Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Summary Basis for Regulatory Action

Date:	June 29, 2026
From:	Silvia De Paoli, Biological Reviewer, Review Committee Chair, OBRR/DBCD Kimberly Bissohong, Regulatory Project Manager, OBRR/RPMS
BLA STN:	125702/0
Applicant:	Vascular Solutions, LLC (a subsidiary of Teleflex)
Submission Receipt Date:	January 28, 2021
*Action Due Date:	July 29, 2026
Proper Name:	Freeze Dried Plasma
Proprietary Name:	EZPLAZ™ Freeze Dried Plasma
Indication:	EZPLAZ™ Freeze Dried Plasma (FDP) is indicated for transfusion in adults when plasma is required and other plasma products are not available. Indications include: (1) Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors [e.g., liver disease, disseminated intravascular coagulation (DIC)] (2) Patients undergoing massive transfusion who have clinically significant coagulation deficiencies (3) Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of the warfarin effect.

*PDUFA = Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of EZPLAZ™ Freeze Dried Plasma (BLA 125702/0). A Phase 4 postmarketing requirement (PMR) safety study with a primary endpoint of thrombotic/thromboembolic events is required.

Anne Eder, MD, PhD
Director, Product Office

Vincent Amatrudo, JD
Director, Office of Compliance and Biologics Quality (OCBQ)

Discipline	Reviewer – Office/Division
CMC Product	Silvia De Paoli, OBRR/DBCD
CMC Facility	Shaina Fullwood, OCBQ/DMPQ
Establishment Inspection Report	Ou (Olivia) Ma, OCBQ/DMPQ
Clinical	Alice Chen, OBRR/DBCD
Postmarketing Safety Pharmacovigilance Review	Firoozeh Alvandi, OBPV/DPV
Statistical	Zhen Jiang, Yuan Hu, OBPV/DB/DNCE
Labeling	Barbara Peoples, OBRR/DBCD/BPB
Promotional, Proprietary Name Review	Kristine Khuc, Oluchi Elekwachi, Micheal Brony, OCBQ/APLB

1. Introduction

Vascular Solutions LLC, a subsidiary of Teleflex Incorporated (6420 Sycamore Lane North, Maple Grove, MN 55369; FEI: 3002827704; U.S. License No. 2135; DUNS: 116901279), submitted Biologics License Application (BLA) 125702 for EZPLAZ™ Freeze Dried Plasma (FDP). EZPLAZ™ FDP is a lyophilized plasma powder manufactured from Fresh Frozen Plasma (FFP) and is regulated as a blood component under 21 CFR Part 606. As a combination product, EZPLAZ™ FDP is also subject to the requirements of 21 CFR Parts 210, 211, 600–640, and 820, pursuant to 21 CFR Part 4.

EZPLAZ™ FDP is indicated for the treatment of multiple coagulation factor deficiencies in adults when plasma is required and other plasma products are not available. Other plasma products (i.e., Fresh Frozen Plasma (FFP), Plasma Frozen within 24 Hours (PF24), and Plasma Frozen within 24 Hours after Phlebotomy Held at Room Temperature up to 24 Hours (PF24RT24)) require continuous frozen storage and must be thawed prior to transfusion, imposing logistical constraints in settings lacking cold-chain infrastructure, including military forward operating environments, remote or resource-limited civilian locations, and pre-hospital or mass casualty emergency scenarios. EZPLAZ™ FDP may be stored for up to 12 months at 2–25 °C (36–77 °F) and reconstituted in less than 2.5 minutes, enabling time-critical administration in such settings.

The review team focused on three principal areas that required interactive review: product quality and stability, clinical safety, and the suitability of the lyophilization bag container. The review included an evaluation that the primary container in which EZPLAZ™ FDP is manufactured and stored, provides adequate aseptic assurance for the finished product. With respect to product quality and stability, the available data demonstrate that lyophilization preserves clinically meaningful coagulation factor activities across the full 12-month shelf life under the approved storage conditions of 2–25 °C. At 4 °C, the greatest observed loss was Factor VIII activity, which decreased approximately 22% from the comparator, FFP, at baseline. At 25 °C, degradation was more pronounced, with Factor VIII decreasing by about 39% and von Willebrand Factor (vWF) activity decreasing by about 40% from FFP at baseline. Notwithstanding the greater degree of degradation at 25 °C, all coagulation factor activity levels met the established acceptance criteria at 12 months under both storage conditions, supporting the labeled shelf life.

With respect to clinical safety, a Phase 1 safety and tolerability dose-escalation study, conducted in 24 healthy adult volunteers, demonstrated an acceptable safety profile across all dose cohorts, with no deaths, serious adverse events (SAEs), suspected unexpected serious adverse reactions or product-related treatment-emergent adverse events (TEAEs) reported. In the highest dose cohort (810 mL), post-infusion coagulation factor levels were comparable to those observed following FFP administration, providing support for clinical benefit.

With respect to container integrity, the lyophilization bag container (b) (4) that serves a dual function: (b) (4) for the finished product. Deficiencies in the validation of the (b) (4) aseptic functionality were identified during the 2021 and 2025 FDA pre-license inspections. To resolve the issues, the sponsor developed a validation framework which demonstrated adequate control of (b) (4) risk under routine manufacturing conditions.

The Review Committee considered the initial submission under an accelerated BLA pathway and granted it Fast Track designation in a rolling BLA in 2019. However, in 2025, FDA determined that there was available clinical experience with freeze dried plasma products and that the confirmatory study in healthy subjects discussed during the initial submission

(i.e., warfarin reversal) would not be informative. Clinical experience includes use in military combat since July 2018 of two different freeze dried plasma products under emergency use authorization (Emergency Use Authorization | FDA). Consequently, FDA determined that approval with a Phase 4 PMR safety study under FDAAA 505(o)(3) was appropriate because of the significant unmet medical need and the restriction of use to settings where other plasma products are not available. Published clinical trials of similar freeze-dried plasma products in patient populations for the same intended use had favorable safety profiles and outcomes and also support the use of this product in a restricted setting where other plasma products are not available.

2. Background

Traumatic hemorrhage and acute traumatic coagulopathy are time-sensitive, medical emergencies in which early plasma transfusion is an essential component of damage control resuscitation. Acute traumatic coagulopathy is a systemic impairment of hemostasis resulting from the consumption and dilution of coagulation factors following severe injury that affects about 40% of transfused combat casualties and is associated with significantly worsened outcomes. Exsanguination from impaired hemostasis is the leading cause of preventable battlefield death, typically occurring within two hours of injury. Timely plasma administration, which replenishes depleted coagulation proteins and supports restoration of hemostasis, is associated with improved survival.

The logistical requirements of plasma products represent a well-recognized and longstanding barrier to timely plasma administration in austere environments. FFP requires continuous frozen storage at ≤ −18 °C and must be thawed — a process requiring 20–30 minutes before transfusion. In settings lacking freezers, devices to thaw frozen plasma, or reliable power sources, these requirements may delay or render plasma effectively unavailable. Delays in plasma administration may worsen coagulopathy and morbidity, thereby increasing the risk of death.

The U.S. has a history of use of freeze-dried plasma in traumatic settings. Freeze-dried plasma was used extensively during World War II, with millions of units transfused to U.S. military forces. Reported at the July 18, 1941, meeting of the Subcommittee on Blood Substitutes, several hundred lots demonstrated a favorable safety profile; observed reactions

after its administration were limited to mild, infrequent urticaria. The absence of sufficient donor screening and pathogen testing at the time, however, led to unacceptable rates of hepatitis transmission, and FDP was withdrawn from use by 1968. Interest in dried plasma resurfaced in the 1990s, driven by the recognized need for a field-ready blood product capable of supporting combat casualty care in austere environments. Advances in donor screening, infectious disease testing, and manufacturing technology have since addressed the hepatitis transmission concerns that led to FDP's withdrawal.

