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Summary Basis for Regulatory Action

Date:	December 16, 2025
From:	Sergey Akimov, PhD, OTP/OPPT/DH/HB2
BLA STN:	125833/0
Applicant:	Grifols Therapeutics, LLC
Submission Receipt Date:	December 27, 2024
Action Due Date:	December 27, 2025
Proper Name:	Fibrinogen, human-chmt
Proprietary Name:	FESILTY
Indication:	FESILTY is a human blood coagulation factor indicated for treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Candace Jarvis OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Consult (E&L) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Sergey Akimov, PhD, OTP/OPPT Andrey Sarafanov, PhD, OTP/OPPT Haarin Chun, PhD, OTP/OPPT Ze Peng, PhD, OTP/OPPT Yideng Liang, PhD, OTP/OPPT Hoda Thai, MS, OCBQ/DMPQ Kouassi Ayikoe, PhD, OCBQ/DBSQC Yen Phan, , OCBQ/DBSQC Parmesh Dutt, PhD, OCBQ/DBSQC George Kastanis, MS, OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Jennifer Dotson, DO, OCE/DCEH Fadi Nossair, MD, OCE/DCEH Shaokui Wei, MD, MPH, OBPV/DPV Jennifer Chan, PharmD, OCBQ/DIS
Statistical • Clinical data (OBPV/DB)	Yuyin Shi, PhD, OBPV/DB
Nonclinical/Pharmacology/Toxicology • Toxicology (Product Office) •	Emily Wires, PhD, OTP/OPT
Clinical Pharmacology	Xing Jing, PhD, OCE/DCEH
Labeling • Promotional (OCBQ/APLB) • USPI Review	Sadhana Khatri, PharmD, MPH, OCBQ/DCM/APLB Kristine Khuc, Pharm D, OCBQ/DCM/APLB Afsah Amin, MD, MPH, OTP/OCE
Other Review(s) not captured above categories, for example: • Consults • Devices	Artur Belov, PhD, OBPV/DABRA/BRAB Samuel Suen, CDER/OSE/OMEPRM/DMEPAII

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1. Introduction

Grifols Therapeutics, LLC (the Applicant) submitted this Biologics License Application (BLA), STN 125833/0, on December 27, 2024, to seek the U.S. licensure of fibrinogen, human-chmt, with the proprietary name of FESILTY. FESILTY is a human blood coagulation factor indicated for treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

FESILTY is a co-packaged Biologics-Drug-Device combination product, which consists of the following components:

- A lyophilized sterile human fibrinogen powder for solution for intravenous injection in a glass vial under vacuum.
- A glass vial of 50 mL sterile Water for Injection (sWFI) for reconstitution, and

- A Nextaro v, 20/20 5 µm transfer device to transfer the sterile WFI to the glass vial for reconstitution of the lyophilizate.

Each single-dose glass vial contains nominally 1 gram of human fibrinogen which is dissolved with 50 mL of sWFI to concentration of approximately 20 mg/mL.

This document summarizes the basis for regular approval of FESILTY. Study 984, a Phase I/III, prospective, single arm, multicenter study provided the primary evidence of safety and effectiveness for the treatment of adult and pediatric patients with congenital fibrinogen deficiency. Our recommendation for approval is based on substantial evidence of effectiveness demonstrated in study 984 which includes pharmacokinetics, pharmacodynamics and clinically meaningful endpoints of hemostasis and supported by preclinical studies. The most common adverse reactions related to FESILTY administration include pain in extremity, back pain, hypersensitivity reactions, pyrexia, thrombosis, fibrin D-dimer increased, headache and vomiting.

The Applicant has provided substantial evidence of effectiveness and safety based on an adequate and well controlled study supported by preclinical studies. The review team agrees with proposed extrapolation of effectiveness from the adult population to the pediatric population, as the number of patients <6 years was limited, and this is a rare disease. The review team recommends traditional approval of this BLA.

The BLA for FESILTY was submitted with two proposed indications for use:

- Treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency

- As fibrinogen supplementation in patients with acquired fibrinogen deficiency.

During the review process, the FDA review team identified substantive issues with (b) (4) that were communicated to the Applicant for the acquired fibrinogen deficiency indication and this indication was withdrawn by the Applicant. There were also several deficiencies identified with manufacturing data. Resolving these issues could have required a Major Amendment and a delay in approval. The FDA exercised flexibility in interactions with the Applicant and in the use of available regulatory approaches to resolve these issues and complete the review process in a timely manner without compromising the safety, efficacy, and quality of the drug product.

Specifically, based on Information Requests (IRs) and discussion with the Applicant at the Late-Cycle meeting, Grifols submitted (on October 10, 2025) a request to withdraw the second indication (acquired fibrinogen deficiency). (b) (4) .

Rather than seeking a Major Amendment, the review team held internal discussions with diverse disciplines (DH, DBSQC and OBPV) and developed a plan to resolve non-critical deficiencies with the manufacturing data as Post-Marketing Commitment (PMC) studies.

The Manufacturing review team used an intercenter consult with CDER (DMEPA2) to review information on the Nextaro Transfer Device, a component of this combination product. The Nextaro device was not used during the clinical studies but will be used in

commercial manufacturing of FESILTY. The non-critical deficiencies identified with Use-Related Risk Analysis (URRA) will be resolved as a PMC. The deficiencies with Comparative Task Analysis (CTA) were satisfactorily resolved via IRs.

Thus, the flexibility of the review team and the use of an arsenal of regulatory tools and approaches enabled resolution of multiple regulatory issues to approve this Biologic License Application in a timely manner.

2. Background

Congenital fibrinogen deficiency is a rare, inherited coagulation disorder that presents as afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia. Bleeding symptoms differ for each patient but can be mild to severe in severity. Human fibrinogen concentrates can be given as on-demand treatment for acute bleeding episodes or on-demand prophylaxis to prevent severe bleeding during or after surgery. Most guidelines recommend maintaining plasma levels of fibrinogen to >1.0g/L for severe bleeding and/or major surgeries. Human fibrinogen concentrates restore fibrinogen levels in these patients. Individualized dosing of human fibrinogen concentrate is based on the extent of bleeding and fibrinogen plasma concentration. Treatment options for congenital fibrinogen deficiency include fibrinogen concentrates, cryoprecipitate, fresh frozen plasma, and anti-fibrinolytic drugs. FESILTY is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma.

