


# Novel Systems for local Preparation of Virus Inactivated Hyper-immune Immunoglobulins in Emergency Situations

Magdy El Ekiaby

28 - 29.09.2015



# The case of EVD epidemic; rationale

- As yet there is no proven treatment available for Ebola virus disease (EVD)
- Whole blood collected from patients in the convalescent phase of infection has been used as an empirical treatment with promising results in a small group of EVD cases
- Whole blood (CWB) and plasma (CP) collected from EVD recovered patients have been prioritized for investigation as one of the treatment modalities

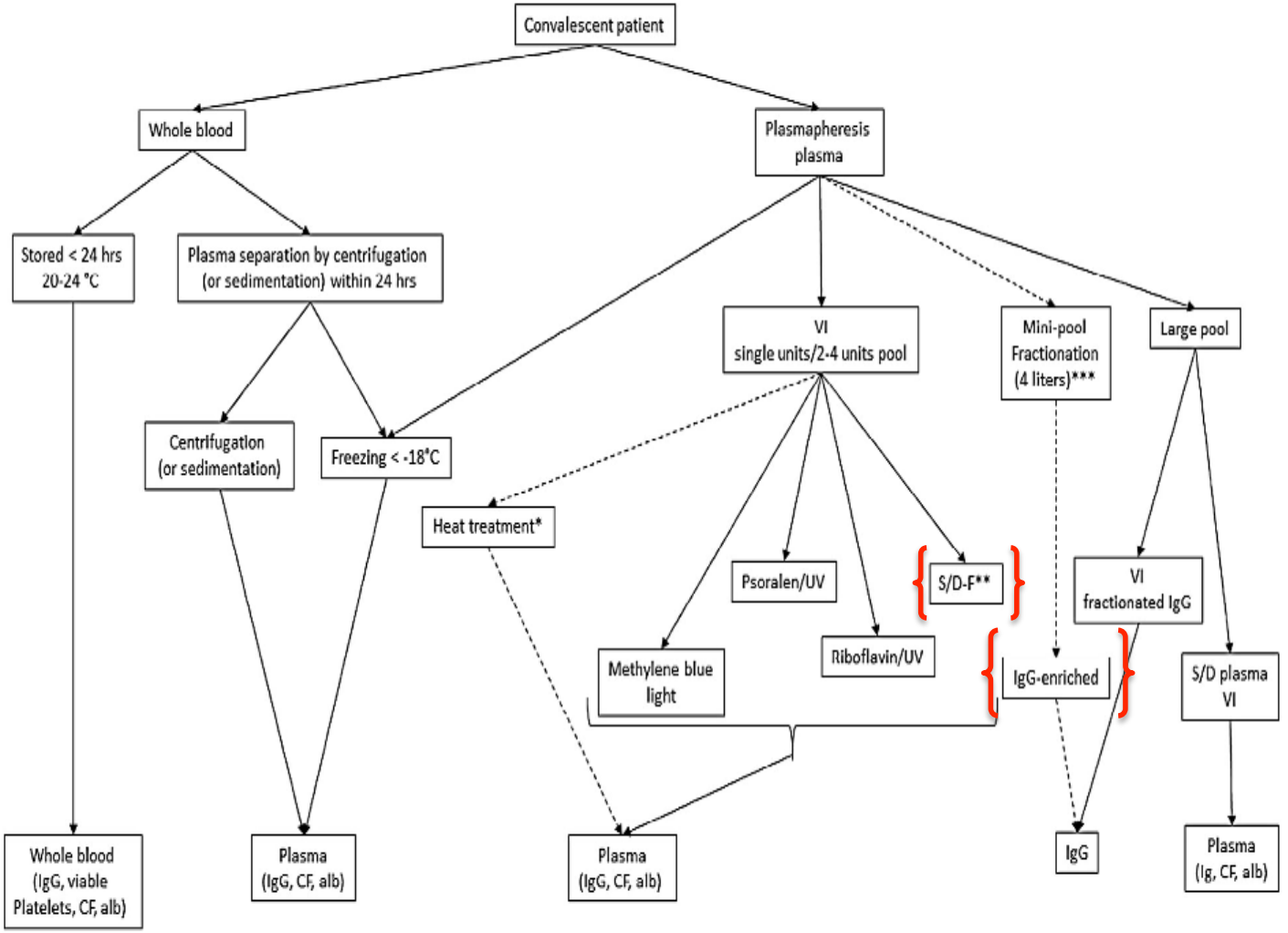



**Fig. 1.** Flow-chart presenting the various technical possibilities that currently can theoretically be considered for producing convalescent blood products. Virally-inactivated plasma and immunoglobulins can also be made from recovered plasma. *unlicensed; **developed in Egypt; ***under clinical trial in immuno-deficient patients; IgG: immunoglobulin G; CF: coagulation factors; alb: albumin; S/D: solvent/detergent; S/D-F: solvent/detergent-filtered; UV: ultraviolet light; VI: virally-inactivated.







Forum on African voice and leadership to accelerate the evaluation of potential treatments and vaccines for Ebola In West Africa

## EVD Patient Experience

- The horror of being a suspect to contract the disease
- Isolation phase
- Recovery phase
- The stigma
- The joy of making it through the disease
- The aftermath:
  - Positive attitude
  - Negative attitude



# Findings

- WB trials have already started in Freetown (40) and Monrovia (10 ),
- Cairo transfusion facility embarking on low technology fractionation for production of Hyper-Immune Caprylic Acid Virus Inactivated Ig Rich Plasma
- Fractionation is very expensive and requires 2 to 5 K liters of collected plasma for production of hyper-immune IVIG
- Plans can take 5 years to be built and operationalized at millions of dollars cost
- Only one African fractionation plant based in South Africa is able to supply enough fractionated products (however for South African domestic use only).

# Main Recommendations

- Developing the infrastructure required to respond to the Ebola outbreak and future epidemics
- Facilitating the work of pharmaceutical companies and research institutions with various foundations
- Implementing the plasma quality control and management procedures

# Main Outcome

- Accelerating the production of convalescent plasma by training local HCPs*:
  - treating plasma with viral inactivation when intended for transfusion
  - producing hyperimmune globulin:
    - Grifols promised a new manufacturing site in US for small scale
    - Mini-Pool option to be implemented on site in each country with help from Cairo

