

Établissement Français du Sang-Alsace
Strasbourg
France



Daniel Kientz, MD
daniel.kientz@efs-alsace.fr
Tel : +33 388212528

Critical Evaluation of Available Pathogen Inactivated Plasma Products in France

Daniel Kientz, MD

Établissement Français du Sang-Alsace, Strasbourg, France

**Presented at the 44th Annual Congress of the
German Society for Transfusion Medicine
and Immunohematology (DGTI)**

Hannover, Germany • September 27th - 30th, 2011



Critical Evaluation of Available Pathogen Inactivated Plasma Products in France

Daniel Kientz, MD

Établissement Français du Sang Alsace, Strasbourg, France



Background

Currently three licensed plasma products, produced in different EFS centers, constitute the approximately 380,000 therapeutic plasma units transfused annually in France (Figure 1): Solvent Detergent plasma (SD FFP; 22% in 2010), Methylene Blue/VIS light plasma (MB FFP; 64%) and Amotosalen/UVA light plasma (IBS FFP; 14%)¹ (Figure 2).

The mechanism of the inactivation process is different for the three products: MB FFP utilizes Visible light to generate reactive oxygen species (ROS) that then destroy the nucleic acid of pathogens, SD FFP utilizes a detergent to disrupt membranes of pathogens in a

bulk process, and IBS uses formation of cross links on nucleic acids mediated by amotosalen after illumination with UVA light.

These three products were used to support the plasma transfusion needs of 555,372 patients in France in 2010.¹ After observation of relatively minor restrictions that are specific to each product, the three products are considered to be interchangeable for patient support and are available for all approved indications (massive hemorrhage, DIC, unusual or complex deficiency clotting factor and plasma exchange).

Figure 1: Production of Therapeutic Plasma in France

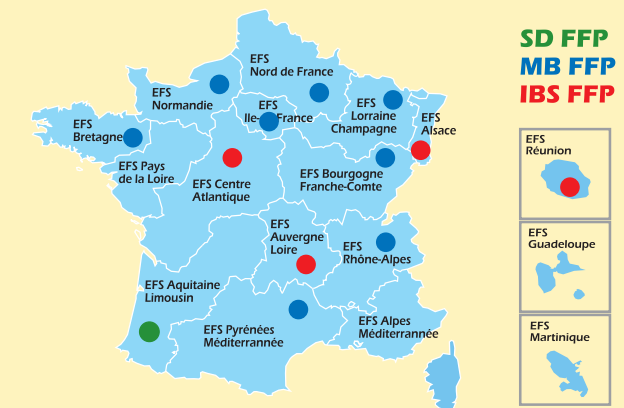
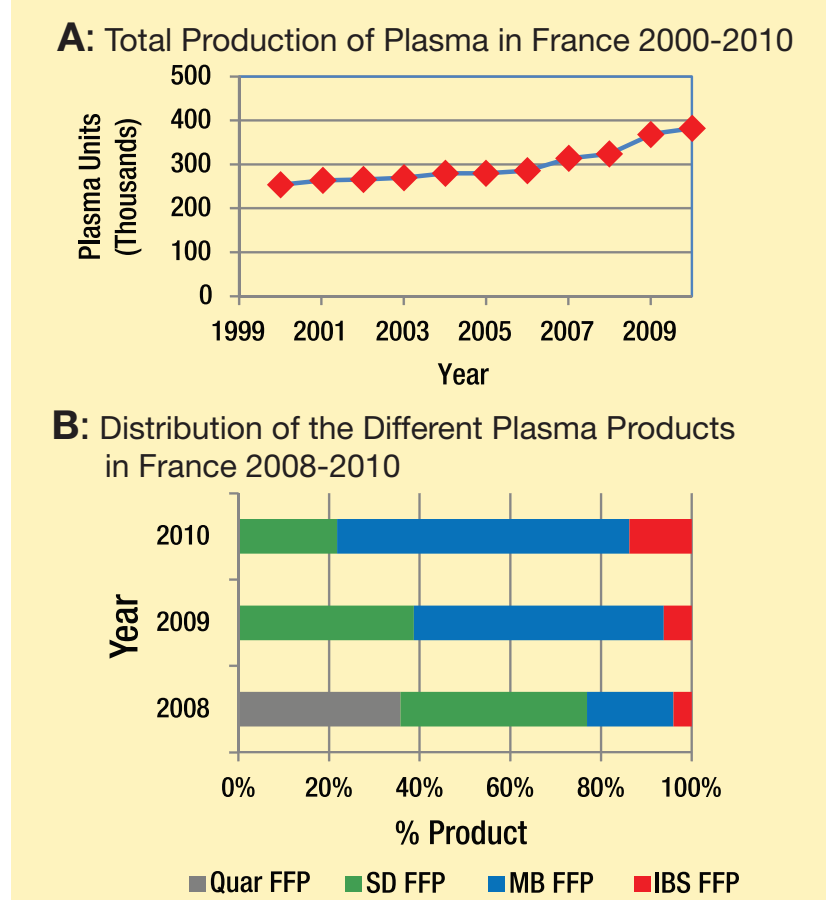


