

CBER CMC BLA Review Memorandum

BLA STN 125833/0

Fibrinogen, human – chmt (BT524) [FESILTY]

CMC Reviewers

Sergey Akimov, PhD, Biologist, OTP/OPPT/DH/HB2

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1. BLA#: STN 125833/0

2. APPLICANT NAME AND LICENSE NUMBER:

Grifols Therapeutics, LLC (Grifols)
U.S. License No. 1871, active

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: Fibrinogen, human – chmt (BT524)
Proprietary Name: FESILTY

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Human blood coagulation factor.
- b. Dosage form: lyophilized powder for solution for intravenous injection.
- c. Strength/Potency: one single-dose glass vial contains nominally 1 gram of human fibrinogen and one 50 mL glass vial of sterile Water for Injection, USP. The actual amount of fibrinogen in milligrams fibrinogen per vial is printed on the vial label and carton. Upon reconstitution, final Fibrinogen concentration is 20 mg/mL.
- d. Route of administration: intravenous use after reconstitution only.
- e. Indication(s): treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

5. MAJOR MILESTONES

Receipt Date: December 27, 2024

- Application Orientation and Dataset Walkthrough Meeting Teleconference: January 29, 2025, 12:00 PM - 1:30 PM ET
- Combined First Committee and Filing Meeting: February 10, 2025, 10:00 AM – 11:00 AM ET
- Filing Notification: February 21, 2025
- Mid-Cycle Meeting Teleconference: June 24, 2025, 1:00 PM - 1:30 PM ET
- Late-Cycle Meeting Teleconference: September 16, 2023, 12:00 PM - 1:00 PM ET
- PDUFA Action Date: December 27, 2025.

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Sergey Akimov, OTP/OPPT/DH/HB2	Drug Substance (Section 3.2.S) Drug Product (Section 3.2.P, Fibrinogen (Human) and Solvent (Diluent)) Environmental Analysis (Section 1.12.14) Regional Information (Section 3.2.R) Reports of Bioanalytical and Analytical Methods for Human Studies (Sections 4.2.2.1 and 5.3.1.4)

Reviewer/Affiliation	Section/Subject Matter
Ze Peng, OTP/OPPT/DH/HB1	Adventitious Agents safety evaluation and validation of viral clearance (Sections 3.2.A.2 and relevant information from Section 3.2.S.2.3 Control of Materials and Section 3.2.P.4.5 Excipients of Human or Animal Origin)
Yideng Liang, OTP/OPPT/DH/HB2	3.2.S.7 Drug Substance Stability, 3.2.S.4.4 Batch Analysis, 3.2.P.8 Drug Product Stability, and 3.2.P.5.4 Batch Analysis
Andrey Sarafanov, OTP/OPPT/DH/HB2, and Haarin Chun, OTP/OPPT/DH/HB2	Analytical assessment of Extractables and Leachables - Section 3.2.P.2.3.8

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Arlesa Hubbard, CDRH/OPEQ/OHTIII/DHTIIC	Human Factors consults / Transfer Device for Fibrinogen (Human) (Section 3.2.R)	N/A (transferred to CDER on August 20, 2025)
Millie Shah, CDER/OSE/OMEPRM/DMEPAII, Samuel Suen, CDER/OSE/OMEPRM/DMEPAII	Human Factors consults / Transfer Device for Fibrinogen (Human) (Sections 3.2.R and 5.3.5.4 (Report BE-201-24); the Use-Related Risk Analysis (URRA) and Comparative Task Analysis	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
27 December 2024	STN 125833/0	Original BLA submission
2 April 2025	STN 125833 /0/12 (response to IR #11 from 20 March 2025)	IR #11 (CMC): provided missing validation protocols

Date Received	Submission	Comments/ Status
7 April 2025	STN 125833 /0/13 (response to IR #8 from 14 March 2025)	IR #8 (CMC): provided the report BE-118-24 for Risk Assessment of Extractables from Rubber Stopper in the DP
30 April 2025	STN 125833 /0/15 (response to IR #14 from 15 April 2025)	IR #14 (CMC): follow-on IR # 8; provided updated leachables study BE-219-24
14 July 2025	STN 125833 /0/25 (response to IR #24 from 27 June 2025)	IR #24 (CMC): provided updated Stability studies reports
14 July 2025	STN 125833 /0/25 (response to IR #25 from 2 July 2025)	IR #25 (CMC): provided updated DP specifications and related commitments
15 July 2025	STN 125833 /0/26 (response to IR #23 from 27 June 2025)	IR #23 (CMC): provided description of the (b) (4) manufacturing process and a summary of detection limits of the viral testing kits
30 September 2025	STN 125833 /0/36 (response to IR #24 from 27 June 2025)	IR #24 (CMC): provided another update to Stability studies reports to complete commitment from 14 July 2025
30 September 2025	STN 125833 /0/36 (response to IR #25 from 2 July 2025)	IR #25 (CMC): provided (b) (4) study report BE-178-24 and report BE-150-24 for (b) (4) spiking experiments to complete commitment from 14 July 2025
6 October 2025	STN 125833 /0/39 (response to IR #33 from 9 September 2025)	IR #33 (CMC): provided updated DP specifications and related commitments
15 October 2025	STN 125833 /0/42 (response to IR #36 from 6 October 2025)	IR #36 (CMC): provided commitment to update the URRAs and Comparative Task Analysis for Nextaro v Transfer Device
17 October 2025	STN 125833 /0/43 (response to IR #33 from 9 September 2025)	IR #33 (CMC): provided the updated method SOP-Q-00454, and the updated method validation report VAL-Q-00246_REP-01 to complete commitments from 6 October 2025
27 October 2025	STN 125833 /0/44 (response to IR #36 from 15 October 2025)	IR #36 (CMC): provided updated URRAs and Comparative Task Analysis for Nextaro v Transfer Device

Date Received	Submission	Comments/ Status
31 October, 2025	STN 125833 /0/47 (response to IR #37 from 21 October 2025)	IR #37 (CMC): updated DP Release and Stability specifications
12 November, 2025	STN 125833 /0/48 (response to IR 38 from 28 October 2025)	IR #38 (DBSQC/CMC): suspended (b) (4) as a method for Residual Moisture testing
18 November, 2025	STN 125833 /0/50 (response to Observation 8 (Form FDA 483))	Observation 8 (CMC): provided Qualification Report BE-232-24 for a new in-house Fibrinogen (Human) control sample batch
19 November, 2025	STN 125833 /0/51 (response to IR 41 from 10 November 2025)	IR #41 (CMC): updated process-related hold times and DP Stability specifications
20 November, 2025	STN 125833 /0/52 (response to email negotiation from 17 November 2025)	CMC PMC #1: to conduct a leachables risk assessment
24 November, 2025	STN 125833 /0/53 (response to IR 42 from 12 November 2025)	IR #42 (CMC): verified proposed DP shelf life via (b) (4) analyses
26 November, 2025	STN 125833 /0/54 (response to email negotiation from 21 November 2025)	CMC PMCs #2 and #3: to complete validation of the (b) (4) assay and to validate the (b) (4) method for the determination of Residual Moisture; changed the submission date for PMC #1
3 December, 2025	STN 125833 /0/59 (response to IRs 49 and 50 from 26 November 2025)	IRs ##49 and 50 (CMC): CMC PMCs #4 and #5 to revise Qualification Report BE-232-24/00 and update URRAs for Nextaro v Transfer Device
5 December, 2025	STN 125833 /0/60 (response to IR 46 from 24 November 2025)	IR #46 (CMC): updated eCTD sections for Reference Standards or Materials and DP Post-Approval Stability protocol
10 December, 2025	STN 125833 /0/62 (response to IR 53 from 8 December 2025)	IR #53 (CMC): updated eCTD section for DP Post-Approval Stability protocol and clarification of the DS process/hold time
10 December, 2025	STN 125833 /0/62 (response to email negotiation from 5 December 2025)	CMC PMC #4 (revised): to revise Qualification Report BE-232-24/00 and provide Qualification Protocol for a Reference Sample