*HCPs: Health Care Providers

# Questions

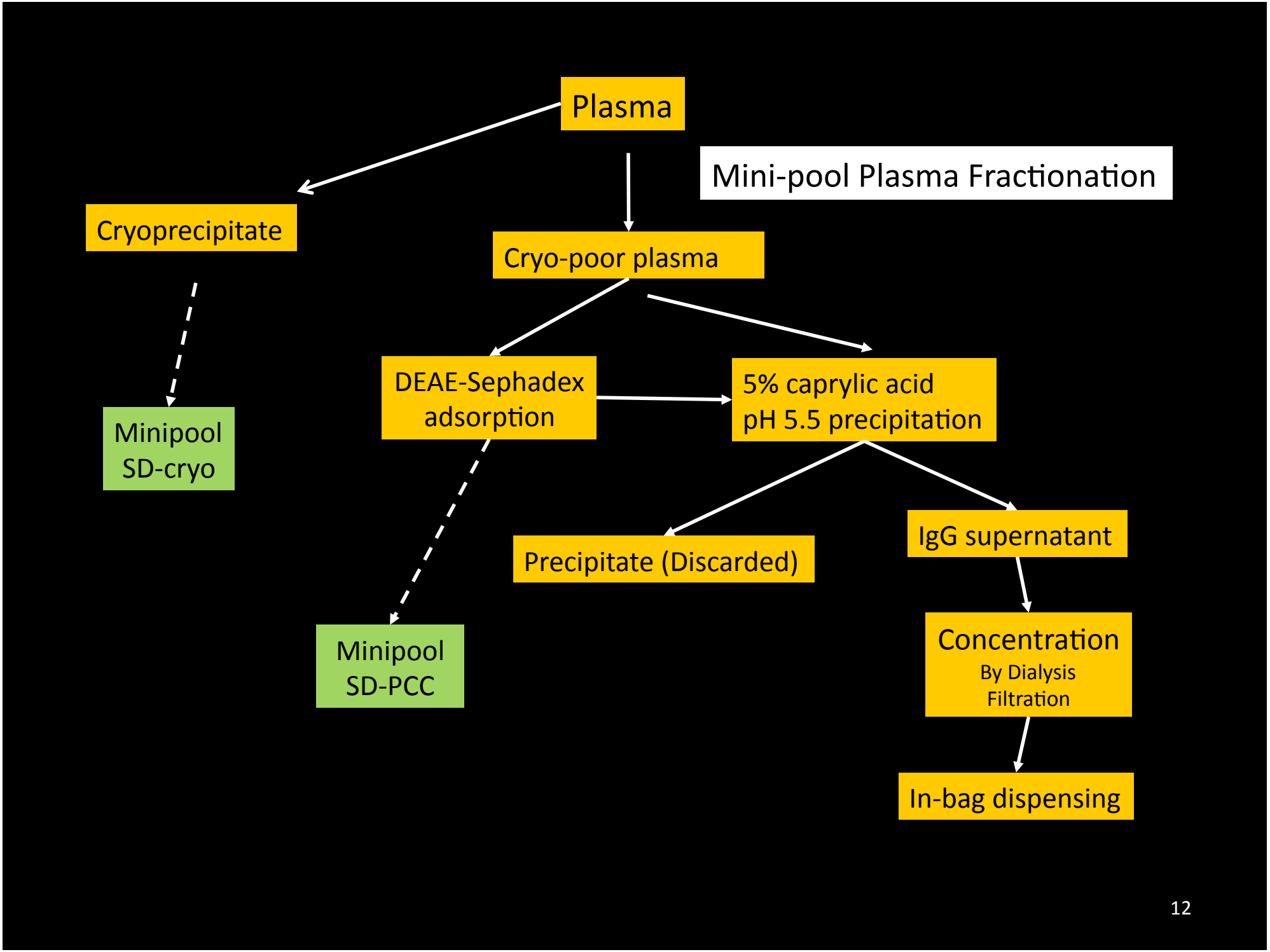
- Will this kind of therapeutic intervention be effective?
- Availability of regulations for cross border movement of plasma and finished plasma products?
- Ownership of plasma product if it is produced from plasma batches that belong to the three affected countries?
- Time frame?
- Other pragmatic approaches that can respond fast to future situations?

# Mini-Pool Plasma Fractionation

Preparation of EV Hyper-Immune Globulins??!!

# Mini-Pool plasma fractionation unit

- Small clean space with access control within a blood transfusion service
- Plasma pool from 20 – 35 donations instead of 100s – 1000s
- Work with validated and licensed single use sterile medical devices
- Small number of technical staff
- Short processing time:
  - Mini-Pool Caprylic Ig Rich Plasma: 12 hours

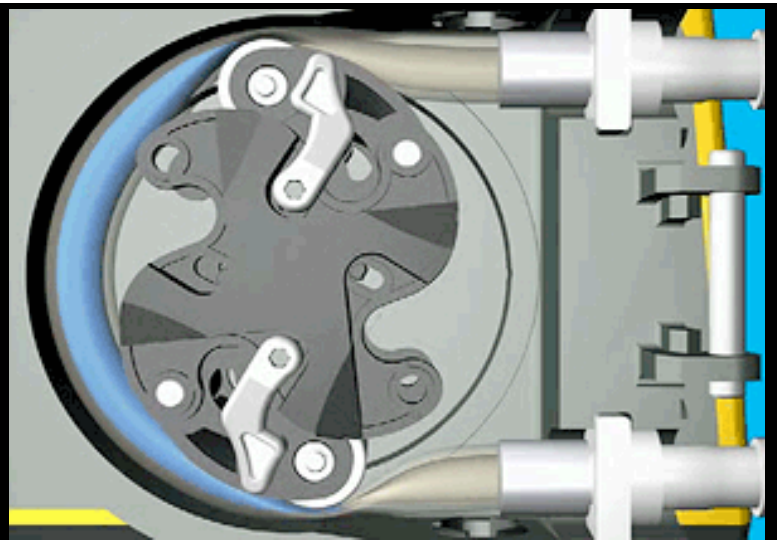

Plasma
Mini-pool Plasma Fractionation
Cryoprecipitate
Cryo-poor plasma
Minipool
SD-cryo
DEAE-Sephadex
adsorption
5% caprylic acid
pH 5.5 precipitation
Precipitate (Discarded)
IgG supernatant
Minipool
SD-PCC
Concentration
By Dialysis
Filtration
In-bag dispensing

# Medical Devices






Pool size: 20 units of cryoprecipitate supernatant plasma



# CE mark of medical devices



ZERTIFIKAT

Nr.: TÜV-A-MT-1/09/Q070

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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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09MT0205WRO
Bericht Nr:
Report No.:

CE 0408

13.07.2009
Erstausstellung
First issue

Dipl.-Ing. Michael Pölzleitner
Zertifizierungsbeauftragter
*Certification representative*

