BLOOD PRODUCTS ADVISORY COMMITTEE
100th Meeting, April 28-29, 2011
The Hilton Washington DC North/Gaithersburg
620 Perry Parkway
Gaithersburg, MD 20877

Issue Summary

Topic II: Current Considerations on Plasma for Further Manufacturing Obtained from Whole Blood Donors

Issue: FDA seeks the advice of the Committee on appropriate manufacturing standards for plasma products collected from Whole Blood donors to make injectable plasma derived products.

Introduction:

FDA seeks advice from the Committee on appropriate standards and labeling for two licensed plasma products (defined below as "Concurrent Plasma," and "Component Plasma") collected under whole blood donor eligibility requirements in 21 CFR 640.3 and intended for use in further manufacturing to make injectable or non-injectable products. This topic was discussed previously with BPAC at the April 2, 2009 meeting.

Background:

Currently, Source Plasma (a licensed product) and recovered plasma (an unlicensed product) are used as source material to manufacture injectable plasma derived products.

Source Plasma (21 CFR 640.60) is an FDA licensed product collected by plasmapheresis, which is labeled at the time of collection as source material for further manufacture into injectable and non-injectable products and is frozen immediately after collection. Source Plasma is primarily collected from paid donors who meet the donor eligibility requirements in 21 CFR 640.63 and 640.65. Source Plasma standards allow collection of plasma twice within a seven day period, and incorporate an annual physical and total protein determination to protect donor health due to the frequency of collection.

Source Plasma can also be collected from donors who meet whole blood donor eligibility requirements every 4 weeks or less frequently as part of an infrequent plasmapheresis program. The donors in this program do not undergo the annual physical and total protein determination required for donors in a frequent Source Plasma collection program. Infrequent Source Plasma collection is approved for individual licensed blood establishments as an alternative procedure under 21 CFR 640.120. With the availability of portable devices, apheresis procedures are now commonly performed at mobile facilities located away from the primary blood collection facility and processing laboratory. The absence of freezing capability at mobile collections generally prevents the manufacture of Source Plasma away from the primary facility because the collected plasma cannot be frozen immediately.

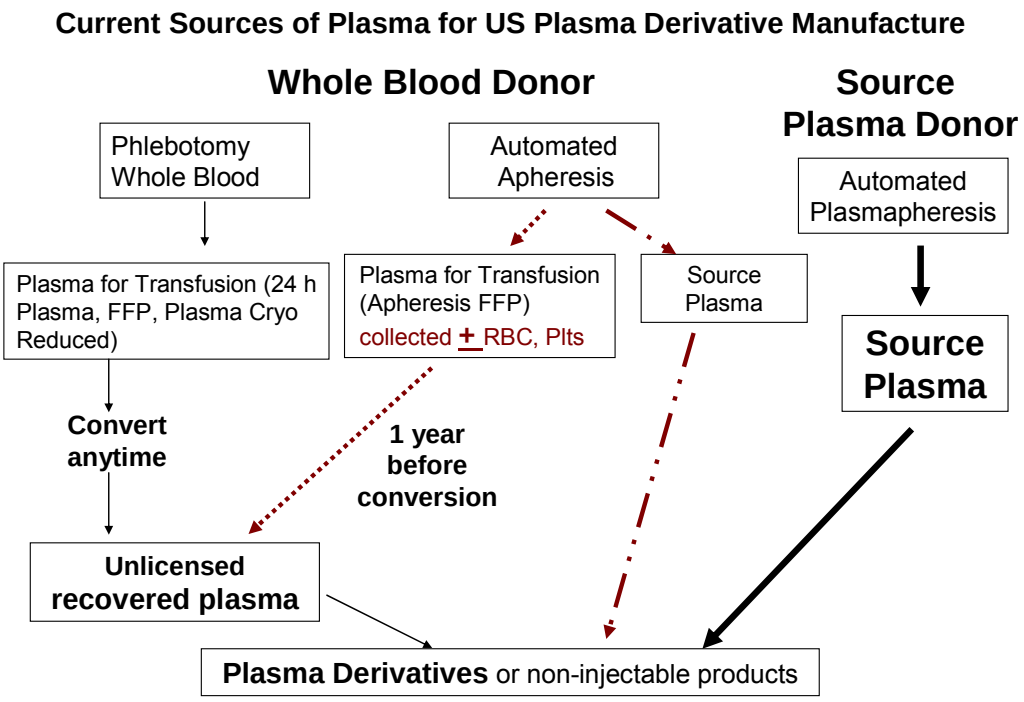


FIG 1

Under current FDA regulations, plasma separated from whole blood collection, whether or not first made into Fresh Frozen Plasma (FFP), may be labeled (or relabeled) at any time as recovered plasma and used in further manufacture into injectable or non-injectable products. FFP collected by automated blood cell separation (apheresis) may also be relabeled as recovered plasma following its one year expiration period.(Fig 1). Distribution of recovered plasma in interstate commerce without a license has historically been permitted under "short supply" regulations. [21 CFR 601.22]