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	Laboratorios Grifols, S.A.	Sterile Water for Injection (sWFI)	yes	DMF is current. Information pertinent to sWFI was reviewed, assessed and documented in the memo by in Section 3.2.P.
510(k) K240748	SFM medical devices GmbH, Germany	needleless <i>Nextaro v, 20/20 5 µm</i> transfer device	yes	Information pertinent to the transfer device was reviewed, assessed and documented in the memo by in Section 3.2.P.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This review is an assessment of the Chemistry, Manufacturing, and Control (CMC) information in the original Biologics License Application (BLA), STN 125833/0, submitted by Grifols Therapeutics, LLC (Grifols), to seek U.S. licensure for Fibrinogen, human-chmt, from a Product Quality perspective. The proprietary name of the product for the U.S. market will be FESILTY.

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. FESILTY Drug Product (DP) is a purified, sterile, non-pyrogenic, lyophilized powder of human fibrinogen concentrate for intravenous injection. FESILTY is a co-packaged Type 9 Biologics/Drug/Device combination product, which includes a 100 mL glass vial with nominally one-gram lyophilized powder, a glass vial of 50 mL sterile Water for Injection (sWFI) as a diluent, and a needleless Nextaro v, 20/20 5 µm transfer device for reconstitution of the lyophilizate. Upon reconstitution with 50 mL (sWFI), final fibrinogen concentration is 20 mg/mL. The Drug Substance (DS) and DP are manufactured at Biotest AG, Dreieich, Germany, a Contract Manufacturing Organization of Grifols.

We present a consolidated review of all the CMC/Product Quality information provided by Grifols in the original BLA, and subsequent amendments submitted in response to the Agency's information requests (IRs). CMC reviewers concluded that the Applicant has adequately characterized the biochemical and functional properties of FESILTY and provided documented evidence that the commercial manufacturing process is adequately validated and controlled to ensure consistent manufacture of FESILTY DP with the intended identity, quality, purity, safety, and

potency. CBER consulted the Center for Drug Evaluation Center (CDER) for evaluation of the Nextaro v 20/20 5 µm transfer device based on the provided Use-Related Risk Analysis and Comparative Task Analysis.

B. RECOMMENDATION

I. APPROVAL

The CMC (Product Quality) reviewers recommend approval of this BLA under STN 125833/0.

- a. List of Drug Substance and Drug Product manufacturing facilities: Refer to sections 3.2.S.2.1 *Manufacturer(s)* and 3.2.P.3.1 *Manufacturer(s)* of this Review Memorandum for a complete list of manufacturing and testing facilities.
- b. List of approvable Comparability Protocols: N/A
- c. There are five (5) Post-Marketing Commitments (PMCs) and no Post-Marketing Requirements (PMRs), from a CMC (Product Quality) perspective for this BLA. The PMCs are stated in Amendments 52, 54, and 62 dated November 20, November 26, and December 10, 2025, respectively, as follows:

PMC #1 (CMC)

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” by February 29, 2028.

PMC #2 (CMC)

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 Date: March 31, 2026

PMC #3 (DBSQC/CMC)

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 Date: May 31, 2026.

PMC #4 (CMC)

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 Date: March 31, 2026.

PMC #5 (CMC)

Grifols commits to update the Use-Related Risk Analysis (URRA) based on 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.

Final Study Report Submission Date: February 28, 2026.

e. Lot release requirements (Yes/No) – Yes, Lot Release Protocol is provided in the DBSQC Memo.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK


Reviewer/Title/Affiliation	Concurrence	Signature and Date
Sergey Akimov, PhD, Biologist, OTP/OPPT/DH/HB2 (Chair)	Concur	
Ze Peng, PhD, Biologist, OTP/OPPT/DH/HB1	Concur	
Yideng Liang, PhD, Biologist, OTP/OPPT/DH/HB2	Concur	
Andrey Sarafanov, PhD, Chemist, OTP/OPPT/DH/HB2	Concur	
Haarin Chun, PhD, Biologist, OTP/OPPT/DH/HB2	Concur	
Natalya Ananyeva, PhD, Branch Chief, OTP/OPPT/DH/HB2	Concur	
Zuben Sauna, PhD, Division Director, OTP/OPT/OPPT/DH	Concur	

Review of CTD
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Module 3


3.2.S DRUG SUBSTANCE

(b) (4)



30 pages determined to be not releasable: (b)(4)

(b) (4)



3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The Dosage form of FESILTY DP is Lyophilized powder for solution for intravenous injection. FESILTY DP is presented as a single-use 100 mL glass vial containing 1 g of lyophilized fibrinogen as a white powder. The lyophilizate is reconstituted with 50 mL of water for injection.

The composition of reconstituted FESILTY DP is provided in Table 11 (adapted from Table 3.2.P.1-1, Section 3.2.P.1)

Table 11. Composition of FESILTY DP

Ingredient	Quantity		Function	Reference
	1 mL reconstituted solution contains	1 vial contains		
<u>Active Ingredient:</u>				
Human fibrinogen	20 mg	1 g	Active substance	N/A
<u>Excipients:</u>				
Arginine hydrochloride	(b) (4)	421.3 mg	(b) (4)	(b) (4)
Polysorbate 80		25.5 mg		
Sodium chloride		292.2 mg		
Sodium citrate dihydrate		73.5 mg		
Trehalose dihydrate		567.5 mg		
Water for Injection		N/A		

The product strength is 20 mg/mL (1 g of human fibrinogen reconstituted with 50 mL of sWFI).

sWFI is prepared from WFI that is sterilized and packaged in single-dose containers. It contains no antimicrobial agent or other added substance.

Container Closure System of FESILTY DP is 100 mL type (b) (4) borosilicate glass vials closed with type (b) (4) bromobutyl stoppers, which are held in place with metal crimps covered with flip-off plastic caps. sWFI is supplied in 20 mm neck type (b) (4) glass 50 mL vials with a chlorobutyl rubber stopper, which is protected by an aluminum flip-off cap.

Reviewers' Assessment: The information provided in Section 3.2.P.1 is sufficient to describe the DP. The active ingredient of FESILTY DP is discussed in the DS sections of this memo. All other components of FESILTY DP are compendial and similar to those found in the formulation of other plasma-derived parenteral protein products.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The active ingredient in FESILTY DP is human fibrinogen described in Section 3.2.P.1 of this review memorandum.

3.2.P.2.1.2 Excipients

All excipients are compendial and their specific functions are described in Table 11.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

There is no difference between clinical and commercial formulations of DP (described in section 3.2.P.1 of this memorandum).

During development, various formulations of FESILTY DP were tested for stability of Fibrinogen during the manufacturing process and for solubility of the lyophilizate.

The formulation was optimized based on:

- Specific fibrinogen activity
- (b) (4) content
- Solubility of the lyophilizate

Based on the performed studies, the following concentrations were chosen:

- (b) (4) arginine hydrochloride
- (b) (4) trehalose dihydrate
- (b) (4) (w/w) polysorbate 80
- (b) (4) tri-sodium citrate at (b) (4)
- (b) (4) sodium chloride (as an electrolyte to ensure physiological osmolality of the DP)

The corresponding excipient concentrations in the reconstituted DP provided in section 3.2.P.1 are about (b) (4) lower because of the difference in filling volume before lyophilization (b) (4) and after reconstitution in 50 mL sWFI.

