EC 21/98

UKBTS/NIBSC STANDING ADVISORY COMMITTEE ON BLOOD COMPONENTS EVALUATION OF NEW FRESH FROZEN PLASMA / CRYOPRECIPITATE COMPONENTS FOR TRANSFUSION

1 Introduction

Currently, FFP for direct use or as start material for cryoprecipitate production is produced either from whole blood donations or by centrifugal apheresis techniques. Novel technologies under assessment include solvent detergent and methylene blue virus inactivation techniques, and plasma produced after leucocyte depletion of whole blood. Apheresis techniques involving filtration have been approved in the past (eg Baxter Autopheresis C).

Current Red Book criteria are as follows (75% of units must meet):

Parameter	Specification
FFP	
Volume	>150 mls and within locally defined normal range
Platelets	$<30 \times 10^9$ /l
Factor VIIIc	>0.7 iu/ml
Cryoprecipitate	
Volume	within locally defined normal range
Fibrinogen	>140 mg/unit
Factor VIIIc	>70 iu/unit

These parameters assume a storage temperature of $<-30^\circ$ C and a 12 month storage period.

2 In vitro evaluation of novel FFP .

2.1 Suggested study design

Because of the wide normal range of some clotting factors and potential inter-batch variation of assays, it is suggested that initially 20 novel units and 20 controls be produced and assayed in parallel, with the novel technology being the only variable. A less costly alternative, if logistics permit, is to do a pooled paired comparison, where 2 units are pooled, and one half processed by the novel technique. This provides greater statistical power for less units assayed, and is particularly important for storage studies. Ideally provision should be made for storing and testing aliquots from each pack at every time point, as thawing out 3 or 4 different packs at each time point introduces excessive variation. However, a pre-validation should be done to ensure that the behaviour of the aliquotted component during storage is the same as that in the main pack.

2.2 Assays required

2.2.1 The extent of any evaluation depends in part on the degree of novelty of the component. The list of assays below need not be applied in every setting. The attached table gives a summary of which assays are recommended in different situations. All evaluations must include the Red Book criteria of Factor VIII and fibrinogen.

2.2.2 Before freezing:

- volume, platelet count, WBC*
- prothrombin time, partial thromboplastin time
- factors I (fibrinogen), II, V, VII, VIII, IX, X, XI, von Willebrand factor (vWf):Ag, vWf:RCof, which measures the functional activity, vWf multimeric analysis (expensive so 2 or 3 packs only).
- inhibitors of coagulation - antithrombin, protein C, protein S

- markers of unwanted activation of coagulation* - prothrombin fragment 1.2, fibrinopeptide A, factor XIIa
- markers of unwanted activation of kinins/complement* - C3a, C5a, bradykinin

* Particularly relevant to plasma which has been collected by any filtration technique, in which case the assays should be performed before and after filtration.

2.2.3 During storage

Consideration should be given to performing storage studies at -20°C as well as -30°C to reflect hospital storage conditions. Samples should be taken at 3, 6, 9, and 12 months. If the 12 month parameters remain well within specification, more prolonged storage and evaluation should be considered (SD FFP has a shelf life of 24 months at -30°C). Ideally, all clotting factors should be assayed at each time point, if only in a few packs. The following should be assayed at each time point as a minimum - factors I, V,VIII, vWf:RCof, IX and X.

Storage parameters may be assayed after the date of implementation of routine production, provided data 'keep ahead' of the age of any clinical product which might be issued.

3. *In vitro* evaluation of novel cryoprecipitate

It is assumed that this will be produced from a 'novel' start plasma so that investigators will be aware of any specific losses of clotting factors which should be particularly considered. _

Assays to be performed before and after production, and during storage:

- fibrinogen, factor VIIIc, vWf:Ag, vWf:RCoF (plus vWf multimeric analysis after production only, on a few units).

vWf multimeric analysis should be performed in a laboratory recognised to be proficient in this technique and which is performing the assay regularly.

4 Cryosupernatant

This component is increasingly used for plasma exchange procedures for patients with thrombotic thrombocytopenic purpura. Analysis of von Willebrand factor multimers is therefore appropriate.

5. *In vivo* studies

Whether or not *in vivo* studies are needed depends on the degree of novelty of the component eg this may not be necessary for plasma which has been leucocyte depleted in the course of producing leucocyte depleted red cells, but would certainly apply in the case of a novel virus inactivated plasma which had been exposed to chemicals. Unlike red cells and platelets, administration to normal volunteers has not been traditional. Suitable patient groups to consider would be:

For FFP - correction of prolonged INR prior to liver biopsy

- liver transplant recipients
- plasma exchange for TTP
- DIC

It is difficult to get permission to study neonates and usually considerable experience has to have been gained with the product in adults.

A randomised design is preferred, with standard FFP as control.

For cryoprecipitate - DIC

- liver disease/transplant
- congenital hypofibrinogenaemia, if maintained on cryoprecipitate.

