

Plasma components: FFP, FP24, and Thawed Plasma

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A rose is a rose, is a rose . . . GERTRUDE STEIN

Plasma intended for transfusion is separated from whole blood or collected by apheresis procedures and frozen according to specific requirements defined by the method of preparation (Table 1).¹⁻³ Fresh frozen plasma (FFP) and plasma frozen within 24 hours of phlebotomy (FP24) differ in the amount of time that is allowed to elapse between collection and frozen storage, which has practical ramifications not only for blood establishments whose collection sites are geographically remote from their manufacturing facilities but also for transfusion services that are often asked about the properties and proper handling of the differently labeled plasma components.

With the time constraints imposed on producing FFP, and the additional demand for plasma collected from male donors for transfusion to mitigate the risk of transfusion-related acute lung injury (TRALI), many blood centers have increased production of FP24. Despite the increasing or exclusive use of FP24 by many hospitals in recent years, questions persist regarding its use in clinical practice, perhaps reflecting deeply ingrained practice or familiarity with FFP at some hospitals, a belief that “fresh is better,” or concern about the unfavorable past experiences with other plasma components such as solvent-detergent (SD) plasma in the United States. Although clinical trials have not been performed to compare the efficacy of FP24 with that of FFP, the available *in vitro* data on the concentration or functional activity of coagulation factors in the plasma components support the use of FP24 and Thawed Plasma for the common and currently accepted indications for plasma transfusion.

Description

FFP and FP24 are U.S. Food and Drug Administration (FDA)-licensed products as defined in 21 CFR 640.34(a) and (b).³ FFP is prepared from a whole blood or apheresis collection and frozen at -18°C or colder

within the time frame required for the anticoagulant or collection process (Table 1). FFP derived from whole blood in CPDA-1, CPD, and CP2D anticoagulant must be separated and placed at -18°C within 8 hours of collection. FFP from apheresis procedures is collected in ACD or sodium citrate anticoagulant and must be placed in the freezer within 6 to 8 hours according to manufacturers' instructions. Most apheresis collection sets are closed or functionally closed systems, but some are open systems, which affects the suitability of converting apheresis FFP to Thawed Plasma (discussed in greater detail in a later section). Licensed FP24 can only be prepared from whole blood and must be placed at -18°C within 24 hours after phlebotomy. The FDA has not yet approved using plasma collected by apheresis procedures for FP24.

The FDA has no finished product quality control requirements for FFP or FP24, provided that the manufacturing, transporting, and storage specifications for time and temperature are met. International standards for final product specifications for frozen plasma components differ. The Council of Europe guidelines specify FFP as being frozen within 8 hours of phlebotomy to -70°C and containing more than 0.70 IU/mL (70%) factor VIII (FVIII) activity. In contrast, the United Kingdom Blood Transfusion Service no longer defines the interval between collection and storage for frozen plasma, provided the quality control specification is achieved.^{4,5} The requirement for standard UK FFP is at least 75 percent of the units contain more than 70 IU/mL of FVIII.^{4,5} Interestingly, lower clotting factor activity (> 50 IU/mL) is accepted for the SD-treated FFP commercially available in Europe, which implicitly sets the lower limit of the normal range as a minimal, clinically acceptable standard that most of the units produced should meet.

As reviewed herein, the vast majority of units of FFP and FP24 contain levels of all clotting factors and inhibitor activity that are above the lower limit of the normal range (≥ 0.50 IU/mL or 50% factor activity) at