Current interest in dried plasma products and innovative blood components is a public health priority. Public Law 115-92 was enacted in December 2017 amends the FD&C Act to expand emergency use authorization, accelerate medical product development, and require joint agency (i.e., FDA and DoD) collaboration. Dried plasma was one of the first products identified under the law as a Department of Defense priority for the military and increased collaboration with FDA, reflecting its strategic importance for national defense and military medical readiness.

Published literature on French lyophilized plasma (FLYP), a pharmacologically related product used in both military and civilian trauma settings, demonstrates faster time-to-transfusion, improved coagulation parameters, and no product-related SAEs across multiple studies. FDA authorized French lyophilized plasma under emergency use authorization in July 2018 (Emergency Use Authorization | FDA). While FLYP and EZPLAZ™ FDP are different freeze-dried plasma products because of different manufacturing steps, the military experience under EUQ and the published literature provides supportive evidence for the safety and efficacy profile of this class of freeze-dried plasma products and informs the benefit-risk assessment for EZPLAZ™ FDP.

The clinical evidence supporting approval of EZPLAZ™ FDP includes a Phase 1 safety study conducted in 24 healthy volunteers at the University of Cincinnati under IND 17154. The study employed an ascending-dose, crossover design, enrolling subjects across three cohorts receiving 270 mL, 540 mL, and 810 mL of FDP. FFP served as the comparator in the highest-dose cohort only. All infusions used autologous plasma. Secondary endpoints — coagulation factor levels assessed as surrogate markers — were evaluated in Cohort 3 only and were found to be comparable between FDP and FFP.

Regarding the safety profile of EZPLAZ™ FDP in this study, no deaths, SAEs, or product-related TEAEs occurred. Nine of 24 subjects experienced 17 mild TEAEs, none of which were attributed to EZPLAZ™ FDP. The independent Data Monitoring Committee (DMC) identified no safety concerns.

The limitations of this clinical program include the size of the study and the population studied. The safety database is small (N=24), the study population (healthy volunteers) does not reflect the intended patient population (trauma patients), and no clinical efficacy data in the intended population are available. However, there is extensive history of use of freeze-dried plasma in clinical settings, with favorable safety profiles and outcomes, including randomized controlled trials for the same intended use and patient population. These limitations are outweighed by the significant unmet medical need, the restriction of use to settings where plasma is not available, and the requirement for a post marketing safety study.

Product Description

EZPLAZ™ FDP is a lyophilized plasma derived from single-donor human plasma (FFP), intended for reconstitution and intravenous or intraosseous transfusion. Each EZPLAZ™ FDP unit is manufactured from single units of approximately 270 mL of FFP collected from male volunteer donors at U.S. licensed blood establishments. The FFP is prepared from either apheresis plasma stored with acid-citrate-dextrose (ACD) anticoagulant or whole blood-derived plasma stored with citrate phosphate dextrose (CPD) anticoagulant. The exclusive use of male donors reduces the risk of transfusion-related acute lung injury (TRALI), because men are less likely to have anti-HLA antibodies than women who might be sensitized to human leukocyte antigens during pregnancy.

EZPLAZ™ FDP contains the same plasma proteins present in FFP. These include coagulation factors (Fibrinogen, Factors II, V, VII, VIII, IX, X, XI, XIII, and von Willebrand Factor antigen), albumin, fibrinolytic proteins, immunoglobulins, Protein C, Protein S, and other plasma proteins. The manufacturing process does not remove or add any proteins, and the finished product contains no additives, excipients, or preservatives. The reviewed data demonstrate that lyophilization preserves clinically meaningful coagulation factors activities across the full 12-month shelf life under the approved storage conditions of 2–25 °C. The

product is available in two blood groups: Group AB and Group A with low-titer anti-B (defined as no agglutination at a 1:200 dilution by saline tube method). Each unit yields approximately 270 mL upon reconstitution with 250 mL Sterile Water for Injection (SWFI, USP). The availability of Group AB and low-titer Group A plasma permits emergency administration before ABO group determination, a clinically important feature for the intended use setting.

EZPLAZ™ FDP is supplied as a complete, self-contained packaged kit containing:

- One unit of EZPLAZ™ FDP sealed in an outer foil pouch (b) (4)
- One 250 mL bag of USP-grade Sterile Water for Injection (SWFI) supplied by (b) (4)
- One sterile Fluid Transfer Set, supplied by (b) (4)
- One sterile Blood Transfusion Set with a 170-micron filter (b) (4)

The kit format will minimize reconstitution errors and support safe use in field or emergency settings where ancillary supplies may not be available. The use of a flexible plastic bag, rather than the bottles used for historical freeze-dried plasma, eliminates the risk of glass breakage during handling, transport, and storage.

EZPLAZ™ FDP is stored at 2–25°C (36–77 °F) with a shelf life of 12 months. Following reconstitution, the product must be infused within 4 hours and must not be refrigerated or refrozen.

Coagulation factor levels over the product shelf life are summarized in Tables 1 and 2, which comprise the stability data in the Teleflex Circular of Information for EZPLAZ™ FDP.

Table 1: Coagulation Protein Levels in FFP and FDP — Storage at 4 °C through 12 Months.

Analyte	**FFP (Mean ± SD)[a]**	**FDP T0 (Mean ± SD)[a]**	**FDP T6M – 4 °C (Mean ± SD)[b]**	**FDP T12M – 4 °C (Mean ± SD)[b]**	**% Change T0 vs. FFP**	**% Change T12M vs. FFP**
FII (IU/dL)	93.7 ± 10.4	86.2 ± 9.7	86.2 ± 9.7	86.2 ± 9.7	8	8
FV (IU/dL)	99.5 ± 16.1	92.0 ± 15.7	88.3 ± 15.7	89.2 ± 15.7	8	10

FVII (IU/dL)	97.9 ± 20.9	92.4 ± 19.6	89.6 ± 19.6	86.9 ± 19.6	6	11
FVIII (IU/dL)	128.7 ± 23.6	108.4 ± 21.4	98.6 ± 21.4	100.8 ± 21.4	16	22
FIX (IU/dL)	120.5 ± 18.4	108.6 ± 17.8	105.3 ± 17.8	102.1 ± 17.8	10	15
FX (IU/dL)	90.6 ± 13.5	86.4 ± 14.5	85.5 ± 14.5	84.7 ± 14.5	5	7
FXI (IU/dL)	93.1 ± 16.6	83.9 ± 15.2	83.9 ± 15.2	83.9 ± 15.2	10	10
FXII (IU/dL)	104.0 ± 22.9	97.3 ± 21.1	96.3 ± 21.1	96.3 ± 21.1	6	7
Fibrinogen (mg/dL)	352 ± 62	338 ± 61	331 ± 61	331 ± 61	4	6
Antithrombin (IU/dL)	94 ± 10	86 ± 10	85 ± 10	86 ± 10	9	9
Protein C (IU/dL)	98 ± 17	91 ± 16	91 ± 16	91 ± 16	7	7
Protein S (IU/dL)	106.6 ± 18.4	100.6 ± 16.6	97.6 ± 16.6	91.5 ± 16.6	6	14
vWF Activity (IU/dL)	142.2 ± 46.3	130.7 ± 40.3	126.8 ± 40.3	121.6 ± 40.3	8	14
vWF Antigen (IU/dL)	150.3 ± 44.9	142.4 ± 41.8	138.1 ± 41.8	138.1 ± 41.8	5	8

[a] Mean and SD from individually tested plasma units pre- and post-lyophilization.
[b] Mean values based on percent change in pooled stability batches; SD assumed from individually tested FDP units at T0.

