Pathogen Inactivation of Cryoprecipitate and Plasma Including Clinical Experience with Patients and other Pipeline Projects for SD PCC and IV Ig

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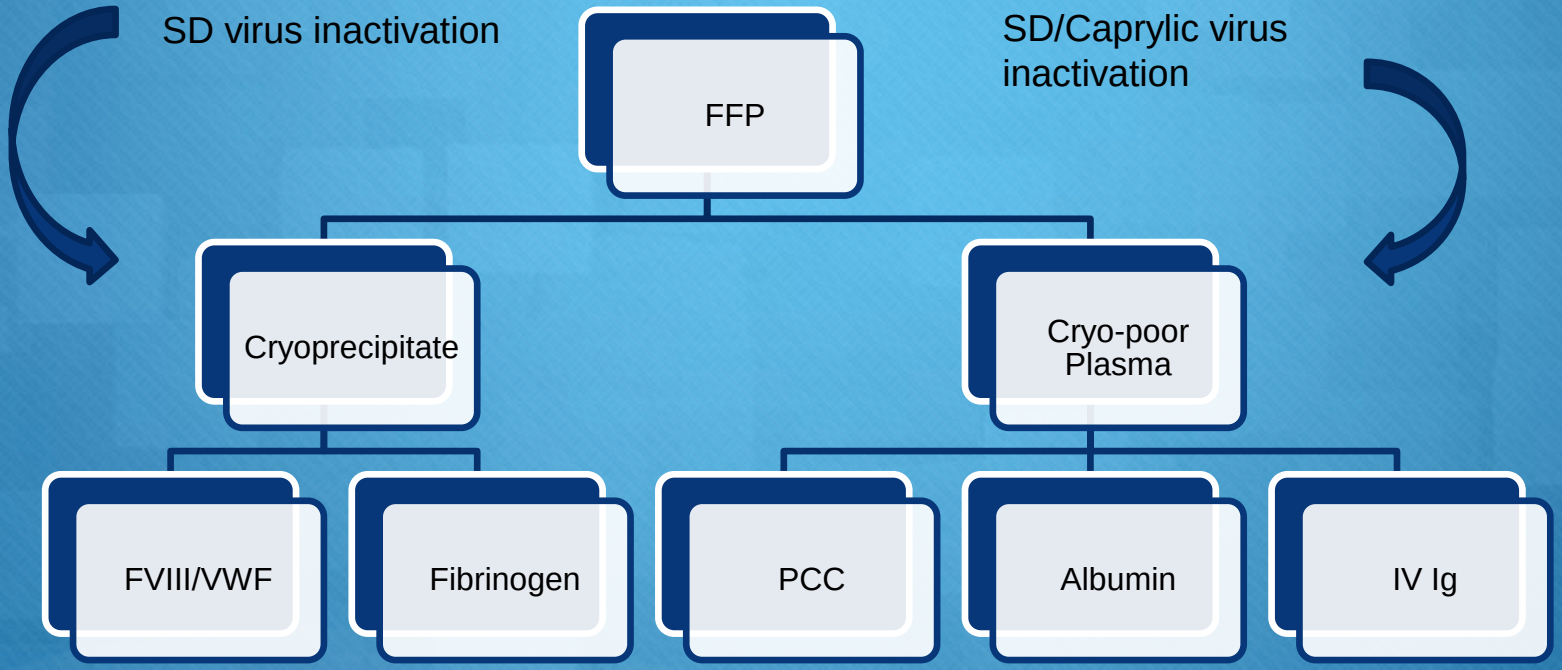
Why such a concept ?

- Non-virally inactivated plasma components are still used to treat patients in many countries for:
  - Coagulation & anticoagulation disorders
  - Immuno-deficiency
  - Blood losses

Mini-pool plasma fractionation

- New concept to process small plasma volumes (2-6 L/batch processing)
- Processed in blood establishment or local service center
- Processing is performed in single use sterile bag systems with special design
- Enriched intermediate purity concentrated plasma proteins
- Virus inactivation
- Final product is liquid and is stored at 4°C or frozen

