ATMF – IPFA

"National Strategies to ensure Safe and Adequate Supply of Blood, Blood Components & PDMPs

Overview of fractionated plasma products for clinical use



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Key Objectives

- Therapeutic importance of plasma protein products (PDMPs) among all blood products
- Specific clinical indications of PDMPs (selective hemotherapy)
- Production, quality and safety criteria of PDPMs affecting their clinical indications and use

Therapeutic blood products

Cellular components

- whole blood & red blood cells for transfusion
- platelets for transfusion (also used for cell therapy/regenerative medicine)

Plasma

Protein compartment

Source of important, clinically proven therapeutic proteins products = PDMPs, several classified as “essential medicines” by WHO

Use of plasma prepared by blood establishments

- Direct transfusion (clinical plasma, FFP)
- Preparation of cryo (& cryo-poor plasma)
  - Cryoprecipitate: source of FVIII, fibrinogen, vWF, FXIII
- Fractionation

Clinical usage of plasma



Direct transfusion

- **Complex deficiencies in plasma proteins (such as coagulation factors or others, associated with liver diseases) leading to bleeding**
- **Plasma exchange (e.g. TTP)**
- **Specific deficiencies in coagulation factors (when purified concentrates are not available)**
- **Transfusion of antibodies (passive immunotherapy, e.g. CCP)**

Fractionation

- **Raw material to isolate a range of purified plasma proteins for selective hemotherapy (PDMPs)**

Plasma suitable for fractionation





Two main types of production procedures of plasma for fractionation

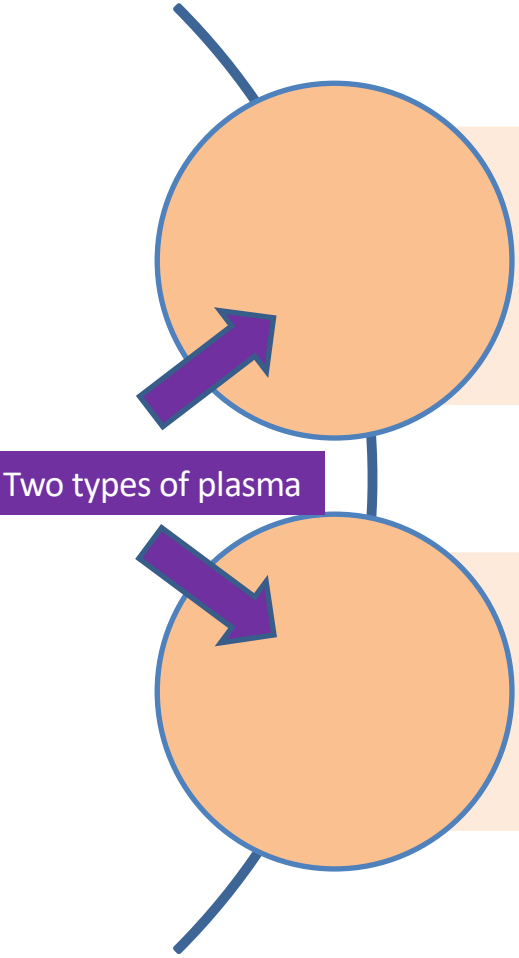
"Recovered"(prepared from whole blood donation)

+ "concurrent" plasma (plateletpheresis)

"Source" (dedicated collection by plasmapheresis)



Two main classes of plasma for fractionation



Two types of plasma

Standard plasma usable to make all PDMPs

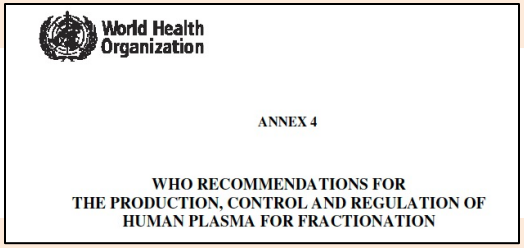
Hyperimmune plasma used to make hyperimmune IgG

- Anti-Rho(D)
- Anti-Hepatitis B
- Anti-rabies
- Anti-tetanus
- Anti-varicella-Zoster
- Etc.