Table 1. Plasma component

Component	Preparation		Expiration*
FFP Prod. Code: 18201 ISBT Codes: E0701V00 E0707V00 E0713V00	Whole blood collection	Separated from whole blood collected in CPD, CP2D, CPDA-1 and placed at -18°C or below within 8 hours.	Frozen state: 12 months stored at ≤ -18°C After thawing: 24 hours, stored at 1°-6°C
FFP Prod. Code: 18211 ISBT Codes: E0869V00 E0909V00 E4142V00	Apheresis	Placed at -18°C or below within 6 or 8 hours according to instructions for storage bags.	Frozen state: 12 months stored at ≤ -18°C After thawing: 24 hours, stored at 1°-6°C FFP, if prepared from open system apheresis collection sets, cannot be converted to Thawed Plasma after 24 hours (see Thawed Plasma)
FP24 Prod. Code: 18101 ISBT Codes: E2619V00 E2555V00 E2587V00	Whole blood collection	Separated from whole blood and placed at -18°C or below within 24 hours.	Frozen state: 12 months stored at ≤ -18°C After thawing: 24 hours, stored at 1°-6°C FDA has not approved apheresis plasma to be frozen within 24 hours of collection.
Thawed Plasma	FFP (prepared in closed system) or FP24	After the initial 24-hour postthaw period, store at 1°-6°C	5 days from date original product was thawed; stored at 1°-6°C FFP, if prepared from open system apheresis collection sets, cannot be converted to Thawed Plasma after 24 hours (see Thawed Plasma) Closed collection system: Baxter (Amicus;Alyx); COBE/Gambro (Spectra;Trima,Trima ACCEL; Haemonetics MCS+ LN8150 and LN9000) Open collection system: Baxter Auto-C, Haemonetic PCSA/PCS2, Model V-50 and Model 30 systems; some kits on Fenwal

*AABB Standards. [FDA has stated: "After thawing: 6 hours [21CFR606.122(m)] or 24 hours if approved for alternative procedure under 21.CFR640.120."]

expiration, suggesting that additional quality control specifications are unnecessary and unwarranted.

Labeling and Managing FFP and FP24 After Thawing

After being thawed and stored at 1° to 6°C for 24 hours, plasma can no longer be labeled as FFP or FP24, but most units can be converted to Thawed Plasma.⁶ First introduced in the 17th edition of AABB Standards, the expiration dating on Thawed Plasma was extended from 24 hours to 5 days. Thawed Plasma is derived from either FP24 or FFP that has been prepared in a closed system and can be stored for up to 5 days at 1° to 6°C.² After the 24-hour expiration for FP24 or FFP, the original license number on the unit should be removed and the product relabeled as Thawed Plasma. Alternatively, FP24 or FFP can be relabeled as Thawed Plasma once thawed and placed at 1° to 6°C, rather than waiting until expiration.

Some hospitals, especially trauma centers, maintain an inventory of Thawed Plasma to avoid the delays in plasma delivery to patients associated with thawing FFP or FP24. Because Thawed Plasma currently has a maximum shelf life of 5 days after the initial thawing, the benefit of maintaining a quickly accessible inventory to treat trauma cases must be weighed against the possible increase in outdating of thawed units. Managing a Thawed Plasma inventory also requires knowledge of the method of collection used by the blood supplier for FFP. Some apheresis collection sets are open systems (e.g., Baxter Auto-C; Table 1), and the resultant FFP cannot be converted to Thawed Plasma and has only a 24-hour shelf life after thawing. Because the same product code may be used by blood suppliers for FFP collected from apheresis both in a closed system and in an open system, hospitals must determine from the supplier the method of collection used when the hospitals are creating Thawed Plasma from FFP with the

intent to possibly store the Thawed Plasma for more than 24 hours. This obstacle will be eliminated with the implementation of ISBT 128, because the method of collection will be evident in the labeling of the unit of FFP (Table 1). Licensed FP24 is currently only prepared from whole blood collections and not apheresis procedures, so there are no special considerations in converting units to Thawed Plasma.