3.2.P.2.2.2 Overages

Overages are not provided as not applicable. With a target value for the total amount of active fibrinogen of 1000 mg per vial, the specified range for fibrinogen content is (b) (4) g/vial as defined at the development phase. This is in accordance with the (b) (4) for human fibrinogen.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of the FESILTY DP are identical to the DS formulation discussed in Section 3.2.S of this memorandum.

3.2.P.2.3 Manufacturing Process Development

The FESILTY DP manufacturing process consists of the following steps: aseptic filling, freeze-drying, and heat treatment.

The following key properties were defined prior to the initial development as targets for the design of the FESILTY DP manufacturing process:

- FESILTY shall be provided as a freeze-dried product
- FESILTY shall have a long shelf life
- FESILTY shall show fast solubility upon reconstitution
- Reconstituted FESILTY shall be stable

The virological/prion safety shall be equal or better compared to other coagulation factor products manufactured by Biotest.

DP Batches Manufactured During the Process Development

(b) (4) batches of FESILTY DP were manufactured to supply the clinical trials. (b) (4) other batches were manufactured to support stability studies, nonclinical research, and consistency. A summary of FESILTY DP batches manufactured in the scope of the process development is provided in Table 12 (adapted with changes from Table 3.2.P.2-4, eCTD Section 3.2.P.2).

Table 12. Summary of FESILTY DP Batches Manufactured in the Scope of the Process Development

(b) (4)

Manufacturing Process Changes

(b) (4)

- (b) (4)

Enhanced environmental monitoring during vial transportation.

Comparability Assessment

A comparability assessment of the DS manufacturing Process P1 versus Process P2 is described in Section 3.2.S.2.6.2 of this memo.

To meet expectations for 100% control of Residual Moisture content in the DP lyophilizate and the vacuum achieved in the DP vials, the respective 100% IPC measurement processes were validated during the PPQ.

Reviewers' Assessment: Results of the comparability assessment demonstrate that none of the changes described above have an impact on the safety, quality, identity, purity, and potency of FESILTY DP. Based on the demonstrated comparability of manufacturing Processes P1 and P2, no further confirmatory non-clinical or clinical studies were required.

3.2.P.2.4 Container Closure System

The Container Closure System is reviewed in section 3.2.P.7.

3.2.P.2.5 Microbiological Attributes

The final DP is filled in vials under aseptic conditions. It is tested for Sterility and Pyrogenicity as part of the release testing (refer to Section 3.2.P.5.1). In accordance with the (b) (4) recommendations for human fibrinogen, no microbial preservative is added.

3.2.P.2.6 Compatibility

The compatibility of FESILTY lyophilizate, solvent, and medical Nextaro v. 20/20 5 µm device is defined in Summary Report BE-202-24/00 "Verification and Review of the Product Requirement Specifications (PRS) of the Combination Product Fibrinogen Concentrate (BT524)" approved on December 6, 2024, as follows:

"The lyophilized powder must be able to be reconstituted with the material provided in the co-package. Co-packed are a vial containing 50 mL of water for injection (WFI) from the manufacturer (b) (4) and a medical device to enable the transfer of the WFI into the lyophilizate (Nextaro transfer device manufactured by the company sfm, based in Germany)."

Summary Report BE-202-24/00 describes the verification and validation activities of the design outputs for all sections of the Product Requirement Specifications (PRS) defined in the design input for the FESILTY combination product (lyophilizate, sWFI, Nextaro transfer device). The compatibility design output is defined as "All products should be used together to produce ready-to-use Fibrinogen Concentrate (BT524) drug product."

FESILTY is compatible with the Nextaro transfer device according to the manufacturer's technical documentation. Results provided in Research Report BE-114-24/00,

"Comparison of the Reconstitution of Fibrinogen Concentrate (BT524) DP Using 50 mL sWFI Bottles from (b) (4) Grifols," dated January 13, 2023, demonstrate that (b) (4) sWFI bottles — (b) (4) Grifols — can be used interchangeably for the reconstitution of FESILTY DP. sWFI from Grifols can be used with (b) (4) transfer device used in clinical trials and the optimized Nextaro transfer device.

However, regarding transfer and reconstitution times, it is highly recommended to use sWFI from either Grifols (b) (4) in combination with the Nextaro transfer device. Therefore, the compatibility and functionality of the Nextaro v, 20/20 5 µm transfer device for reconstitution of FESILTY DP with sWFI from Laboratorios Grifols has been demonstrated.

Reviewers' Assessment: Adequate information has been provided with respect to the pharmaceutical development of the DP and is acceptable as submitted. All steps in the manufacturing process were appropriately evaluated for adequate controls, and the compatibility of the FESILTY DP with the diluent (sWFI) and Nextaro v, 20/20 5 µm transfer device has been adequately evaluated.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

FESILTY DP Manufacturing

Sites associated with the proposed commercial FESILTY DP manufacturing, quality control, and storage are provided in Table 13 according to the information in eCTD Section 3.2.P.3.1.

Table 13. FESILTY DP Manufacturing and Testing Sites and Responsibilities

Site Name FDA Establishment Identifier (FEI)	Address	Manufacturing or Testing Responsibilities
Biotech AG, FEI# 3001034985	Landsteinerstr. 5 63303 Dreieich, Germany	<ul style="list-style-type: none"> - Commercial FESILTY DP manufacturing and quality control, labelling and packaging of the DP, and batch certification of the labelled and packaged DP - Primary labelling of sWFI vials and sWFI batch release
Grifols Therapeutics LLC, (b) (4)	(b) (4)	<ul style="list-style-type: none"> - Batch release of the final product with all necessary co-packaged components including sWFI
(b) (4)	(b) (4)	<ul style="list-style-type: none"> - Contract laboratory for pyrogen testing (primary testing laboratory)
(b) (4)	(b) (4)	<ul style="list-style-type: none"> - Contract laboratory for pyrogen testing (alternative testing laboratory) - Storage Warehouse in the US
(b) (4)	(b) (4)	<ul style="list-style-type: none"> - Contract laboratory for trehalose determination
(b) (4)	(b) (4)	<ul style="list-style-type: none"> - Contract laboratory for water determination (by (b) (4))
(b) (4)	(b) (4)	<ul style="list-style-type: none"> - Additional external storage site of the DP

Manufacturing site responsible for sWFI manufacture, IPC testing, bulk testing, and filling into vials (without labelling, packaging, and batch release):

(b) (4)

Manufacturing site responsible for sWFI component testing, sterility testing, testing of DP, shipping release of sWFI vials, and stability sample storage and testing:

(b) (4)

3.2.P.3.2 Batch Formula

One batch of FESILTY DS of approximately (b) (4) batch size (b) (4) protein) is used to manufacture one batch of the DP. The DS is processed within (b) (4) (b) (4) to DP and (b) (4). The minimum and maximum batch size of FESILTY DP is presented in Table 14 (adapted from Table 3.2.P.3.2-1, eCTD Section 3.2.P.3.2).