Table 2: Coagulation Protein Levels in FFP and FDP — Storage at 25 °C through 12 Months.

Analyte	**FFP (Mean ± SD)[a]**	**FDP T0 (Mean ± SD)[a]**	**FDP T6M – 25 °C (Mean ± SD)[a]**	**FDP T12M – 25 °C (Mean ± SD)[b]**	**% Change T0 vs. FFP**	**% Change T12M vs. FFP**
FII (IU/dL)	93.7 ± 10.4	86.2 ± 9.7	79.3 ± 9.7	71.5 ± 9.7	8	24
FV (IU/dL)	99.5 ± 16.1	92.0 ± 15.7	79.1 ± 15.7	70.8 ± 15.7	8	29
FVII (IU/dL)	97.9 ± 20.9	92.4 ± 19.6	84.1 ± 19.6	77.6 ± 19.6	6	21
FVIII (IU/dL)	128.7 ± 23.6	108.4 ± 21.4	85.6 ± 21.4	78.0 ± 21.4	16	39
FIX (IU/dL)	120.5 ± 18.4	108.6 ± 17.8	91.2 ± 17.8	81.5 ± 17.8	10	32
FX (IU/dL)	90.6 ± 13.5	86.4 ± 14.5	76.9 ± 14.5	67.4 ± 14.5	5	26

FXI (IU/dL)	93.1 ± 16.6	83.9 ± 15.2	78.0 ± 15.2	78.0 ± 15.2	10	16
FXII (IU/dL)	104.0 ± 22.9	97.3 ± 21.1	80.8 ± 21.1	72.0 ± 21.1	6	31
Fibrinogen (mg/dL)	352 ± 62	338 ± 61	301 ± 61	277 ± 61	4	21
Antithrombin (IU/dL)	94 ± 10	86 ± 10	83 ± 10	80 ± 10	9	15
Protein C (IU/dL)	98 ± 17	91 ± 16	87 ± 16	86 ± 16	7	12
Protein S (IU/dL)	106.6 ± 18.4	100.6 ± 16.6	84.5 ± 16.6	73.4 ± 16.6	6	31
vWF Activity (IU/dL)	142.2 ± 46.3	130.7 ± 40.3	103.3 ± 40.3	85.0 ± 40.3	8	40
vWF Antigen (IU/dL)	150.3 ± 44.9	142.4 ± 41.8	129.6 ± 41.8	121.0 ± 41.8	5	20

[a] Mean and SD from individually tested plasma units pre- and post-lyophilization.
[b] Mean values based on percent change in pooled stability batches; SD assumed from individually tested FDP units at T0.

Mechanism of Action

EZPLAZ™ FDP acts by replenishing deficient human plasma proteins, principally coagulation factors, to restore hemostasis in patients with multiple coagulation factor deficiencies. The reconstituted product contains the same plasma proteins present in FFP, including pro-coagulant factors (FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, and fibrinogen), anticoagulant proteins (Protein C, Protein S, and antithrombin), and other plasma proteins (albumin, fibrinolytic proteins, immunoglobulins, and von Willebrand factor [vWF]). The reviewed data demonstrate that lyophilization preserves clinically meaningful coagulation factors activities across the full 12-month shelf life. This broad protein complement supports hemostasis across multiple pathways and is appropriate for the management of complex, multi-factor coagulopathies such as those associated with trauma, liver disease, DIC, and anticoagulant therapy.

Indications for Use

EZPLAZ™ Freeze Dried Plasma (FDP) is indicated for transfusion in adults when plasma is required and other plasma products are not available.

Indications include:

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors [e.g., liver disease, disseminated intravascular coagulation (DIC)]
- Patients undergoing massive transfusion who have clinically significant coagulation deficiencies
- Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect

The restriction to settings where plasma is not available ensures that EZPLAZ™ FDP is used in the contexts for which it was developed, and not as a routine substitute in settings where FFP or other plasma products are readily accessible.

Regulatory History

Table 3. Regulatory History

Regulatory Event / Milestone	Date
IND 17154 — Submission of protocol for exploratory study FDP-1 (S-14-12 v1.0): *"A Phase 1, single-center, partial double-blind, randomized, controlled (versus FFP in Cohort 3 only) clinical study of the safety of ascending doses of autologous FDP in healthy volunteers"*	October 14, 2016
Submission of S-14-12 Clinical Study Report	January 23, 2019
BL 125702/0, FDA acknowledges Fast Track designation in the initial part of the rolling BLA submitted March 29, 2019	April 8, 2019
Agreed Initial Pediatric Study Plan (iPSP)	September 19, 2019
Study sponsorship transferred to Teleflex	December 7, 2020
Final part of the BL 125702/0 application was submitted, and the official review clock began as a priority review, due 6 months from filing date (September 28, 2021).	January 28, 2021
Pre-License Inspection #1 — Form FDA 483 issued with 14 observations	May 24–28, 2021

Complete Response Letter issued — manufacturing deficiencies only; no clinical or statistical deficiencies identified	September 2, 2021
○ CR extension request #1 received to extend the resubmission of the application to September 2, 2024. ○ CR extension request #2 received to extend the resubmission of the application to January 31, 2026.	August 24, 2022 May 24, 2024
Type B face-to-face meeting (BL 125702/0.61; Meeting ID 21559) — FDA communicated that the FDP-2 warfarin reversal study in healthy volunteers was no longer considered an appropriate confirmatory study; application transitioned from an accelerated approval pathway consideration to a traditional BLA approval pathway with a Phase 4 Title IX safety study PMR	July 30, 2025
BLA resubmission (BL 125702/0.67) includes CRL/483 responses; updated documentation; revised subsections and equipment/validation records; proposed labeling (clean/redline); advertising and promotional materials	September 29, 2025
Pre-License Inspection #2 — Form FDA 483 issued with 5 observations; all observations subsequently resolved	December 15–19, 2025
IR Letter issued — communicating revised Phase 4 PMR parameters and updated pediatric study milestones	May 29, 2026
Sponsor response — agreement to revised Phase 4 non-inferiority margin (OR <2.0) and incorporation of group sequential interim analysis design	June 8, 2026
EZPLAZ™ FDP (BL 125702) licensed	July 29, 2026

Total Time in Review:

- Initial Submission to CR/Manufacturing 483s: January 28, 2021, to September 2, 2021. Time in Review: 7 months, 5 days
- Resubmission received on September 29, 2025, following two extensions (total elapsed time: 4 years 27 days) with a 6-month review clock and original due date March 31, 2026; however, the lapse in FDA appropriations (i.e., the government shutdown) from October 1, 2025, to November 12, 2025, as well as a major

amendment extended the review deadline to July 29, 2026. Total review time for resubmission: 10 months.

3. Chemistry, Manufacturing, and Controls (CMC)

The CMC program presented two significant manufacturing challenges during the review: the adequacy of the lyophilization bag container as an aseptic manufacturing system, and the control of foreign material (FM) in the lyophilization bag container prior to use. Both issues have been satisfactorily resolved. The CMC program is considered adequate to support licensure, and all CMC reviewers recommend approval.

a. Product Quality

Fresh Frozen Plasma (FFP) Starting Material

EZPLAZ™ FDP is manufactured from FFP prepared by U.S. licensed blood establishments. The plasma is collected from male volunteer donors only and stored with ACD or CPD anticoagulant.