With recent growth in the targeted collection of cellular blood components by apheresis, whole blood collection establishments have sought changes in FDA regulations that would permit plasma collected concurrently during the apheresis procedure to be distributed immediately for further manufacturing. Such a change would provide flexibility to blood collectors to manufacture either FFP or plasma for further manufacturing use based on current need, without concern that excess apheresis FFP might need to be held for one year or else discarded. Some blood collectors are also interested in improving the negative perceptions associated with the term "recovered" plasma by changing the name and having it recognized as a licensed product.

The current state of plasma storage/freezing conditions for recovered plasma varies widely and is specified in the short supply agreements between collectors and

fractionators or other further manufacturers. FDA does not routinely review short supply agreements. It is known that conditions of freezing, thawing, time in contact with cells and time in the liquid state bear a relationship to preservation, activation and inactivation of labile proteins (e.g. yields of Factor VIII). For this reason, we are considering establishing limiting conditions for plasma used in fractionation to ensure minimum quality suitable for the manufacture of injectable plasma derivatives.

At the April 2, 2009 meeting of the Blood Products Advisory Committee, FDA described a proposal for licensing Concurrent Plasma (CCP) as a licensed plasma product collected concurrently with a cellular transfusion product, either by whole blood collection or by apheresis. CCP could be labeled immediately at the time of collection, or by one-way conversion (at any time) of previously collected Fresh Frozen Plasma (or other plasma intended for use in transfusion) into a product for further manufacturing. The Committee endorsed this concept, but recommended simplification of the proposed labeling scheme.

FDA described another potential product, Component Plasma (CMP), collected as a stand-alone plasmapheresis product or converted from FFP collected as a stand-alone product and intended for further manufacturing. Members of the Committee expressed concern that licensing of CMP could undermine the system of community based voluntary donation under which donors generally provide donations to meet patient needs for transfusion rather than to be used primarily for further manufacturing.

FDA has considered the advice of the BPAC and now brings forward a revised proposal.

FDA's current considerations for these new products are as follows (Fig 2):

Concurrent Plasma (CCP): a new licensed plasma product collected under whole blood donation standards (including by apheresis), to be defined by modifications to existing regulations and associated guidance. FDA's current considerations for CCP include the following parameters:

- CCP would be plasma intended for further manufacturing obtained from: i) licensed Whole Blood collected manually, or ii) licensed plasma collected concurrently with cellular components by apheresis, or iii) conversion at any time from licensed FFP or WB-PF24 collected concurrently with a cellular product. This definition of Concurrent Plasma reflects the concept that blood obtained from community whole blood donors is intended primarily to serve transfusion needs.

- CCP shelf life would be 3 years from date of collection

- Licensed WB-derived FFP, PF24, and apheresis FFP could be converted to Concurrent Plasma at any time, but Concurrent Plasma, once labeled, could not be re-labeled as a transfusable product.

Component Plasma (CMP): a new licensed plasma product intended for further manufacturing obtained by relabeling of expired licensed FFP collected under whole blood standards as a stand-alone plasmapheresis product This product would also be defined by modifications to existing regulations and associated guidance.

- CMP shelf life would be 3 years from date of collection

Under FDA's proposal, CCP and CMP would be suitable for manufacture of injectable end products (subject to certain additional restrictions discussed below) but also could be made into non-injectable end products. Plasma products not meeting the standards of CCP or CMP would not be subject to licensure requirements and could continue to be distributed as "recovered plasma" under short supply agreements, but only for use to make non-injectable end products.