13.07.2009
Datum der Ausstellung
*Date of issue*

02.03.2014
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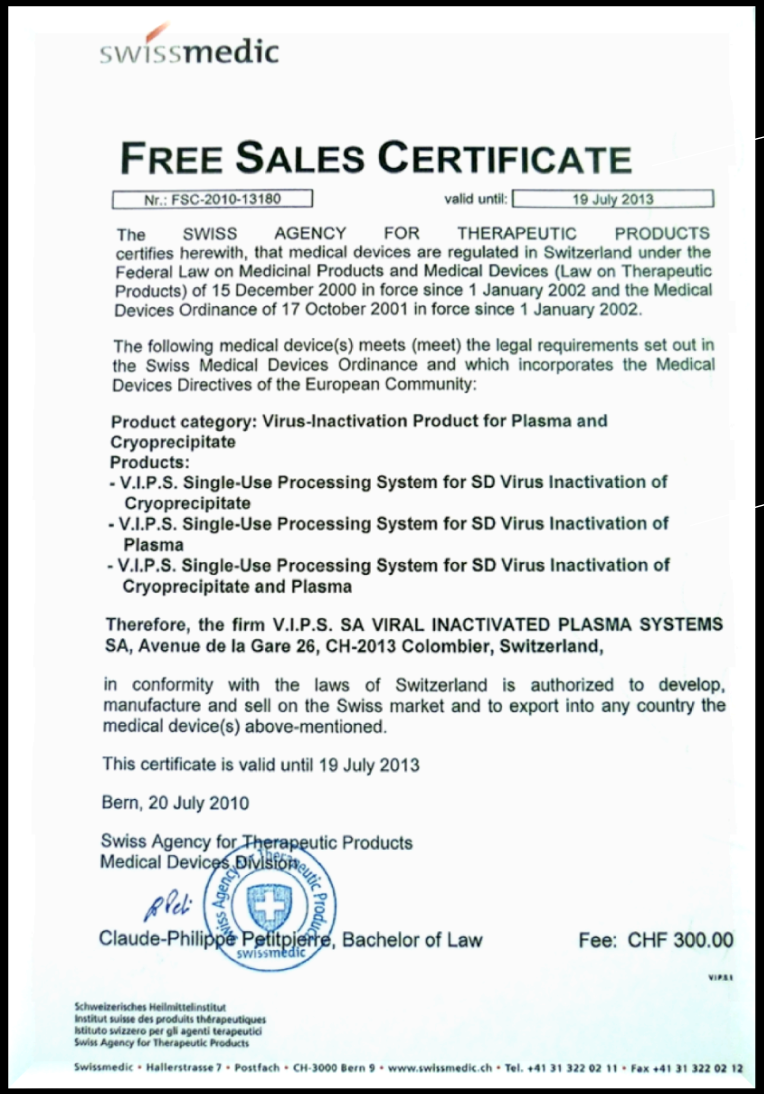
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# Free Sales Certificate



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## 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:**
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- **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.

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Bern, 20 July 2010

Swiss Agency for Therapeutic Products
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# MEDICAL DEVICE VALIDATION

# Viral Validation

## STUDY REPORT

**VIRAL CLEARANCE STUDY ASSOCIATED**
**TO INCUBATION AND PRECIPITATION WITH CAPRYLIC ACID AT LOW PH**
**DURING THE PURIFICATION PROCESS OF**
**IMMUNOGLOBULIN G ANTIBODIES FROM CRYO-POOR PLASMA**

Project number: **395/02**
Study report number: **395/02/5511-A1/01**

Study report for:

**Sponsor: RESEARCH FOUNDATION FOR MEDICAL DEVICES (RFMD)**
**Authorized Representatives:** Olivier FLEURY and Nicolas GUHL

Multifiduciaire Fribourg SA
Rue Faucigny 5
CH-1705 Fribourg
Switzerland

**France sponsor representative: Human Protein Process Sciences (HPPS)**
**Scientific coordinator:** Thierry BURNOUF, Ph.D.

18 Rue Saint-Jacques,
59000 Lille
France

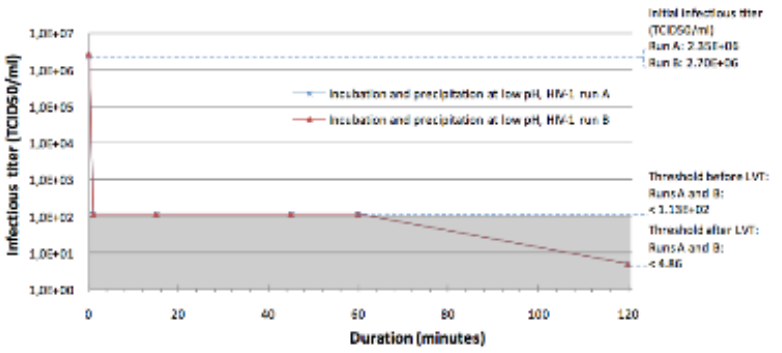
Submitted by:

**Test Facility: TEXCELL**

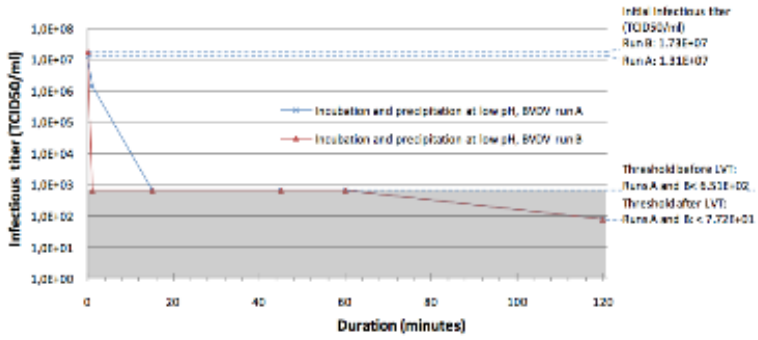
**Study Director:** Yasmina AGUEMON-GAILLARD