Donor screening and infectious disease testing are performed in accordance with 21 CFR § 630.10 (donor eligibility) and 21 CFR § 610.40 (testing for relevant transfusion-transmitted infections). EZPLAZ™ FDP is provided as blood groups AB or A, with low titer anti-B (< 1:200 by saline tube method). In the emergency treatment of hemorrhage or coagulopathy, group A and group AB EZPLAZ™ FDP may be administered to any patient prior to determining their ABO blood group.

Manufacturing Process

The EZPLAZ™ FDP manufacturing process is built around the custom-designed lyophilization bag container, which serves the dual function of lyophilization vessel and primary container closure system. The lyophilization bag container is manufactured by (b) (4)

(b) (4)

lyophilization bag containers are subsequently shipped to Vascular Solutions for use in manufacturing.

The manufacturing process proceeds in (b) (4) stages:

(b) (4)

(b) (4)

Control Strategy

The control strategy for EZPLAZ™ FDP is designed to ensure product quality, safety, and traceability at each stage of the manufacturing process from FFP receipt through finished product distribution. It encompasses electronic batch record management, raw material qualification, in-process monitoring, and 100% unit-level lyophilization bag container testing, as described below.

Traceability and Batch Records

The Blood Establishment Computer Software (BECS) — specifically (b) (4) serves as the primary electronic manufacturing record, tracking each unit from FFP receipt through distribution in compliance with 21 CFR Parts 210–211, 600–640, and Part 11. Commercial units maintain 1:1 donor-to-FDP traceability, linking each finished unit to its source FFP donor. Quality control and stability units are traced to the FFP pool and individual Donor Identification Numbers (DINs).

Key Process Controls and In-Process Tests

(b) (4)

Product Stability and Shelf Life

Stability studies demonstrate that EZPLAZ™ FDP retains clinically meaningful coagulation factor activity throughout the approved 12-month shelf life under both 4 °C and 25 °C storage conditions. The primary stability program evaluated coagulation protein levels at four time points — T0, T3, T6, and T12 months across three batches stored under both temperature conditions, with results compared against the FFP starting material baseline. As shown in Tables 1 and 2 of the Circular of Information, reconstituted FDP retains, on average, more than 80% of the coagulation factor levels of the starting FFP at T0.

Storage temperature has a pronounced effect on coagulation factor stability. At 4 °C, degradation is modest: most factors retain greater than 85% of FFP baseline activity at 12 months, with Factor VIII demonstrating the greatest loss at approximately 22%. At 25 °C, degradation is substantially greater after 12 months of storage compared to the FFP baseline, with Factor VIII decreasing by about 39%; vWF activity, by about 40%; Factor IX by about 32%; Factor XII, by about 31%; and Protein S, by about 31%. Despite this greater

degree of degradation during 12-month storage compared to FFP, all coagulation factor activity levels in EZPLAZ™ FDP met the established acceptance criteria at 12 months under both storage conditions, supporting the labeled shelf life and the product's suitability for clinical use.

The acceptance criteria were established to ensure that reconstituted EZPLAZ™ FDP retains sufficient coagulation factor activity to provide clinically meaningful hemostatic support. Key thresholds include FVIII (b) (4) FV (b) (4) FIX (b) (4) Protein S (b) (4) and vWF (b) (4) factor activity. These thresholds are consistent with levels of coagulation factor activity associated with hemostatic effects.

Post-reconstitution stability data demonstrate that the product must be infused within 4 hours of reconstitution. The data show that Factor VIII may decrease further by up to 12% during the 4-hour post-reconstitution hold at 25 °C. However, there is minimal change (decrease of less than 5%) for all other factors change.

Safety Concerns and Manufacturing Risk Management

Four principal manufacturing-related safety concerns were identified during the review**:**

1. Lyophilization Bag Container Integrity and Aseptic Manufacturing

The most significant manufacturing challenge identified during the review was the lyophilization bag container integrity and aseptic manufacturing. EZPLAZ™ FDP is manufactured under aseptic not sterile conditions; the product is not (b) (4) . The sterility of the finished product depends on the integrity of the lyophilization bag container as an aseptic manufacturing system throughout the lyophilization process. The (b) (4) is the critical element of this system. (b) (4)

Deficiencies in the validation of the (b) (4) aseptic functionality were identified during both the 2021 and 2025 pre-license inspections. These deficiencies were resolved through a layered, four-part validation framework:

(b) (4)

(b) (4)

These four lines of evidence, considered in combination, provide a layered demonstration that (b) (4) risk is adequately controlled under routine manufacturing conditions.

This issue is considered resolved.

2. Foreign Material in Lyophilization Bag Container

During the 2021 pre-license inspection, a high rate of lyophilization bag container discard due to foreign material (FM) was identified as a significant manufacturing concern. Investigation identified both intrinsic FM sources (b) (4) and extrinsic FM sources (b) (4) The root cause of the problem was the absence of FM design requirements and controls in Vascular Solutions procedures, compounded by contributing factors at each supplier. Vascular Solutions implemented comprehensive corrective and preventive actions (CAPAs) across the company and its suppliers, including elimination of uncontrolled FM sources, establishment of robust FM specifications and inspection requirements, and implementation of enhanced incoming inspection procedures. In summary, Vascular Solutions' procedures confirms that the lyophilization bag containers are free of visible particulates before use. **This issue is considered resolved.**

3. (b) (4) ***Analytical Interference During Development-Phase Stability Testing***

During R&D feasibility stability testing, Vascular Solutions observed atypical (b) (4) results in samples stored at 25 °C at the 6-month timepoint and at (b) (4) °C at the 3-month timepoint. Beginning in April 2018, parallel testing was initiated using both the (b) (4) method and the (b) (4) method on the (b) (4) to characterize the anomalous findings. Vascular Solutions initially attributed the atypical results to interference from (b) (4) degradation products. However, subsequent trend analysis further informed during a teleconference with FDA on June 26, 2019 (BL 125702/SN0002) determined this hypothesis to be inconsistent with the observed data: rather than decreasing as expected with progressive degradation, (b) (4) values in samples stored at 25 °C or higher appeared to increase over time, a result that is not physiologically plausible.

The root cause was identified as an (b) (4)

(b) (4)

Following completion of this investigation, Vascular Solutions discontinued use of the (b) (4) method and transitioned exclusively to the validated (b) (4) method (b) (4) measurement in FDP stability and release testing. The (b) (4) method has been validated and verified in accordance with (b) (4) (b) (4) and (b) (4) demonstrating specificity, accuracy, precision, and robustness in the FDP (b) (4). All commercial stability and batch release (b) (4) data presented in this BLA were generated using the (b) (4) method. **This issue is considered resolved.**

4. Infectious Disease Transmission

The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard. The risk is present with all blood components and not unique to EZPLAZ™ FDP. This risk is managed through the exclusive use of FFP sourced from U.S. licensed blood establishments. Donor screening and infectious disease testing are performed in accordance with 21 CFR §630.10 (donor eligibility) and 21 CFR §610.40 (testing for relevant transfusion-transmitted infections). The current risk of transfusion-transmitted HIV, HCV and HBV are less than 1 in 2 million transfusions (Transfusion 2025; 65:2128-2143). The risk is outweighed by the potential benefit in the context of the intended use setting and is addressed in labeling.

b. Testing Specifications

Analytical methods used for batch release and stability testing were validated and/or verified in accordance with (b) (4) and applicable internal standard operating

procedures (SOPs). All methods have been found acceptable for their intended purpose, demonstrating specificity, accuracy, precision, and robustness.