The Agency had a pre-IND meeting on September 8, 2022, to discuss the acceptance of foreign clinical data not conducted under an IND for Study 984. The Agency had a pre-BLA meeting on September 19, 2024, with the Applicant to discuss the proposed plan for format and content of the BLA submission.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	September 8, 2022
2. Pre-BLA meeting	September 19, 2024
3. BLA 125833/0 submission	December 27, 2024
4. BLA filed	February 25, 2025
5. Mid-Cycle communication	June 25, 2025
6. Late-Cycle meeting	September 1, 2025
7. Action Due Date	December 27, 2025

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Description

FESILTY Drug Product (DP), proper name: fibrinogen, human–chmt, company code: BT524, is formulated as a purified, sterile, non-pyrogenic, lyophilized powder of human fibrinogen for reconstitution for intravenous administration. It is a biological component of

the final combination product which is co-packaged with the drug (Diluent, sWFI, for reconstitution) and a Nextaro v, 20/20 5 µm transfer device.

The active ingredient in FESILTY is plasma-derived Fibrinogen, human blood coagulation Factor I, a soluble plasma protein which plays a critical role in the coagulation process. Fibrinogen is a heterohexamer with a molecular weight of 340 kDa composed of two sets of alpha, beta, and gamma polypeptide chains. Because of its natural human origin, FESILTY has the biological and immunological characteristics of plasma fibrinogen.

Fibrinogen is activated by thrombin. Thrombin cleavage at specific sites on the alpha and beta chains removes fibrinopeptide A (FPA) and fibrinopeptide B (FPB) leading to the formation of fibrin monomers and their subsequent polymerization. The resulting fibrin clot is stabilized by activated coagulation Factor XIII which catalyzes crosslinking of fibrin polymers and makes the fibrin clot more resistant to fibrinolysis. Additionally, soluble fibrinogen mediates platelet aggregation by binding to the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on the platelet surface activated following blood vessel injury. This interaction acts as a bridge between platelets, facilitating their aggregation, i.e., formation of primary platelet plug. The end product of the coagulation cascade, cross-linked fibrin, stabilizes and reinforces the primary platelet plug to achieve secondary hemostasis and stop bleeding.

Manufacturing Process Summary

The starting material for manufacturing FESILTY Drug Substance (DS) is pooled human US Source Plasma collected from healthy volunteer donors in FDA-licensed facilities. The plasma conforms to the regulations of the FDA for Source Plasma 21 CFR Part 640 Subpart G, FDA memoranda, and (b) (4) Each unit (plasma donation) included in a manufacturing pool is tested according to FDA requirements using validated FDA licensed kits at licensed laboratories. All compendial and non-compendial raw materials are sourced from approved suppliers and are released to production based on vendor certificates of analysis and results of incoming testing. Compendial materials are qualified per the monographs of United States Pharmacopeia (USP)/ National Formulary (NF) and European Pharmacopeia (Ph.Eur.). Non-compendial raw material ingredients are subjected to the internal quality control systems.

Pooled plasma is processed to Cryoprecipitate fraction (Steps (b) (4) at (b) (4) contract manufacturing sites, Grifols Therapeutics LLC (Grifols Therapeutics), U.S.A. (b) (4)

FESILTY DS and Drug Product (DP) are manufactured at Biotest AG, Germany, a Contract Manufacturing Organization (CMO) of Grifols Therapeutics, LLC, which is a multi-product facility.

FESILTY DS is purified from the pooled Cryoprecipitate fraction using a combination of aluminum hydroxide purification, solvent/detergent (S/D) treatment (polysorbate 80 / (b) (4) for virus inactivation, anion exchange chromatography (AEX) (Steps (b) (4), glycine precipitation (b) (4), virus inactivation by UV-C irradiation, cation exchange chromatography (CEX), (b) (4), and adjustment of protein concentration, pH, (b) (4) filtration, and quality control testing of the DS (Steps (b) (4)). Steps (b) (4) are

performed in Biotest Production Site (b) (4) Steps (b) (4) are performed in Biotest Production Site (b) (4) DS is further processed into DP within (b) (4) .

DP manufacturing process is performed at Biotest Production Site (b) (4) and includes glycine precipitation, aseptic filling, lyophilization, dry heat treatment for virus inactivation, quality control testing (Steps (b) (4) in Building (b) (4), and packaging and visual inspection (Step (b) (4) in Building (b) (4)).

FESILTY is supplied in single-dose vials containing nominally 1 gram of fibrinogen. The actual amount of fibrinogen is printed on the vial label and carton in milligrams fibrinogen per vial. When reconstituted in 50 mL sterile water for injection, FESILTY contains approximately 20 mg/mL protein, of which not less than 80% is purified human fibrinogen. Additional ingredients in FESILTY include the excipients arginine hydrochloride, sodium chloride, sodium citrate dihydrate, polysorbate 80, and trehalose dihydrate.

Description of the Applicant's control strategy

The DS manufacturer Biotest has established an adequate control over the Fibrinogen DS manufacturing process steps monitored by in-process controls (IPC) to ensure the process consistency and product quality. Critical quality attributes (CQAs) were defined according to (b) (4) guideline as "physical, chemical, biological, or microbiological properties or characteristics that should be within appropriate limits, range, or distribution to ensure the desired product quality". Each quality attribute was evaluated according to its severity for the patient and the extent of available knowledge.

The Failure Mode and Effects Analysis (FMEA) risk analysis was used to categorize process parameters into critical process parameters affecting production process (CPPs), key process parameters (KPPs), and non-key process parameters (non-KPPs) according to their impact on CQAs and process performance indicators (PPI, e.g., yield).

The following steps, linked to effective virus inactivation, were defined as critical steps:

- Treatment with polysorbate 80 / (b) (4) (Step (b) (4)
- UV-C irradiation (Step (b) (4).

Controls of critical steps of Fibrinogen DS manufacturing process were reviewed and found adequate.

There are (b) (4) in the manufacturing process of Fibrinogen DS – (b) (4) . Specifications for both intermediates were reviewed and found adequate.

The critical steps in the manufacture of FESILTY DP are the following:

- Step (b) (4)- final filling into vials by sterile filtration through (b) (4) filter under aseptic conditions

- Step (b) (4) - virus inactivation with dry heat.

Controls of CPPs for DP process at Step (b) (4) Final filling into sales units (sterile filtration), include control of Filter (b) (4) before and after sterile filtration by (b) (4) test. Controls at Step (b) (4) Virus inactivation with dry heat, include Residual moisture determination (b) (4) to Heat treatment by (b) (4), Heat treatment temperature, and Heat treatment duration. In response to FDA IR, Biotest replaced (b) (4) for determination of Residual moisture, since (b) (4) method was not adequately validated.

There are no intermediates in the manufacturing process of Fibrinogen DP.