Proposed Sources of Plasma for US Plasma Derivative Manufacture

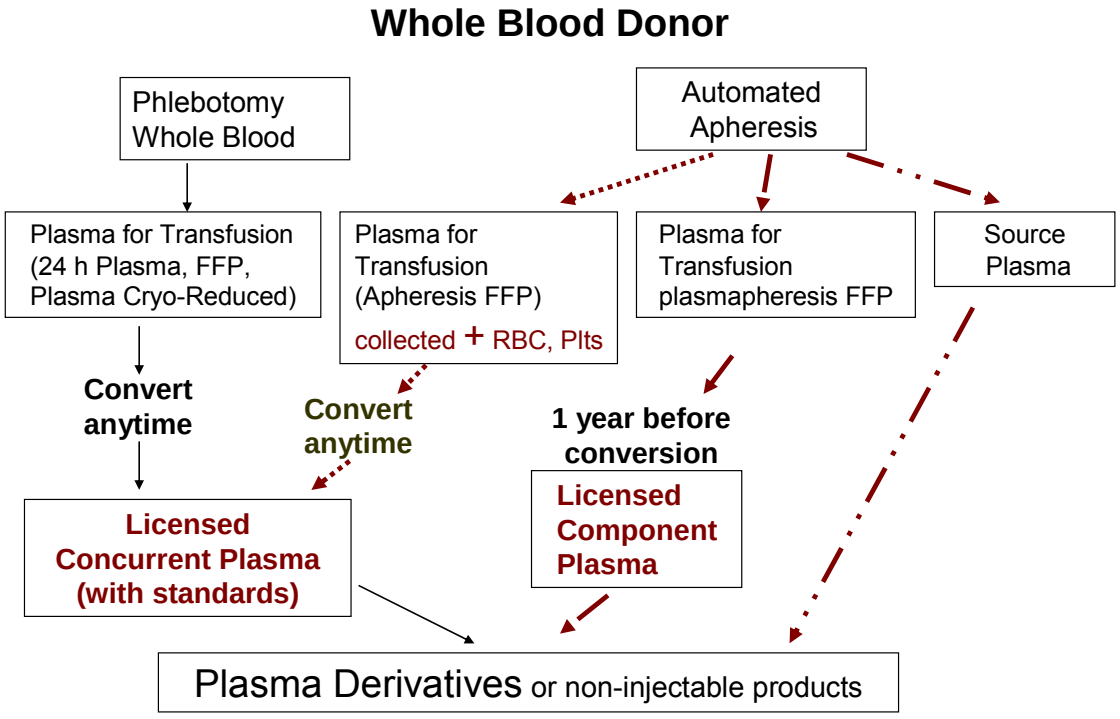


Fig 2

Discussion:

General Features of the Revised Proposal

Manufacturing conditions for Concurrent Plasma would reflect current practices
FDA believes that plasma derivatives made under current practices are safe and effective. Therefore, FDA would establish standards for Concurrent Plasma that for the most part reflect current industry practices for the preparation and use of recovered plasma, an unlicensed product. Establishing these practices as standards for Concurrent Plasma, will enable FDA to provide regulatory oversight that will ensure consistency and limit the extent to which plasma with unknown or inferior properties could be used for manufacturing. Concurrent Plasma standards will include specified limits for the collection, freezing and storage of plasma, as well as labeling criteria that will provide fractionators with information about the conditions under which the plasma was manufactured, and the classes of products for which the plasma is suitable as a raw material.

Redefinition of Component Plasma

FDA has modified the proposed definition of Component Plasma based upon the April, 2009 Committee recommendations. FDA's current consideration is for Component Plasma to be a licensed plasma component intended for further manufacturing into injectable or non-injectable products obtained from expired licensed FFP collected under whole blood standards as a stand-alone plasmapheresis product. Because standards for transfusion help to ensure a high quality frozen plasma product, FDA considers it important to preserve a pathway for suitable but untransfused plasma to be relabeled for further manufacturing into injectable or non-injectable final products.

Discussions with the blood community have indicated that this redefinition of Component Plasma is unlikely to cause undue burden to blood collection centers, since the number of apheresis collections where plasma is the sole product is limited, and most of these collections would be Group AB and/or plasma from male donors which would likely be transfused prior to outdate.

Rationale for Establishing Quality Standards

Since Concurrent Plasma would be collected from donors meeting whole blood donor eligibility standards, the primary consideration for additional product standards lies in the conditions of collection, freezing process, and storage that would be reflected in product labeling.

Plasma quality is a relative term that is linked to the purpose for which the plasma will be used. FVIII is commonly used as an indicator of plasma quality because it is one of the most labile of plasma proteins and because there is commercial interest in preserving its activity in high-yield for use as a therapeutic agent. The parameters for obtaining high quality plasma to make labile FVIII in good yield may not be the same as those for

making the more stable immunoglobulins or albumin. However, in all cases, plasma should not contain substances that, if not removed or neutralized during the manufacturing process, could have an untoward effect on the safety or efficacy of the final product.

Once blood is drawn, the molecular composition of plasma will change, depending on environmental conditions, resulting in greater heterogeneity than occurs in vivo, including activation, inactivation, aggregation or fragmentation of enzymes and other proteins. In the Cohn-Oncley plasma fractionation process, a commonly used manufacturing procedure to prepare fractions of proteins for further purification, proteins are separated according to their solubilities under specified conditions of temperature, pH, ionic strength and alcohol concentration (Fig 3). The output of one step is dependent on the input from the previous step.