Verified Methods (b) (4) *FDA-Cleared)*

- (b) (4)

- Total Protein: (b) (4)
  - Moisture Content: (b) (4)
  - pH: (b) (4)
  - (b) (4)
  - (b) (4)

Validated Methods (b) (4)

- (b) (4)
- Reconstitution Time and Appearance: Internally developed by Vascular Solutions
- (b) (4) Test Procedure: (b) (4)
- Foil Pouch (b) (4) : Validated for accuracy, precision, intermediate precision, linearity, and range

FDP commercial stability specification and batch release specification tests and acceptance criteria are described in Tables 4-6.

Table 4. FDP Commercial Stability Specification.

Test	**Acceptance Criteria**
Description (Appearance)	Off-white to dark amber dry powder; no chunks or hard spots
Post-Reconstitution Appearance	Near-uniform, cloudy liquid
Reconstitution Time	≤ 2.5 minutes (150 seconds)
Moisture Content (%)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
pH	6.5–7.5

(b) (4)	(b) (4)
(b) (4)	(b) (4)
Fibrinogen – (b) (4)	(b) (4)
FV Activity (%)	(b) (4)
FVIII Activity (%)	(b) (4)
FIX Activity (%)	(b) (4)
FX Activity (%)	(b) (4)
FXI Activity (%)	(b) (4)
FXII Activity (%)	(b) (4)
Protein S Activity (%)	(b) (4)
vWF Activity (%)	(b) (4)
vWF Antigen (%)	(b) (4)
(b) (4)	(b) (4)
FVIII Activity – (b) (4)	(b) (4)
Protein S Activity – (b) (4)	(b) (4)

Table 5. FDP Batch Release Specification — (b) (4)

Test	(b) (4)	
(b) (4)	(b) (4)	
FVIII Activity	(b) (4)	
Protein S Activity	(b) (4)	
Total Protein	(b) (4)	

[a] QC units manufactured from a minimum of (b) (4) FFP units.

Table 6. FDP Batch Release Specification — Individual Result from Each (b) (4) .

Test	**Lower Limit**	**Upper Limit**
Description (Appearance)	Off-white to dark amber dry powder; near-uniform cloudy liquid upon reconstitution	—
pH	6.5	7.5
(b) (4)		
(b) (4)		
Reconstitution Time	N/A	≤ 2.5 min
Moisture Content	N/A	(b) (4)
(b) (4)		

[a] QC units manufactured from a minimum of (b) (4) thawed and (b) (4) FFP units.

c. CBER Lot Release

This product is a blood component and therefore will not be subject to CBER lot release.

d. Facilities Review / Inspection

FDA conducted two pre-license inspections at Vascular Solutions LLC (6420 Sycamore Lane North, Maple Grove, MN 55369; FEI: 3002827704), the sole manufacturing site for EZPLAZ™ FDP, where all manufacturing, lyophilization, primary labeling and packaging, final release testing, and product storage and distribution activities are performed.

The first pre-licensure inspection was conducted on May 24-28, 2021. FDA issued a Form FDA 483 with 14 observations, covering deficiencies in process validation, lyophilization bag container qualification, closed system demonstration, equipment cleaning and qualification, incoming material controls, (b) (4) controls, labeling, shipping validation, and facility cleanliness. These deficiencies were significant and the basis for the FDA Complete Response Letter issued September 2, 2021.

The second pre-license inspection was conducted on December 15-19, 2025, following resubmission of the BLA. FDA issued a Form FDA 483 with 5 observations, addressing residual concerns related to lyophilization bag container (b) (4) validation, equipment cleaning procedures and hold times, cleaning agent effectiveness, (b) (4) placement and monitoring, and shipping temperature monitoring. The reduction from 14 to 5 observations reflected substantial progress in the sponsor's manufacturing program. All remaining observations were resolved through sponsor responses and are considered satisfactory.

All observations from both inspections have been satisfactorily resolved. The facility is considered acceptable for the purpose of licensure.

e. Container Closure

The lyophilization bag container serves the dual function of lyophilization vessel and primary container closure system (CCS) for the finished FDP product throughout its 12 month shelf life. The lyophilization bag container is constructed primarily of (b) (4) . Following lyophilization, (b) (4)

(b) (4)

. The (b) (4) lyophilization bag container is then hermetically sealed within an outer foil pouch (b) (4), which serves to maintain a near-neutral reconstituted pH of 6.5–7.5 throughout the shelf life.

Lyophilization bag container suitability is supported by biocompatibility evaluation, chemical characterization, and extractables and leachables assessment per (b) (4) series of standards. Performance and integrity testing under simulated shipping (b) (4) 12-month accelerated aging (b) (4) and real-time aging studies at 4 °C and 25 °C confirmed that all acceptance criteria were met.

Established acceptance criteria span three areas:

- Lyophilization Bag Container Protection and Performance: (b) (4)
- Lyophilization Bag Container Safety: (b) (4)
- (b) (4) Lyophilization Bag Container Post-Manufacturing Integrity and Outer Foil Pouch: (b) (4)

f. Environmental Assessment

In accordance with 21 CFR 25.31(j) and 21 CFR 25.21, Vascular Solutions, LLC claims a categorical exclusion from the requirement to prepare an Environmental Assessment. The application is for marketing approval of a biologic product for transfusable human blood or blood components and plasma, and to the applicant's knowledge, no extraordinary circumstances exist.

4. Nonclinical Pharmacology/Toxicology

EZPLAZ™ FDP is a freeze-dried plasma product regulated as a blood product under 21 CFR Part 606 and the Public Health Service (PHS) Act. It does not contain added drugs or pharmacologically active excipients and functions solely by replenishing deficient plasma proteins and coagulation factors through a physiological replacement mechanism. Formal nonclinical pharmacology and toxicology characterization is therefore not applicable to EZPLAZ™ FDP, and no animal studies have been conducted. This is consistent with the established regulatory framework for blood components including plasma and does not represent a gap in the safety evaluation of this application.

5. Clinical Pharmacology

N/A

6. Clinical/Statistical

All clinical and statistical reviewers recommend approval.

a. Clinical Program

The clinical program was conducted under IND 17154. The BLA was officially submitted on January 28, 2021, under Fast Track Designation pursuant to Section 506(b) of the FD&C Act. A Complete Response Letter was issued on September 2, 2021, citing manufacturing deficiencies only; no clinical or statistical deficiencies were identified. Following resolution of the manufacturing deficiencies, the BLA was resubmitted on September 29, 2025.

The clinical program consists of a pivotal Phase 1 safety study. As discussed in the non-clinical section above, no animal studies were conducted. The available data are accepted in the context of the significant unmet medical need, the restriction of use to settings where plasma is not available, and the supportive class-level evidence from pharmacologically related products. Additionally, FDA is requesting that the sponsor conduct a Phase 4 PMR.

Before and during the Phase 1 safety study, the sponsor engaged in multiple formal meetings with CBER: a Type C meeting (October 27, 2017) to discuss the investigational plan for FDP-1 and the planned Phase 2 study (FDP-2); a Type A meeting (April 9, 2018) to address regulatory, administrative, CMC, and labeling issues; and FDA concurrence (July 27, 2018) with the sponsor's request for the same indications as conventional plasma. The protocol

underwent multiple revisions (v1.0 through v6.0) between 2016 and 2018, reflecting iterative engagement with CBER.