Process Validation for DS

(b) (4)

(b) (4)

Process Validation for Drug Product

The PPQ studies for FESILTY DP manufacture were conducted at (b) (4)

All pre-defined acceptance criteria for DP quality were met during the PPQ campaign. The validation of the DP manufacturing process was performed as planned, and the expected process performance was achieved with one exception. The rejection rate of vials due to (b) (4)

In summary, the PPQ study results demonstrate that the manufacturing process of FESILTY DP is adequately validated.

Specifications for FESILTY DS and DP

The specification parameters were selected from CQAs determined in process development studies and risk assessments. Acceptance ranges/limits are established based on applicable pharmacopoeia requirements (European Pharmacopoeia (Ph. Eur.) and United States Pharmacopeia (USP)), statistical analysis of release manufacturing data for clinical and conformance batches/lots, analytical variability, and stability data.

During the review process, in response to the FDA requests, the following modifications were made to the DS and/or DP Specifications to assure their quality:

- (b) (4) was added as additional parameter for *Identity* in DP Specification.
- Acceptance criteria for *Specific Fibrinogen* (b) (4) were tightened from (b) (4) in (b) (4) DP Specifications.
- The parameter (b) (4) was extended in DP Specifications to include *Monomer*, (b) (4) (originally only (b) (4) were monitored) with acceptance criteria for *Monomer* ≥ 80 % (release and shelf-life); for (b) (4) tightened from (b) (4) (release) and (b) (4) (shelf-life); and for (b) (4) (release) and (b) (4) (shelf-life).
- Acceptance limit for *Residual Moisture content* was tightened from (b) (4) in DP Specifications. (b) (4) will be used for the determination of *Residual Moisture* in DP release and stability testing because of deficiencies identified with the calibration model used for validation of the (b) (4) method. The Applicant will re-validate the (b) (4) method as a quantitative method based on FDA advice under a Postmarketing Study Commitment (PMC #3).
- The modified (b) (4) assay was added as a reference method to (b) (4)-based method for the determination of Fibrinogen (b) (4) in DP Stability Specification.

The final DS Release specifications include the following quality attributes: (b) (4) distribution/aggregates). There are no DS Stability specifications because DS is processed to DP within (b) (4) in a (b) (4) process.

The final DP release specifications in Table 2 reflect revisions made per the FDA requests.

Table 2. Specifications of Drug Product

Test Parameter/ Quality Attribute	Acceptance Criteria	Justification for Specification
Potency		
Fibrinogen (b) (4)	20 g/L (b) (4)	(b) (4)
Identity		
Fibrinogen (b) (4)	20 g/L (b) (4)	
(b) (4) - monomers	Complies	
Appearance and description		

Test Parameter/ Quality Attribute	Acceptance Criteria	Justification for Specification
Coloration of solution	Equal or less colored than reference solution (b) (4))	(b) (4)
Clarity and opalescence	(b) (4)	
Solubility[2]	(b) (4)	
Stability of the solution	(b) (4)	
pH	7.0 (6.5 - 7.5)	
Osmolality	≥ 240 mosmol/kg	
Quantity		
Total protein	20 g/L (b) (4)	
Total amount of active fibrinogen per vial (calculated)	(b) (4)	
Purity and contaminations		
Specific fibrinogen (b) (4) (calculated)	(b) (4)	
Water / residual moisture[3]	(b) (4)	
(b) (4)		
- (b) (4)	(b) (4)	
- monomers	≥ 80 % (release) ≥ 80 % (shelf-life)	
- (b) (4)	(b) (4)	
Sterility	Sterile	
Pyrogens	pyrogen free	
Excipients		
Polysorbate 80	(b) (4)	

Test Parameter/ Quality Attribute	Acceptance Criteria	Justification for Specification
Arginine	(b) (4)	
Trehalose		
Sodium		
Chloride		
Citrate		

[1]The modified (b) (4) assay was added as a reference method to (b) (4)-based method in DP Stability Specification. [2] – corresponds to the lyophilizate; [3] - analyzed in the lyophilizate; [4] - tested as IPC at Step (b) (4) Quality Control of the DP batch; [5] - Biotest replaced (b) (4) with (b) (4) for determination of Residual moisture in response to FDA IR, since (b) (4) method was not adequately validated (PMC #3).

In conclusion, the current proposed commercial release specifications for (b) (4) DP sufficiently reflect product quality requirements and are considered adequate to control the identity, quality, purity, potency, and safety of FESILTY (b) (4) DP.

Analytical Methods Used for FESILTY Drug Substance and Drug Product

Analytical methods utilized for FESILTY DS release testing include (b) (4)

(b) (4)

Control of Impurities

The Applicant evaluated process- and product-related impurities during development of the Fibrinogen manufacturing process and developed a control strategy with adequate testing. An assessment of potential impurity sources and data showing the degree of removal for all considered impurities throughout the process was provided.

Process-related impurities are derived from either the source material (human plasma) or the manufacturing process.

Process robustness studies showed that glycine precipitation consistently removes plasma proteins, such as albumin and immunoglobulins. Other impurities originating from source plasma, such as von Willebrand Factor (vWF) and proteases, are removed by subsequent CEX chromatography.

All plasma-derived impurities in DS were below or close to detection/quantitation limits except for known impurities vWF and fibronectin. However, the residual vWF content showed very low activity in a (b) (4) assay. Additionally, the NaPTT revealed no shortening of the coagulation time for the Fibrinogen product compared to a reference control. The test for (b) (4) in FESILTY DP PPQ batches thus confirming efficient removal of proteases present in plasma.

Process-related Impurities were evaluated for the PPQ batches in samples from Process Step (b) (4), fibrinogen-containing eluate fraction of CEX chromatography, and (b) (4) in the DS. Residues from materials used during manufacturing of Fibrinogen, such as (b) (4) in PPQ DS batches. No potential risk was identified; these impurities will not be tested regularly, but on a risk-based approach (e.g., after process or equipment modifications).

Product-related Impurities: Fibrinogen (b) (4) formed during the manufacturing process are the main product-related impurities.

(b) (4)

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In response to FDA Information Requests, the acceptance limit for (b) (4) DP Specifications. To ensure product purity, the Applicant added (b) (4) additional parameters in DP Specification which can detect potential Fibrinogen (b) (4), as determined by (b) (4)

- Monomers: ≥ 80 % (release); ≥ 80 % (shelf-life)
- (b) (4)

Results of PPQ batch analysis for (b) (4) comply with (b) (4) DP Specifications.

Fibrinogen breakdown products fibrinopeptide A and D-dimer were determined to be at very low levels or not detectable in PPQ batches, underlining the integrity of the fibrinogen molecule in the DP.

Overall, the manufacturing process for FESILTY is robust in consistently removing process- and product-related impurities and their residual levels do not raise safety concerns. Those impurities found to be critical are included as release specifications for DS and DP.