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91058 Evry cedex
France

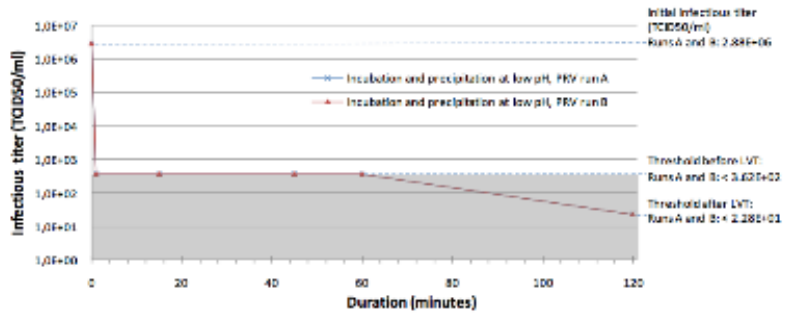
**HIV-1**



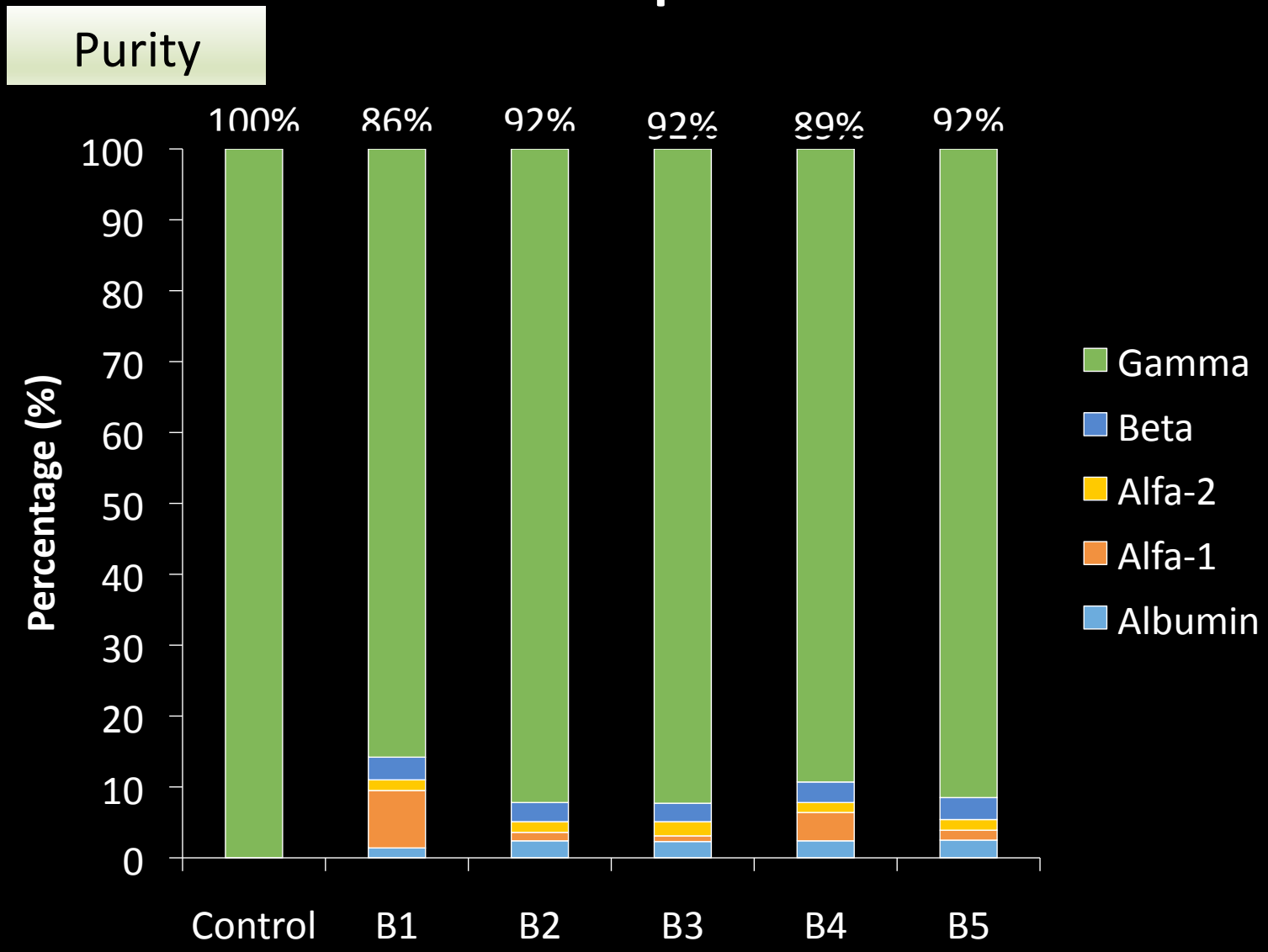

**BVDV**




**PRV**



# Protein profile: zone electrophoresis

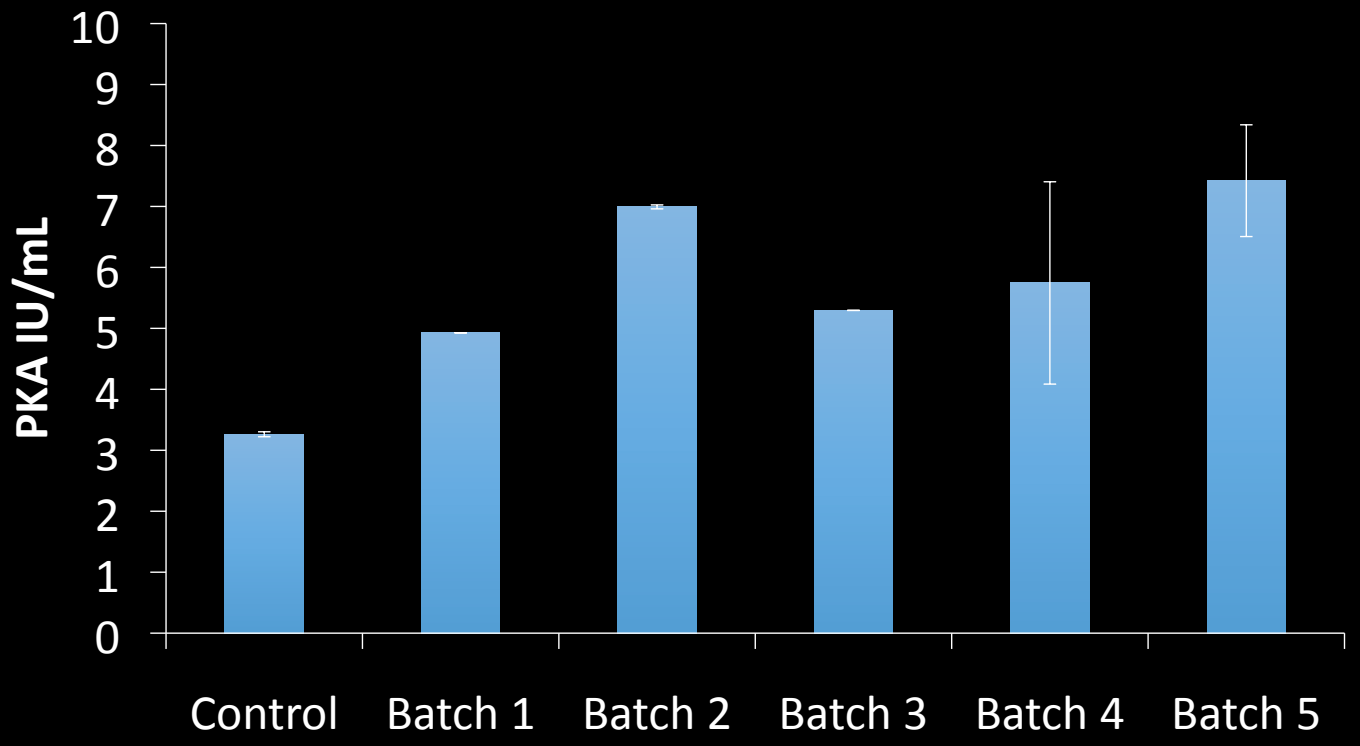


## Anti-HBs in 20 pools

Mean Anti-HBs IU/gm IGs 10.1 (range 0.66 – 22) in 5% Caprylic Ig Rich Plasma Fraction

| batch no | Anti-HBs |
|---|---|
| 25 | 3.81mlu/ml |
| 26 | >1000mlu/ml |
| 27 | >1000mlu/ml |
| 28 | >1000mlu/ml |
| 29 | 380.95mlu/ml |
| 30 | 11.31mlu/ml |
| 31 | 383.22mlu/ml |
| 32 | 19.10mlu/ml |
| 33 | 3.53mlu/ml |
| 34 | 60.17 mlu/ml |
| 35 | 67.15 mlu/ml |
| 36 | 663.37 mlu/ml |
| 37 | >1000 mlu/ml |
| 38 | 160.94mlu/ml |
| 39 | 33.03mlu/ml |
| 40 | 8.41mlu/ml |
| 41 | 110.70mlu/ml |
| 42 | 671.93mlu/ml |
| 43 | 60.18mlu/ml |
| 44 | 450.35mlu/ml |