Enriched plasma components



Cryoprecipitate

Dry Cryo

- Deplete cryoprecipitate from plasma
- Re-suspend in 5% glucose saline

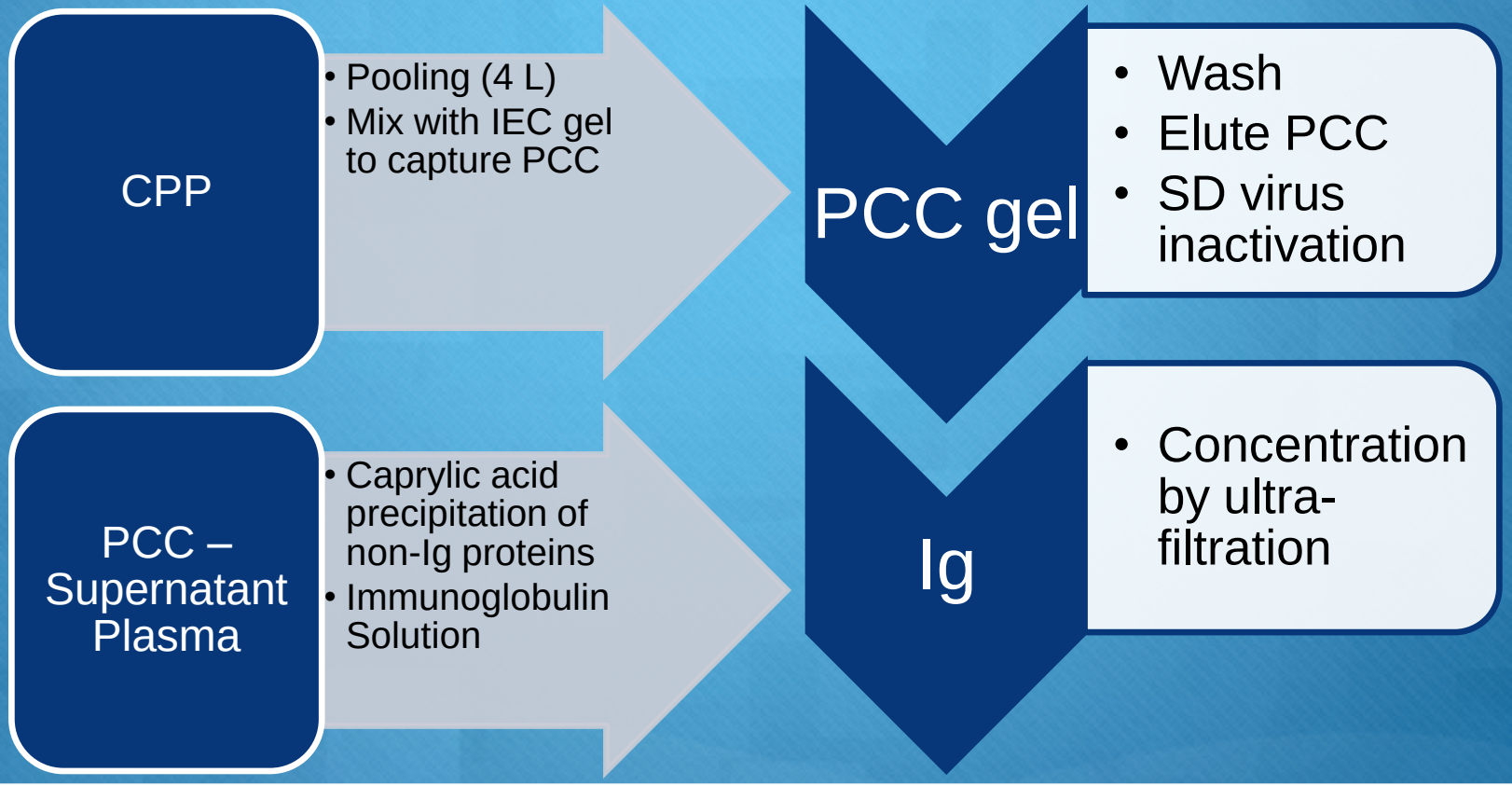
SD Virus Inactivation

- Pool 30 units of dry cryo
- SD treatment

Final product

- Concentrated Solution of:-
- FVIII, Fibriniogen, vWF and FXIII

Cryoprecipitate poor plasma (CPP)



Solvent-Detergent Virus Inactivation

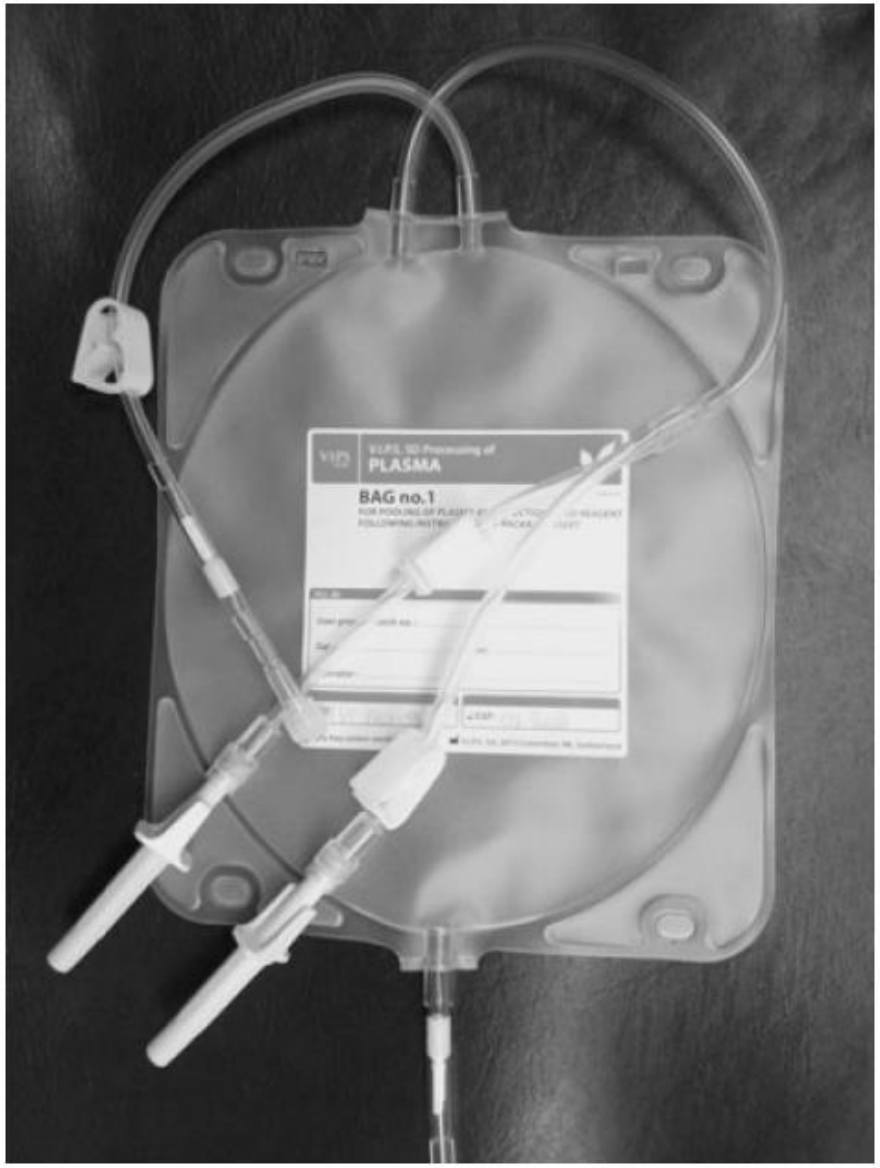
- Developed by the New York Blood Center
- The major breakthrough in the safety of industrial plasma products in the last 25 years
- No HIV, HBV, HCV transmission by SD-treated products in the last 25 years