Figure 2: Evolution of the Plasma Distribution in France



Results and Methods

We compared the efficacy and safety literature data of the products, and evaluated hemovigilance data obtained after routine use in France.

Comparative studies² of the three products demonstrated that the coagulation factors meet EU standards, however MB FFP Fibrinogen and SD FFP Protein S are reduced (Table 1).^{2,3} Modification of HIS residues on Fibrinogen in MB FFP through the generation of ROS may be responsible for the reduction.^{4a,b} It is not known which part of the SD process is responsible for the reduction of protein S, however recent data from the French liver patient transfusion study NCT00235183, showed a two-fold increased incidence of Hepatic Artery Thrombosis for SD plasma vs. quarantine plasma or MB plasma. Similar thromboembolic adverse reactions had been observed after SD plasma transfusions in the US led to a "box" warning by the FDA and had been correlated with complete absence of protein S.^{4c}

The ability to inactivate pathogens met basic requirements for all products and IBS-FFP had the broadest spectrum of inactivation for viruses, bacteria and parasites (Table 2).⁵ Even though the three products have been in the market for different amounts of time and the prior human experience reflects that fact, randomized clinical trial data prior to regulatory approval are only available for IBS FFP based on 3 trials demonstrating equivalence to control plasma for the support of congenital and acquired clotting factor deficiencies and TTP (Table 3).⁶ In prior studies, SD FFP was equivalent to control FFP⁷ for patient support, while MB FFP was found to require more exchanges, or larger volume to support patient needs in TTP or surgery (Liver or Cardiovascular Disease patients).

Concerns over allergic reactions with MB FFP arose from hemovigilance reports of a higher rate per 10⁴ products for allergies (5,56 vs. 3,05 (SD FFP) and 3,36 (PCT FFP)) and a significant number of severe allergic reactions (0,58 vs. 0,28 for SD FFP and 0 for PCT FFP).¹ Three severe reactions were also reported separately⁸ and in follow up investigations proven to be connected to MB (Table 4).

Table 2: Inactivation Spectrum of Viruses and Parasites

Pathogen	SD FFP	MB FFP	IBS FFP
HAV	0	N/A	0
HIV (extra cellular)	>5	≥4	>6,8
HIV (cell associated)	N/A	4,9	>6,7
Influenza A	N/A	N/A	>5,7
Porcine parvovirus	0	N/A	0
Vesicular Stomatitis Virus	>8	N/A	>6,0
West Nile Virus	≥6	5,75	≥6,8
Chikungunya Virus	N/A	N/A	≥7,6
Sindbis Virus (HCV model)	>6	N/A	N/A
Bovine Viral Diarrhoea Virus (HCV model)	>6,1	N/A	≥5,4
Pseudorabies Virus (HBV model)	>7	≥5,5	N/A
Duck Hepatitis B Virus (HBV model)	N/A	N/A	4,4-4,5
<i>Trypanosoma Cruzi</i>	N/A	>3,4	>5
<i>Babesia microti</i>	N/A	N/A	≥5,3
<i>Plasmodium falciparum</i>	N/A	N/A	≥6,9

Conclusions

- SD FFP, MB FFP and IBS FFP have been implemented to reduce the risk of transfusion-transmitted infection
- All products meet basic requirements for pathogen inactivation
- Some differences have been found for the coagulation factors after MB treatment and HAT events associated with SD FFP, while significant concerns remain over severe anaphylactic reactions strongly associated with transfusion of MB FFP

Table 1: Comparison of Selected Pro-coagulant and Anti Thrombotic Factor Levels^a

	Normal Values	SD FFP	MB FFP ^b	IBS FFP ^c
Fibrinogen (g/L)	2-4	2,5-3,1	1,57-2,11	2,7-3,3
Factor V (UI/mL)	0,7-1,3	0,72-0,98	0,73-1,37	1-1,2
Factor VIII (UI/mL)	0,5-1,5	0,67-0,94	0,55-0,88	0,8-0,9
Factor XI (UI/mL)	0,5-1,5	0,11-0,39	0,52-1,30	0,7-1,1
Protein C (UI/mL)	0,7 - 1,2	1,05 (4)	0,89-1,03 (1)	0,9-1,1 (1)
Protein S (UI/mL)	0,65-1,4	0,62 (4)	0,99-1,11 (1)	1-1,4(1)
ATIII (%)	-	81(2)	102,3 (2)	92,3 (2)
ADAMTS 13 (%)	-	100 (3,4)	100 (3,4)	98 (3,4)