The Phase 1 study (S-14-12) measured key hemostatic analytes as secondary endpoints, including procoagulant factors (II, V, VII, VIII, IX, X, XI), anticoagulant proteins (Protein C, Protein S, AT-III), and fibrinolytic and activation markers (Fibrinogen, vWF, PT/INR, aPTT, D-dimer, PF 1+2, TAT, Alpha-2 Antiplasmin, C3a). Coagulation factor activity levels (surrogate endpoints) are reasonably likely to predict clinical benefit for the following reasons:

- Pathophysiologic relevance: Acute traumatic coagulopathy is directly caused by depletion of clotting factors. Up to 38% of transfused combat casualties develop severe hemostatic abnormalities shortly after injury, and exsanguination from impaired hemostasis is the leading cause of preventable battlefield death, typically occurring within two hours of injury. Restoration of coagulation factor levels is the mechanistic basis for plasma transfusion therapy.

- Established mechanism of action: Replacement of coagulation factors by plasma transfusion is the clinically accepted mechanism of action for FFP

- Biological plausibility: In vitro analysis confirmed that the coagulation protein composition of FDP lyophilized in plastic bags is similar to thawed FFP, supporting the biological plausibility that restoration of coagulation factor levels will correlate with clinical benefit.

- Precedent: Coagulation factor levels have been used in the regulatory evaluation of plasma products and are established indicators of hemostatic capacity.

Clinical Study — S-14-12 (FDP-1)

S-14-12 was a single-center, partial double-blind, crossover, randomized, ascending-dose, controlled Phase 1 safety study conducted at Hoxworth Blood Center/University of Cincinnati, Cincinnati, OH, under IND 17154. The study enrolled 24 healthy adult volunteers across three ascending dose cohorts. All infusions used autologous plasma — subjects donated their own plasma via whole blood donation or plasmapheresis prior to the infusion visit. An independent DMC oversaw subject safety throughout the trial.

Cohort assignments were as follows:

- Cohort 1 (N=8): Single infusion of 270 mL (1 unit) FDP-CPD or FDP-ACD
- Cohort 2 (N=8): Single infusion of 540 mL (2 units) FDP-CPD or FDP-ACD
- Cohort 3 (N=8): Crossover infusion of 810 mL (3 units) FDP-ACD versus FFP, with approximately a two-week washout period; subjects followed for 28 days post-infusion #2

For the first five subjects in each cohort, infusions were staggered to allow the principal investigator and research monitor to independently review all data through the 24-hour follow-up visit before proceeding to the next subject.

The study enrolled 24 healthy male and female volunteers aged 18 - 55 years (mean age 34 years across cohorts). The population was predominantly white males. No subjects from special populations — pediatric, geriatric, pregnant, or immunocompromised — were enrolled, consistent with the Phase 1 safety focus of the study. The use of autologous plasma instead of allogenic plasma as the starting material for the Phase 1 study eliminated the risk of infectious disease transmission.

The primary endpoint was the safety of ascending doses of FDP, assessed by the incidence of SAEs, FDP-related TEAEs, suspected unexpected serious adverse reactions, and clinically significant changes in vital signs and laboratory parameters. The primary endpoint was met:

- No deaths or SAEs occurred in any cohort.
- No TEAEs led to product discontinuation.
- Nine of 24 subjects experienced 17 TEAEs; 16 were mild and one (bursitis) was moderate. None were considered related to FDP. The only possibly related TEAEs (elevated PF 1+2 and TAT) were associated with FFP infusion in Cohort 3, not with FDP.
- No clinically significant safety signals were identified in vital signs, hematology, coagulation analytes, chemistry, or urinalysis.
- No dose-response relationship for adverse events was evident across cohorts.

The independent DMC identified no safety concerns. TEAEs observed included: nasal congestion, temperature regulation disorder, positive direct Coombs test, hyperglycemia,

glycosuria, drug-induced liver injury (attributed to concomitant acetaminophen use), dysgeusia, oropharyngeal pain, pulmonary congestion, rhinorrhea, elevated TAT, headache, seasonal allergy, elevated D-dimer, and bursitis.

Secondary endpoints, assessed in Cohort 3 only, included the safety of 3 units FDP versus FFP and post-infusion recovery rates of coagulation factors and laboratory measures. These endpoints were met and served as the primary surrogate marker basis for this regulatory action:

- Coagulation factor levels were comparable between the FDP and FFP arms in Cohort 3.
- Minor, transient excursions outside the normal range were observed for Factor V, Factor X, Protein C, and Protein S in selected subjects; these were not considered clinically significant and resolved without intervention.
- The safety profile of FDP was indistinguishable from that of FFP.

Safety Database and Limitations

The safety database consists of 24 healthy volunteers who enrolled in a Phase 1 safety study. This database supports a conclusion that EZPLAZ™ FDP has an acceptable safety profile in healthy adults at doses up to 810 mL. The intended patient population for EZPLAS (i.e., critically ill adults with trauma, coagulopathy, or active bleeding) may have different baseline risk for adverse events, including TTE events; consequently, the safety profile of EZPLAZ™ FDP has not been fully characterized. Based on published data TTE may occur at rates of 3–15% with conventional plasma and 1.3–12% with FDP products, Teleflex will conduct the Phase 4 PMR SAFE-PLASMA study.

The following issues with the safety database are noted:

- The safety study used autologous plasma, limiting generalizability of conclusions about safety to the allogeneic transfusion setting.
- The study was conducted in healthy volunteers, not in the intended patient population.

- The study was not designed to assess clinical efficacy; coagulation factor levels served as surrogate markers of factor replacement.
- No clinical studies were conducted in special populations (pediatric, geriatric, pregnant, or immunocompromised).

These issues are accepted in the context of the significant unmet medical need, the restriction of use to settings where plasma is not available, and the requirement for a postmarketing safety study.

Risk-Benefit Assessment

The clinical reviewers concluded that the benefit-risk profile supports approval. The significant unmet medical need for an ambient-temperature-stable plasma product particularly in austere and remote military and civilian settings where FFP is unavailable outweighs the limitations of the small safety database, given the restriction of use to situations where plasma is not available. Clinical experience with similar freeze- dried plasma products available under Emergency Use Authorization | FDA include French FDP, available since July, 2018, and Octaplas LG Powder, available since June, 2025, as well as published clinical studies of other freeze dried plasma products which provide additional context for the safety and efficacy profile of the product class. The restriction to adults only and to situations where plasma is not available is a key risk mitigation measure embedded in the approved indication.

Statistical Review

No statistical issues were identified in the original Phase 1 submission or in the CR Letter. Descriptive statistics were used to present Phase 1 study data, which was appropriate given the small sample size and the safety-focused nature of the study. The statistical review for this submission focused primarily on the proposed Phase 4 postmarketing safety study protocol (SAFE-PLASMA).

The statistical reviewer identified four deficiencies in the original Phase 4 protocol submitted under IND 17154/75: hypothesis testing was not defined; sample size was not verifiable; the primary analysis population was not defined; and a missing data strategy was not specified. These issues were addressed by the sponsor in the response submitted under IND 17154/77, with the exception of the proposed sample size, which required further revision.

The original sample size of 482 subjects (across both arms, accounting for 10% attrition) was calculated based on an OR < 2.5 non-inferiority margin, assuming 80% power, a 10% event rate in the conventional plasma arm, a 22% event rate in the FDP arm, a cluster design size of 2, and an intraclass correlation coefficient of 0.05. The clinical reviewer recommended revising the OR margin to 2.0, reflecting a more clinically meaningful threshold for non-inferiority. The IR Letter dated May 29, 2026, communicated this recommendation, along with a suggestion to incorporate a group sequential interim analysis design. In their response dated June 8, 2026, the sponsor agreed to revise the OR margin to 2.0 and to incorporate an interim analysis. A revised protocol and Statistical Analysis Plan (SAP) are to be submitted by August 30, 2026.