Main Process Steps

- Pooling plasma/CPP or 30 units of dry cryoprecipitate solubilized in 5% glucose saline solution (400 ml) :
- SD treatment
- SD Removal
  - Oil extraction
  - SD adsorption filter
- 0.2 µm filtration
- Dispensing in dose labeled bags and freezing

Medical Device for Virus Inactivation by SD

B



C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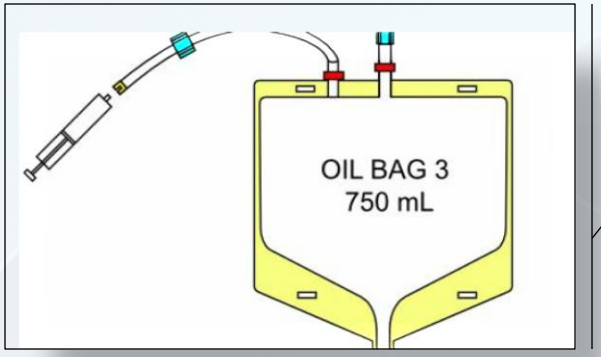
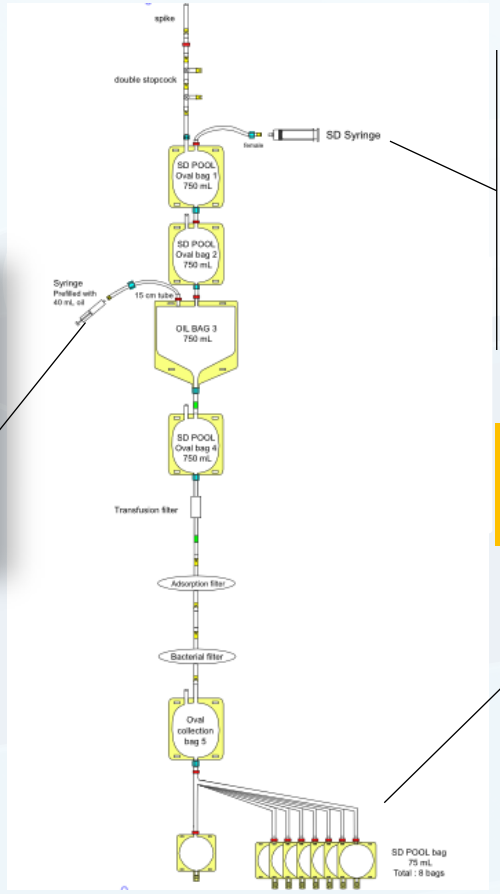
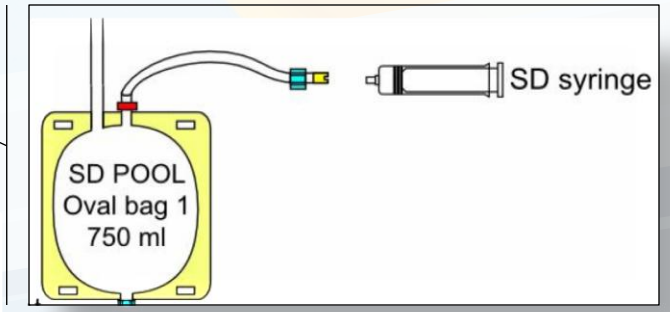
Oil decantation step

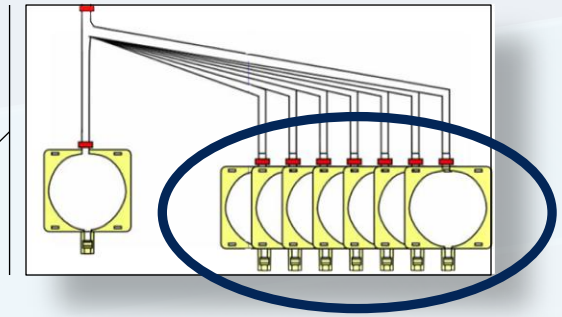




SD treatment



Distribution into therapeutic doses



2 units of plasma or 30-32 cryo units= **380 +/- 20 mL**
S/D-plasma or Cryo

Each dose:
200 IU FVIII
300 IU VWF
350 mg fibrinogen

ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/Q070

TÜV AUSTRIA

Vollständiges Qualitätssicherungssystems - *Full quality assurance system*
93/42/EWG Anhang II Abschnitt 3 – *93/42/EEC Annex II section 3*

Hersteller:
Manufacturer:

V.I.P.S. SA
Viral Inactivated Plasma Systems SA
Avenue de la Gare 26
2013 Colombier, Switzerland

Produktkategorie:
Product category:

Virus-inaktivierungs Produkt für Plasma und Kryopräzipitat (-)
Virus-inactivation product for plasma and cryoprecipitate (-)

Dieses Zertifikat gilt nur für Produkte und Fertigungsstätten die im Anhang zum Zertifikat angeführt sind. - *This certificate is valid for products and facilities listed in annex to certificate only.*

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Bericht Nr:
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CE 0408

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13.07.2009
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Date of issue

Dipl.-Ing. Michael Pölzleitner
Zertifizierungsbeauftragter
Certification representative

02.03.2014
Ende der Gültigkeit
End of validity

QFM-MT-MP30_Zertifikat_Anh II Rev. 02

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ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/Q070