Drug Substance and Drug Product Stability and Shelf Lives

The Fibrinogen DS is processed to DP within (b) (4) in a (b) (4) process. Stability testing was performed for the (b) (4) Cryoprecipitate (Step (b) (4) and the (b) (4) (Step (b) (4). These studies showed no significant stability trends and supported the proposed shelf lives of (b) (4) for: (i) The (b) (4) Cryoprecipitate manufactured at (b) (4) when stored at (b) (4). (ii) The i(b) (4) Cryoprecipitate manufactured at Grifols Therapeutics LLC when stored at (b) (4) and a shelf life of (b) (4) for (iii) The (b) (4) when stored at (b) (4)

The DP stability is supported by testing (b) (4) PPQ lots and (b) (4) comparable supportive lots stored at room temperature (5°C to 30°C) for up to 12 months and for 36 (b) (4) months, respectively. Based on available long-term stability data and results of limited regression analysis of primary (PPQ) stability lots and combined analysis of all stability data, the proposed 36-month shelf life is adequately supported for the lyophilized Drug Product when stored between 2°C and 30°C. Stability studies for the PPQ lots are ongoing, and data will be submitted to the BLA as they become available. This approach is considered acceptable given the demonstrated comparability of products manufactured by Process P1 and Process P2. For clinical use, the reconstituted product should be administered within four (4) hours.

CMC Comparability Assessment / Process 1 (Clinical) versus Process 2 (Commercial) Comparison

The comparability of clinical Process P1 and commercial Process P2 was demonstrated by results of risk-based assessment following the (b) (4) Guideline. Clinical material (P1) and commercial material (P2) were compared by:

- (b) (4)

As part of the comparability assessment between P1 and P2 processes, a (b) (4) was performed to compare FESILTY batches manufactured at the (b) (4) and the production plant in Building (b) (4) and to identify stability-indicating CQA parameters.

The (b) (4) study results demonstrated that P1 DP batches exhibited a higher sensitivity to (b) (4) for quality attributes Fibrinogen (b) (4) and (b) (4) compared to most P2 batches. This difference was attributed to the higher residual moisture content in the P1 batches and not to differences in the manufacturing process. In response to the FDA request, the Specification limit for (b) (4) was lowered from (b) (4)

In an additional study conducted by the Applicant per an FDA request, it was determined that the traditional (b) (4) assay (for Fibrinogen (b) (4) is more sensitive to Fibrinogen degradation under various stress conditions than the assay that relies on the change in (b) (4). The Applicant committed to adding the (b) (4) assay as a reference method, in addition to monitoring (b) (4), for measuring Fibrinogen (b) (4) in Stability studies as part of a post-marketing commitment (PMC #2).

Overall, analytical comparability was successfully demonstrated between P1 and P2 materials, confirming that Process (b) (4) product can be used without additional preclinical or clinical studies. Therefore, the comprehensive development program successfully established a robust, scalable manufacturing process with defined control strategies supporting the commercial production of FESILTY.

Adventitious Agents Control

For non-viral adventitious agents, such as bacteria, fungi, and mycoplasma, the potential for contamination of these agents is controlled through validated cleaning and sanitization procedures, and in-process filtration steps. The final product is further tested to ensure it is free of non-viral adventitious agents through sterility and pyrogens testing. Biotest manufactures FESILTY in accordance with Current Good Manufacturing Practice (CGMP) regulations.

(b) (4)

The potential for viral contamination of FESILTY is mitigated through (b) (4) dedicated viral clearance steps integrated into the manufacturing process: (i) Solvent/Detergent (b) (4); (ii) Ultraviolet C (UV-C) (b) (4) (iii) Lyophilization (b) (4). The enveloped viruses selected in these studies were human immunodeficiency virus (HIV), pseudorabies virus (PRV, model virus for enveloped DNA viruses including hepatitis B virus (HBV)), and bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies were hepatitis A virus (HAV) and porcine parvovirus (PPV, model virus for

human parvovirus B19 (B19V)). These studies resulted in cumulative virus log_{10} reduction factors shown in Table 3.

Table 3. Cumulative virus reduction factors (log_{10}) for FESILTY manufacturing process

Manufacturing step	**Virus reduction factor (log_{10})**				
	Enveloped virus			Non-enveloped virus	
	HIV	PRV	BVDV	HAV	PPV
S/D treatment	≥ 4.51*	≥ 5.39*	≥ 5.21*	Not done	Not done
UV-C irradiation	Not done	1.63*	1.87*	2.47*	4.19*
Lyophilization and dry heat treatment	≥ 4.86*	≥ 5.36*	≥ 4.29*	≥ 4.34*	1.09*
Total virus reduction factor (log_{10})	**≥ 9.37**	**≥ 12.38**	**≥ 11.37**	**≥ 6.81**	**5.28**

*: Selected log reduction value was the most conservative (lowest) from the respective viral clearance study.

In conclusion, the information provided for valuation of safety regarding adventitious agents is adequate, sufficient and acceptable.

Extractables and Leachables

The assessment of components (b) (4) classified with medium leachables risk and components classified with high leachables risk ((b) (4) were assessed individually using the manufacturers' extractables data as a worst-case scenario. The toxicological assessment of extractables exposure levels from each component were found to be below the Permitted Daily Exposure (PDE) values confirming their safety.

An additional extractables study and a simulated leachables study were performed for the CCS Stopper under accelerated conditions using standard methodology for analysis of organic and elemental compounds.

For organics, Analytical Evaluation Threshold (AET) was calculated based on (b) (4) were calculated based on (b) (4) unidentified organic leachables and one elemental leachable (b) (4) were found above the AET. However, the respective levels were below the generic limit of (b) (4) for (b) (4) products, and the Applicant concluded that there is no risk of leachables to patients from the stopper and the manufacturing components.

This assessment was found insufficient as the cumulative effect of leachables was not assessed, thus underestimating the resulting leachables profile. Through a series of information requests, the design of the study was optimized and the Applicant committed to analyze leachables in the actual DP in the ongoing stability study to cover the shelf-life storage of 36 months (PMC #1).

In conclusion, the Applicant adequately addressed major issues identified in the analytical assessment of leachables. The provided data are acceptable for the intended clinical application of the product and sufficient to recommend approval of this BLA from the E/L analytical review perspective. The toxicological reviewer confirmed the safety of the leachables in DP. The complete leachables assessment over the product shelf life will be submitted as a post-marketing commitment (PMC #1).

Bioanalytical Assays Used in Clinical Trials

In clinical trials, the Applicant used the following methods for determination of fibrinogen in patients' samples from Study 984:

- Fibrinogen immunological (antigen) method using the (b) (4) system to measure immune complexes with specific anti-fibrinogen antibodies provided by the manufacturer.