EVALUATION OF NOVEL PLASMA COMPONENTS

x *Recommended* - *Not needed* # *Consider individually*	**Fresh Frozen Plasma**						**Cryo-precipitate**	**Cryo-supernatant**
	Leucocyte Depleting Filter	**New Centrifuge/ Component Extractor**	**Novel Anti-Coagulant**	**Novel Apheresis System**	**Novel Apheresis + Anti-Coagulant**	**Virus inactivated**		
Volume	x	x	x	x	x	x	x	x
Factor VIII	x	x	x	x	x	x	x	x
Platelets	x	x	x	x	x	x	-	-
PT/INR	x	-	-	x	x	x	-	-
PTTK	x	-	-	x	x	x	-	-
Fibrinogen	x	-	-	x	x	x	x	x
II, V, VII, IX, X, XI	x	-	-	x	x	x	-	-
vWf : Ag	x	-	x	x	x	x	x	x
vWf : RiCof	x	-	x	x	x	x	x	x
AT III, Prot C, Prot S	-	-	-	x	x	x	-	-
Frag 1.2 / FPA/XIIa	x	-	x	x	x	x	Omit if not elevated in source plasma	
C3a + C5a + bradykinin	x	-	x	x	x	x		
vWf Multimers	x	-	x	x	x	x	x	x
Clinical trial	-	-	#	#	#	x	#	#

6.22 Fresh Frozen Plasma, Methylene Blue Treated (for direct clinical use)

6.22.1 General Description

Fresh frozen plasma Methylene Blue Treated (MBT), is plasma that has been obtained from whole blood or by apheresis, has been ~~filtered~~ to remove white blood cells and treated with methylene blue and exposure to white light to inactivate viruses.

Following MBT the plasma is rapidly frozen to a temperature that will maintain the activity of labile coagulation factors.

6.22.2 Technical Information

1 Ideally the plasma should be separated (at 22°C ± 2°C) before the red cell component is cooled to its storage temperature.

2 The method of preparation should ensure the component has the maximum level of labile coagulation factors with minimum cellular contamination.

3 ~~The~~ white blood cells in the plasma are reduced to $<5x10^6$ per unit prior to exposure to methylene blue and ~~white~~ light.

4 A rapid freezing process should be used to ensure that a core temperature of -30°C or below is achieved within 2 hours of commencing the freezing process.

5 The maximum time period from venepuncture to obtaining a core temperature of -30°C or below is normally 8 hours.

6 The MBT process reduces the factor VIII content by approximately ~~20~~% ~~(ie MBT FFP has 20% less factorVIII than stanard FFP)~~.

6.22.3 Labelling (For general guidelines see 5.6)

The following shall be included on the label:

- fresh frozen plasma methylene blue treated and volume
- the producer's name in eye readable and UKBTS approved barcode format
- the donation number
- the ABO group
- the RhD group stated as positive or negative
- the date of preparation and expiry date of the frozen component
- the temperature of storage
- a warning that the component should be used within 4 hours of thawing

In addition the following statements should be made:

CAUTION
Always check patient/component compatibility
Do not use if there are signs of deterioration or damage
Use a standard transfusion set
Risk of adverse reaction/infection
Please contact your blood bank/BTC for further information

6.22.4 Storage (for general guidelines see 5.7)

1 Fresh frozen plasma methylene blue treated should be stored at a core temperature of -30^{0}C or below for a maximum of 12 months.

2 Although a storage temperature below -30^{0}C improves the preservation of labile coagulation factors, lower temperatures increase the fragility of plastic. Particular care must be taken when handling such packs.

3 Once thawed, fresh frozen plasma methylene blue treated must not be refrozen and should be stored at ambient temperature and used within 4 hours.

6.22.5 Testing

1 In addition to the mandatory and other tests required for blood donations and which are described in Annex 3, the manufacturer must ensure (eg by a recognised process control methodology or by performing leucocyte counts on all components) that plasma for methylene blue treatment is consistently leucocyte depleted to <5x10^6 prior to being exposed to the methylene blue/~~white~~ light process. Furthermore, a minimum of 75% of those components tested for the other parameters shown at 6.22.5.2 below shall meet the specified values.

2 Additional Tests

PARAMETER	FREQUENCY OF TEST	SPECIFICATION
Volume	1% or 10 per month whichever is greater. If less than 10 per month, every component	Within locally defined nominal volume range and within any limits specified for the MBT process used
Platelets		≥30x10^9/l #
Factor VIIIc		>0.55IU/ml #
Leucocyte count	As per 6.22.5.1	< 5x10^6 / unit

Prefreeze

6.22.6 Transportation (for general guidelines see 5.11)

Every effort should be made to maintain the core storage temperature during transportation. Unless the component is to be thawed and used straight away it should be transferred immediately to storage at the recommended temperature.