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Product category:

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Virus-inactivation product for plasma and cryoprecipitate (-)

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CE
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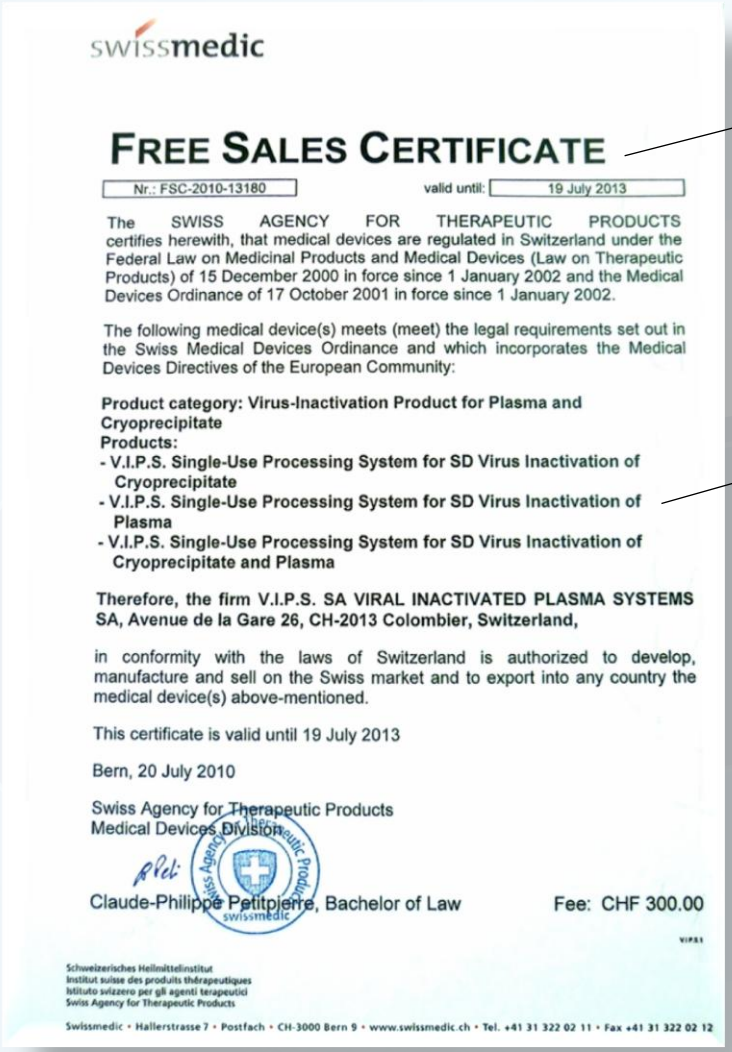
VIPS for life



swissmedic

FREE SALES CERTIFICATE

Nr.: FSC-2010-13180 valid until: 19 July 2013

The SWISS AGENCY FOR THERAPEUTIC PRODUCTS certifies herewith, that medical devices are regulated in Switzerland under the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products) of 15 December 2000 in force since 1 January 2002 and the Medical Devices Ordinance of 17 October 2001 in force since 1 January 2002.

The following medical device(s) meets (meet) the legal requirements set out in the Swiss Medical Devices Ordinance and which incorporates the Medical Devices Directives of the European Community:

Product category: Virus-Inactivation Product for Plasma and Cryoprecipitate
Products:
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate**
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Plasma**
- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate and Plasma**

Therefore, the firm V.I.P.S. SA VIRAL INACTIVATED PLASMA SYSTEMS SA, Avenue de la Gare 26, CH-2013 Colombier, Switzerland,

in conformity with the laws of Switzerland is authorized to develop, manufacture and sell on the Swiss market and to export into any country the medical device(s) above-mentioned.

This certificate is valid until 19 July 2013

Bern, 20 July 2010

Swiss Agency for Therapeutic Products
Medical Devices Division

Claude-Philippe Petitpierre, Bachelor of Law Fee: CHF 300.00

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- **V.I.P.S. Single-Use Processing System for SD Virus Inactivation of Cryoprecipitate and Plasma**

VIPS
for life

ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/E111

TÜV AUSTRIA

Qualitätsmanagementsystem - *quality management system*

Unternehmen:
Company:

V.I.P.S. SA
Viral Inactivated Plasma Systems SA
Avenue de la Gare 26
2013 Colombier, Switzerland

Geltungsbereich:
Scope:

Design und Entwicklung, Herstellung und Vertrieb von nicht-aktiven Medizinprodukten für die Transfusionsmedizin
Design and development, manufacture and distribution of non-active medical devices for transfusion medicine

Norm:
Standard:

EN ISO 13485:2003+AC:2007
Qualitätsmanagementsystem Medizinprodukte
Quality management system medical devices

Bemerkungen:
Remarks:

Hiermit bescheinigt die TÜV Austria Services GmbH, dass das Qualitätsmanagementsystem im Zuge eines Audits überprüft wurde und im angeführten Geltungsbereich den Anforderungen der oben angeführten Normengrundlage entspricht.
TUV Austria Services GmbH certifies that the quality management system in the above mentioned scope has been examined and meets the relevant requirements of the above mentioned standard.