Indications for Plasma Transfusion

Plasma transfusion is indicated to treat preoperative or bleeding patients who require replacement of multiple plasma coagulation factors, such as patients with liver disease or disseminated intravascular coagulation (DIC). Acquired coagulation factor deficiencies may also result from massive transfusion through dilution or warfarin therapy, which decreases the vitamin K-dependent factors (FII, FVII, FIX, FX, protein C, protein S). Plasma transfusion may be indicated to reverse the effect of warfarin in bleeding patients or patients at significant risk of bleeding during invasive procedures whenever time does not permit reversal of warfarin anticoagulation with vitamin K administration. Finally, plasma is often lifesaving for patients with thrombotic thrombocytopenic purpura (TTP) who are deficient in ADAMTS13 (von Willebrand factor [vWF]-cleaving protease) activity. As contraindications, FFP and FP24 should never be given to FVIII-deficient patients, or any patient with known hereditary coagulation deficiencies for whom specific clotting factor concentrates are available. An international registry of commercially available clotting factor concentrates is maintained by the International Society on Thrombosis and Hemostasis.⁷

In a population of healthy adults, plasma coagulation factor and inhibitor activity occur within a wide reference range (0.50–1.50 U/mL; 50–150% factor activity), reflecting normal biologic variability. The heterogeneity observed for some clotting factors is linked to blood group and race. Plasma collected from group O individuals contains less vWF and FVIII than plasma collected from group A individuals, and Caucasians generally have lower levels than African Americans.⁸ This interindividual variability should be taken into account when evaluating the factor activity in plasma components collected from healthy volunteer blood donors. For example, a unit of FP24 collected from a group A individual could have more vWF:VIIIc at expiration than a unit of FFP prepared from a group O individual; yet both products are clinically acceptable.

Many patients who require plasma transfusion have normal or high levels of FVIII, because it is an acute phase protein and is often increased by liver disease and other common inflammatory diseases. Individual coagulation proteins and inhibitors also demonstrate maturation during infancy and childhood, with most factors reaching adult levels by 6 months of age in both term and preterm infants.^{9,10} Notably, the level of FVIII at birth is the same as for an adult, even in premature infants, but the vitamin K-dependent factors and coagulation inhibitors fall below the lower limit of the reference range for adults. Despite these differences, healthy infants are not coagulopathic, and the levels reflect the normal hemostatic balance for the developmental stage. Consequently, the same considerations apply to infants being given plasma transfusion for acquired multiple coagulation factor deficiencies and related clinical indications as for adults.

Plasma transfusion is typically given as 10 to 20 mL/kg and expected to deliver a hemostatic dose of coagulation factors and inhibitors. The minimum levels of coagulation factors required to maintain hemostasis (e.g., 50 mg/dL fibrinogen; 15–30 % factor activity) are about 3- to 10-fold below the amount normally present in healthy adults. Plasma containing physiologic amounts (e.g., ≥ 0.50 IU/mL) of coagulation proteins will increase deficient clotting factor activity to at least 30 percent in patients with acquired coagulopathy when dosed appropriately. The biologic variability that is observed in the normal content of plasma products does not affect the clinical effectiveness of the product. Similarly, FFP, FP24, and Thawed Plasma used at 5 days retain sufficient functional content during production and storage to deliver a hemostatic dose that is expected to correct acquired coagulation defects.^{11–17}

Functional Content of Plasma Components

The relative functional protein content of FFP, FP24, and Thawed Plasma is affected by the method of preparation, temperature, and duration of storage. The 2002 Circular of Information states that FP24 contains reduced amounts of FV compared with FFP, but several studies have demonstrated minimal or no reductions in the levels of FV and other plasma clotting factors and inhibitors, with the exception of FVIII, which is reduced by 16 to 24 percent (Table 2). The 2002 Circular of Information is currently under revision and is expected to clarify this point.

FV and FVIII in plasma or whole blood are retained to variable degrees in different studies under the

Table 2. Effect of FFP and FP24 processing conditions on FV and FVIII activity

Factor	FFP conditions 8 hours, 4°C		FP24 conditions 24 hours, 4°C		% units in FFP reference range	Reference
	n	Mean (%) (SD or 2 SD range)	n	Mean % (SD or 2 SD range)		
FV	10	98.6 (3.2)	10	101.4 (2.5)	NR	11
	10	102 (15)	-	100 (14)	-	12
	66	94 (35-148)	60	80 (53-112)	100	13
FVIII:C	10	89.8 (1.9)	10	75.9 (2.4)	-	11
	10	84 (16)	10	64 (13)	-	12
	66	100 (48-185)	60	77 (38-140)	98	13
vWF activity	10	103.3 (18.1)	-	95.0 (13.2)	-	11
	-	-	-	-	-	12
	66	101 (57-163)	60	97 (30-185)	87	13