Table 14. Batch size of FESILTY DP

Container	Filling volume in mL	Active substance (human fibrinogen) per vial	Number of vials
Vial	(b) (4)	1 g	(b) (4)

Reviewers' Assessment: The information provided in Sections 3.2.P.3.1 and 3.2.P.3.2 is acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process and 3.2.P.3.4 Controls of Critical Steps and Intermediates

FESILTY DP is manufactured from the DS under controlled conditions. The manufacturing process of the DP consists of the following (b) (4) steps:

(b) (4)

A flow diagram of the manufacturing process is provided as Figure 3.2.P.3.3-2 in eCTD Section 3.2.P.3.3. A summary of the DP manufacture IPCs is provided in Table 15 (adapted from Table 3.2.P.3.3-2, eCTD Section 3.2.P.3.3).

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

No (b) (4) are manufactured during the FESILTY DP manufacturing process.

Reviewers' Assessment: The description of the manufacturing process and control strategy for the FESILTY DP is acceptable as submitted.

3.2.P.3.5 Process Validation and/or Evaluation

The validation program for FESILTY DP was based on the categorization of critical quality attributes (CQAs), critical process parameters (CPPs), and process risk analysis. The process validation included studies of the final filling, including sterile filtration (a critical step), and studies of other important steps during DP manufacture. An overview of the DP process validation studies is provided in Table 17 (adapted from 3.2.P.3.5-1, eCTD Section 3.2.P.3.5) in a chronological order.

(b) (4)

- (b) (4)

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

Reviewers' Assessment: The description of the FESILTY DP process validation is acceptable as submitted. All predefined acceptance criteria for the DP quality were met during the PPQ campaign. In summary, the PPQ study results demonstrate that the FESILTY DP manufacturing process is adequately validated. A detailed analysis of the lyophilization process was performed by the DMPQ reviewers.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

All excipients used in the manufacture of FESILTY DP are compendial grade and are listed in Table 18 below (adapted from Table 3.2.P.4.1, Section 3.2.P.4.1 *Specifications - Excipients*):

Table 18. Excipients Used in the Manufacture of FESILTY DP

Material	Specification	Function
Arginine hydrochloride	(b) (4)	(b) (4)
Polysorbate 80		
Sodium chloride		
Sodium citrate dihydrate		
Trehalose dihydrate		

Certificates of Analysis for the excipients are provided in eCTD Section 3.2.S.2.3 because the (b) (4).

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

All procedures performed for quality control of excipients are routine procedures described in current editions of the (b) (4). The analytical procedures are tested in accordance with (b) (4) standards and are therefore considered validated and suitable for their intended use. Potential differences between (b) (4) are described in Table 19 below (adapted from Table 3.2.P.4.2-1, eCTD Section 3.2.P.4.2).

Table 19. Analytical Procedures for Compendial Excipients

Material	Analytical procedure	Specification
Arginine hydrochloride	All procedures performed for quality control of arginine hydrochloride are according to (b) (4) for arginine hydrochloride and (b) (4).	(b) (4)
Polysorbate 80	All procedures performed for quality control of polysorbate 80 are according to (b) (4) for polysorbate 80 and (b) (4).	
Sodium chloride	All procedures performed for quality control of sodium chloride are according to (b) (4) for sodium chloride and (b) (4) (b) (4).	

Material	Analytical procedure	Specification
Sodium citrate dihydrate	All procedures performed for quality control of sodium citrate dihydrate are according to (b) (4) for sodium citrate dihydrate (alternative test to pyrogens: (b) (4) .	(b) (4)
Trehalose dihydrate	All procedures performed for quality control of trehalose dihydrate are according to (b) (4) for trehalose dihydrate and (b) (4) .	

sWFI

This section is not applicable for the diluent sWFI as it does not contain any excipients.

3.2.P.4.4 Justification of Specifications

All test parameters for arginine hydrochloride, sodium chloride, sodium citrate dihydrate, polysorbate 80, and trehalose dihydrate are specified in the (b) (4) . There are no specific requirements for the excipients used in the manufacturing process of FESILTY that exceed the specifications defined in (b) (4) . The tests are conducted in compliance with current editions of (b) (4) .

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin are used in the manufacture of the FESILTY DP.

3.2.P.4.6 Novel Excipient

No novel excipients are used in the manufacture of the FESILTY DP.

Reviewers' Assessment: All excipients are compendial and there are no novel excipients or those of human or animal origin. This section adequately describes the control of excipients.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The Applicant defined specifications for the critical quality attributes in accordance with applicable pharmacopoeia requirements (b) (4) . The specifications of FESILTY DP and their justifications are provided in Table 3.2.P.5.1-1, eCTD Section 3.2.P.5.1. The specifications refer to FESILTY DP solution after reconstitution of the lyophilizate in 50 mL of sWFI.

A summary of the DP release specifications and their changes throughout development is provided in Table 20.

Table 20. Summary of Changes to the Release Specification of FESILTY DP

Test Parameter/ Quality Attribute	Analytical Procedure	Final Acceptance Criteria	Clinical Material Acceptance Criteria	PPQ/ Validation Acceptance Criteria		
Potency						
Fibrinogen activity	SOP-Q-00438	20 g/L (b) (4)	(b) (4)	(4)		
Identity						
Fibrinogen activity	SOP-Q-00438 (b) (4)	20 g/L (b) (4)				
	SOP-Q-00018 (b) (4)	n/a				
(b) (4)	SOP-Q-00454	(b) (4)				
Appearance and description						
Coloration of solution	SOP-Q-00311	Equal or less colored than reference solution (b) (4)				
Clarity and opalescence	SOP-Q-00515	(b) (4)				
	SOP-Q-00017	n/a				
Solubility	SOP-Q-00384	(b) (4)				
Stability of the solution	SOP-Q-00384	(b) (4)				
pH	SOP-Q-00050	7.0 (6.5 - 7.5)				
Osmolality	SOP-Q-00336	≥ 240 mosmol/kg				
Quantity						
Total protein	SOP-Q-00438	20 g/L (b) (4)				
	SOP-Q-00238	n/a				
Total amount of active fibrinogen per vial (calculated)	SOP-Q-00438	(b) (4)				

Test Parameter/ Quality Attribute	Analytical Procedure	Final Acceptance Criteria	Clinical Material Acceptance Criteria	PPQ/ Validation Acceptance Criteria
	SOP-Q-00018 (b) (4)	n/a	(b) (4)	
Purity and contaminations				
Specific fibrinogen activity (calculated)	SOP-Q-00438	(b) (4)		
	SOP-Q-00018 (b) (4)	n/a		
Water / residual moisture	V_1910E (b) (4)	(b) (4)		
	SOP-P-00403 (b) (4)	n/a		
	SOP-Q-00285 (b) (4)	n/a		
(b) (4)	SOP-Q-00454	(b) (4)		
	SOP-P-00006	n/a		
(b) (4) - monomers	SOP-Q-00454	≥ 80 %		
(b) (4)	SOP-Q-00454	(b) (4)		
Sterility	SOP-Q-00417	Sterile		
Pyrogens	IG_MA- 000011C_ING	Pyrogen free		
	SOP-Q-00035/ TM\BAB\548	n/a		
Excipients				
Polysorbate 80	SOP-Q-00098	(b) (4)		
Arginine	SOP-Q-00255	(b) (4)		
Trehalose	SAA 490-036	(b) (4)		
Sodium	SOP-Q-00558	(b) (4)		

Test Parameter/ Quality Attribute	Analytical Procedure	Final Acceptance Criteria	Clinical Material Acceptance Criteria	PPQ/ Validation Acceptance Criteria
	SOP-Q-00323	(b) (4)	(4)	
	C.52.S927			
Chloride	SOP-Q-00236			
Citrate	SOP-Q-00220			

⁹ (b) (4) ¹³ No limit specified, ¹⁴ (b) (4) ¹⁶ Retrospective investigations showed that the (b) (4) method used as the reference method for (b) (4) the residual moisture in the lyophilizate because water extraction was incomplete. The specification limit set earlier was therefore defined incorrectly. ¹⁷ The residual moisture content after freeze-drying was measured with (b) (4). Additionally, (b) (4) model was suitable for the measurement but was not completely validated.