Standard plasma for fractionation

Frozen within 24h

Full range of plasma products including labile coagulation factors



World Health Organization

ANNEX 4

WHO RECOMMENDATIONS FOR THE PRODUCTION, CONTROL AND REGULATION OF HUMAN PLASMA FOR FRACTIONATION

Frozen within 24 to 72h

Immunoglobulin G and albumin

Quality of Plasma for fractionation

Audits and inspections (GMPs)

- Epidemiological surveillance
- Donor's screening (interview)
- Individual donation testing
- Mini-pool NAT testing

Plasma of equivalent quality and safety when pooling takes place



- "Recovered"(prepared from whole blood donation)
- "Source" (dedicated collection by plasmapheresis)

Summary of blood products for clinical use

- Close to 120 million blood donations/year
- +/- 54 million L plasma fractionated/year





Single-donor donations

Pooled plasma donations

> 4000 L



Cellular products

Plasma

Fractionated protein products

Red blood Cells*

Platelets*

Plasma*

Cryo

Coagulation Factors*

Protease Inhibitors

Albumin

Immunoglobulins*

Intravenous use

Intravenous
Sub-cutaneous
Intramuscular
use

*WHO list of Essential Medicines

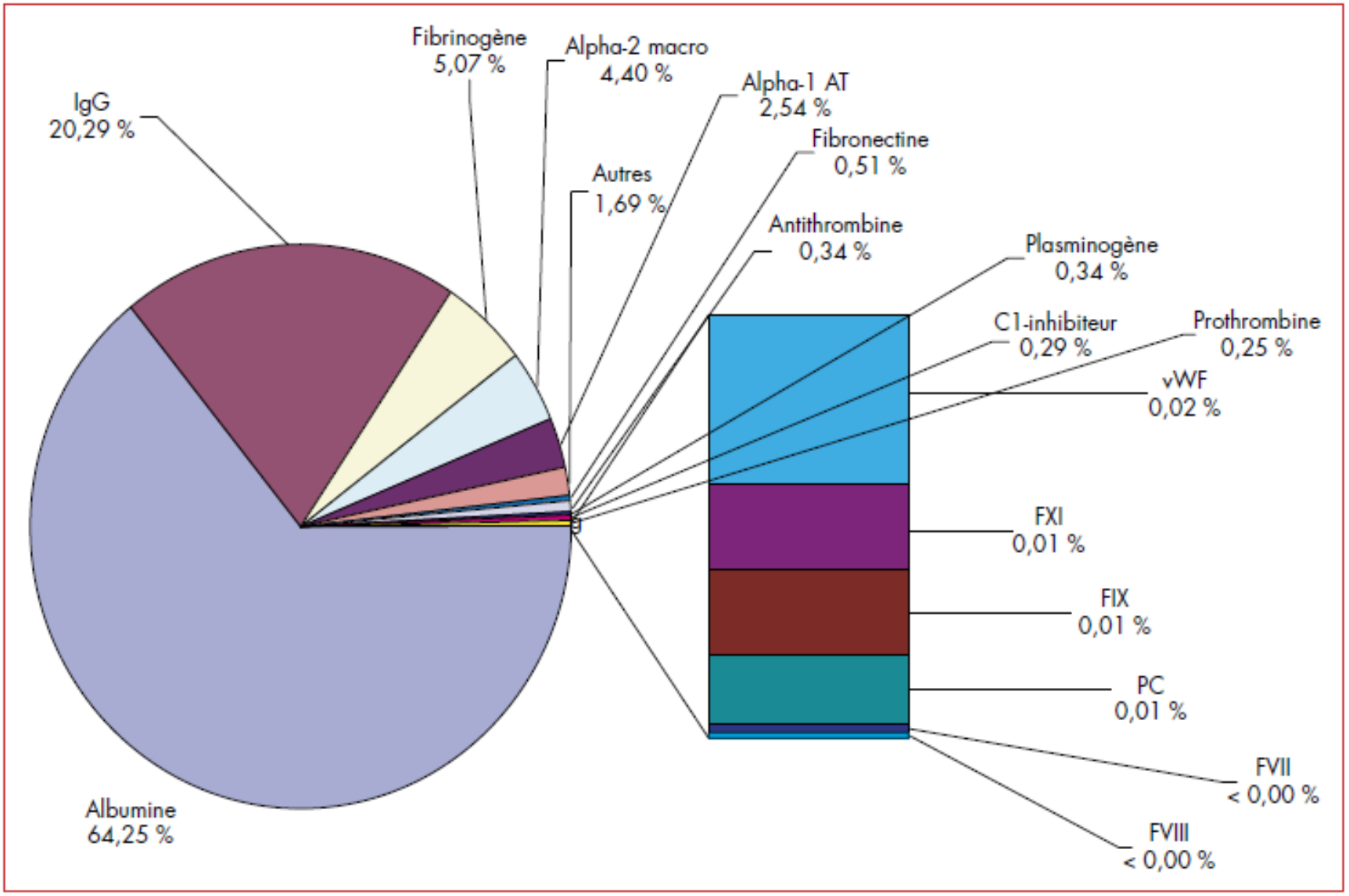
Plasma unique source of therapeutic proteins (which should not be wasted)