SD = standard deviation

conditions used to prepare FFP and FP24 (Table 2). Smith et al.¹¹ compared the effect of extending the storage time from 8 hours to 24 hours on the level of labile coagulation factors in plasma derived from CPD-whole blood held at 1° to 6°C. Their results showed no significant changes in FV, vWF:Ag, FIX, and ristocetin activity at the different times, but there was a statistically significant decrease (16%) in FVIII activity at 24 hours compared with 8 hours. The level of FVIII activity, however, at 24 hours (76%) was still above the lower limit of the reference range. O'Neill et al.¹² evaluated the coagulation activity in whole blood stored for 24 hours at 4°C before separation into plasma. At expiration after thawing (24 hours), FP24 contained an average of 64 percent FVIII activity, whereas FFP contained an average of 84 percent, a reduction of 24 percent. Cardigan et al.¹³ also evaluated coagulation factor activity in whole blood stored overnight (18-24 hours) at 4°C before separation into plasma, and likewise observed a 23 percent reduction in FVIII, but reported that the vast majority of units (98%) were within the same range as for 8-hour plasma (0.40 to 1.60 IU/mL).

The activity of coagulation factors in Thawed Plasma from FFP is stable for 5 days at 1° to 6°C, except for FVIII which is reduced by 35 to 41 percent at expiration.¹⁴ Thawed Plasma on day 5 had on average 41 to 63 percent FVIII activity, depending on ABO blood group.¹⁴ The relative amounts of coagulation factor and inhibitor activity in Thawed Plasma on day 5 prepared from whole blood or apheresis collections compared with FFP are shown in Table 3. Plasma collected by apheresis has slightly higher factor levels than plasma prepared from whole blood collection, likely because of less anticoagulant dilution, lower citrate concentrations, earlier mean freezing times, or differences in laboratory assays.¹⁵ This tendency, however, may explain the lower observed decreases in factor activity with Thawed

Plasma prepared from apheresis FFP compared with whole blood FFP.¹⁵

The factor content of Thawed Plasma prepared from FP24 throughout the 5-day storage period has not been reported, although Nifong et al.¹⁸ measured the coagulant activity in thawed FP24 stored under less

Table 3. Relative factor activity in FP24, Thawed Plasma, and SD plasma

Reference	% Difference in factor activity*					
	FP24			Thawed Plasma (from whole blood FFP), day 5 [†]	Thawed Plasma (from apheresed FFP), day 5 [†]	SD-plasma [‡]
	[13]	[12]	[11]	[14]	[15]	[19]
Fibrinogen	12	6	-	0	2	-
FV	15	2	+3	16	9	9
FVII	+6	5	-	20	4	-
FVIII	23	24	15	41 (group A, O) 35 (group B)	14	20
FIX	+7	-	+11	-	-	3
FX	+18	0	-	6	0	-
FXI	7	-	-	-	0	17
vWF activity	4	-	8	-	-	6
Protein C (U/dL)	2	3	-	-	-	11
Protein S (U/dL)	8	1	-	-	-	51
ATIII	1	0	-	-	-	9
α2-Antiplasmin (plasmin inhibitor)	5	-	-	-	-	76
ADAMTS13 activity	-	-	-	-	-	0
ADAMTS13 activity * [Ref 16]	10			11	-	-

*Differences are expressed as a percentage decrease or increase (+) in mean factor activity compared with FFP or other standard, as indicated; (-), not reported.

†Day 5 compared with day 1

‡SD, solvent/detergent-treated plasma, compared with untreated plasma

favorable conditions (i.e., 20°C rather than 1° to 6°C). The average FVIII activity measured in 15 units of FP24 stored at 20°C was 59 percent on day 5, which was decreased by 34 percent compared with the activity on day 1 of storage, but was still within the normal reference range for human plasma.