- The (b) (4) fibrinogen and derived fibrinogen method which measures fibrinogen (b) (4) (clot formation) using the (b) (4) system.

The Applicant performed validation of the test methods according to the EMA guideline on bioanalytical methods. The following validation parameters were used for the Fibrinogen antigen method: Selectivity, Carry Over, Lower Limit of Quantification (LLOQ), Calibration Curve, Accuracy, Precision, Dilution Integrity, and Stability. The same validation parameters except for Dilution Integrity were used for validation of the Fibrinogen (b) (4) -based test method.

The results obtained for all validation parameters met the predefined acceptance criteria for both test methods. Therefore, the method validation confirmed that both test methods are suitable for their intended use to measure Fibrinogen Antigen and Fibrinogen (b) (4) in samples of Study 984.

Device and Drug Components and their Assessments

- ***Device Component***

FESILTY is a Type (b) (4) co-packaged Biologics-Drug-Device combination product. The device component is the needleless Nextaro v, 20/20 5 µm transfer device which is used for reconstitution of the lyophilized DP. The device is manufactured at sfm medical devices GmbH, Wachtersbach, Germany, and is FDA cleared with K240748 Device 510 (k) clearance letter.

During the review process FDA identified that a different device for product reconstitution, the (b) (4) device from (b) (4) , was used in clinical trial 984. The Nextaro v, 20/20 Transfer Device obtained 510(k) clearance after completion of the clinical phase and is proposed for commercial distribution of the combination product.

The Applicant conducted a study aimed at reducing (b) (4) in reconstituted Fibrinogen DP. This study demonstrated that including a (b) (4) filter in the Nextaro transfer device effectively reduced the number of (b) (4) (both (b) (4)

µm) formed during the DP production. Notably, the (b) (4) filter of the (b) (4) device effectively removes (b) (4) but is incapable of effectively reducing the number of (b) (4). Therefore, the Nextaro device with a (b) (4) filter and a pressure valve was proposed as an alternative to the (b) (4) device, for commercial product due to its ability to reduce the number of (b) (4).

A consult reviewer was requested from the Division of Medication Error and Prevention Analysis II (DMEPA II), CDER, via an Inter-Center Consult Request (ICCR) to evaluate the use-related risk analysis (URRA) and comparative task analysis (CTA) reports to determine the needs of additional human factors validation study (HFVS) to support the marketing application.

Through Information Requests, both documents, URRA and CTA, were revised. Based on the review of the revised URRA and CTA, DMEPA II determined that human factors validation study results do not need to be submitted to the BLA. DMEPA II provided additional recommendations to update the URRA to appropriately capture the clinical impact associated with identified use errors or task failures. The revised URRA report will be submitted under a Postmarketing Study Commitment (PMC #5).

- ***Drug Component***

The sterile WFI (sWFI) supplied for reconstitution of the lyophilized DP is manufactured by (b) (4). DMF No. (b) (4) of (b) (4) sWFI is prepared from water for injection that is sterilized and packaged in single-dose 50 mL containers, 20 mm neck Type (b) (4) glass vials, which are stoppered with a chlorobutyl rubber stopper protected by an aluminum flip-off cap. sWFI does not contain any antimicrobial agent or other added substance.

The specification of sWFI complies with the current edition of the USP monograph *Sterile Water for Injection* and all other applicable requirements.

Certificates of Analysis (CoA) from (b) (4)., were provided for (b) (4) current lots of sWFI which met specifications for all tested parameters.

The shelf life and storage conditions for sWFI have been established in the accelerated and long-term stability studies conducted with (b) (4) production batches. Based on the results, the shelf life of (b) (4) months is established for the 50/50 mL format when stored at 5 ºC and 30 ºC.

Brief Rationale for CMC-related PMCs

The remaining issues were discussed in respective sections of SBRA and will be addressed as Postmarketing Commitments as detailed in section 11. They do not impact our recommendation of approval.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the FESILTY drug substance and drug product were found to be adequate for their intended use, except for the outstanding issue related to the residual moisture method using (b) (4) for the FESILTY drug product. Grifols has committed to providing

a full validation of (b) (4) as a quantitative method for residual moisture content determination in in-process control, release, and stability drug product samples. This will be submitted as a post marketing commitment (PMC #3) in a Prior Approval Submission (PAS) by May 31, 2026.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

DMPQ

Facility information and data provided in the BLA STN 125833/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of FESILTY, fibrinogen, human–chmt are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 4 Manufacturing Facilities Table for FESILTY, fibrinogen, human–chmt

Name / Address	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
(b) (4) *DS intermediate manufacturing*	(b) (4)		Waiver	ORA / OBPO (b) (4) VAI (b) (4) GMP Inspection
Grifols Therapeutics LLC. (b) (4) *DS intermediate manufacturing and batch release of final co-packaged product*	(b) (4)		Waiver	CBER / DMPQ (b) (4) VAI
Biotest AG Landsteinerstraße 3-5 63303 Dreieich, Hesse, Germany *DS and DP manufacturing, batch release of intermediate and DS, and primary labeling / packaging*	3001034985	315031799	Inspection	CBER / DMPQ June 2025 VAI
(b) (4) *DP pyrogen batch release testing*	(b) (4)		Waiver	CDER / OC (b) (4) VAI (b) (4) GMP Inspection

Name / Address	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
(b) (4) *DP pyrogen batch release testing*	(b) (4)		Waiver	CBER / DMPQ (b) (4) NAI
(b) (4) *DP batch release trehalose determination*	(b) (4)		Waiver	ORA / OPQO (b) (4) NAI (b) (4) GMP Inspection
(b) (4) *DP batch release water determination*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI (b)(3),(b)(4) GMP Inspection
Laboratorios Grifols, S.A. (b) (4) *Diluent manufacturing and sterilization; Diluent sterility testing and shipping release*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI

Abbreviations: CBER: Center for Biologics Evaluation and Research; CDER: Center for Drug Evaluation and Research; DMPQ: Division of Manufacturing and Product Quality; DP: Drug product; DS: Drug substance; NAI: No Action Indicated; NC: North Carolina; OBPO: Office of Biological Products Operations; OC: Office of Compliance; OPQO: Office of Pharmaceutical Quality Operations; ORA: Office of Regulatory Affairs; PAI: Pre-Approval Inspection; PLI: Pre-License Inspection; VAI: Voluntary Action Indicated

(b) (4) is a contract manufacturing facility for (b) (4) production. The (b) (4) performed an inspection in (b) (4), resulting with an issuance of a GMP certificate.