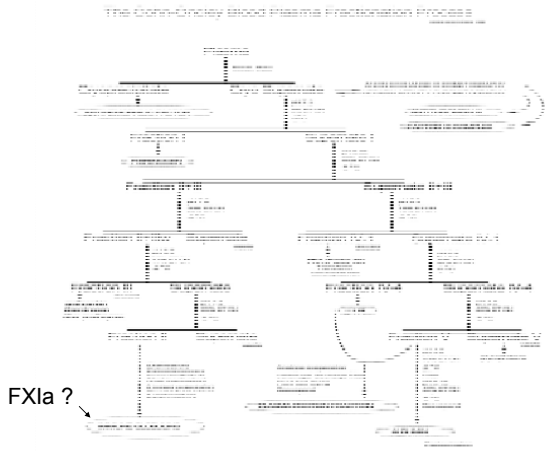


Fig 3. Cohn-Oncley Fractionation Scheme

Novel heterogeneous materials generated in the starting plasma may co-purify and become concentrated within various Cohn fractions. If not removed or neutralized in manufacturing, these materials could potentially affect the safety of the final product. For example, if raw plasma has a high Factor XIa content that is not cleared during manufacturing, the activated enzyme could co-purify with an immunoglobulin product and cause thrombotic adverse events. Setting limits to plasma preparation conditions will reduce raw material variability, increase manufacturing consistency and predictability, and decrease the potential for plasma raw material to have an untoward effect on final plasma derivative product composition or safety.

Parameters That Affect Plasma Quality

Among the conditions that affect plasma quality, as defined by causing a decrease in the quantity of a desired therapeutic activity and an increase in molecular heterogeneity, are: time and temperature of separation of plasma from cells, anti-coagulant, freezing process, storage and thawing conditions, and the post- thawing environment.

Plasma contact with or without cells. Plasma quality is affected by the amount of time that plasma stands in contact with cells. For example, plasma proteolytic activity

increases, the longer that plasma is in contact with platelets and leukocytes (Wallvik et al) (Fig 4).

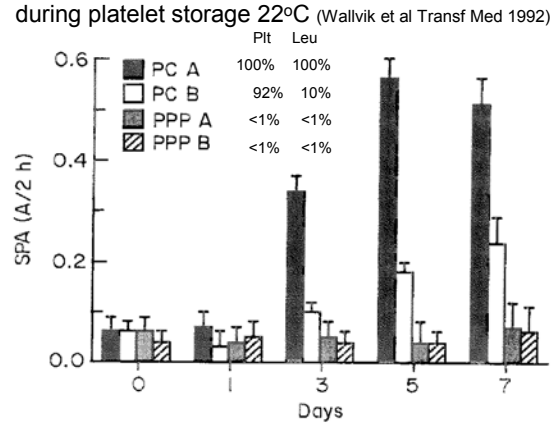


Fig 4. Plasma in contact with platelets and leucocytes, over time has increased levels of proteolytic activity. PRP was stored at 22°C over a period of days, and the plasma was tested for proteolytic activity using a synthetic substrate S-2288. Taking platelet concentrate (PC) A to contain 100% platelets and 100% leucocytes, then a second preparation of PC contains 92% and 10%. Platelet poor plasma A and B are controls. Non-specific proteolysis increased over time dependent primarily on the concentration of leucocytes.

Even when plasma is not in contact with cells it can undergo changes in enzymatic activity and heterogeneity, including thrombin activation, fibrin formation, and kallikrien generation (Fig 5.).

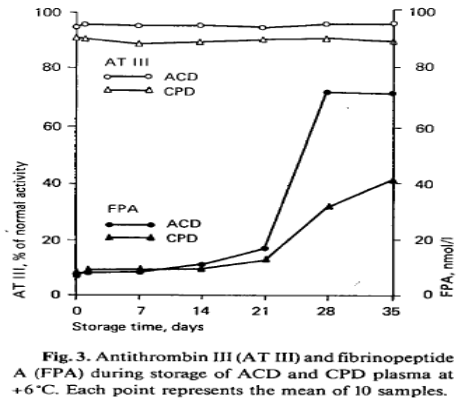
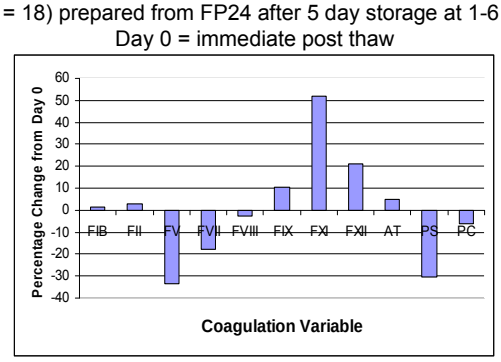


Fig 5. Changes in ATIII and Fibrinopeptide A in plasma collected in ACD or CCPD and stored over 35 days at 6°C. FPA is released over this time both in ACD and CCPD plasma, suggesting activation of the coagulation system. These storage conditions can result in activation of the coagulation, fibrinolytic, and kallikrein systems. Note that Liquid Plasma is a licensed product that can be separated up to 5 days after expiration from Whole Blood, and Whole Blood can be stored up to 35 days depending on the anticoagulant.