Scott et al.¹⁶ compared the ADAMTS13 activity in therapeutic plasma components used in the treatment of TTP (Table 3). FP24 and FFP as well as Thawed Plasma at 5 days all had equivalent ADAMTS13 activity, which was stable under the different processing and storage conditions.

In summary, the levels of coagulation factors and inhibitors in FP24 are minimally or not different compared with those of FFP, with the exception of FVIII, which is variably reduced by about 16 to 23 percent. For comparison, the functional effect of solvent-detergent treatment on plasma is included in Table 3 because of the striking difference in anticoagulant proteins in SD plasma compared with FP24 and FFP.^{18,19} The SD process reduces transmission of lipid-enveloped viruses but also adversely affects the amount of protein S and plasmin inhibitor in the final product, causing a 51 percent and 76 percent loss in activity, respectively.¹⁹ The reduced coagulation factor and inhibitor levels did not impair efficacy of SD-plasma in clinical studies, but likely accounted for the uncommon but serious adverse events associated with its use.²⁰⁻²⁵ Thrombotic complications in several patients with TTP undergoing plasma exchange with SD-plasma were attributed to depletion of protein S; excessive bleeding and fibrinolytic complications described in patients undergoing liver transplant were attributed to lower levels of plasmin inhibitor in the group treated with SD-plasma compared with FFP.^{22,24,25} In the United States, SD-plasma was linked to the deaths of six patients who experienced thrombotic events or excessive bleeding during orthotopic liver transplantation.²³ SD-plasma is no longer commercially available in the United States, but is presently an approved product in Europe for all of the same indications as FFP (Octaplas, Octapharma, Vienna, Austria). Interestingly, the risk of TRALI may be potentially lower for SD-plasma than for FFP and FP24 because it is prepared from pools of plasma from 500 to 1600 donors, although a difference has not been substantiated.

In conclusion, FFP, FP24, and Thawed Plasma can be safely used to effectively treat the coagulopathy of liver disease, TTP, and DIC, to reverse the effect of warfarin, and to manage massive traumatic blood loss. Most units

of FFP and FP24 contain coagulation factor activity within the normal reference range, and even Thawed Plasma on day 5 retains sufficient levels of coagulation factor activity to deliver a hemostatic dose of all factors except, in some cases, FVIII. Being an acute phase protein, however, FVIII is not deficient in many patients who are candidates for plasma transfusion. If there is clinical concern about the relative degree of FVIII deficiency in the setting of multiple clotting factor deficits, the use of Thawed Plasma should be carefully considered or its use should be limited to the first few days of storage.¹⁴ In contrast, Bostrom et al.²⁶ have proposed extending storage of Thawed Plasma to 14 days for clinical use, despite the observed mean 25 percent and 50 percent decrease in FV and FVIII levels, respectively.

Utilization Trends in the United States

In the United States, the use of FFP and FP24 has changed with time and varies across the country. A recent review of monthly transfusable plasma shipments to hospital customers by the American Red Cross (ARC) from July 1, 2005, to March 31, 2007, showed a shift in the percentage of hospital customers using predominantly (defined as > 80% of the plasma distributed to the hospital) FP24 from 31 percent of hospital customers in the second half of 2005 to 45 percent of hospital customers in the first quarter of 2007 (Fig. 1). Conversely, the percentage of hospital customers using predominantly FFP decreased from 59 percent in the second half of 2005, to only 40 percent in the first quarter of 2007 (Fig. 1).

In addition to a progressive shift in overall distributions from FFP to FP24, the number of geographic regions using predominantly FP24 increased 63 percent in this time period. By March 2007, FP24 accounted for more than 90 percent of the transfusable plasma shipments in 13 of the 35 ARC regions. These regions represented shipments to 657 hospitals in 23

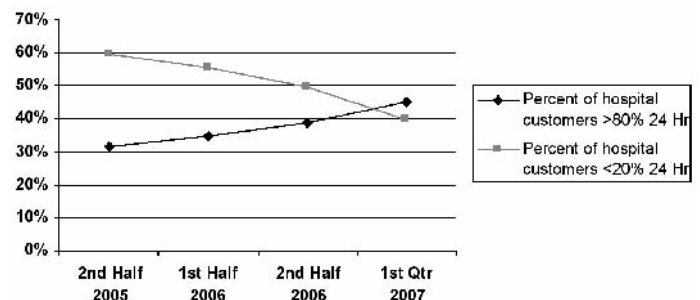


Fig. 1. Shift in transfusable plasma shipment types.

