

ISSUE SUMMARY
BLOOD PRODUCTS ADVISORY COMMITTEE MEETING
MARCH 17, 2005
Gaithersburg, MD

**Topic II: REVIEW OF STANDARDS FOR PLASMA PRODUCTS FOR
TRANSFUSION**

ISSUE: FDA seeks advice from the Committee on the extent to which the available scientific data may support potential changes to further standardize processing of plasma products for transfusion, and on additional scientific studies that would be helpful to resolve current areas of uncertainty.

BACKGROUND:

Currently, plasma products for transfusion as described in the CFR and in the AABB Circular of Information lack definition and/or specifications for many processing conditions. Furthermore, scientific uncertainty exists on the extent to which conditions of plasma product preparation may affect the final products. We therefore are seeking to evaluate data acquired from all available sources in order to consider the possible development of minimal standards for these products that would further ensure their clinically relevant safety, purity and potency.

At a recent FDA workshop on plasma standards, data were presented suggesting that multiple parameters can affect the composition and potentially the quality of plasma products for transfusion, e.g. Fresh Frozen Plasma and Cryoprecipitate. These include the time and temperature of separation of plasma from cells, the anticoagulant used, conditions of freezing, storage, thaw, and post thaw. Subsequent to the workshop, FDA has engaged in a more detailed review of the literature on plasma processing, and obtained additional information from industry.

This session will consist of a review of the key literature on plasma processing and a presentation on the clinical use of plasma products.

DISCUSSION:

On August 31- September 1, 2004, FDA sponsored a workshop on Plasma Standards. One objective of the workshop was to obtain information that would help in the development of standards for recovered plasma. Another goal was to review scientific data, regulatory requirements, and current industry practices

regarding the freezing, storage, and shipping of plasma to ensure the safety, purity, and potency of both labile and non-labile plasma components. We also explored the possibility of harmonizing our requirements with those of other regulatory bodies.

This meeting and subsequent review of the literature indicated that there are multiple parameters that potentially could affect the quality, and safety of plasma products used for transfusion. These parameters include the time and temperature of separation of plasma from cells, the anticoagulant used, conditions of freezing, residual cellular content of plasma, storage, thaw and post thaw conditions.

Plasma products for transfusion as described in the Code of Federal Regulations (CFR) and AABB Circular of Information do not have specifications for many of these parameters. We are in the process of reviewing scientific evidence that might help in the potential development of minimal standards. We will discuss the current definition of plasma products in the CFR and AABB Circular of Information, the labeled uses of these plasma products, safety hazards associated with transfusion of these products, and potential areas to consider in improving current standards. A major focus will be on temperature related parameters that affect plasma quality.

Products under review include the following, as defined in the CFR and the AABB, ABC, ARC Circular of Information for the Use of Human Blood and Blood Components

Fresh Frozen Plasma (FFP) 21CFR 640.34 (b) The plasma shall be separated from the red blood cells, and placed in a freezer within 8 hrs or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system, and stored at -18 °C or colder.

The AABB circular includes additional information: [FFP] Consists of the fluid portion of blood that is separated and placed at ≤ -18 °C or below within 8 h of collection of whole blood if the anticoagulant is CPD....Plasma collected in ACD ... must be placed at ≤ -18 °C within 6 h. Plasma components may be prepared from whole blood collection or by apheresis.

Thawed Plasma is derived from FFP prepared in a way that ensures sterility (closed system), thawed at 30-37 °C, and maintained at 1-6 °C for 1-5 days. Note that this product, unlike others in this list, is not a licensed product and is not described in the CFR.

Cryoprecipitate: Prepared by thawing FFP between 1-6 °C and recovering the precipitate. Each unit should contain ≥ 80 IU FVIII and the Circular, but not the CFR, also indicates that the product should contain ≥ 150 mg fibrinogen in approximately 15ml plasma.

Plasma, Cryoprecipitated Reduced is prepared from FFP that is thawed and centrifuged, with the cryoprecipitate removed by centrifugation.

Plasma frozen within 24 hours after phlebotomy must be separated and placed at $\leq -18^{\circ}\text{C}$ within 24 hours of whole blood collection.