# PreKallikrein activator (PKA)



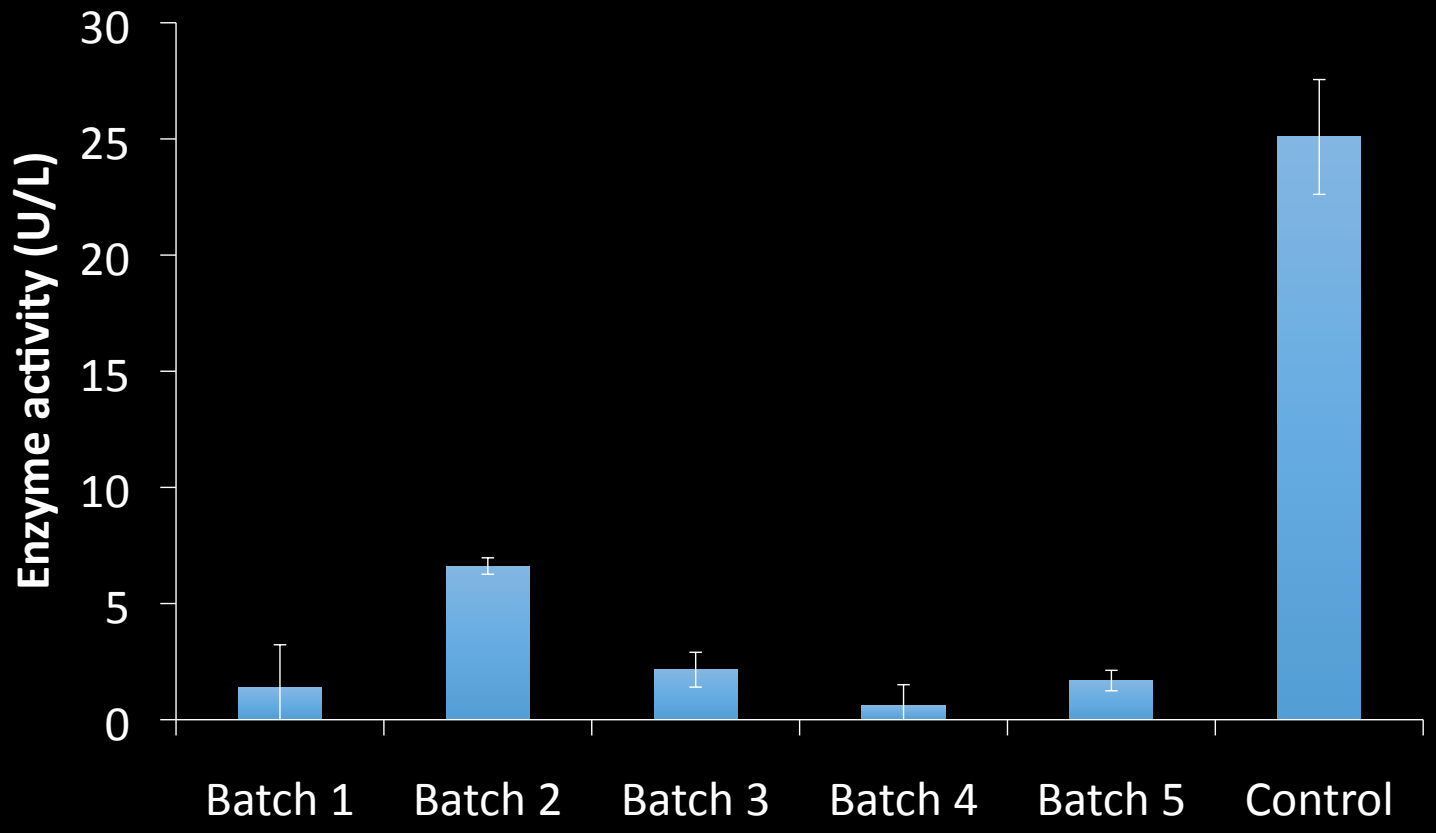

European pharmacopia specification for PKA ≤ 35 IU / ml
for a solution containing 3% protein