Acceptance criteria were justified based on batch release data from representative batches used for clinical trials, non-clinical studies, process transfer, and process validation (PPQ).

To establish the acceptance limits, the applicant used a statistical approach based on the mean value \pm 3 standard deviations. This interval captures 99.7% of process variability and ensures that virtually all routine manufacturing fluctuations are accommodated while flagging true out-of-specification events.

Additional justification factors included alignment with (b) (4) requirements, demonstrated process performance across multiple manufacturing scales, stability considerations, successful use in clinical trials, and formulation studies.

Reviewers' Assessment: The Applicant proposed commercial release specifications based on product quality requirements that reflect the product CQAs and established adequate acceptance criteria. These criteria are based on the manufacturing process development and clinical experience, process validation data, release and ongoing stability data, and regulatory compliance.

In response to Question 1, FDA IR #25, the Applicant added a category/quality attribute Potency (Fibrinogen activity, previously used only as an Identity test) to FESILTY DP specifications. Additionally, in response to Question 1, FDA IR #33, the Applicant added (b) (4) analytical method by (b) (4) as an additional Identity test for FESILTY DP.

In response to Question 3, FDA IR #33, and to harmonize the specifications between US and non-US batches, the Applicant updated and tightened FESILTY DP specifications compared to clinical and PPQ specifications for the following select parameters: Fibrinogen activity, Specific fibrinogen activity, (b) (4) (by including parameters Monomer (b) (4), in addition to (b) (4)), Water/Residual moisture upper limit.

The specifications for FESILTY DS were harmonized with the specifications for the DP for (b) (4) ” and for (b) (4) ” in eCTD Sections 3.2.S.2.6.1, 3.2.S.4.1, 3.2.S.4.4, and 3.2.S.4.5. Additionally, the upper limit for the (b) (4) was aligned with the adapted residual moisture specification for the DP. Consequently, this specification range was (b) (4)

We consider the changes for updating and tightening FESILTY DP specifications to be an improvement (refer to Table 20).

The statistical methods employed in the specification setting strategy are appropriate and align with (b) (4) guidance on acceptance criteria for biotechnological products. The multi-faceted approach used by the Applicant ensures that the currently proposed specifications for FESILTY DP are acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

DBSQC reviewers are responsible for the review of all FESILTY DP release and stability analytical procedures and method validations, except for:

- Potency/Identity- Fibrinogen Activity
- Appearance – Solubility and Stability of the Solution
- Purity/Impurities - Specific Fibrinogen Activity (calculated).

The DBSQC reviewers concluded that the analytical methods and their validations and/or qualifications reviewed for FESILTY DP release and stability testing were adequate for their intended use, except for an outstanding issue related to the residual moisture method using (b) (4) for the FESILTY DP. Their rationale is included in an independent review memo. The Applicant has provided a written commitment to address the issue with the Residual Moisture method as a post-marketing commitment (PMC #3).

The analytical procedures for FESILTY DP release and stability testing reviewed by OTP/OPPT/DH CMC reviewers are the same as for DS release testing and are listed in Table 21 (modified from Tables 3.2.P.5.2-1 and 3.2.P.5.3-1, eCTD Sections 3.2.P.5.2 and 3.2.P.5.3, respectively). For detailed description and validation of the methods refer to sections 3.2.S.4.2 and 3.2.S.4.3 of this memorandum.

Table 21. Overview of FESILTY DP Analytical Procedures Reviewed by CMC Reviewer

Quality attribute	Test method	SOP and Validation / verification report numbers	Summarized results	eCTD section
Fibrinogen activity	(b) (4)	SOP-Q-00438, VAL-Q-00232 REP-01	Validation passed	3.2.P.5.2.1, 3.2.P.5.3.1
Solubility	Visual	SOP-Q-00384, RA-T:A-0688	N/A*	3.2.P.5.2.4, 3.2.P.5.3.4
Stability of the solution	Visual	SOP-Q-00384, RA-T:A-0688	N/A*	3.2.P.5.2.5, 3.2.P.5.3.5
Specific fibrinogen activity	Calculation	SOP-Q-00438, VAL-Q-00232 REP-01	Validation passed	3.2.P.5.2.10, 3.2.P.5.3.10

*no validation / verification of the compendial method is required

Fibrinogen Activity and Specific Fibrinogen Activity analytical test methods used for FESILTY DP release and stability testing are the same as for FESILTY DS release testing.

Reviewers' Assessment: The analytical procedures and validation studies for the determination of Fibrinogen Activity, Specific Fibrinogen Activity, Solubility, and Stability of the Solution were reviewed and evaluated in the DS sections of this memorandum. All procedures meet the acceptance criteria established in the validation protocols and are suitable for their intended purpose of controlling DP quality. In response to FDA IR #37, the modified (b) (4) assay will be added as a reference method to (b) (4) method in stability studies (refer to PMC #2).

3.2.P.5.4 Batch Analyses

(b) (4) PPQ batches of FESILTY DP derived from (b) (4) different suppliers of (b) (4) were evaluated. (refer to the memorandum of Dr. Yideng Liang)

3.2.P.5.5 Characterization of Impurities

The Applicant evaluated the product- and process-related impurities during development of FESILTY manufacturing processes.

Product-related impurities are defined as unwanted activities or unwanted states of the product itself (e.g., (b) (4)), whereas process-related impurities are substances that are derived from the human plasma source material (e.g., von Willebrand Factor) or from the production process. An overview of main impurities and corresponding process steps for their removal is provided in Table 6 "Overview of Main Impurities and Corresponding Process Steps for their Removal" in section 3.2.S.3.2 of this memorandum.

(b) (4) and (b) (4) are product-related impurities. No significant (b) (4) formation was observed. Additionally, (b) (4) are monitored as part of

the release testing of the (b) (4) DP. (b) (4) are monitored as part of the release testing for FESILTY DP.

Impact of Manufacturing Conditions

The (b) (4) content as a product manufacturing-related impurity is influenced by the residual moisture content, freeze-drying, and heat treatment. Only a (b) (4) in the (b) (4) content (but below the specification limit) was observed after freeze-drying and heat treatment.

Compliance and Additional Testing

(b) (4) comply with the DP specifications.

In response to FDA information requests and to ensure product purity, the Applicant added (b) (4) additional parameters capable of detecting potential Fibrinogen (b) (4) as determined by (b) (4)

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

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

For the PPQ batches, the main protein constituents of human plasma (i.e., albumin and immunoglobulins), residual coagulation factor activities, fever-inducing cytokines, tests for procoagulant activity (non-activated partial thromboplastin time – NaPTT), and total (b) (4) were determined. Furthermore, other safety-relevant impurities such as residual amounts of (b) (4) were determined to demonstrate depletion of impurities by the FESILTY manufacturing process.

The main potential impurities from plasma are predominantly removed by glycine precipitation. Process robustness studies showed that glycine precipitation is robust and consistently removes accompanying proteins such as albumin and immunoglobulins. Remaining impurities such as von Willebrand Factor (vWF) and proteases, can be further removed by subsequent CEX chromatography.

An overview of impurities and corresponding process steps for their removal is provided in Table 6, section 3.2.S.3.2 of this memorandum.