Statistical Reviewer Conclusion

The statistical reviewer recommends approval and has no additional statistical comments. A full statistical review of the revised Phase 4 SAP will be provided upon submission.

Clinical Efficacy Review

EZPLAZ FDP demonstrated a safety profile indistinguishable from FFP in the Phase 1 study; the surrogate marker data support the biological plausibility of clinical benefit; and the benefit-risk profile supports approval, including completion of a postmarketing safety study.

No substantive internal disagreements were identified between the clinical and statistical reviewers; both are aligned in recommending approval.

Rationale for PMR/PMC Recommendations

Regulatory Basis

A Phase 4 PMR safety study is required under Section 505(o)(3) of the FD&C Act (Title IX of FDAAA), based on the following statutory findings:

- Section 505(o)(3)(A): Available data indicate the potential for a serious risk — specifically, TTE events following transfusion of EZPLAZ™ FDP. Published data from plasma and pharmacologically related FDP products document TTE event rates of 3–15% for conventional plasma and 1.3–12% for FDP products. This risk cannot be adequately characterized from the existing Phase 1 safety database.

- Section 505(o)(3)(D)(i): Adverse event reporting alone will not be sufficient to identify this potential serious risk. Surveillance systems for blood products are fragmented, and no single system captures information on every transfusion.
- Section 505(o)(3)(D)(ii): A postmarketing observational study would not be sufficient
- A randomized controlled trial is necessary to provide a concurrent controlled comparison, randomization to balance baseline thrombotic risk in trauma patients, and standardized adjudicated event detection for TTE events.

Clinical Reviewer Perspective

The Phase 4 PMR is required because the Phase 1 safety database (N=24 healthy volunteers) is insufficient to characterize TTE risk in the intended patient population critically ill adults with trauma, coagulopathy, or active bleeding, who are at substantially elevated baseline risk for TTE events. The clinical reviewer recommended a randomized, controlled, prospective trial (SAFE-PLASMA) with a primary endpoint of the proportion of subjects experiencing TTE events within 7 days of infusion, comparing FDP to conventional plasma. Pediatric patients are excluded from this study; their evaluation will be addressed separately under the Pediatric Study Plan (required under the Pediatric Research Equity Act (PREA)).

Statistical Reviewer Perspective

The Phase 4 PMR must address the following methodological requirements to generate valid and interpretable data:

- Non-inferiority margin revised to OR < 2.0
- Prospectively defined interim analysis using a group sequential design, with appropriate Type I error control, conditional power-based futility assessment, sample size re-estimation as appropriate, and a prespecified maximum enrollment cap
- Revised sample size calculation based on OR 2.0 margin
- Independent DMC oversight with blinded, standardized endpoint adjudication
- Clearly defined primary analysis population, missing data strategy, and hypothesis testing framework in the revised SAP

The statistical reviewer will provide a full review of the revised Phase 4 protocol and SAP upon submission.

SAFE-PLASMA Study Key Parameters	
Parameter	*Detail*
Study Design	Phase 4, cluster-randomized, prospective, multicenter, open-label, non-inferiority
Population	Adults only (pediatric patients excluded)
Primary Endpoint	Proportion of subjects with TTE events within 7 days of infusion
Non-Inferiority Margin	OR <2.0
Interim Analysis	Yes, group sequential design
Final Protocol Submission	August 30, 2026
Study Completion	September 30, 2030
Final Report Submission	December 31, 2030

b. Bioresearch Monitoring (BIMO)

Study S-14-12 (FDP-1) was conducted at a single clinical site: Hoxworth Blood Center/University of Cincinnati, Cincinnati, Ohio. The sponsor attested that the Phase 1 volunteer study was conducted in compliance with Good Clinical Practices (GCP) and the principles set forth in 21 CFR Parts 50, 54, 56, 312, and 314; ICH Guidelines for Good Clinical Practice; and applicable local and national regulatory requirements.

c. Pediatrics

PeRC Meeting Outcome and Pediatric Study Plan

An Agreed Initial Pediatric Study Plan (iPSP) was agreed upon on September 19, 2019, following PeRC presentation on April 3, 2019, and receipt of the agreed draft iPSP on June 20, 2019. The iPSP established a deferral for completion of a postmarketing pediatric study covering the full pediatric age range of neonates to < 17 years (0–16 years). The deferred pediatric study is an open-label, multicenter, single-arm safety study in pediatric subjects (N=50) aged neonates to < 17 years. Updated milestones, as communicated in the IR Letter of May 29, 2026, are:

- Final Protocol Submission: December 2026

- Study Completion: December 2030
- Final Report Submission: December 2031

Key Pediatric Issue — Exclusion from Phase 4 PMR

A critical pediatric issue arose during the current review cycle. The sponsor initially proposed including pediatric patients in the Phase 4 SAFE-PLASMA PMR study and requested a labeling exemption on the basis that the approved indication is for adults only. FDA did not grant this exemption and directed that the Phase 4 PMR must not include children, and that pediatric evaluation must be addressed exclusively through the Pediatric Study Plan. The sponsor agreed to remove pediatric subjects from the Phase 4 PMR study and acknowledged that a dedicated pediatric study will require pediatric-specific protocol development, age-appropriate safety considerations, pediatric site identification and engagement, ethical and regulatory review, enrollment feasibility assessment, and statistical planning. The sponsor confirmed that pediatric evaluation will be addressed separately under the Pediatric Study Plan.

Rationale for Deferral of Pediatric Study Submission

The deferral for the pediatric (PREA) final protocol submission until 2031 is appropriate for the following reasons:

- The Phase 1 study was conducted exclusively in healthy adult volunteers; no clinical data in pediatric populations are available.
- The product is indicated for adults only, and the clinical program was designed and powered for the adult population.
- Completion of a pediatric study prior to adult approval is not feasible given the unmet medical need and the logistical complexity of pediatric-specific protocol development.
- A dedicated pediatric study with age-appropriate design, safety monitoring, and enrollment considerations cannot be adequately addressed within the adult Phase 4 PMR framework.

No waivers for any pediatric age subgroup have been granted. No pediatric age range is being approved at this time. The full pediatric age range (0–16 years) remains subject to

deferral under the Agreed iPSP, pending completion of the deferred postmarketing pediatric safety study.

d. Other Special Populations

N/A

7. Safety and Pharmacovigilance

The safety database from the clinical program is limited to 24 subjects enrolled in a single Phase 1 safety study in healthy volunteers. This database is insufficient to characterize the safety profile of EZPLAZ™ FDP in the intended patient population and is inadequate to detect or characterize the risk of TTE events. These limitations are acknowledged and are the primary driver of the Phase 4 PMR SAFE-PLASMA study.

The following safety concerns have been identified and are addressed through labeling and/or postmarketing requirements:

Thrombotic and Thromboembolic (TTE) Events

TTE events represent the primary uncharacterized safety risk associated with EZPLAZ™ FDP. Published data from plasma and pharmacologically related FDP products document TTE event rates of 3–15% for conventional plasma and 1.3–12% for FDP products. The intended patient population — critically ill adults with trauma or coagulopathy is at elevated baseline risk for TTE events, making attribution without a concurrent controlled comparison unreliable. This risk will be characterized through the Phase 4 SAFE-PLASMA PMR study.

Infectious Disease Transmission

The risk of transmitting infectious agents from human plasma is consistent with the risk profile of plasma products for transfusion and is managed through donor screening and infectious disease testing in accordance with applicable regulations.

Hemolytic Transfusion Reactions (ABO Incompatibility)

The risk of hemolytic transfusion reactions due to ABO incompatibility is addressed through ABO compatibility guidance in the labeling and through the isoagglutinin screening program for blood type A units.