# Thrombin Generation Assay (TGA)

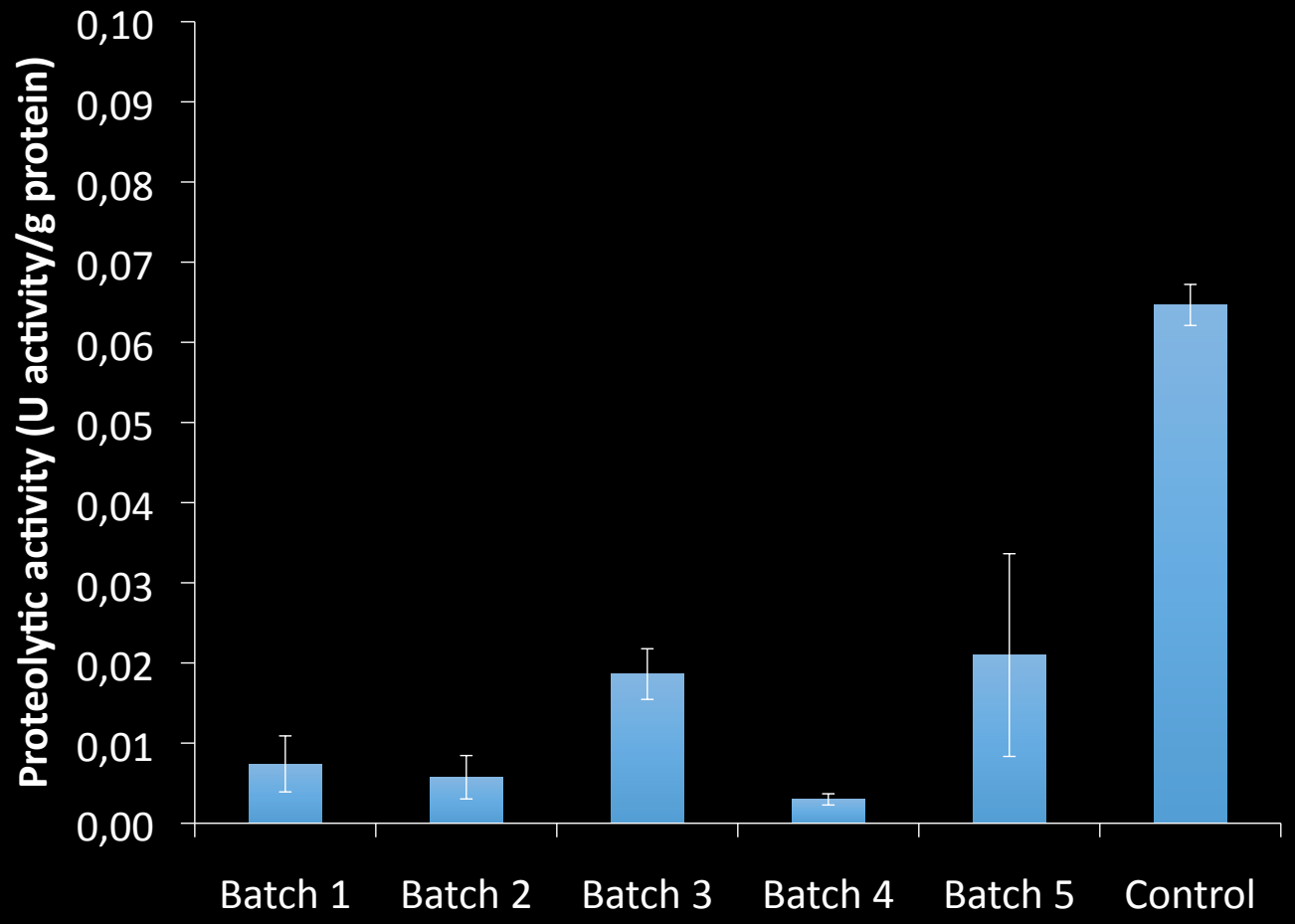
| Sample* | lag phase time (min) | Thrombin [nM] | Time to peak [min] |
|---|---|---|---|
| Batch 1 | 38 ± 0 | 0 | 0 |
| Batch 2 | 9.5 ± 2.1 | 222.8 ± 135.4 | 19.0 ± 5.7 |
| Batch 3 | 45.5 ± 13.4 | 0 | 0 |
| Batch 4 | 19.0 ± 5.7 | 50 ± 0 | 28.5 ± 9.2 |
| Batch 5 | 45.0 ± 14.1 | 0 | 0 |
| Control | | | |

Specification: Peak thrombin < 350 nM

# Thrombin


Enzyme activity (U/L)
30
25
20
15
10
5
0
Batch 1
Batch 2
Batch 3
Batch 4
Batch 5
Control

# Thrombin-like proteolytic activity



PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

# Minipool Caprylic Acid Fractionation of Plasma Using Disposable Equipment: A Practical Method to Enhance Immunoglobulin Supply in Developing Countries

**Magdy El-Ekiaby[1], Mariángela Vargas[2], Makram Sayed[3], George Gorgy[1], Hadi Goubran[4], Mirjana Radosevic[5], Thierry Burnouf[6]***

**1** Shabrawishi Blood Bank, Shabrawishi Hospital, Cairo, Egypt, **2** Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, San José, Costa Rica, **3** Environmental and Food Pollutant Laboratory, Fayoum University, Fayoum, Egypt, **4** Saskatoon Cancer Center, College of Medicine, University of Saskatchewan, Saskatoon, Canada, **5** Human Protein Process Sciences, Lille, France, **6** Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

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# Plasma for preparation of Caprylic Ig Rich Plasma

- Voluntary non remunerated whole blood or apheresis donors/ convalescent donors
- Plasma is prepared from whole blood or collected by apheresis
- Tested for serological markers of HCV, HBV, HIV and Syphilis
- ID or Mini-Pool NAT for HCV, HBV & HIV