Grifols Therapeutics LLC. in (b) (4) (USA) is an alternative facility for (b) (4) production. Release testing of DP is also performed here. DMPQ performed a PAI in (b) (4).. Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

(b) (4) DP. OCBQ / DMPQ performed a PLI in (b) (4) under BLA STN 125833/0 for FESILTY. Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

(b) (4) is a contract testing laboratory for pyrogen release batch testing. (b) (4) performed an inspection in (b) (4), resulting with an issuance of a GMP certificate. CDER performed a PAI in (b) (4). Form FDA 483 list of observations was issued at the end of both inspections. All inspectional issues have been resolved, and both inspections were classified as VAI. The facilities were waived of an inspection.

(b) (4) is an alternative testing laboratory for batch release pyrogen testing. DMPQ performed a PAI in (b) (4). No Form FDA 483 list of observations was issued, and the inspection was classified as NAI.

(b) (4) is a contract testing laboratory for batch release trehalose determination. (b) (4) authority performed an inspection in (b) (4), resulting with an issuance of a GMP certificate. ORA performed a surveillance inspection in (b) (4). No Form FDA 483 list of observations was issued, and the inspection was classified as NAI.

(b) (4) is a contract testing laboratory for batch release water determination testing. (b) (4) of (b)(3),(b)(4) performed an inspection in (b) (4), resulting with an issuance of a GMP certificate. ORA / OPQO performed an MRA Inspection Review. No observations were issued, and the inspection was classified as NAI. ORA performed a surveillance inspection in (b) (4) Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

(b) (4) is an in-house facility that performs manufacturing, packaging, and terminal sterilization of the diluent. ORA performed a surveillance inspection in (b) (4). Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

(b) (4) is an in-house facility that performs diluent batch release testing. ORA performed a surveillance inspection in (b) (4). Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

e. Container/Closure System

The lyophilized FESILTY drug product (DP) is presented in 100 mL type (b) (4) borosilicate glass vials (b) (4) closed with 20mm type (b) (4) bromobutyl stoppers (b) (4) and sealed with aluminum crimps covered with 20mm flip-off plastic caps (b) (4). Grifols Therapeutics LLC. conducted the container closure integrity testing (CCIT) at Biotest AG, employing the (b) (4) method; all acceptance criteria were met.

The Nextaro v, 20/20 5 µm transfer device is co-packaged. It is used for reconstitution of the product and is manufactured by sfm medical devices GmbH, Germany.

The diluent, co-packaged for reconstitution of the product, is sterile water-for-injection (sWFI), manufactured by (b) (4) . The sWFI is presented in a 50 mL clear Type (b) (4) moulded glass vial (b) (4) with 20mm type (b) (4) chlorobutyl stopper (b) (4) and sealed with a 20mm aluminum flip-off cap with a polypropylene lid (b) (4) conducted CCIT for the sWFI using a (b) (4) method; all acceptance criteria were met.

f. Environmental Assessment

The BLA includes a request for categorical exclusion from preparation of an Environmental Assessment under 21 CFR 25.31(c) for naturally occurring substances. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require preparation of an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The nonclinical studies provided in this BLA submission evaluated the activity, thrombogenicity, local tolerance, and safety pharmacology of FESILTY compared to human fibrinogen product, Haemocomplettan P, which is identical to the FDA approved product RiaSTAP. In vitro clot firmness was similar between both products when used at physiological relevant levels of 2.0-2.5 g/L. FESILTY and Haemocomplettan P also demonstrated similar clot activity in vitro. A single IV injection of FESILTY at 200 mg/kg in the ear vein of rabbits resulted in the formation of clots similar in frequency and size to those observed in animals administered Haemocomplettan P at the same dose level. This dose level is representative of a high dose given to humans in extreme situations such as severe hemorrhage. For local tolerance studies, 10 mL of FESILTY and Haemocomplettan P at 20 mg/mL (based on the clinical resuspension of 1 g into 50 mL of water for injection) was administered via an IV infusion pump. For safety pharmacology studies, FESILTY and Haemocomplettan P were administered at 50 mg/kg or 200 mg/kg, with the latter representing a high clinical dose level. No differences in local tolerance or safety pharmacology were observed between FESILTY and Haemocomplettan P following IV administration in rabbits.

Studies to evaluate the developmental and reproductive toxicity and carcinogenicity/ tumorigenicity of FESILTY were not conducted. These studies are not warranted based on product characteristics.

5. Clinical Pharmacology

The clinical pharmacology of FESILTY was evaluated in a Phase I/III, prospective, single arm, multicenter study (Study 984) to assess the pharmacokinetics (PK),

pharmacodynamics (PD), efficacy and safety of FESILTY in patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia).

Pharmacokinetics (PK)

The PK of FESILTY was evaluated based on both fibrinogen antigen (FiAg) and fibrinogen activity (FiAc) levels in plasma after single IV administration of 70 mg/kg BW in children, adolescents, and adults with congenital afibrinogenemia or severe congenital hypofibrinogenemia (Study 984). Since the FiAc levels cannot be measured as frequently in young children as in adults, a population PK (popPK) and PK/PD modeling/simulation-based approach was employed to estimate FiAc levels based on measured plasma FiAg levels in children and in adults. The clinical pharmacology review focuses on FiAc levels.

A two-compartment popPK model with first order elimination was fit for integrated assessment of fibrinogen antigen (FiAg) and fibrinogen activity (FiAc) levels. The model adequately described the FiAg and FiAc levels across a wide age range (1 – 40 years). Administration of FESILTY resulted in an increase of systemic FiAg (from 0 g/L at pre-dose up to 1.86 g/L at the end of infusion) in patients. Fibrinogen activity (FiAc) also increased (up to 1.28 g/L in pediatric groups and 1.34 g/L in adults).

PK parameters of FESILTY are summarized in Table 5. The popPK model estimated 28% and 14% lower AUC for the <6 and 6-<12 year of age groups as compared to adults, respectively. Cmax was comparable across all age groups. These differences in FiAc levels were not considered significant given the observed inter-subject variability in adults (28.9% $AUC_{0-\infty}$ and 35.3% Cmax).

Table 5. Summary of Pharmacokinetic Parameters of FESILTY by Age Groups (Fibrinogen Activity Levels Based on popPK model)

		< 6 years N = 6	6 to < 12 years N = 3	12 to < 18 years N = 3	18 to 75 years N = 15
Fibrinogen Antigen					
C_{max} (g/L)	gMean	1.69	1.87	1.68	1.79
	gCV (%)	10.6	16.0	8.76	34.5
$AUC_{0-\infty}$ (g·h/L)	gMean	144	153	154	184
	gCV (%)	10.6	7.25	17.7	28.9
Fibrinogen Activity					
C_{max} (g/L)	gMean	1.15	1.30	1.03	1.23
	gCV (%)	10.7	22.0	18.1	44.9
$AUC_{0-\infty}$ (g·h/L)	gMean	86.4	93.3	82.9	110
	gCV (%)	8.99	13.2	26.2	35.3

Abbreviations: $AUC_{0-\infty}$ = area under the curve (AUC) from time 0 to infinity; C_{max} = maximum concentration; CL = clearance; N = number of patients

Pharmacodynamics (PD)

To evaluate the exposure-response relationship, a popPK model-based simulation was employed. The modeling-based approach was also used to evaluate the relationship between FiAc and maximum clot firmness (MCF), which is a secondary efficacy

endpoint, and the relationship between MCF and overall hemostatic response (OHR). Refer to Section 6 Clinical/Statistical for more details.