^a Results expressed in log reduction after Rock^{3b}, but corrected from the primary sources

^c Amotosalen inactivates many bacterial species², and in PFC-SD are removed (sterile filtration)¹

^b Methylene Blue is not effective in bacterial inactivation¹

Table 3: Randomized Clinical Trials (RCT) for Plasma Products

Study	Design	Clinical Setting	Key Result
Randomized Clinical Trials for IBS FFP^a			
Hambleton ⁹	X-Over; N=27	Warfarinized Volunteers	No Difference PT, FVII Kinetics
	X-Over; N=16, N=17	Warfarinized Volunteers	No Difference C & S Kinetics
De Alarcon ^{6a}	RCT; N=34, 107 Tx	Patients, Multiple factors	Recovery Tolerance and Efficacy Acceptable
Mintz ^{6b}	RCT; N=121	Acquired Coagulopathy	Non-inferiority for PT
Mintz ^{6c}	RCT; N=35	TTP Patients	No Clinical Difference
Selected Randomized Clinical Trials for MB FFP^a			
Simonsen ¹⁰	X-Over; N=12	Healthy Volunteers	No Difference
Wieding ¹¹	RCT; N=71 vs. MB	Cardiopulmonary bypass surgery patients	No Clinical Problems; For SD Arm, Low S, Low Antitrypsin
Selected Randomized Clinical Trials for SD FFP^a			
Williamson ¹²	N=49 vs. FFP	Complex coagulopathy: liver disease or transplantation	No Difference
Beck ¹³	N=40	Severe Coagulopathy	No Difference
Lerner ¹⁴	N=45	Severe Coagulopathy	No Difference

^a For a more comprehensive list of studies see the review by Prowse^{3a}

Table 4: Adverse Event Comparison for Plasma Components in 2009²

	SD FFP	MB FFP - MB	IBS FFP
Units Transfused	142,533	204,814	22,933
Serious Adverse Events (SAE) Imputability 2-4 (per 10 ⁴)	57 (3,99)	136 (6,64)	12 (5,23)
Allergies (per 10 ⁴)	48 (3,36)	114 (5,56)	7 (3,05)
SAE Grade 3-4 and Imputability 3-4 (per 10 ⁴)	4 ^b (0,28)	12 ^c (0,58)	0/0

^a Allergies

^b 8 Allergies, 2 Volume Overloads, 1 TRALI, 1 Unknown

References

1 Le Rapport Annuel de l'Hémovigilance, 2009 and 2010 Afssaps
 2 Naegelen C, et al., Transfus Clin Biol 2009; 16: 179-189
 3 a) Prowse C, Transfus Med Rev 2009; 23: 124-133
 b) Rock G, Vox Sang 2011; 100: 169-178
 4 a) Altance R, et al., Transfusion 2001; 41: 1548-1552
 b) Inada Y, et al., Biochim Biophys Acta 1978; 532: 161-170
 5 Salge-Bartels U, et al., Transfus Med 2006; 16: 266-275.
 6 Stramer SL, et al., Transfusion 2009; 49 Suppl 2:1S-29S
 7 de Alarcon P, et al., Transfusion 2005; 45: 1362-1372
 b) Mintz PD, et al., Blood 2006; 107: 3753-3760
 c) Mintz PD, et al., Transfusion 2006; 46: 1693-1704

7 a) Beck KH, et al., Infus Ther Transfus Med 2000; 27:144-148,
 b) McCarthy LJ, et al., Apheresis and Dialysis 2003; 8: 80-86
 c) Rock G, et al., British Journal of Haematology 2005;129, 79-86
 8 a) Nubret K, et al., Transfusion, 2011; 51, 125,
 b) Dewachter P, et al., British Journal of Anaesthesia 2011; 106, 687
 9 Hambleton et al., Transfusion 2002; 42,1302-1307
 10 Simonsen and Sorensen, Vox Sang, 1999; 77, 210-217
 11 Wieding et al., Transfusion 39(suppl): 23s (abstract)
 12 Williamson et al., Transfusion 1999; 39,1227-1234
 13 Beck et al., Infusionsther. Transfusionsmed 2000; 27, 144-148
 14 Lerner et al., Vox Sang 2000; 79,161-167