# Caprylic Immunoglobulin (Ig) Rich Plasma

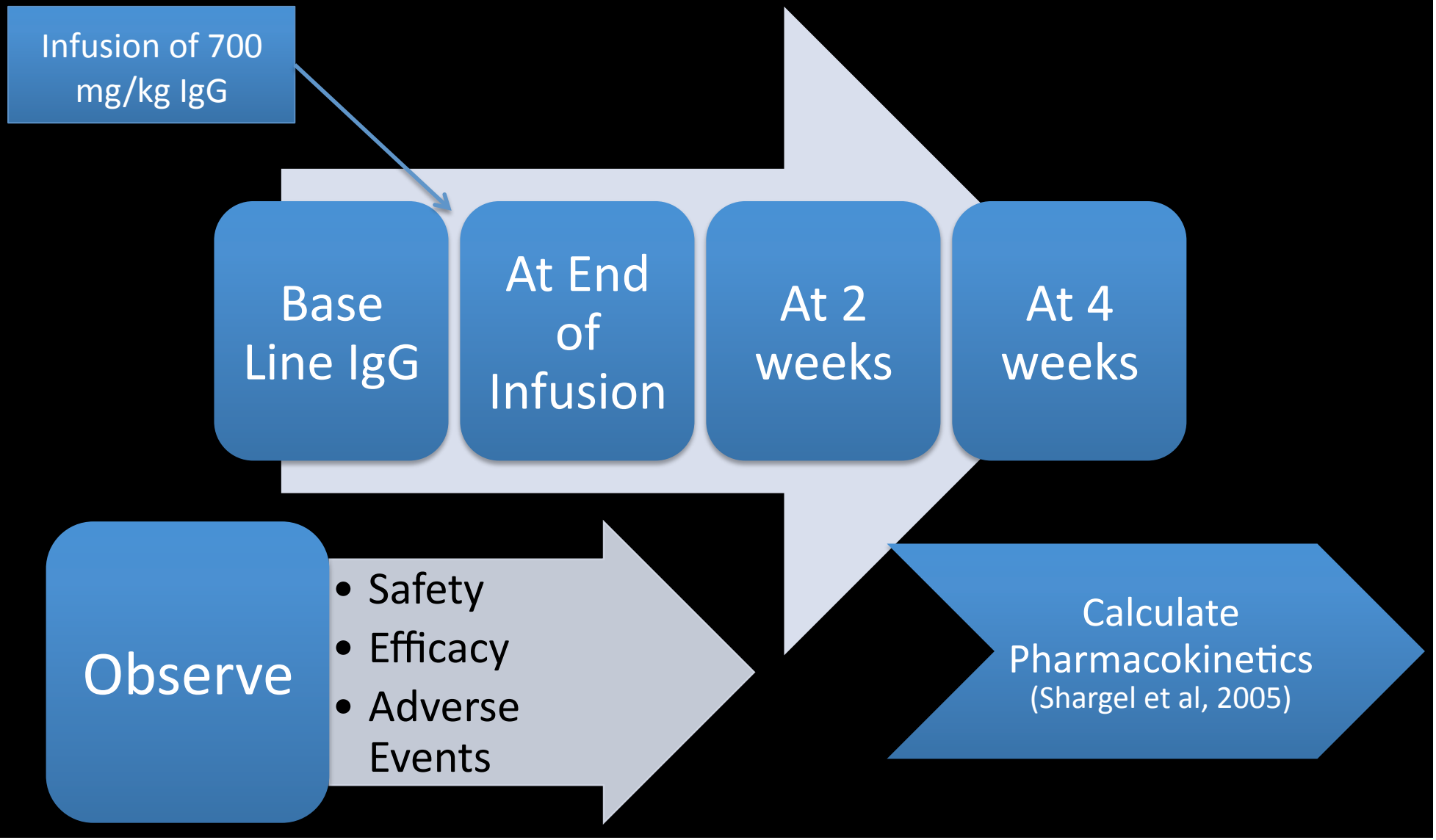


| Product Characteristic | European Pharmacopia | Mini-Pool IG Plasma Fraction |
|---|---|---|
| Physical condition | Liquid or FD | Liquid |
| pH | 4 – 7.4 | 5.5 ✔ |
| Osmolality m Osmol/kg | >240 | ≅295 |
| Total protein (>85% IgG) | >30 gm/L | ≅59.8 gm/L ✔ |
| Molecular size distribution | >90% monomer & dimer, <3% polymer & aggregates | ✔ |
| Prekallikrein activator iu/ml for 3% protein solution | <35 | ✔ |
| ABO isoagglutinins | <1/32 | ✔ |
| Anti-HBs Ab | >0.5 IU/gm | 10.1 IU/gm |
| Sterile and apyrogenic | ✔ | ✔ |
| Thrombin Generation Assay | <350 nM | ✔ |

# Clinical Evaluation of Mini-Pool Caprylic Ig Rich Plasma

- Aim:
  - To demonstrate the safety, tolerance and efficacy of this mini-pool Ig rich plasma in patients with primary immune deficiency
  - Immune modulatory effect in early diagnosed ITP as a first line of therapy

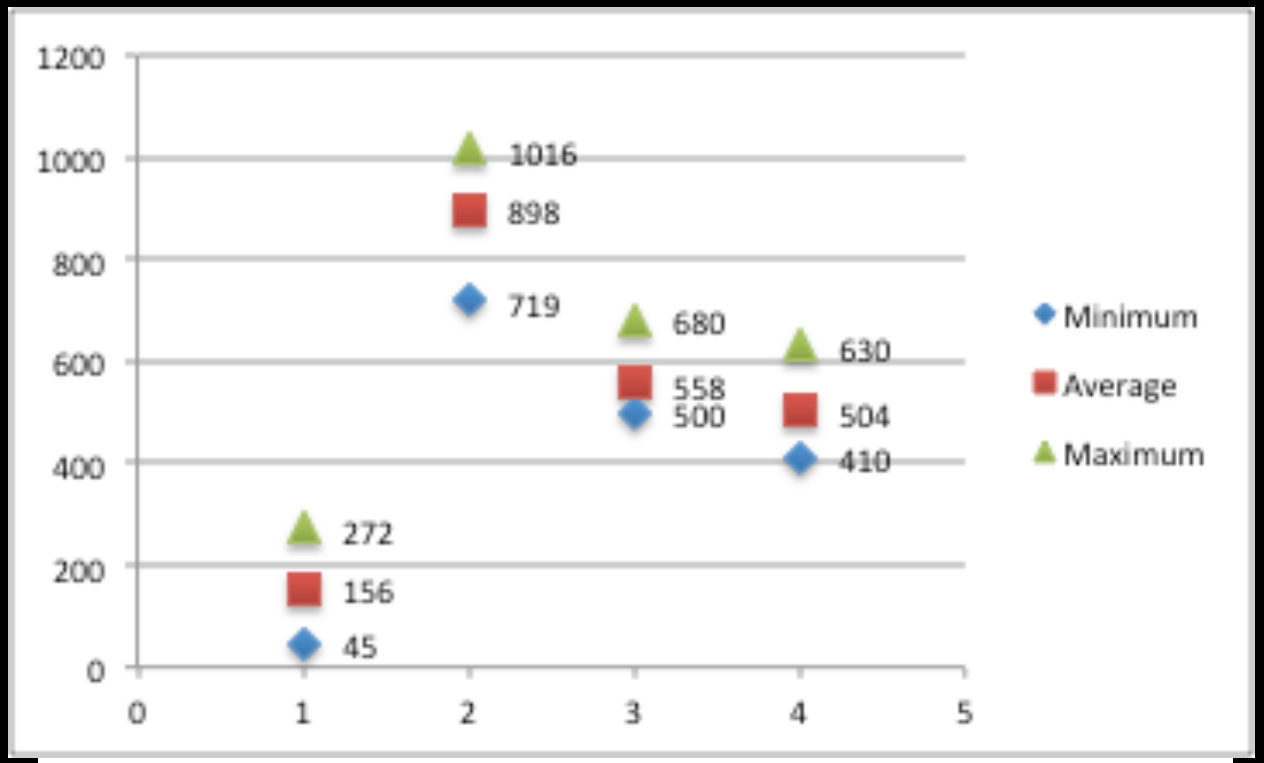
# Study Design in Primary Immunodeficiency Patients



# Patients

- Number of patients: 11
- Average age/years: 10.18 (6 – 16)
- Sex: Males
- Average weight/Kg: 27.4 (12 – 55)
- Diagnosis:
  - Agammaglobulinemia (5)
  - Hypogammglobulinemia (3)
  - Hypergammaglobulin M Syndrome (1)
  - Combined Immunodeficiency (2)
- Average baseline serum IgG mg/dl: 156 (45 – 272)

IgG mg/dl




Data from 7 patients who completed 4 weeks post infusion observation:

1 Basal level

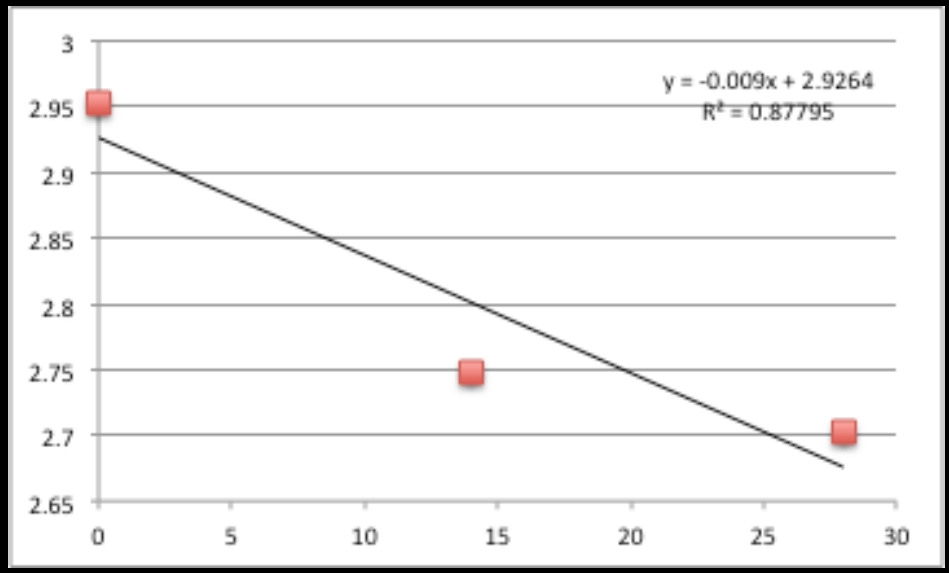
2 Post infusion level

3 Two weeks post infusion level

4 Four weeks post infusion level

# Igg plasma fraction pharmacokinetics

- IgG half life is 34.65 days
- Total Clearance rate is 1.5 ml/kg/day



# A Prospective, Two-Phase Study of Intravenous Immunoglobulin (IVIG) in Hypogammaglobulinemia: Pharmacokinetic Characterization and a Dosing Nomogram