Plasma; Liquid Plasma is separated no later than 5 days after the expiration date of the Whole Blood. Plasma may be stored at $\leq -18^{\circ}\text{C}$. Liquid Plasma is stored at refrigeration temperature ($1-6^{\circ}\text{C}$).

The AABB Circular describes the uses of these products.

FFP:

- ?? Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (e.g., liver disease).
- ?? Patients with massive transfusion who have clinically significant coagulation deficiencies.
- ?? Patients on warfarin who are bleeding or need to undergo an invasive procedure...
- ?? For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).
- ?? Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available
- ?? Management of patients with rare specific plasma protein deficiencies, such as C-1-esterase."

24 h Plasma; Thawed Plasma; Liquid plasma: Serve as a source of defective or deficient plasma proteins except for FV and FVIII. Indications are the same as for FFP except not to be a source of FV or FVIII.

Cryoprecipitate: Provides FVIII, fibrinogen, vWF, FXIII. Used as second-line therapy for vWD and hemophilia A. Control of bleeding associated with fibrinogen deficiency, and to treat FXIII deficiency.

Plasma, Cryoprecipitate Reduced: Provides for defective or deficient plasma proteins except fibrinogen, FVIII, vWF, FXIII. Used for TTP refractory to FFP.

Side effects and hazards of plasma transfusion components

The transfusion of plasma components is associated with a number of potential side effects and hazards (AABB Circular). Immediate immunologic complications include febrile nonhemolytic reactions, allergic reactions, anaphylactoid reactions, and transfusion-related acute lung injury (TRALI). Delayed immunologic complications include alloimmunization to antigens of red cells, white cells, platelets, or plasma proteins. Besides these complications, there is always the potential of human blood products to transmit infectious agents, because of viral, bacterial, or prion contamination. Transfusions also carry the risks of circulatory overload, hypothermia, or metabolic complications.

Given these risks, transfusion of blood components should be appropriately minimized. To that end, increasing the potency of products could help to reduce exposure to products.

Parameters to consider that might improve the quality of plasma.

The CFR and AABB standards do not specify many conditions of plasma collection, freezing, storage, thaw and post thaw conditions that could affect the quality and safety of plasma components. At an international forum on critical factors that affect the quality of FFP, held in 1983, [Allain, 1983] the following parameters were highlighted as being significant. They are not inclusive and further suggestions are welcome.

Anticoagulant: CPD or ACD: The literature is mixed on the differing effect of these anticoagulants on FVIII recovery. Some studies indicate FVIII activity is reduced in ACD compared to CPD. Is there an anticoagulant-related difference in coagulation factors or other plasma proteins in frozen or liquid plasma that develop over time?

Cellular content in plasma components. Residual cells and cellular breakdown products in plasma have the potential of causing immunological reactions and release of proteolytic enzymes, leading to some side effects seen in plasma product transfusions. There are no standards for the cellular content of plasma products, but plasma products must be ABO compatible. Plasma separation techniques can vary widely yielding differing quantities of residual cells.

Plasma contact with cellular components—Temperature effects Cold activation of the coagulation and plasma kinin system is of concern [Over, 1990]. A recent study [Favaloro, 2004] suggests that significant reduction in FVIII and vWF activity can occur in plasma separated from whole blood after 3.5 hr at 4 °C, compared to plasma separated after 3.5 hr at 22 °C.

Time, Temperature from draw to freezing Allowable times and temperatures vary among different regulatory bodies [see tables below]. Importantly, conditions that are optimal for plasma collection may or may not be optimal for cellular components [Hogman, 1998; Pietersz, 1989]. In evaluating the literature and considering the development of standards, we need to be mindful that these standards can affect both plasma products and cellular components.

Rate of freezing plasma, final temperature of freezing, storage time and temperature, thawing and post thawing conditions are additional factors that can affect the quality of plasma products. They were discussed extensively at the Plasma Standards workshop. [Slide sets and a transcript of the workshop are available at <http://www.fda.gov/cber/summaries.htm>, and <http://www.fda.gov/cber/minutes/workshop-min.htm> respectively.]