09MT0205WRO
Bericht Nr:
Report No.:

03.03.2009
Erstausstellung
First issue

03.03.2009	Dipl.-Ing. Michael Pölzleitner	02.03.2014
Datum der Ausstellung *Date of issue*	Zertifizierungsbeauftragter *Certification representative*	Ende der Gültigkeit *End of validity*

QFM-MT-QM30_Zertifikat_13485 Rev. 02

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ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/E111

Geltungsbereich: *Scope:*	Design und Entwicklung, Herstellung und Vertrieb von nicht-aktiven Medizinprodukten für die Transfusionsmedizin *Design and development, manufacture and distribution of non-active medical devices for transfusion medicine*
Norm: *Standard:*	EN ISO 13485:2003+AC:2007 Qualitätsmanagementsystem Medizinprodukte *Quality management system medical devices*

Viral validation studies

- Texcell/Pasteur Institute (France)
- Conducted following CPMP/EMEA guidelines
- Worst case conditions (low % range of SD, low temperature; no transfer to second viral inactivation bag)
- >4 log reduction of HBV, HCV & HIV virus models in cryoprecipitate (as well as plasma, and cryo-poor plasma) in two minutes

Viral validation studies: conclusion

- The TnBP-Triton X-45 is very effective
- Virus inactivation is very fast
- The shape and design of the bag is appropriate to ensure good mixing between plasma and SD

Removal of solvent and detergent

- SD residual after oil extraction, SD adsorption filter and bacterial filter:-
  - TnBP <0.3 ppm
  - Triton X 45 <10 ppm

Transfusion Medicine, 2010, **20**, 48–61 doi: 10.1111/j.1365-3148.2009.00963.x

ORIGINAL ARTICLE

Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system

M. El-Ekiaby,[1] M. A. Sayed,[2] C. Caron,[3] S. Burnouf,[4,5] N. El-Sharkawy,[7] H. Goubran,[8] M. Radosevich,[6] J. Goudemand,[3] D. Blum,[4,5] L. de Melo,[9] V. Soulié,[9] J. Adam[9] & T. Burnouf[6] [1]*Shabrawishi Hospital Blood Bank, Giza, Egypt,* [2]*Fayoum University, Fayoum, Egypt,* [3]*Laboratoire d'hématologie, Hôpital Régional et Universitaire Lille,* [4]*INSERM, U837,* [5]*Université Lille-Nord de France, IMPRT, Jean-Pierre Aubert Research Centre,* [6]*Human Protein Process Sciences, Lille, France,* [7]*National Cancer Institute,* [8]*Faculty of Medicine, Cairo University, Cairo, Egypt, and* [9]*V.I.P.S. SA Virus Inactivation of Plasma Systems, 2013 Colombier, Switzerland*

Transfusion Medicine, 2010;20:48-61

Quality control of SD-cryoprecipitate

Table 3. Protein composition of cryoprecipitate minipools before and after S/D + filtrations (Mean ± SD : $N = 5$)

	Start				Final				P
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Factor VIII : c (IU/mL)	8·66	0·97	7·27	9·62	9·21 (106%)	1·51	7·11	11·23	NS
Factor VIII : Ag (IU/mL)	12·08	1·74	10·80	14·60	12·40 (103%)	1·77	10·20	14·40	NS
Fibrinogen (mg/mL)	17·4	2·7	13·6	21·0	15·0 (86%)	3·7	12·3	21·2	NS
Factor XIII (IU/mL)	2·26	0·26	2·03	2·69	2·46 (109%)	0·29	2·18	2·82	<0·05
VWF : Ag (IU/mL)	17·5	1·7	16·2	19·8	17·1 (97·5%)	1·0	15·8	18·0	NS
VWF : RCo (IU/mL)	13·5	2·2	10·0	15·6	14·3 (106%)	2·2	11·2	16·6	NS
RCo/Ag	0·77	0·13	0·61	0·96	0·84 (109%)	0·14	0·69	1·04	NS
VWF/CB (IU/mL)	14·6	3·9	10·1	19·1	14·9 (102%)	3·4	11·3	18·8	NS
CB/Ag	0·83	0·16	0·62	1·02	0·87 (105%)	0·17	0·65	1·04	<0·05
Percentage of >15 mers	7·8	1·6	5·6	10·0	7·8 (99·5%)	1·3	5·5	8·8	NS
>15 mers/control plasma ratio	0·8	0·2	0·6	1·0	0·8 (100%)	0·1	0·6	0·9	NS
Percentage of >10 mers	23·8	2·0	21·4	26·4	23·5 (99%)	1·7	21·4	25·2	NS
>10 mers/control plasma ratio	0·9	0·08	0·8	1·0	0·9 (99%)	0·07	0·8	0·1	NS

ABO iso-agglutinins titer in concentrated SD-cryoprecipitate

- ABO iso-agglutinins :
  - Anti-A titer: o
  - Anti-B titer: o

Haemophilia

Haemophilia (2011), 1–5

DOI: 10.1111/j.1365-2516.2011.02511.x

ORIGINAL ARTICLE

Pharmacokinetic study of minipooled solvent/detergent-filtered cryoprecipitate factor VIII

M. EL-EKIABY,* H. A. GOUBRAN,†‡ M. RADOSEVICH,§ A. ABD-ALLAH,* A. EL-EKIABY* and T. BURNOUF§¶

**Shabrawishi Hospital Blood Bank, Giza, Egypt; †Saskatoon Cancer Centre, University of Saskatoon, Saskatoon, Canada; ‡Faculty of Medicine, Cairo, Egypt; §Human Protein Process Sciences, Lille, France; and ¶College of Oral Medicine, Taipei Medical University, Taipei, Taiwan*

Patients and methods

- 11 severe hemophilia A patients, <1% FVIII level
- Negative for inhibitors
- Infusion of SD cryoprecipitate FVIII 40 units/kg
- Study of SD cryoprecipitate FVIII pharmacokinetics and tolerance

Pharmacokinetics of FVIII in SD Cryoprecipitate

- SD Cryoprecipitate has t1/2 of 14.2 hrs
- It has a clearance rate of 2.6 ml/hr/kg
- Thus it has a behavior similar PD FVIII as well as Recombinant FVIII
- Patients reported 8 – 22 days free from bleeding episodes after the infusion
- It is well tolerated by the severe hemophilia A patients with no record of any adverse event