Coagulation protein activity in thawed plasma can change over time. In one study (Yazer et al) (Fig 6a.) the activities of Factors IX, XII and most notably factor XI were found to increase, while Factors V, VI, VIII, Protein C and Protein S decreased over five day storage at 1- 6°C. Activation of Factor XI and a decrease in Protein S were most notable

after 48 and 24 hours respectively (Fig 6b). Limiting the amount of time that plasma can remain un-frozen will reduce potential safety threats.



Data from Yazer et al, Transfusion, 2008 48:2525-2530

Fig 6a

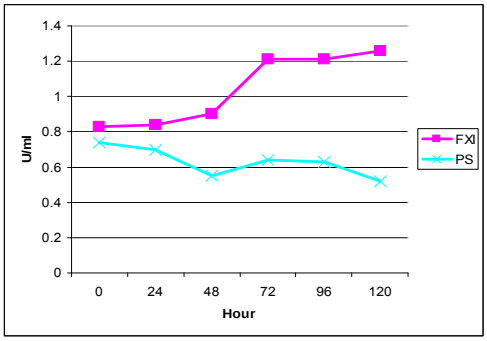


Fig 6b

Temperature affect. The temperature at which plasma is in contact with cells affects plasma quality. In the United States plasma can be in contact with cells at 20-24°C, for up to 8 hours (for the production of platelets). In other cases plasma is cooled down toward 1-10 °C or held at 2-6°C, in contact or not with cells, before being placed in a freezer within 24 hours of collection (FP24). Given the current lack of regulations for recovered plasma, plasma derivative products could be made from any of the plasmas cited below, such as plasma that had been in contact with cells for an extended period of time, e.g. Liquid Plasma that was 40 days old, in contact with cells for 35 days. The quality of some such plasma for manufacture of injectable products is questionable.

Plasma Definitions (per the CFR)

- **Plasma**. Plasma shall be separated from the red blood cells and shall be stored at -18°C or colder within six hours after transfer to the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system unless the product is to be stored is Liquid Plasma. [21 CFR 640.34(a)]
- **Fresh Frozen Plasma (FFP)** [21 CFR 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
- **Plasma, Cryoprecipitate Reduced:** is prepared from FFP that is thawed and centrifuged, with the cryoprecipitate removed by centrifugation. [21 CFR 640.34(e)(2)]
- **Liquid Plasma** is separated no later than 5 days after the expiration date of the Whole Blood [**expiration can be 21 or 35 days depending on anticoagulant]**.

Plasma may be stored at ≤- 18°C. Liquid plasma is stored at refrigerator temperature 1-6°C. [21 CFR 640.34(c)]

Plasma Definitions (per the AABB Circular of Information)

- **Fresh Frozen Plasma** is prepared from whole blood or apheresis collection and frozen at -18°C or colder within the time frame as specified in the directions for use for the blood collection, processing, and storage system.
- **Plasma frozen within 24 hours after phlebotomy:** must be separated and placed at ≤-18°C within 24 hours of whole blood collection.
- **Thawed Plasma** is derived from FFP and PF24 prepared in a way that ensures sterility (closed system), thawed at 30-37°C, and maintained at 1-6°C for 1-5 days. *A product not in the CFR, not a licensed product.*

However, in practice, United States licensed plasma derivative manufacturers use plasma placed in a freezer within 24 hours of collection (see below Current Manufacturing Practices) for the manufacture of labile products e.g., FVIII. Table 1 shows the results of several studies that monitored FVIII activity in plasma held in contact with cells at the given times and temperatures. The results of this review suggests that holding Whole Blood for up to 24 hours from collection to freezing to yield plasma containing at least 70 IU/100 ml of FVIII is somewhat inconsistent but was obtainable in most cases.