All parameters were below or close to their respective detection/quantitation limits except for the known impurities vWF and fibronectin. However, the residual vWF content showed no or only very low activity. Moreover, the NaPTT revealed no shortening of the coagulation time compared to a reference control. In addition, the test for total (b) (4) confirms the results obtained from the NaPTT, showing no measurable (b) (4) in FESILTY DP PPQ batches.

Residual proteins from human plasma, fibronectin, FVIII, wWF, fever-inducing cytokines (IL-1 β , IL-6, and TNF- α), were all at levels well below their concentration in human plasma. Furthermore, NaPTT at normal plasma levels and no (b) (4)

underscore no residual coagulation factor activity and no thrombogenic risk of FESILTY DP.

Product-related impurities of FESILTY were analyzed for breakdown products fibrinopeptide A and (b) (4) were at very low levels or undetectable in PPQ batches.

Residues from materials used during manufacturing of FESILTY, such as polysorbate 80, (b) (4) were depleted during the manufacturing process and were not detectable.

Reviewers' Assessment: The information and data described in Section 3.2.P.5 demonstrate that adequate controls are in place to ensure the safety, efficacy, and quality of FESILTY DP. The Applicant provided lot release information from (b) (4) PPQ DP batches manufactured from the PPQ campaign. All FESILTY PPQ DP batches met all release specification acceptance criteria. The batch analysis data support the consistency of FESILTY DP process for commercial manufacturing.

FESILTY shows only very low amounts of impurities, which do not raise any safety concerns. Therefore, only those impurities found to be critical are routinely tested for release of the DP. Further impurities will not be tested regularly, but on a risk-based approach (e.g., after process or equipment modifications).

3.2.P.6 Reference Standards or Materials

Information regarding the reference standards used for analytical procedures for the FESILTY DP is provided in Table 22 (reproduced from Table 3.2.P.6-1, Section 3.2.P.6).

Table 22. Reference Standards or Materials

Analytical procedure	Method	Primary reference standard	Working reference standard	Information about the reference standard
Polysorbate 80 3.2.P.5.2.15	SOP-Q-00440	(b) (4) polysorbate 80	Polysorbate 80 working standard	Certificate of Analysis
Arginine 3.2.P.5.2.16	SOP-Q-00255	(b) (4) arginine hydrochloride	Arginine working standard	Certificate of Analysis
Sodium 3.2.P.5.2.18	SOP-Q-00558	(b) (4)	Sodium standard solution	Certificate of Analysis
Trehalose 3.2.P.5.2.17	SAA 490-036	Trehalose dihydrate (b) (4)	Same as primary reference standard	Information leaflet EDQM

Reviewers' Assessment: The Applicant did not include any information regarding in-house secondary reference standards or materials for FESILTY DP in Section 3.2.P.6 in the original BLA submission. However, the section was updated in response to FDA IRs # 37 and #46. Also, Table 3.2.P.6-2 was added to revised eCTD Section 3.2.P.6. For more details refer to section 3.2.S.5 *Reference Standards or Materials* in this memorandum.

3.2.P.7 Container Closure System

The primary container closure system (CCS) of FESILTY DP consists of the following components:

- 100 mL Glass Vials: Clear, colorless Type (b) (4) borosilicate glass vials with specific dimensions (flange diameter (b) (4), height (b) (4), outside diameter (b) (4)). The vials comply with (b) (4) requirements and are manufactured by (b) (4).
- 20 mm Rubber Stoppers: Grey-colored Type (b) (4) bromobutyl rubber stoppers compliant with (b) (4) manufactured by (b) (4). The stoppers are purchased pre-washed and pre-sterilized.
- 20 mm Flip-off Caps: Aluminum crimp caps with flip-off plastic discs manufactured by (b) (4).

Review of technical aspects of the CCS including dimensional drawings and CoAs referenced for each component is covered by the DMPQ reviewers.

CCS Suitability and Protection Properties

The Applicant confirms the following:

- Materials of construction meet pharmaceutical standards with Type (b) (4) glass providing high hydrolytic resistance and Type (b) (4) rubber stoppers meeting requirements for aqueous parenteral preparations and freeze-dried powders.
- Compatibility studies are described in section 3.2.P.2 and stability reports in section 3.2.P.8.3 of this memorandum.

The Applicant performed DP stability studies using the same CCS that is used for the final DP to assess compatibility of DP with the CCS. For results of the stability studies refer to section 3.2.P.8 of this memorandum.

Reviewers' Assessment: The information provided for DP container closure system is acceptable from a Product Reviewer perspective. The in-depth analysis of this information is provided in the memorandum of the DMPQ reviewer who confirmed its acceptability.

Extractables and Leachables

Information on risk assessment for Extractables and Leachables including the whole CCS (vials and stoppers), lyophilized protein diluent (sWFI in CCS), and transfer device (for in-use preparation) is provided in Section 3.2.P.2.3.8 of eCTD. Detailed analysis of

this information is presented in the memorandum of Dr. Andrey Sarafanov and is summarized below:

The initial assessment was performed for potential of contact materials to release leachables into the production stream. Components classified as having low leachables risk were excluded from the investigation. 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. Compounds calculated to have (b) (4) dose, corresponding to single-use product, were subjected to toxicological analysis to compare these values to Permitted Daily Exposure (PDE) for each compound. The extractables exposure levels from each component were found to be below the 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 Threshold of Toxicological Concern (TTC) of (b) (4). For elementals, AETs 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 upstream process high-risk materials were omitted from the assessment and 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 (PPQ lots (b) (4) in the ongoing stability study to cover the shelf-life storage of 36 months (PMC #1). This study will mimic actual in-use conditions.

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 post-marketing as stated in amendment 52 dated November 20, 2025 (PMC #1).

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The proposed shelf life for FESILTY DP is 36 months when stored at 2°C to 30°C. Detailed analysis of stability data provided in support of DP shelf life is presented in the memorandum of Dr. Yideng Liang and is summarized as follows:

FESILTY DP Storage Conditions

The following storage conditions were investigated to evaluate the stability profile of FESILTY DP:

- Long-term room temperature storage conditions: at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / (b) (4)
- Long-term room temperature storage conditions: at 30°C (b) (4) RH
- Accelerated storage conditions: (b) (4)

Stability-indicating specification parameters are included in the stability testing program used to determine the shelf life of FESILTY DP. The DP stability specifications are based on DP release specifications presented in Section 3.2.P.5.1 except some parameters specified in Table 3.2.P.8.2-19, eCTD Section 3.2.P.8.2. For (b) (4) parameters, the difference is the following:

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

Primary FESILTY DP Stability Study

The primary FESILTY DP stability study investigated (b) (4) PPQ batches under long-term storage conditions, comprising (b) (4) batches each manufactured with Cryoprecipitate separated from US plasma at (b) (4) and Grifols Therapeutics LLC, respectively. The test results demonstrated that all parameters remained within the updated version of the specification limits for the currently available 12 months under long-term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 30°C (b) (4) and 6 months under accelerated conditions (b) (4). No adverse trends were detected across any storage conditions.

Linear regression analysis was conducted for PPQ stability studies to assess Fibrinogen Activity, Specific Fibrinogen Activity, and (b) (4), Monomers, (b) (4) based on real-time data from long-term storage conditions. Predictive modeling based on the current data indicates that both parameters will remain within specification limits for up to 36 months.

Supportive/Supplementary DP Stability Study

The DP supportive/supplementary stability study included (b) (4) technical batches manufactured using process P2 with non-US plasma and (b) (4) additional batches manufactured using process P1 that were used in clinical trials.