Table 1. Recovered plasma: protein biochemical composition before and after S/D + filtrations (Mean ± SD : $N = 10$)

	Recovered plasma								
	Start				Final				*P*
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Fibrinogen (mg/mL)	2·93	0·52	2·20	3·81	2·77 (95%)	0·54	1·90	3·37	NS
Factor II (IU/mL)	0·94	0·12	0·78	1·13	0·95 (101%)	0·14	0·76	1·11	NS
Factor V (IU/mL)	1·27	0·17	0·98	1·50	1·12 (88%)	0·17	0·83	1·33	< 0·01
Factor VII (IU/mL)	1·02	0·14	0·86	1·32	0·99 (97%)	0·13	0·86	1·26	NS
Factor VIII (IU/mL)	1·24	0·25	1·01	1·80	1·27 (102%)	0·26	0·93	1·8	NS
Factor IX (IU/mL)	0·98	0·13	0·81	1·21	0·85 (87%)	0·19	0·60	1·23	NS
Factor X (IU/mL)	0·87	0·17	0·56	1·08	0·69 (79%)	0·20	0·41	0·94	NS
Factor XI (IU/mL)	0·61	0·12	0·44	0·76	0·55 (90%)	0·12	0·36	0·69	NS
Factor XIII (IU/mL)	0·83	0·26	0·55	1·27	0·84 (101%)	0·26	0·52	1·24	NS
VWF : Ag (IU/mL)	1·12	0·21	0·9	1·5	1·11 (99·1%)	0·21	0·9	1·5	NS
VWF : RCo (IU/mL)	1·10	0·25	0·64	1·28	1·10 (100%)	0·31	0·64	1·28	NS
Protein S (IU/mL)	0·86	0·23	0·50	1·07	0·96 (112%)	0·08	0·88	1·08	NS
Protein C (IU/mL)	0·76	0·13	0·64	1·04	0·80 (105%)	0·11	0·70	1·04	NS
Antithrombin (IU/mL)	0·88	0·14	0·67	1·07	0·91 (103%)	0·11	0·77	1·07	NS
Alpha 2-antiplasmin (U/mL)	0·89	0·16	0·63	1·19	0·81 (91%)	0·19	0·55	1·22	0·005
C3 (mg/mL)	719	156	539	988	686 (95%)	125	547	932	NS
IgG (mg/mL)	8·9	2·2	5·7	12·6	9·1 (103%)	1·8	6·9	12·7	NS
IgA (mg/mL)	1·46	0·15	1·17	1·68	1·46 (100%)	0·20	1·16	1·72	NS
IgM (mg/mL)	1·22	0·35	0·91	2·04	1·16 (95%)	0·28	0·86	1·66	NS
Albumin (mg/mL)	33·2	4·8	27·3	40	32·3 (97%)	4·3	24·6	38·3	NS
Protein (mg/mL)	55·4	4·8	49·0	62·4	58·7 (106 %)	8·26	43·2	70	NS
PT (s)	13·8	0·5	13·3	14·9	14·3 (104%)	0·7	13·7	16·0	<0·01
aPTT (s)	29·6	2·5	26·3	34·4	30·9 (104%)	1·7	28·3	33·3	NS
Cholesterol (mg/mL)	0·84	0·13	0·73	1·14	<0·02	–	<0·02	<0·02	<0·0001
Triglycerides (mg/mL)	0·82	0·50	0·51	1·96	0·20	0·06	0·13	0·34	<0·001

Table 2. Apheresis plasma: protein biochemical composition before and after S/D + filtrations (Mean ± SD : $N = 10$)

	Apheresis plasma								
	Start		Final		Start		Final		P
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Fibrinogen (mg/mL)	2·76	0·51	2·26	3·75	2·60 (94%)	0·42	2·09	3·30	NS
Factor II (IU/mL)	0·98	0·19	0·76	1·27	0·95 (97%)	0·12	0·77	1·13	NS
Factor V (IU/mL)	1·28	0·22	0·95	1·51	1·05 (82%)	0·25	0·82	1·55	0·009
Factor VII (IU/mL)	1·13	0·13	0·97	1·32	1·09 (96%)	0·11	0·95	1·24	NS
Factor VIII (IU/mL)	1·21	0·35	0·90	1·80	1·27 (105%)	0·35	0·74	1·8	NS
Factor IX (IU/mL)	1·09	0·20	0·85	1·38	1·04 (95%)	0·20	0·74	1·46	NS
Factor X (IU/mL)	0·98	0·20	0·59	1·21	0·96 (98%)	0·15	0·79	1·22	NS
Factor XI (IU/mL)	0·80	0·18	0·61	1·12	0·77 (96%)	0·15	0·60	1·00	NS
Factor XIII (IU/mL)	0·77	0·22	0·53	1·19	0·75 (97%)	0·22	0·48	1·15	NS
VWF : Ag (IU/mL)	1·19	0·32	0·80	1·70	1·22 (102%)	0·33	0·86	1·84	NS
VWF : RCo (IU/mL)	1·04	0·33	0·64	1·28	1·12 (107%)	0·33	0·64	1·28	NS
Protein S (IU/mL)	0·75	0·20	0·48	0·98	0·94 (125%)	0·12	0·76	1·18	NS
Protein C (IU/mL)	1·00	0·32	0·89	1·68	1·04 (104%)	0·31	0·80	1·62	NS
Antithrombin (IU/mL)	1·09	0·08	0·98	1·21	1·03 (94%)	0·12	0·85	1·18	0·01
Alpha 2-antiplasmin (U/mL)	0·98	0·15	0·75	1·24	0·90 (92%)	0·15	0·79	1·24	NS
C3 (mg/mL)	779	101	664	946	827 (106%)	70	745	918	NS
IgG (mg/mL)	7·2	2·1	3·5	10·7	7·1 (98%)	2·4	4·2	11·5	NS
IgA (mg/mL)	1·0	0·3	0·8	1·7	1·02 (97%)	0·3	0·7	1·6	NS
IgM (mg/mL)	0·97	0·26	0·71	1·50	1·05 (108%)	0·28	0·64	1·48	NS
Albumin (mg/mL)	30·0	2·3	25·3	32·3	29·9 (99%)	2·3	26·7	33·2	NS
Protein (mg/mL)	49·5	3·3	43·4	53·5	49·1 (99%)	3·2	43·9	53·4	NS
PT (s)	13·3	0·9	12·4	15·3	14·2 (106%)	1·6	13·0	17·7	<0·05
aPTT (s)	26·4	2·1	24·1	29·3	29·4 (111%)	3·9	22·9	36·1	<0·05
Cholesterol (mg/mL)	1·06	0·07	0·92	1·15	0·03	0·08	<0·02	0·20	<0·0001
Triglycerides (mg/mL)	1·17	0·47	0·24	1·92	0·23	0·05	0·17	0·29	<0·001