Table 1. Plasma Separated from Whole Blood and Placed in a Freezer within 24 Hours: Literature Review

Time (h) with Cells	Time without cells	Temperature	FVIII (IU/100 ml)
8		1-6 ^{0}C	64 (O'Neill)
	16	1-6 ^{0}C	
8		22-24 ^{0}C	71 (O'Neill)
	16	1-6 ^{0}C	
24		1-6 ^{0}C	76 ± 2 (Smith)
?	?	1-6 ^{0}C	72 ± 14 (Yazer)
18-20		1-6 ^{0}C	55 ± 20 (Kakaiaya)
16-20		22 ^{0}C	77± 8 (Pietersz)
24		24 ^{0}C (18-25 ^{0}C)	75 (Cardigan)
24		20 - 24 ^{0}C	64 (Study Submitted to FDA)

FDA has received data from three studies of apheresis plasma held at ---b(4)---------- that had mean levels of FVIII ---b(4)--- ml in each case, suggesting that apheresis plasma collected under these conditions would be suitable for manufacturing labile plasma derivatives. The effect of processing conditions on the quality of apheresis plasma (such as time at room temperature prior to freezing) is not well established at this time. In general, apheresis plasma would appear to be of higher quality than a similar volume of whole blood plasma, if the measure of quality was based on the average level of FVIII activity alone. However, this apparent higher quality is in part an artifact of the higher anticoagulant dilution of whole blood (14 ml/100 ml collected whole blood) compared to apheresis plasma (6.3 ml to 11 ml/100 ml blood, depending on the collecting device) (Laub). Thus, the measured higher concentration of FVIII in apheresis plasma, while correct relative to the standard may not necessarily indicate that apheresis plasma is of higher quality, i.e. more intact protein and less heterogeneity, than whole blood plasma. Potentially this artifact could be dealt with by using a correction factor that would take into account the volume of anticoagulant used in the apheresis device relative to the whole blood plasma standard.

However a study by Runkle et al supports the idea that apheresis plasma is in fact of higher quality than whole blood plasma when considering other indicators of active hemostasis and proteolysis. Coagulation activation and proteolysis markers including F1+ 2, PF4 and neutrophil elastase were significantly higher in whole blood plasma placed in a freezer three and 15 hours after collection when compared to apheresis plasma placed in a freezer three hours after collection.

Table 2. Apheresis Plasma		
Hold time (hr)	Temperature	FVIII (IU/100 ml)
-b(4)-	-b(4)-	----b(4)---------
-b(4)-	-b(4)-	
-b(4)-	-b(4)-	----b(4)---------
24	24^0C	86± 27(Study C, Snyder)
Studies A, B, and C were submitted to FDA, and each included more than 50 study subjects		

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

Freezing rate. The rate at which plasma is frozen will influence FVIII activity levels more than the temperature at which plasma is frozen. Early studies (Akerblom) showed that rapidly freezing plasma at -40°C, within 40 min resulted in a loss of about 8% FVIII from pre to post freeze, while a slow freeze at the same chamber temperature resulted in a 14% loss. When plasma was slowly frozen at -20°C, FVIII activity decreased by 20%. Other studies have shown similar results (Bravo; Farrugia; Carlebjork). Interestingly, however, one study (Bravo) showed that the yield of FVIII from cryoprecipitate obtained from plasma frozen at -20°C was no different from plasma frozen at -30° or at -25°C. FIX recovery was significantly better from plasma frozen at -20°C compared to that

frozen at -30°C. These observations suggest that the yield of final product for the manufacture of FVIII and FIX derivatives may be no worse from plasma frozen at -20°C than from plasma frozen at a lower temperature. FDA is not specifying a rate of freezing in our proposals for Concurrent Plasma standards.

Storage temperature. The temperature at which plasma is stored could potentially affect plasma quality. An extensive study by Kotitschke et al showed no difference in blood plasma constituents, including Factors VIII, IX, V, among others, in plasma stored at -20°C versus -40°C over 36 months.

Industry Practices for Time to Placement in the Freezer and Use of Recovered Plasma in the Manufacture of Plasma Derivatives

Source Plasma, collected by apheresis and frozen immediately, is used by all US licensed manufacturers to make all classes of plasma derivatives and accounts for nearly 90% of plasma used in plasma derivative production (Marketing Research Bureau, 2009).

At the FDA sponsored 2004 Workshop on Plasma Quality, a number of plasma derivative manufacturers described the kinds of recovered plasma (time to freezer placement) they used to manufacture labile and non-labile products (Table 3.)

Table 3.