For DP technical batches, all parameters remained within specified ranges with no observable trends for up to 12 months under storage conditions of 25°C to 30°C as well as under accelerated storage conditions at (b) (4). In (b) (4) supportive batches, all stability-indicating parameters remained within specified requirements for up to (b) (4) months (36-(b) (4) months) when stored at 5°C to 30°C and for up to (b) (4) under accelerated conditions at (b) (4) showed a slight increase but remained well within specification limits.

A linear regression analysis performed for the technical batches was inconclusive for shelf-life prediction pending additional data collection. A linear regression analysis was also performed for supportive batches for the parameters Fibrinogen Activity and (b) (4) data from storage under long-term conditions of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$, and 30°C (b) (4). A slight decline in Fibrinogen Activity was observed over the monitored time period, but all data remained within specification limits for up to (b) (4) months. The Specific Fibrinogen activity data demonstrated variability over time and (b) (4) data showed slight increases over time; however, both parameters remained within specification limits for up to (b) (4) months.

Reviewer's Assessment: The DP stability is supported by testing (b) (4) PPQ lots and comparable supportive lots stored at room temperature (5°C to 30°C) for up to 12 and (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, a 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 at the two different facilities (process P1 and P2). In-use stability testing demonstrated that the reconstituted product is stable for 24 hours at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. For clinical use, the Applicant defined that the reconstituted product should be administered within four (4) hours.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The stability program for FESILTY DP, including (b) (4) PPQ batches, (b) (4) technical batches, and all existing stability studies, will be monitored for up to (b) (4) months. The Applicant commits to finalizing the stability studies and to informing the FDA in the event of unexpected issues that may affect shelf life and require corrective actions (refer to eCTD Section 3.2.P.8.2).

In addition, the Grifols commits to placing (b) (4) at least (b) (4) commercial batch of FESILTY DP on long-term stability for the duration of the intended shelf life. Stability data will be included in annual reports, and any out-of-specification results will be reported according to established timelines.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

CBER/OCBQ/Division of Manufacturing and Product Quality (DMPQ) CMC reviewers are responsible for the review of all facilities and equipment information.

3.2.A.2 Adventitious Agents Safety Evaluation

A detailed evaluation of controls in place to ensure safety of FESILTY DP with regard to adventitious agents is presented in the memorandum of Dr. Ze Peng. It is summarized as follows.

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)

All plasma donations, (b) (4), and manufacturing pools undergo comprehensive testing for viral markers in accordance with FDA requirements. The manufacturing process for FESILTY uses no raw materials of human or animal origin, except for Source Plasma as the starting material and heparin sodium as an anticoagulant during manufacturing. The heparin sodium is porcine-derived and complies with all applicable (b) (4) requirements. The excipients used in FESILTY DP formulation were selected to minimize contamination risk. These manufacturing approaches collectively minimize the potential risk of contamination by adventitious viruses or TSE agents/prions.

Additionally, the potential for viral contamination of FESILTY is mitigated through three dedicated viral clearance steps integrated into the manufacturing process: (i)

Solvent/Detergent (S/D) treatment (b) (4)

(ii)

Ultraviolet C (UV-C) irradiation ((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 log₁₀ reduction factors shown in Table 23 and demonstrate sufficient viral clearance to support the proposed commercial manufacturing process for FESILTY.

Table 23. Cumulative virus reduction factors (log₁₀) 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 (log₁₀)	≥ 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.

3.2.A.3 Novel Excipients

Not applicable.

3.2.R Regional Information (USA)

❑ Executed Batch Records

The submission includes completed and fully executed batch record documentation for the PPQ batches listed in Table 21, Section 3.2.P.5.4 of this memorandum. The batch record documentation is hybrid documentation consisting of a mixture of paper-based and electronic documentation. A batch tree overview is provided for each batch.

❑ Method Validation Package

In eCTD Section 3.2.R.2 (Method Validation Package), Grifols references Section 3.2.P.5.2, which includes a detailed description of the analytical methods used, and Section 3.2.P.5.3, which includes validation of the analytical methods performed. No additional information regarding method validation protocols and reports is provided in this section.

❑ Combination Products

FESILTY is a co-packaged Type (b)(4) Biologics/Drug/Device combination product, which includes a 100 mL glass vial of one-gram lyophilized FESILTY DP powder, a glass vial of 50 mL sWFI as a diluent, and a needleless Nextaro v, 20/20 5 µm transfer device to transfer sWFI to the 100 mL glass vial of the DP for reconstitution of the lyophilizate.

The Nextaro v, 20/20 5 µm transfer device was developed by sfm medical devices GmbH, Germany, as a customized solution for FESILTY combination product and is FDA cleared with K240748 Device 510-K clearance letter (REF number 20040). Letter of Authorization from sfm medical devices GmbH is provided in eCTD Section 1.4.2.

To demonstrate compliance with the applicable device Quality Support regulations specified in 21 CFR 4.4(b)(1) for the combination product which includes a device constituent part and a drug constituent part, Grifols provided the following documents that were in compliance with 21 CFR 820.20 “Management responsibility”, 21 CFR 820.30 “Design controls” and 21 CFR 820.50 “Purchasing controls”.

The following Research Reports were also provided:

- BE-104-24/00 “Reducing (b) (4) particles in the Fibrinogen Concentrate (BT524) drug product using a transfer device including (b) (4) filter”
- BE-114-24/00 “Comparison of the reconstitution of Fibrinogen Concentrate (BT524) DP using 50 mL WFI bottles from (b) (4) Grifols”
- BE-207-24/00 (b) (4) testing of Fibrinogen Concentrate (BT524) drug product vials and integrity testing of Nextaro transfer devices after a representative transport for distribution”.

The Transfer Device Design Change and Design History

The Nextaro v represents an evolution from the standard Nextaro device, with specific modifications for large volume (50 mL) applications. The Design History File (DHF) documents all design activities and changes throughout the product lifecycle, maintained by Manufacturing Development per SOP-S-00193.

The design of the customized (optimized) Nextaro v transfer device addressed known issues with the standard Nextaro device, including the following:

- Incomplete solvent transfer due to vacuum formation: a laboratory testing at Biotest revealed that the standard Nextaro device had incomplete water transfer when used with the large 50 mL reconstitution volume required for FESILTY DP
- High physical effort during syringe withdrawal
- Particle contamination risks

The improved design incorporated:

- A venting system to prevent vacuum formation during 50 mL transfers
- A (b) (4) filter to reduce particle contamination
- Robust construction to minimize damage during transportation

Design Inputs and Design Outputs

Design Inputs are provided in document BE-200-24 describing the Product Requirements Specification (PRS) of the combination product.

Design Outputs are provided in document BE-202-24 summarizing the verification and validation activities of the design outputs for all sections of the PRS defined in the design input for the combination product.

Design Verification

Verification confirmed design outputs met design inputs through extensive testing.

Design Validation

Design Validation was performed under actual use conditions.

Purchasing Controls

Purchasing controls are established through comprehensive supplier management procedures.