The popPK model was extended via a proportional slope model to describe maximum clot firmness (MCF) levels as the PD endpoint as a function of FiAc levels. The MCF to FiAc ratio was estimated to be 11.9 mm x L/g at FiAc levels of 1g/L, with slight decreases observed as FiAc increased, but was challenging to characterized due to limited MCF measurements.

Dosing justification

The aforementioned popPK analyses demonstrated comparable FiAc exposure across age groups support body weight-based dosing for FESILTY, supporting the pediatric dosing. The PK analyses also estimated incremental recovery (IR) values (1.8 for 6 years and older, 1.6 for < 6 years) for different age groups, as shown in Table 6. This estimation is appropriate.

The proposed dosing strategy is acceptable.

Table 6. Summary of BT524 IR (based on modeling and simulation)

Age group	N evaluated	Observed incremental recovery	
		mg/dL per mg/kg dose	CV (%), geometric mean
Overall	27	1.78	37.1
Adults aged ≥ 18 years	15	1.87	46.8
Adolescents aged 12 to < 18 years	3	1.54	30.7
Children aged 6 to < 12 years	3	2.00	23.9
Children aged < 6 years	6	1.59	12.2

CV = coefficient of variation; N = number of subjects

6. Clinical/Statistical

The clinical review team's recommendation for traditional approval of FESILTY for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- of afibrinogenemia, is based on one clinical study, Study 984.

a. Clinical Program

The clinical study provided in this BLA submission evaluated the pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of FESILTY in a two-part prospective, single arm study (Study 984) evaluating patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia). PK/PD were evaluated with a single dose of FESILTY in part I of the study, and efficacy and safety of FESILTY were evaluated in part II for on-demand prophylaxis and on-demand treatment of bleeding events. The BLA was evaluated in a traditional approval pathway. This study was not conducted under an IND. Study 984 was conducted outside of the United States. The foreign study population in Study 984 for congenital fibrinogen deficiency was comparable to the United States population due to similar treatment modalities and underlying disease phenotypes in both populations.

The key clinical efficacy endpoints from Study 984 included measurement of maximum clot firmness and evaluation of the overall hemostatic response (OHR) for each bleeding event on a 4-point scale: “none,” “moderate,” “good,” or “excellent. Secondary endpoints included total blood loss, units of fibrinogen or transfusion products infused and safety events. The key clinical efficacy findings formed the basis for the regulatory action being recommended.

There were no major review issues during the BLA review. The key clinical endpoints were adequate for evaluation of hemostasis in patients with congenital fibrinogen deficiency. There were 36 patients evaluable in part II for clinical efficacy, and 45 patients in parts I and II evaluable for safety. The adverse events reported in the study are consistent with similar fibrinogen containing products.

Key clinical efficacy results showed consistent improvements in maximum clot firmness (MCF) 1 hour after FESILTY infusion during bleeding events. The mean change from pre-dose was 10.8 mm for the overall population, with age-specific mean changes of 8.7 mm, 11.1 mm and 9.8 mm in patients <6 years, 6 to <12 years, and 12 to <18 years, respectively. For the overall population of adults and pediatric patients, the majority of bleeding events were reported as excellent (85.7%) or good (13.1%) OHR, with no notable differences between age groups or between major and minor bleeding events.

The basis of FDA’s conclusion of substantial evidence of effectiveness comes from one adequate and well controlled study supported by confirmatory evidence in the preclinical studies, with persuasive results on the benefit of overall hemostatic response. This evidence supports traditional approval for FESILTY.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

A Bioresearch Monitoring (BIMO) inspection assignment was issued for one foreign clinical study site that participated in the conduct of Protocol 984. The inspection did not reveal significant issues that impact the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

The Applicant’s pediatric plan was presented to the FDA Pediatric Review Committee (PeRC) on September 17, 2024. The committee agreed with the Applicant’s request for pediatric assessment, including proposed extrapolation of effectiveness from the adult population to the pediatric population, as the number of patients <6 years was limited and this is a rare disease. The Applicant conducted a semi-mechanistic PK/PD modeling (fibrinogen antigen/fibrinogen activity) with subsequent link to efficacy outcome of maximum clot firmness. The Applicant did not request a waiver or deferrals. The product is ready to be approved for adults and pediatric patients age 0 to <16 years.

7. Safety and Pharmacovigilance

Safety

The safety population consisted of 45 patients who received FESILTY in parts I (pharmacokinetics/pharmacodynamics) and II (efficacy and safety evaluation) of the study. In part I of the trial, 27 patients received a single dose of FESILTY which evaluated 14-day PK/PD and maximum clot firmness. In part II of the trial, 36 patients received single or repetitive doses of FESILTY as on-demand prophylaxis and on-demand treatment for bleeding events and surgical procedures. Eighteen patients participated in parts I and II.

A total of 174 treatment-emergent adverse events (TEAEs) were reported. Most patients reported mild or moderate TEAEs. Nine (20%) of patients experienced a serious adverse event (SAE). There were four (9%) patients with SAEs considered by the Agency as related or possibly related: 1 event of deep vein thrombosis, 1 event of portal vein thrombosis, 1 event of pain in extremity with clinically suspected thrombosis, and one patient with events of epilepsy and extradural hematoma four weeks after FESILTY administration, which was fatal.

The most common adverse reactions occurring in >2% of patients included pain in extremity (7%), back pain (7%), hypersensitivity reactions (7%), pyrexia (4%), thrombosis (4%), fibrin D-dimer increased (4%), headache (4%), and vomiting (2%).

Four patients withdrew from the study after a TEAE. These TEAEs included pain in extremity with clinically suspected thrombosis, portal vein thrombosis, deep vein thrombosis and pregnancy.

Six (13%) patients had infusion reactions considered related or possibly related to FESILTY. There were 3 (7%) of patients with hypersensitivity reactions. Two (4%) of patients had AEs of thrombosis. There were no patients with fibrinogen inhibitory antibodies or transmission of infective agents.

