and has adequately addressed the requests from all CMC reviewers in their responses. The manufacturing process for Fibrin Sealant (Human) is considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the justified release specifications. The implemented control strategy for plasmatic and other raw materials and the developed manufacturing processes for Fibrinogen and Thrombin components provide acceptable safety margins with regard to adventitious agents. The analytical methods are adequately validated and are suitable for their intended use as lot release tests.

One remaining CMC deficiency will be addressed as a Post-Marketing Commitment as detailed in Dr. Peng's memorandum.

The Applicant provided sufficient information to demonstrate the safety and effectiveness of the device constituent parts of this combination product. The Applicant committed to performing a new Human Factors validation study as part of the deferred pediatric clinical trial as detailed in the memorandum of the CDRH consult reviewer.

All 483 observations from the PLI have been adequately addressed.

Thus, the information on Chemistry, Manufacturing, and Controls is sufficient and satisfactory, and I recommend **APPROVAL** of Grifols' BLA for Fibrin Sealant (Human). The Clinical reviewer concluded that the submitted clinical data demonstrate safety and efficacy of FS Grifols in the adult population for the proposed indications. The recommendation for **APPROVAL** is shared by all members of the review committee.

APPENDIX: HISTORY OF INFORMATION REQUESTS AND RESPONSES

Date of Information Request	Communicated Review Issues from FDA or Additional Information from the Applicant	Amendment/ Date of Response
December 15, 2016	Validation of the assembly of the combination product and Human Factors study reports	125640/0.7 (December 23, 2017); 125640/0.9 (January 11, 2017)
January 2, 2017 (Filing Letter)	Changes in the manufacturing process (from clinical material to commercial production lots) with comparability reports; hold times; request for Design History File reports	125640/0.11 (February 15, 2017) 125640/0.15 (March 9, 2017)
April 4, 2017	Additional reports related to the Design History File, including reports on device functionality and usability (Human Factors studies)	125640/0.23 (April 11, 2017)
April 26, 2017	To address process-related deficiencies identified in the course of review and Pre-License Inspection (filling process, Sepharose resin lifetime, hold times, reprocessing; syringe holder design issue)	125640/0.30 (May 30, 2017)
May 1, 2017	To address deficiencies identified with validation of analytical methods	125640/0.28 (May 23, 2017)
June 15, 2017	To address deficiencies identified with Drug Product Specifications	125640/0.33 (July 05, 2017)
August 3, 2017	To revise Lot Release Protocol template	125640/0.38 August 4, 2017
August 18, 2017	To develop Study Protocol for validation of Sepharose lifetime for commercial manufacture To submit consolidated lists of CPPs and IPCs	125640/0.49 (September 27, 2017)
August 29, 2017	To revise Lot Release Protocol template	125640/0.43 (September 8, 2017)
September 8, 2017 September 18, 2017	To justify proposed long-term storage conditions, submit Final Stability Report, and revise Stability Protocol	125640/0.48 (September 25, 2017)
From April 26 IR	Addressing Design issue: investigational report IG_ITEC-003057_ING, functionality report IG_ITEC-003053_ING	125640/0.51 (September 29, 2017)
From August 18, 2017	Updated Report IG_VS-001435 submitted	125640/0.51 (September 29)
October 3, 2017 October 18, 2017 October 25, 2017	Labeling negotiations (product-related sections)	125640/0.56 (October 11, 2017) 125640/0.59 (October 23, 2017) 125640/0.63 (October 27, 2017)