Corrective and Preventive Action (CAPA)

CAPA management follows SOP-S-00065 with structured processes:

- CAPA initiation: Triggered by nonconformities, deviations, or inspection findings related to the transfer device
- Process flow: Systematic approach including CAPA plan definition, action implementation, effectiveness evaluation, and closure
- Responsibilities: Defined roles for Process Owner, QA Coordinators, and action owners
- Documentation: Electronic tracking in SAP QM system (Z4 reports) with defined timelines
- Effectiveness evaluation: Required assessment to ensure implemented actions successfully address root causes
- Integration: Links with deviation management and change control systems for comprehensive quality management

Risk Analysis

Comprehensive risk analysis was conducted at multiple levels:

- Device-Level Risk Analysis (conducted by sfm).
- Combination Product Risk Analysis (conducted by Biotest).
- Key Risk Findings and Mitigations:
 - Particle contamination risk: Mitigated through (b) (4) filter integration
 - Incomplete transfer risk: Addressed through venting system design
 - User error risks: Reduced through intuitive design features (color coding, tactile feedback)
 - Contamination risks: Minimized through sterile packaging and clear user instructions
 - Physical injury risks: Addressed through spike protection and robust housing design

Reviewers' Assessment: In the course of review, FDA noted that during clinical trials, the lyophilized investigational medicinal product FESILTY was reconstituted using a device that was different than Nextaro, i.e., either a (b) (4) transfer device from (b) (4) . The Nextaro v, 20/20 Transfer Device from SFM Medical devices GmbH was to be introduced after completion of the clinical phase and proposed for commercial distribution of the combination product. The standard Nextaro transfer device and the optimized version of the Nextaro (Nextaro v) were characterized in Research Report BE-104-24/00. The optimized Nextaro v device contains a (b) (4) filter (instead of (b) (4) in the (b) (4) device) and a ventilation valve directed to the water vial.

A study conducted by the Applicant for reducing (b) (4) in FESILTY DP using a transfer device including a (b) (4) filter showed that the number of (b) (4) formed during the DP production can be efficiently reduced by filtration. However, the (b) (4) of the (b) (4) was incapable of effectively reducing the number of (b) (4), whereas (b) (4) were removed (refer to Research Report BE-104-24/00). Therefore, the Nextaro v device with a (b) (4) filter was proposed as an alternative to the (b) (4) device. Results of the study confirmed that the Nextaro transfer device with (b) (4) filter can reduce the number of (b) (4), even from very high initial numbers, below their specification limits for the reconstituted DP.

Moreover, according to Research Report BE-114-24/00, with regards to the transfer and reconstitution times, it is highly advised to use the optimized Nextaro device.

Since a different device was used in the clinical trials, CBER consulted the Center for Drug Evaluation Center (CDER)/OSE/OMEPRM/DMEPAII for an assessment of human factors (HF), specifically, the Use-Related Risk Analysis (URRA) and Comparative Task Analysis for evaluation of the Nextaro v 20/20 5 µm transfer device to transfer the sWFI to the glass vial for reconstitution of the FESILTY lyophilizate.

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 # 01102794) to evaluate the use-related risk analysis (URRA) and comparative task analysis to determine whether the Applicant needs to submit human factors validation study (HFVS) results in support of the marketing application.

The DMEPA II determined that URRA and comparative analyses (CA) should be revised. The following on review of the revised URRA and CA provided by Grifols in response to the FDA IR did not identify any new, differing, or unique risks between the proposed Nextaro v, 20/20 5 µm transfer device and (b) (4) transfer device.

Grifols commits to further update the URRA based on Human Factor Advice in FDA IR #50 to appropriately capture the clinical impact associated with identified use errors or task failures (refer to PMC #5).

The physicochemical compatibility of reconstituted FESILTY DP is evaluated under section 3.2.P.2.6 *Compatibility* of this review memorandum.

❑ **Comparability Protocols**

Not applicable. Section 3.2.S.2.6 contains comparability studies performed during product development upon the changes in manufacturing process or manufacturing site.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

In Section 1.12.14, the Applicant submitted a claim for a Categorical Exclusion (CE) from the requirement to prepare an Environmental Assessment (EA) pursuant to 21 CFR 25.31(c) for “naturally occurring” products:

“Food and Drug Administration action on an application for marketing approval of a biological product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.”

Grifols also states that no extraordinary circumstances exist that would warrant the preparation of an EA.

Reviewer’s Assessment: According to 21 CFR 25.15(a), the Applicant submitted a request for a CE from EA under the appropriate category and provided adequate justification. The CE claim is accepted.

B. Reference Product Designation Request

Not applicable.

C. Labeling Review

Full Prescribing Information (PI):

In Section 1.14 *Draft Labeling*, the Applicant provided draft *US Prescribing Information* (USPI) and *Instructions for Use* (IFU) documents.

We reviewed the CMC-related information in USPI sections 3, “*Dosage Forms and Strengths*”, 11, “*Description*”, 12.1, “*Mechanism of Action*”, and 16, “*How Supplied/Storage and Handling*”. Our proposed edits and comments were communicated to Grifols by the Regulatory Project Manager. The final version received on December 11, 2025, is acceptable.

Carton and Container Label:

In Section 1.14 *Draft Labeling*, Grifols provided draft vial labels (FESILTY and sWFI) and carton labels information. We reviewed the CMC-related information from a Product Quality perspective. Our proposed edits and comments were communicated to Grifols, and the labels received on December 11, 2025, were found acceptable.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

In Clinical studies the Applicant used the following methods for determination of fibrinogen in patient’s samples – primary endpoints:

- Fibrinogen Antigen (FiAg)
- Fibrinogen Activity (FiAc)

“Fibrinogen Antigen” method was used for the measurement of fibrinogen antigen in samples of study 984 by immunological (b) (4) using (b) (4) system. (b) (4) diagnostic reagents were used for the quantitative determination of coagulation factors (fibrinogen) in human plasma. The Lower Limit of Quantification (LLOQ) for the method is (b) (4).

“Fibrinogen Activity” is (b) (4) assay-based method used for the measurement of Fibrinogen activity in samples of study 984 using (b) (4) analyzer. The Lower Limit of Quantification (LLOQ) for the method is (b) (4) (for activity validation) / (b) (4) (mentioned in pharmacokinetic report).

The Applicant performed validation of the Fibrinogen Antigen and Activity test methods according to the EMA guideline on bioanalytical methods.

The following validation parameters were assessed for both analytical methods:

- Selectivity - using fibrinogen-depleted plasma from multiple lots
- Carry Over - alternating high concentration and blank samples
- Lower Limit of Quantification (LLOQ) - Accuracy and Precision testing
- Calibration Curve - back-calculation accuracy assessment
- Accuracy - within-run and between-run testing at multiple concentration levels
- Precision - Coefficient of variation assessment
- Stability – including the following:
 - Reagent on-board stability
 - Sample handling/pipetting stability
 - Bench time stability
 - Long-term storage stability (b) (4)
 - Freeze/thaw cycle stability

For “Fibrinogen Antigen” method the additional Validation parameter was used:

- Dilution Integrity - testing internal dilutions from (b) (4)

The following Acceptance Criteria were applied:

- Accuracy: (b) (4) for most parameters; (b) (4) at LLOQ
- Precision: (b) (4) CV for most parameters; (b) (4) CV at LLOQ
- Selectivity: Response
- Carry Over: Response
- Stability: (b) (4) recovery for most conditions; (b) (4) for long-term stability

Both methods underwent additional robustness validation to ensure reliability across different reagent and standard batches, demonstrating method stability over time.

Both methods included incurred sample reanalysis (ISR) with (b) (4) of study samples reanalyzed, meeting the acceptance criterion of (b) (4) of samples within (b) (4) of their mean values.

Reviewers' Assessment: The provided information regarding analytical or bioanalytical methods used to test clinical study endpoints and the method validations are acceptable as submitted. The results obtained for all the validation parameters met the predefined acceptance criteria for both test methods used in the Clinical studies. Therefore, the method validation confirmed that both test methods are suitable for their intended use to measure Fibrinogen Antigen and Fibrinogen Activity in samples of study 984.