Recovered Plasma Time From Blood Collection to Placement in Freezer, and Plasma Use Data from FDA 2004 Workshop on Plasma Quality				
	≤8 hr	≤ 24 hr	≤72 hr	≤120 hr
Grifols		IGIV, Albumin		
CSLB		FVIII, vWF, Albumin, IGIV		Albumin, IGIV
Octapharma	SD Plasma	FVIII, Albumin, IGIV	Albumin, IGIV	
Bayer (now Talecris)	Recovered plasma used only to make Fraction IV-1 paste for Alpha1 PI; time to placement in freezer not given			
ARC	Plasma placed in freezer within 8 and 24 hr, but products made from 8 and 24 hr plasma were not identified			

Manufacturers reported that they used recovered plasma to make labile and non-labile products from ≤ 24 hr plasma, and that only one company used ≤ 120 hr Liquid Plasma to make non-labile products.

Current United States and European Standards for Plasma

US Standards

	Source Plasma	Recovered plasma
Collection method	Plasmapheresis	Whole blood or Plasmapheresis
Time from collection to freezing	Immediately	Undefined
Freezing conditions, temperature	≤-20 °C	Undefined
Storage, expiration	≤-20 °C, 10 yr	Undefined
Shipping temperature	≤-5 °C	Undefined
Allowable deviation	Can exceed -20 °C for ≤ 72 h total Never > -5 °C, always frozen	Undefined

European Pharmacopoeia			
Purpose	**Labile proteins for fractionation**	**Non labile protein for fractionation**	
Collection method	Plasmapheresis or Plasma from whole blood	Plasmapheresis	Plasma from whole blood
Time from collection to freezing	≤24 hrs	≤24 hrs	≤72 hrs
Freezing conditions, temperature	Frozen to a core temp of ≤-25 °C in ≤12 hr	Chamber at ≤-20 °C	Chamber at ≤-20 °C
Storage	≤-20 °C		
Shipping temperature	≤-20 °C		
Allowable deviation	Exceeds -20 °C not more than 72 h total One time > -15 °C, Never > -5 °C		

In Europe, unlike in the United States, recovered plasma used for manufacturing labile or non- labile products has requirements, as stated in the European Pharmacopoeia, for conditions of time from collection to placement in a freezing chamber, freezing conditions, storage and shipping temperatures, and allowable temperature deviations. FDA is describing similar requirements for Concurrent Plasma that would be within the boundaries of current industry practice.

The European Pharmacopeia Guidelines for the Preparation of Plasma for Manufacturing vol 2, 7.0, pg 2181 discusses the activity of FVIII in plasma to be used for labile products:

"It is not intended that the determination of … factor VIII shown below to be carried out on each unit of plasma. They are rather given as guidelines for good manufacturing practice, the test for factor VIII being relevant for plasma intended for use in the preparation of concentrates of labile proteins.

Preservation of factor VIII in the donation depends on the collection procedure and the subsequent handling of the blood and plasma. With good practice, 0.7 IU /ml can usually be achieved, but units of plasma with the lower activity may still be suitable for use in the production of coagulation factor concentrates. The aim of good manufacturing practices is to conserve labile proteins as much as possible."

Factor VIII. *Carry out the test using a pool of not fewer than 10 units. Thaw the samples to be examined, if necessary, at 37°C. Carry out the assay of factor VIII using a reference*

plasma calibrated against the international standard for human coagulation factor VIII plasma. The activity is not less than 0.7 IU /ml."

Standards for Collection, Processing, Labeling and Storage of Concurrent Plasma

FDA currently is considering labeling for Concurrent Plasma that can be created, using computer software, by the blood establishment for key conditions of storage and freezing, so that purchasers in the US and abroad will know the salient characteristics of the product. Other categories may be established based on evidence showing that safe and effective products can be produced from plasma manufactured under specified conditions. We would limit the conditions of manufacturing and product use in the following ways:

Concurrent Plasma Category	**Examples of injectable product**	**Separation from cells**	**Freeze**	**Store and Ship**
A	FVIII, vWF IGIV, Albumin, Labile and Non-labile products (Average FVIII ≥70 IU/100 ml in QC testing under GMP)	≤24 hr	Freezer at ≤ -20 °C	≤ -20 °C
B	IGIV, Albumin Non-labile products	≤72 hr	Freezer at ≤ -20 °C	≤ -20 °C

Conditions under consideration for the manufacture of Concurrent Plasma include the following:

Labile products made only from plasma held for ≤ 24 hours, at specified temperatures, from collection to placement in freezer.
Rationale: This is in accordance with current US industry practice.

Average FVIII level ≥ 70 IU/100 ml for plasma used to make labile products as Quality Control testing under GMP.
Rationale: This proposed GMP requirement is the same as that in the European Pharmacopoeia. The FVIII activity of ≥70 IU/100 ml *is an achievable benchmark, a desirable level of activity for manufacturing purposes, and is one marker, albeit an imperfect measure, of plasma molecular integrity. As in the European Pharmacopoeia, it is not intended that the determination of FVIII be carried out on each unit of plasma, and units of plasma with lower activity may be used. The test would be carried out*

periodically using a pool of ten or more units and the international standard for human FVIII as a calibration reference. (It remains to be determined how often quality control testing for FVIII would be performed and by which establishments.)