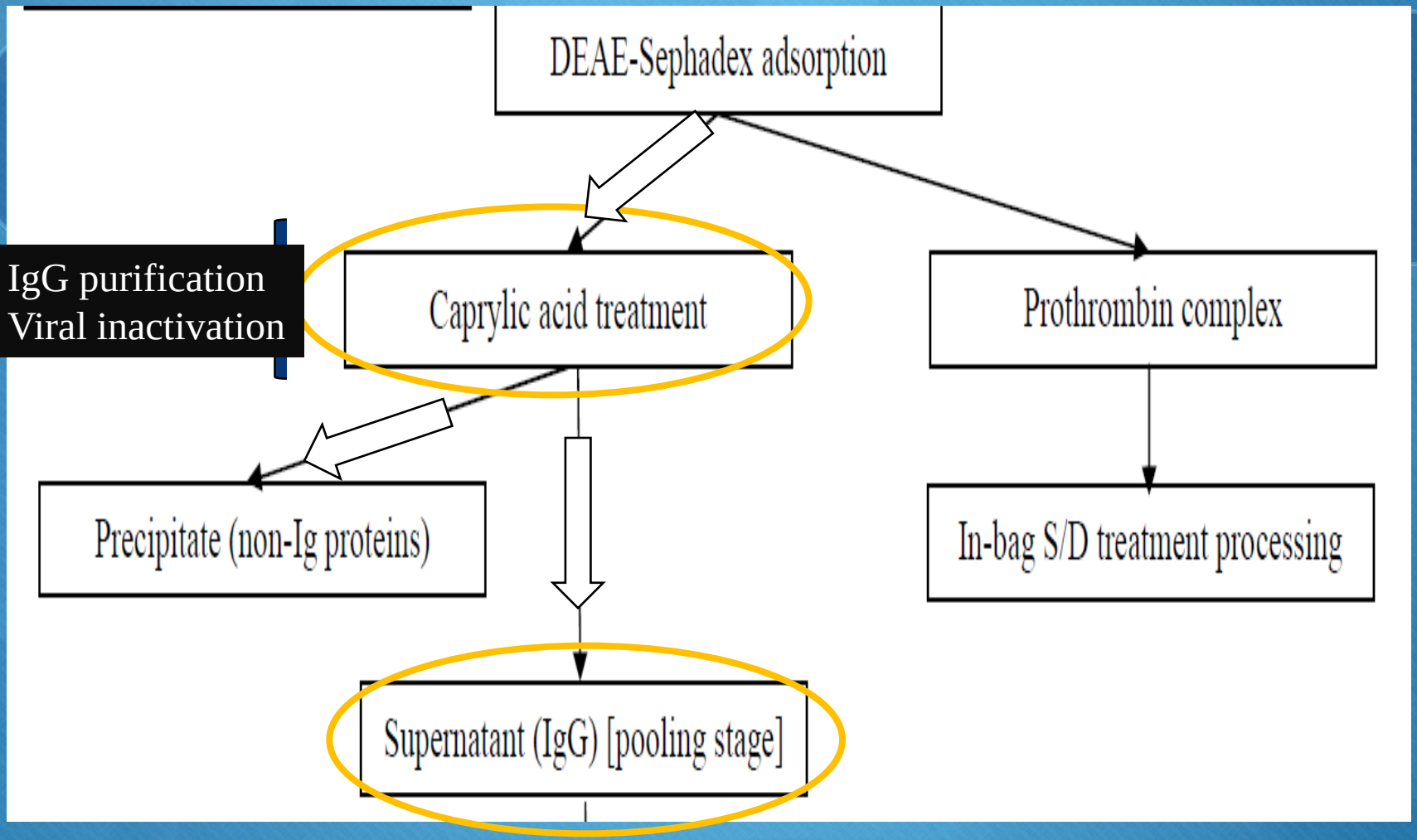
Over all quality of SD-plasma

- Excellent protein recovery, e.g.:
  - all coagulation factors (FVIII, fibrinogen, etc.)
  - protease inhibitors, including alpha 2-AP and Protein S
- TnBP < 0.3 ppm; Triton X-45 < 10 ppm
- 0.2µm filtration:
  - Sterile
  - Cell-free "shiny" plasma