Results from the workshop and review of the literature suggest the following:

Time and temperature from collection until freezing affects yield of labile products. FVIII is the most labile protein, and changes in its activity may reflect unmeasured changes in other labile factors. FVIII activity may be better preserved in blood held at 20°C than at 4 °C before separation [**Over**, 1990]

Labile factors, particularly FVIII, are preserved better if plasma is frozen rapidly compared to plasma frozen more slowly. The Council of Europe has recommended that plasma for transfusion be frozen **to** ≤ -30 °C within 1 hour. This is in contrast to the CFR requirement that such plasma be frozen, stored and shipped at ≤ -18 °C. (see tables below).

While the data shows that rapid freezing preserves more factor VIII than slower freezing, the magnitude of this effect depends on the details of the processing conditions and may have more effect on cryoprecipitate than FFP. One study concluded that there was little difference in FVIII activity in FFP between slow and fast frozen plasma, [**Farrugia**, 1985], while another [**Akerblom**, 1992] did find a difference.

Higher concentrations of FVIII, fibrinogen and vWF were present in cryoprecipitate prepared from rapidly frozen plasma and correspondingly less in cryosupernatant [**Farrugia**, 1985]. This may be advantageous when using Cryoprecipitate Reduced plasma to treat thrombotic thrombocytopenic purpura. These results may or may not be generalized to other methods of preparing cryoprecipitate.

Some studies report that little if any loss of clotting factor activity occurs when quick frozen plasma is stored at ≤ -20 °C for 3 years [**Kotitschke**, 2000; **Koerner**, 1982]. Other investigators [**Woodhams**, 2001] have reported losses.

Fluctuations in the storage temperature of frozen plasma can alter yield of some proteins in cryoprecipitate, such as fibrinogen. [**Farrugia**, 1985]

While slow freezing reduces the efficacy of FFP reflected in FVIII activity, the effect on safety is unknown.

Plasma for transfusion in the US is regularly shipped at ≤ -20 °C according to meeting participants.

In evaluating scientific evidence that might support potential modifications of existing standards, such as extending the dating period of FFP beyond 1 year, care should be taken to examine the experimental details supporting the data, especially in cases where results differ among studies. Laboratory conditions might not reflect those achievable in blood processing centers. It is also

important to consider that parameters optimal for production of one product may not be the best for others.

Questions for the Committee:

- Please discuss the extent to which the available literature on plasma processing may support changes to improve the clinically relevant safety, purity, potency or consistency of various plasma products for use in transfusion, e.g. time to plasma separation, time from collection or separation to freezing, freezing rate and target temperature, storage temperature, allowed temperature variations during shipping and storage, cellular content.
- What additional scientific studies are needed?
- What recommendations do you have for the next steps forward?

Summary of European Plasma Standards

European Pharmacopoeia				Council of Europe	
Purpose	Labile proteins for fractionation	Non labile protein for fractionation	Non labile protein for fractionation	For transfusion	
Collection method	Plasmapheresis Or Plasma from whole blood	Plasmapheresis	Plasma from whole blood	Whole blood plasma	apheresis
Time from collection to freezing	≤24 hrs	≤24 hrs	≤72 hrs	≤18 hrs, (≤6 hrs optimal) if +20 – 24 °C, then ≤24 hrs	≤6 hrs if +20 – 24 °C, then ≤24 hrs
Freezing conditions, temperature	Chamber at ≤-30 °C	Chamber at ≤-20 °C	Chamber at ≤-20 °C	To < -30 °C within 1 hr	
Storage, expiration	≤-20 °C			If -18 °C to -25 °C, 3 months If <-25 °C, 24 months	
Shipping temperature	≤-20 °C			-18 °C to -25 °C, or <-25 °C (see above)	
Allowable deviation	Exceeds -20 °C not more than 72 h total One time > -15 °C, Never > -5 °C			none	

US Standards

	Source Plasma	FFP	Recovered plasma
Collection method	Plasmapheresis	Whole blood or Plasmapheresis	Whole blood or Plasmapheresis
Time from collection to freezing	Immediately	if +20 – 24 °C for platelet prep, then ≤8 hrs	Undefined
Freezing conditions, temperature	≤-20 °C	≤-18 °C	Undefined
Storage, expiration	≤-20 °C, 10 yr	≤-18 °C, 1 yr	Undefined
Shipping temperature	≤-5 °C	≤-18 °C	Undefined
Allowable deviation	Can exceed -20 °C for ≤72 h total Never > -5 °C, always frozen	None	Undefined

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