Non-labile products made from plasma held for ≤ 72 hours, at specified temperatures, from collection to placement in freezer.
Rationale: Only one manufacturer reported using plasma older than 72 hours from the time of collection to freezing at the 2004 FDA Workshop. Considering the observed generation of proteolytic activity and increased protein heterogeneity as described in this summary, it is prudent to limit the time that plasma for manufacturing remains unfrozen to 72 hr. (Note: An exemption could potentially be made to make non-labile factors from Plasma, Cryoprecipitate Poor Plasma.)

Replacing ≤-20°C for ≤-18°C for all conditions of freezing, shipping and storage
*Rationale: The temperature limit of ≤-20°C for all conditions is the current industry practice and is supported by data (*Kotitschke)*, unlike ≤-18°C. The actual set-point temperature will be lower than -20°C to reduce the chance of exceeding this upper limit.*

Allowable shipping and storage temperature deviation can exceed - 20°C ≤ 72 hours total, never greater than -5°C (never refrozen).
Rationale: These are the current FDA standards for Source Plasma.

Storage up to 3 years from collection.
*Rationale: Data (*Kotitschke) *support the stability of plasma held at ≤-20°C for this time period.*

Plasma that has been thawed and refrozen would not be used for injectable products.
Rationale: There is a concern about the quality of such plasma based on potential for changes in some proteins. Source Plasma has similar limitations.

Labeling will include an intended use statement:

For plasma that can be used to make injectables:

> For labile products:
> "Caution: For Manufacturing Use Only.
> Placed in freezer ≤ 24 hours. May be used for labile or non-labile injectable products."
> (Note: Process control would assure an average FVIII ≥70 IU/100 ml)
>
> For non-labile products:
> "Caution: For Manufacturing Use Only. Placed in freezer ≤ 72 hours. May be used only for non-labile injectable products."

For plasma that can only be used to make non-injectables: "Caution: For Use in Manufacturing Noninjectable Products Only."

Regulatory Pathway
Definition of Concurrent Plasma would require changes to current regulations and guidances to support licensure of the new product. Should FDA develop a regulatory pathway for conversion of in-date apheresis Fresh Frozen Plasma for use in further manufacture, the FDA may consider variances under 21 CFR 640.120 to allow blood establishments to implement these changes prior to publication of the final regulations.

Risks and Benefits
One public health benefit of defining Concurrent Plasma as a new product would be to establish minimum standards for the collection, storage and freezing for plasma intended for further manufacturing into injectable end products. This would reduce the present uncertainty regarding the quality of recovered plasma used to make these products. The approach is consistent with the FDA requirement for licensure of Source Plasma.
A second public health benefit of the proposed new plasma products will result from the likely collection of more FFP on mobile collection sites due to the elimination of the one year storage requirement. This development will make increased volumes of male AB plasma available for transfusion to reduce the incidence of TRALI, and will also increase the overall supply of plasma available for fractionation into life-saving products.

The main benefit of rapid conversion of apheresis Fresh Frozen Plasma for blood establishments into a plasma for further manufacturing lies in reduction of plasma storage volumes, allowing blood establishment to gain flexibility in the management of their inventory. However, since conversion of Fresh Frozen Plasma under the proposed paradigm would be uni-directional, blood establishments will need to carefully monitor FFP supplies to ensure adequate availability of plasma for transfusion.

Questions for the Committee:

Q1. Please comment on FDA's proposed standards for Concurrent Plasma

Labile products made only from plasma held at ≤ 24 hours from collection to placement in freezer.

Average FVIII level ≥ 70 IU/100 ml for plasma used to make labile products as Quality Control testing under GMP.

Non-labile products made from plasma held at ≤ 72 hours from collection to placement in freezer.

Replacing ≤-20°C for ≤-18°C for all conditions of freezing, shipping and storage

Allowable shipping and storage temperature deviation can exceed - 20°C ≤ 72 hours total, never greater than -5°C (never refrozen).

Storage up to 3 years.

Plasma that has been thawed and refrozen would not be used for injectable products (with the possible exception of cryo-poor plasma).

Q2. Does the Committee agree with FDA's proposed labeling categories?

Placement in freezer ≤20°C	Labile	Non Labile	Non Injectable
≤24 hr (avg FVIII ≥ 70 IU/100 ml)	x	x	x
≤72 hr or ≤24 hr but avg. FVIII ≤ 70 IU/100 ml)		x	x
>72 hr			x

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