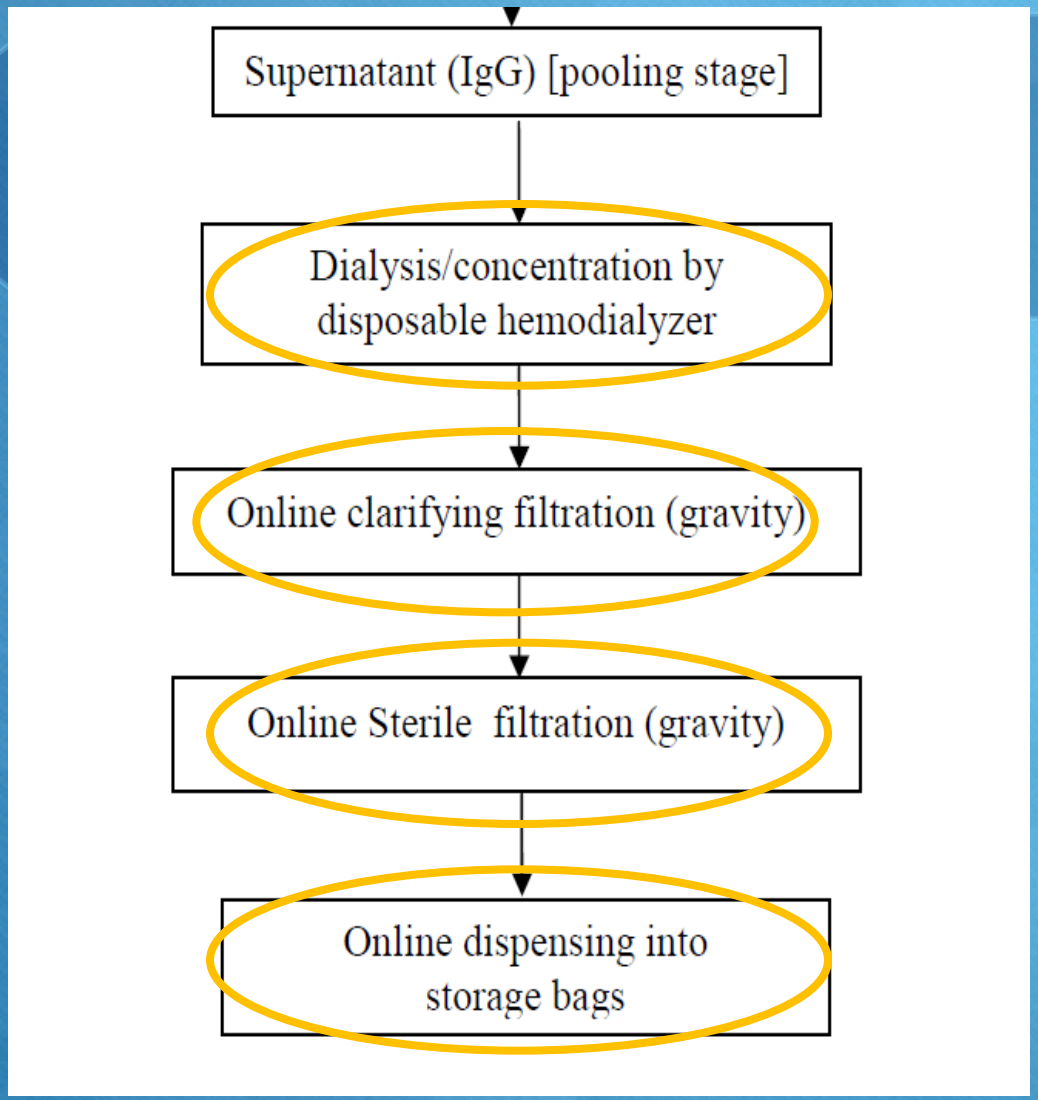
SD-virally inactivated PCC (FII,FVII,FIX & FX)

Factor	CPP volume ml	Factor concentration iu/ml	Factor content iu	PCC volume ml	Factor concentration iu/ml	Factor content iu	% recovery
FII	44oo	1.2	5280	360	6.5	2340	44
FVII	4400	1	4400	360	4.3	41548	35
FIX	4400	0.95	4180	360	3.3	1188	28
FX	4400	1.18	5192	360	7	2520	48

Purification & viral inactivation of IgG



Concentration, dialysis & filtration



- 3-4 x IgG concentration
  Dialysis
  Removal of caprylic acid
- Clarification
  Removal of caprylic acid
- Bacterial sterility
- Storage (frozen or liquid)

IgG fraction properties

Parameters	Results	Methods
Appearance	Very clear, not turbid	Visual
pH	5.4 – 5.7	Potentiometer
Osmolality, mosm/kg	≥ 240	Osmometer
Total proteins, g/L	25 - 30	Biuret
IgG, g/L	22 – 25	Immunonephelometry
IgA, g/L	2 - 3	Immunonephelometry
IgM, g/L	0.5 – 1	Immunonephelometry
Albumin, g/L	<1	Photometric method
Aggregates, %	< 1	HPLC
Monomers and dimers, %	> 95	HPLC
Proteolytic activity	0 – 2 IU/L	Chromogenic assay (S-2288)
Caprylic acid	<700 ppm	HPLC

Optional additional purification step

- IgA removal using single-use processing
- Under development

Viral safety: caprylic acid treatment

- Robust viral inactivation/removal treatment
- Applied recently to 2 commercial IVIG preparations (different intermediate fractions)

Viral validation study

- Texcell, France
- Following CPMP/EMEA guidelines
- Duplicate runs
- Worst-case conditions (pH & temperature)
- 3 enveloped viruses
  - HIV
  - BVDV
  - PRV

Viral validation data

- > 5 logs of inactivation/removal of lipid-enveloped viruses (BVDV & PRV) in less than 15 minutes of caprylic acid treatment
- Total duration: > 1hr