*Crystal L. Amos, Mary H.H. Ensom, David Pi, and R. Robert Schellenberg*

**Can J Hosp Pharm 2005;58:71-8**

**Table 3. Pharmacokinetic Parameters of IV Immunoglobulin (n = 14)**

| | $C_{max}$ (g/L) | $C_{min}$ (g/L) | k ($h^{-1}$) | $t_{1/2}$ (days) | AUC (g • h/L) | Dose-Normalized AUC* (g • h/L) |
|---|---|---|---|---|---|---|
| Mean | 14.7 | 8.0 | 0.0009 | 34.9 | 6382.4 | 300.6 |
| Median | 15.2 | 8.5 | 0.0008 | 37.5 | 5950.0 | 290.9 |
| SD | 2.0 | 2.2 | 0.0004 | 12.4 | 1688.9 | 96.2 |
| Minimum | 11.8 | 4.8 | 0.0005 | 16.2 | 3699.7 | 148.0 |
| Maximum | 19.1 | 12.9 | 0.0018 | 56.4 | 9866.1 | 493.3 |

$C_{max}$ = maximum serum concentration of immunoglobulin G (IgG) , $C_{min}$ = minimum (trough) serum IgG concentration,
k = elimination rate constant, $t_{1/2}$ = elimination half-life, AUC = area under the serum concentration–time curve, SD = standard deviation.
*Determined as the quotient of AUC and the actual dose.

# Clinical Efficacy

- Clinical and laboratory observation showed that the product successfully prevented microbial infections during the 4 weeks observation
- Patients reported improved general health status and less absence from school

# Adverse events

- During Ig rich plasma infusion:
  - Transient fever (39 - 39.5°C) in 3 patients was managed by anti-pyritic and infusion was completed
- One month post infusion follow up:
  - No clinical or laboratory observation of adverse events

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion

# Novel Blood Products

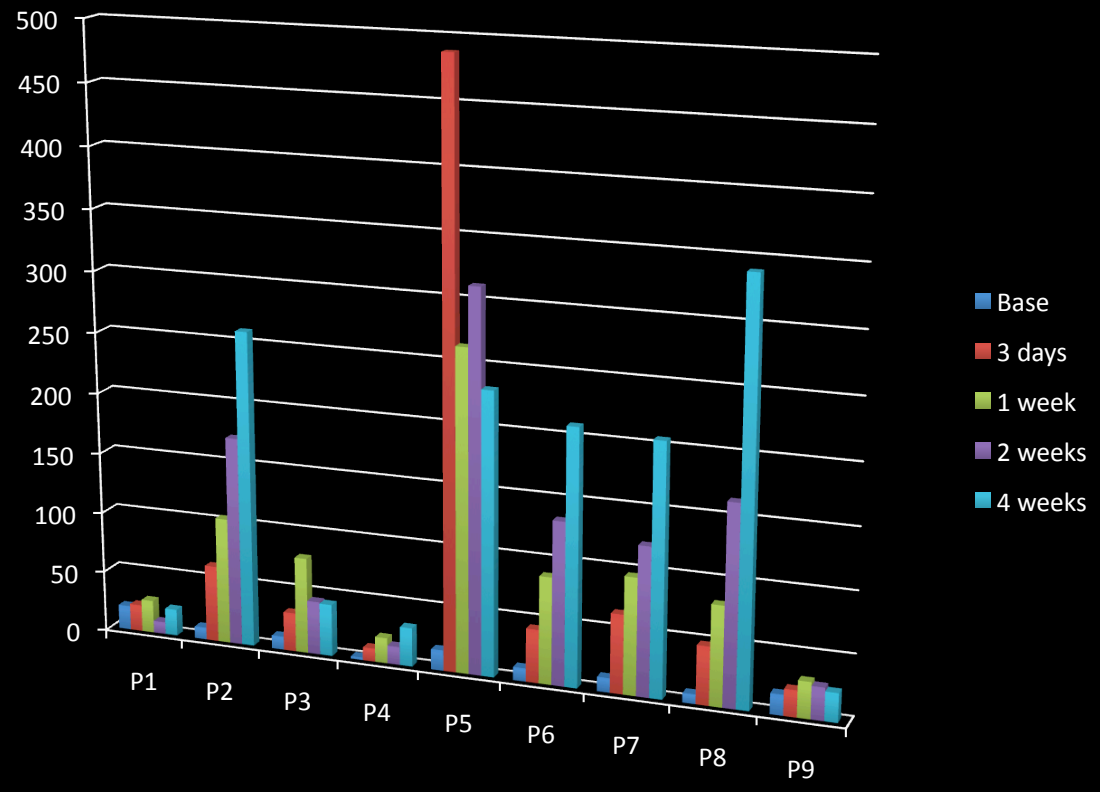
5A-S42-02

## CLINICAL EVALUATION OF MINIPOOL IMMUNOGLOBULIN PLASMA FRACTION IN PRIMARY IMMUNODEFICIENCY PATIENTS

El Ekiaby M[1], Burnouf T[2], El Marsafy A[3], Galal N[3], Goubran H[4] and Radosevic M[5]

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*Vox Sanguinis* (2014) 107 (Suppl. 1), 1–56

# Clinical Trial in Early ITP
# As 1st Line Therapy
## Interim Results



# Conclusion

- Pharmacological characteristics of Caprylic Ig Rich Plasma conforms with European Pharmacopia requirements for IVIG
- Ig rich plasma pharmacokinetics are similar to commercial IVIG
- Interim results of on going study of immune modulation effect in ITP is promising

# Conclusion

- Medical device is underway of CE Mark in 2016
- This new medical device offers:
  - Validated technology
  - Access to use domestic plasma for production of safe and effective plasma products in developing countries
  - Rapid access to prepare hyper-immune Ig from convalescent patients during periods of epidemics; such as EVD epidemic
- Less stringent regulatory requirements with no compromise on safety and efficacy profiles
- Less residual risk due to the small pool size when compared to large pools of classical fractionation