Table 4. Shift in shipments of transfusable plasma

% of transfusable plasma shipments 24 hours	2nd half 2005			1st half 2006			2nd half 2006			1st qtr 2007		
	Number of hospitals	Average shipments	% of hospitals	Number of hospitals	Average shipments	% of hospitals	Number of hospitals	Average shipments	% of hospitals	Number of hospitals	Average shipments	% of hospitals
100%	377	252	21%	449	276	24%	498	259	27%	621	322	36%
> 80-< 100%	207	629	11%	197	668	11%	232	664	12%	158	934	9%
> 60-80%	72	378	4%	67	335	4%	69	533	4%	99	505	6%
> 40-60%	49	357	3%	36	591	2%	50	322	3%	85	349	5%
> 20-40%	41	701	2%	75	533	4%	92	497	5%	75	530	4%
> 0-20%	210	722	11%	203	756	11%	231	657	12%	152	698	9%
0%	888	275	48%	822	254	44%	697	268	37%	534	337	31%

*Average shipments for 1st quarter 2007 have been multiplied by 2 to estimate 6-month figures to be comparable with other periods shown.

states and the District of Columbia in March 2007. The percentage of hospitals using any FP24 increased from 52 percent to 69 percent; in contrast, the percentage of hospitals transfusing exclusively FFP decreased from 48 percent to 31 percent during the study period (Table 4).

The temporal trends in plasma component use in the community indicate the general acceptance of the therapeutic equivalence of FP24 and FFP for most indications, as supported by the *in vitro* studies of functional coagulation activity and protein levels in plasma components. Thawed Plasma is not an FDA-licensed plasma component, and the extent of its use in the community has not been assessed.

Audits of Plasma Use in the United States

The United States transfuses far more plasma than European countries, both on a per capita basis and when normalized for RBC use.^{27,28} The United States was second only to Germany in the per capita usage of FFP among seven European countries in one survey,^{27,28} and the ratio of FFP to RBC use in the United States was 1:3.6 compared with 1:6.0 in Europe.²⁸

Audits of transfusion practice in American hospitals have demonstrated the overuse and misuse of plasma. Dzik and Rao²⁹ evaluated the usage of FFP at Massachusetts General Hospital for 3 months in 2003, and found that 31 percent of the orders for FFP were to correct an abnormal coagulation test result (i.e., international normalized ratio [INR]) before an invasive procedure. Several studies have shown, however, that plasma transfusion does not correct mildly elevated coagulation tests most of the time, and the preoperative prothrombin time to INR values do not predict postsurgical bleeding.^{30,31} Given the risks associated with plasma transfusion, including TRALI, as well as the cost of maintaining a safe and adequate supply of

transfusable plasma, the AABB recently emphasized the importance of appropriate evidence-based hemotherapy practices to minimize unnecessary transfusion.³² Clinical trials have been initiated to better define appropriate plasma transfusion practice.³³

Conclusions

The levels of coagulation factors and inhibitors in FP24 are minimally or not different when compared with FFP, with the exception of FVIII, which is variably reduced by about 16 to 23 percent but remains above the lower limit of the reference range in most units. Thawed Plasma throughout the 5-day storage period has progressive and more pronounced loss of FVIII activity, and decreased levels of all other factors except fibrinogen, yet still retains sufficient factor activity for clinical use. FFP and FP24 are considered by many to be therapeutically equivalent choices for the common and accepted indications for plasma transfusion. Thawed Plasma prepared either from FFP (if collected in a closed system) or from FP24 is also an acceptable component to treat patient coagulopathy of liver disease, TTP, and DIC and to reverse the effect of warfarin when clinically indicated.

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