8. Labeling

APLB

The proposed proprietary name, FESILTY, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on March 13, 2025, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 26, 2025. A designated suffix (-chmt) was assigned to the proper name on September 9, 2025, making the proper name fibrinogen, human-chmt.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information and package and container labels on October 16, 2025, and found them acceptable from a promotional and comprehension perspective.

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Plasma Protein Therapeutics (OPPT) reviewed the package and container labels and determined they meet regulatory/statutory requirements.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to

ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Several significant labeling changes were made to enhance clarity and completeness of prescribing information. The indication was revised to specify that FESILTY is indicated for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia. Administration in Section 2 was revised to include appropriate infusion rates for FESILTY. The Adverse Reactions section was revised to include list of serious adverse reactions and most common adverse reactions (incidence ≥2%). Additionally, the Clinical Studies section was restructured to provide a comprehensive description of the pivotal study that established substantial evidence of FESILTY's efficacy with clinically meaningful endpoints.

9. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to an Advisory Committee.

10. Other Relevant Regulatory Issues

Not applicable.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on a prospective, single arm, multicenter clinical trial with supportive evidence from the d pharmacokinetic and pharmacodynamic studies and preclinical studies. The evidence of treatment effect is based on a clinically meaningful benefit in the overall hemostatic response in patients treated with FESILTY either as on-demand prophylaxis or treatment for bleeding events and surgeries, as well as a significant mean increase in maximum clot firmness in patients treated with FESILTY.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends traditional approval of FESILTY, a human fibrinogen concentrate for treatment of acute bleeding episodes and for perioperative management of bleeding in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

b. Benefit/Risk Assessment

FESILTY has demonstrated efficacy with improvement in overall hemostatic response. The majority of bleeding events in patients treated with FESILTY were

reported as excellent (85.7%) or good (13.1%) OHR, with no notable differences between age groups or between major and minor bleeding events. The most common moderate or severe adverse reactions occurring in >2% of patients included pain in extremity (7%), back pain (7%), hypersensitivity reactions (7%), pyrexia (4%), thrombosis (4%), fibrin D-dimer increased (4%), headache (4%), and vomiting (2%). Serious adverse reactions included thrombosis in 2 patients (portal vein thrombosis and deep vein thrombosis in one subject each), pain in extremity with suspected thrombosis in one patient, and one patient with epilepsy and extradural hematoma four weeks after FESILTY administration, which was fatal.

Thus, considering the effect on bleeding events, and the fact that the risks are generally mild, infrequent, and/or easily mitigated, the overall benefit-risk profile favors traditional approval of FESILTY for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- and afibrinogenemia.

c. Recommendation for Postmarketing Activities

The Applicant will conduct routine pharmacovigilance activities as outlined in the Pharmacovigilance Plan, version 2.

In amendments 52, received November 20, 2025, 54 received November 26, 2025, 59 received December 3, 2025, and 62 received December 10, 2025, the Applicant agreed to five non-section 506B PMCs:

CMC PMC #1:
Grifols commits to conduct a leachables risk assessment (b) (4) for the Drug Product (DP) using actual DP lots (b) (4) PPQ lots: (b) (4) to be tested in the ongoing stability study. This assessment will cover storage at 25°C for the 36-months DP shelf life. In this study, for DP reconstitution, actual diluent supplied in the kit and aged to not less than the DP at the respective time point will be used. The reconstituted DP will be held in the Nextaro Transfer Device under in-use (clinical preparation) conditions at maximal hold time and temperature until sample preparation and analysis. The final results will be submitted as a “Postmarketing Study Commitment - Final Study Report”.

Final Study Report Submission: February 29, 2028

CMC PMC #2:
Grifols commits to complete validation of the (b) (4) assay, according to (b) (4) as a reference method for Fibrinogen (b) (4) determination in FESILTY Drug Product to be used on stability testing, in addition to the (b) (4) assay. Grifols also commits to update SOP-Q-00227 with description of verification of the (b) (4) results for Fibrinogen (b) (4) by the (b) (4) method in stability studies.

The Method Validation Report and updated SOP-Q-00227 will be submitted as a Prior Approval Supplement (PAS) titled as a “Postmarketing Study Commitment – Final Study Report” to fulfill the commitment by March 31, 2026.

Prior Approval Supplement Submission: March 31, 2026

CMC PMC #3:
Grifols commits to:

a) Develop and validate a calibration model based on the statistical advice in the FDA Information Request dated October 28, 2025. For the calibration model validation, (b) (4) The validation will determine where the model applies "as suitable for the circumstances" and specify situations requiring model (b) (4) with the reference method.

   The results of this development and validation will be submitted to FDA for review prior to starting method validation as a "Postmarketing Study Commitment – Status Update" by March 2, 2026.

b) Validate the (b) (4) method as a quantitative method for the determination of Residual Moisture for release and stability testing of FESILTY Drug Product. The method validation will be performed according to (b) (4), including assay specificity, linearity, precision (repeatability and intermediate precision), limits of quantitation, accuracy, and robustness. The method validation will be conducted using a (b) (4) assay suitability and performance.

   The Method Validation Protocol will be submitted to FDA for review prior to starting method validation as a "Postmarketing Study Commitment – Status Update" by March 2, 2026.

   The Method Validation Report will be submitted as a Prior Approval Supplement (PAS) titled as a "Postmarketing Study Commitment – Final Study Report" to fulfill the commitment by May 31, 2026.

   Prior Approval Supplement Submission: May 31, 2026

CMC PMC #4:
Grifols commits to revise Qualification Report BE-232-24/00 "Control sample establishment of Fibrinogen Concentrate (BT524) for SOP-Q-00438" dated November 14, 2025. The revised version of the Report will include the following sections:

a) Preparation
b) Characterization/Qualification with predefined Acceptance Criteria
c) Qualification of the in-house Fibrinogen control sample (reference sample) Lot (b) (4) for determination of Fibrinogen (b) (4) using the current (b) (4) as control.
d) Stability Program/Storage of the in-house reference material.

The submission will also include a Qualification Protocol for implementation of future lots of the in-house Fibrinogen control sample (reference sample).

The updated Qualification Report BE-232-24/00 and the Qualification Protocol will be submitted as a Prior Approval Supplement titled “Postmarketing Study Commitment – Final Study Report” to fulfill the commitment by March 31, 2026.

Final Study Report Submission: March 31, 2026

CMC PMC #5:
Grifols commits to update the Use-Related Risk Analysis (URRA) based on the Human Factor Advice in FDA Information Request dated November 26, 2025, to appropriately capture the clinical impact associated with identified use errors or task failures. The updated URRA will be submitted as “Postmarketing Study Commitment – Final Study Report” to fulfill the commitment by February 28, 2026.A

Final Report Submission: February 28, 2026