Transfusion-Related Acute Lung Injury (TRALI)

The risk of TRALI is mitigated by the exclusive use of male donors, consistent with established TRALI mitigation strategies for plasma products.

Labeling Warnings and Precautions

The EZPLAZ™ FDP Circular of Information includes the following warnings and precautions:

- The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard
- May be less effective than targeted therapies for specific coagulopathies
- Not intended for routine volume expansion
- May not meaningfully correct minimally elevated INR (1.5–1.7)
- Refer to the FDA-recognize Circular of Information (COI) for further details on potential transfusion-related adverse reactions, including hemolytic, alloimmunization (to plasma proteins), transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), allergic and anaphylactic reactions, and metabolic complications (e.g. citrate toxicity)

8. Labeling

The labeling for EZPLAZ™ FDP encompasses the Circular of Information (COI), container and kit labels, and associated labeling components. No patient labeling or Medication Guide was required or included, as EZPLAZ™ FDP is administered exclusively by healthcare professionals.

Proprietary Name

The proposed proprietary name, EZPLAZ™, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on May 21, 2019, and found acceptable. CBER communicated acceptability to the applicant on May 28, 2019.

Circular of Information (COI)

The COI serves as a required extension of the container labels under 21 CFR 606.122. EZPLAZ™ FDP is a blood component derived from FFP.

FFP is described in the standard Circular of Information (An Acceptable Circular of Information for the Use of Human Blood and Blood Components | FDA; link to the COI for standard FFP: Circular of Information for the Use of Human Blood and Blood Components)

The EZPLAZ™ FDP COI includes all required elements that are unique to freeze-dried plasma or require emphasis for its safe administration and refers to the standard blood component COI for items that relate to FFP.

The EZPLAZ™ FDP COI contains the following elements:

- Product Description: EZPLAZ™ FDP is identified as a lyophilized unit of apheresis or whole blood-derived human plasma manufactured from approximately 270 mL of FFP from a single donor, using either ACD or CPD anticoagulant.
- Indications: The product is indicated for transfusion in adults when plasma is required and other plasma products are not available, including management of coagulation factor deficiencies (e.g., liver disease, DIC), massive transfusion, and urgent warfarin reversal.
- Dosage and Administration: Intravenous (IV) and/or intraosseous (IO) use only; reconstitution using the 250 mL SWFI included in the kit via aseptic technique; infusion must be completed within 4 hours of reconstitution, with unused product discarded thereafter.
- Compatibility: ABO compatibility guidance (group AB and group A with low-titer anti-B); no Rh type matching required; emergency use prior to recipient's ABO group determination is addressed.
- Warnings and Precautions: Infectious Disease Warning: The required verbatim warning statement per 21 CFR 606.122(f) regarding infectious agent transmission risk is included; Hemolytic transfusion reactions, Cross-references to the AABB Circular are included to also address TRALI, anaphylaxis, alloimmunization, TACO, and metabolic complications.

- Storage and Handling: Storage at 2–25 °C (36–77 °F) prior to reconstitution; 12-month shelf life from the date of final labeling; infusion within 4 hours of reconstitution; product must not be refrigerated or frozen post-reconstitution.
- Coagulation Factor Activity Data: Tables comparing coagulation factor activity levels in thawed FFP and reconstituted EZPLAZ™ FDP at baseline, 6 months, and 12 months at both 4 °C and 25 °C are included to support clinical use and to inform clinicians of the greater factor degradation that occurs at 25 °C storage.

Quick Reference Guide

A Quick Reference Guide providing clear pictorial reconstitution instructions is included in each packaged kit alongside the Prescribing Information, supporting accurate reconstitution in field or emergency settings.

Package and Immediate Container Labels

The container label is presented in standard ISBT 128 four-quadrant format, meeting the requirements of 21 CFR 606.121. It includes all required elements: product name, Donation Identification Number (DIN), ABO group, Rh type, expiration date, storage temperature, facility identification, FDA registration number, U.S. License Number (2135), and reference to the COI. Additional labeling components — kit label, outer foil pouch, fold-over label, bubble mailer, and shipper label — consistently display required product and manufacturer information. The labeling components submitted are acceptable.

Patient Labeling / Medication Guide

No patient labeling or Medication Guide was required or included. EZPLAZ™ FDP is administered exclusively by healthcare professionals.

9. Advisory Committee Meeting

An Advisory Committee was not held.

10. Other Relevant Regulatory Issues

None

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Review Committee recommends approval of BLA 125702/0 for EZPLAZ™ Freeze Dried Plasma.

b. Integrated Benefit/Risk Assessment

Benefits

EZPLAZ™ FDP addresses a well-documented and longstanding unmet medical need: the absence of a licensed, ambient-temperature-stable plasma product for use in settings where frozen plasma is unavailable. Traumatic hemorrhage and acute traumatic hemorrhage are leading causes of preventable death in military and civilian trauma settings, and early plasma transfusion is a cornerstone of damage control resuscitation. The logistical requirements of conventional plasma products — frozen storage and thawing — have historically precluded their use in resource-constrained and austere environments.

EZPLAZ™ FDP eliminates these logistical barriers through its 12-month ambient-temperature shelf life, 2.5-minute reconstitution time, complete kit design, and flexible plastic bag packaging. Stability data confirm that the product retains clinically meaningful coagulation factor activity across a 12-month shelf life under approved storage conditions. The Phase 1 safety profile is acceptable and comparable to FFP. Clinical experience included emergency use access of other freeze dried plasma products support the safety and efficacy of the product class in real-world trauma settings.

Risks

The risks of EZPLAZ™ FDP are those inherent to any plasma product —hemolytic transfusion reactions, TRALI, TACO, hypersensitivity reactions, infectious disease transmission, and metabolic complications, plus the specific and incompletely characterized

risk of TTE events in the intended patient population. The TTE risk is the primary unresolved safety concern and will be characterized through the Phase 4 SAFE-PLASMA PMR study.

Benefit-Risk Conclusion

The benefit-risk balance for EZPLAZ™ FDP is favorable. In the approved indication, adults requiring plasma transfusion in settings where plasma is not available, the clinical benefit of timely plasma administration outweighs the potential risks associated with the product, and are consistent with those of other plasma products and are addressed through mitigations, labeling and monitored through a postmarketing requirement. The restriction of use to settings where plasma is not available is a key risk mitigation measure that limits exposure to the product's incompletely characterized risks to the population most likely to benefit. The Phase 4 SAFE-PLASMA PMR study will provide the confirmatory safety data needed to fully characterize the TTE risk in the intended patient population.

c. Recommendation for Postmarketing Activities

The Review Committee considered the initial submission under an accelerated BLA pathway and granted Fast Track in a rolling BLA in 2019, requiring a confirmatory study. However, FDA determined in 2025 that there was available clinical experience with freeze dried plasma products and a confirmatory study in healthy subjects would not be informative. Clinical experience with similar freeze- dried plasma products available under Emergency Use Authorization | FDA include French FDP, available since July 9, 2018, and Octaplas LG Powder, available since August 8, 2024, providing product class-level supportive evidence. Consequently, FDA determined that a Phase 4 PMR safety study was the appropriate regulatory pathway for approval under FDAAA 505(o)(3) because of the significant unmet medical need and the restriction of use to settings where plasma is not available. Clinical trials of similar freeze-dried plasma products in patient populations for the same intended use had favorable safety profiles and outcomes and also support the use of this product in a restricted setting where plasma is not available.

FDA will conduct a full review of the revised Phase 4 SAFE-PLASMA protocol and SAP upon submission, which is expected by September 30, 2026.