- 60 g proteins/litre

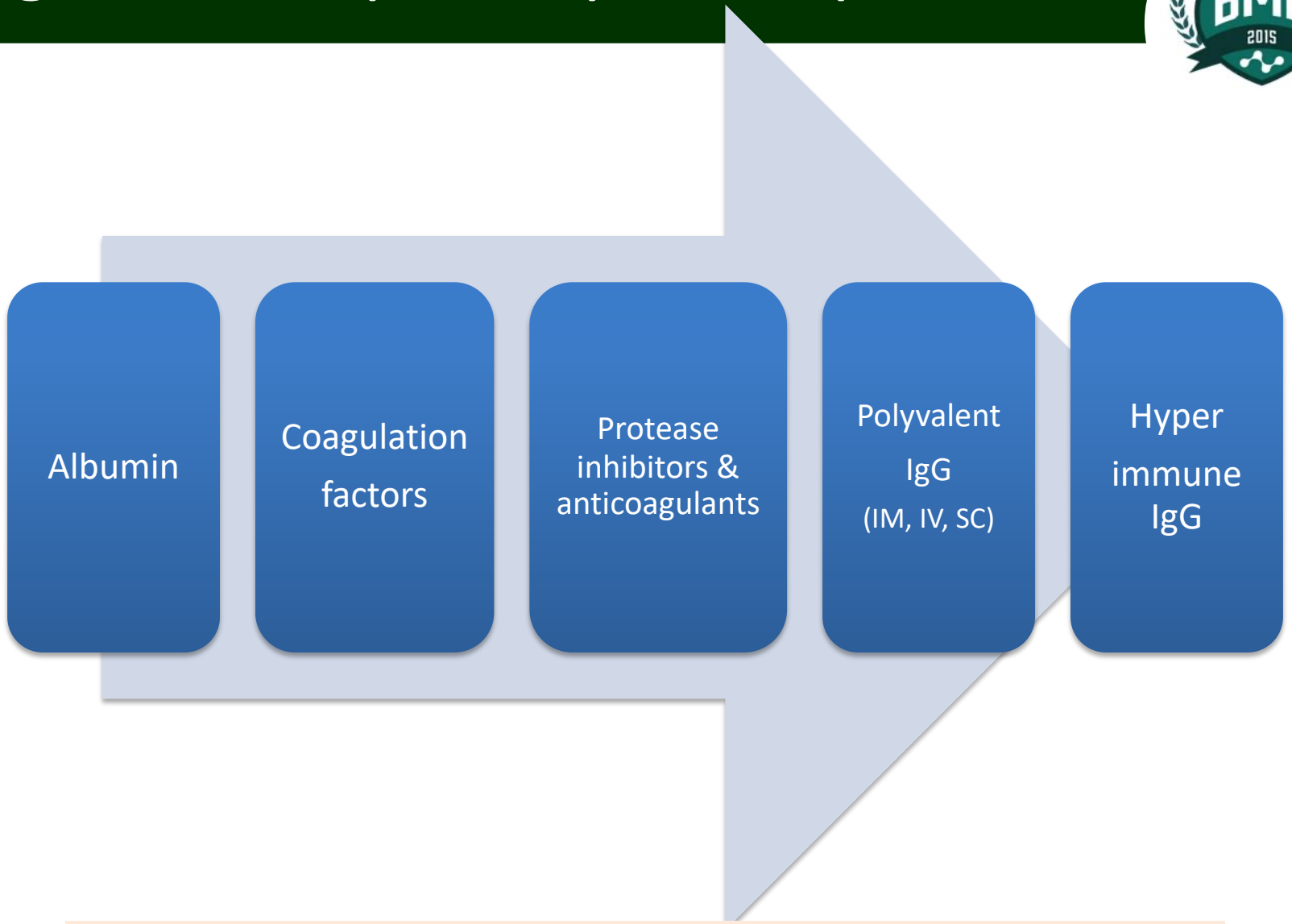


- 3 abundant proteins: albumin, immunoglobulins, fibrinogen
- Multiple less abundant, functional proteins, e.g. coagulation factors, anticoagulant proteins, …
- > 25 distinct licensed protein therapeutics

Plasma proteins



Range of therapeutic plasma products



Over 25 protein therapeutics

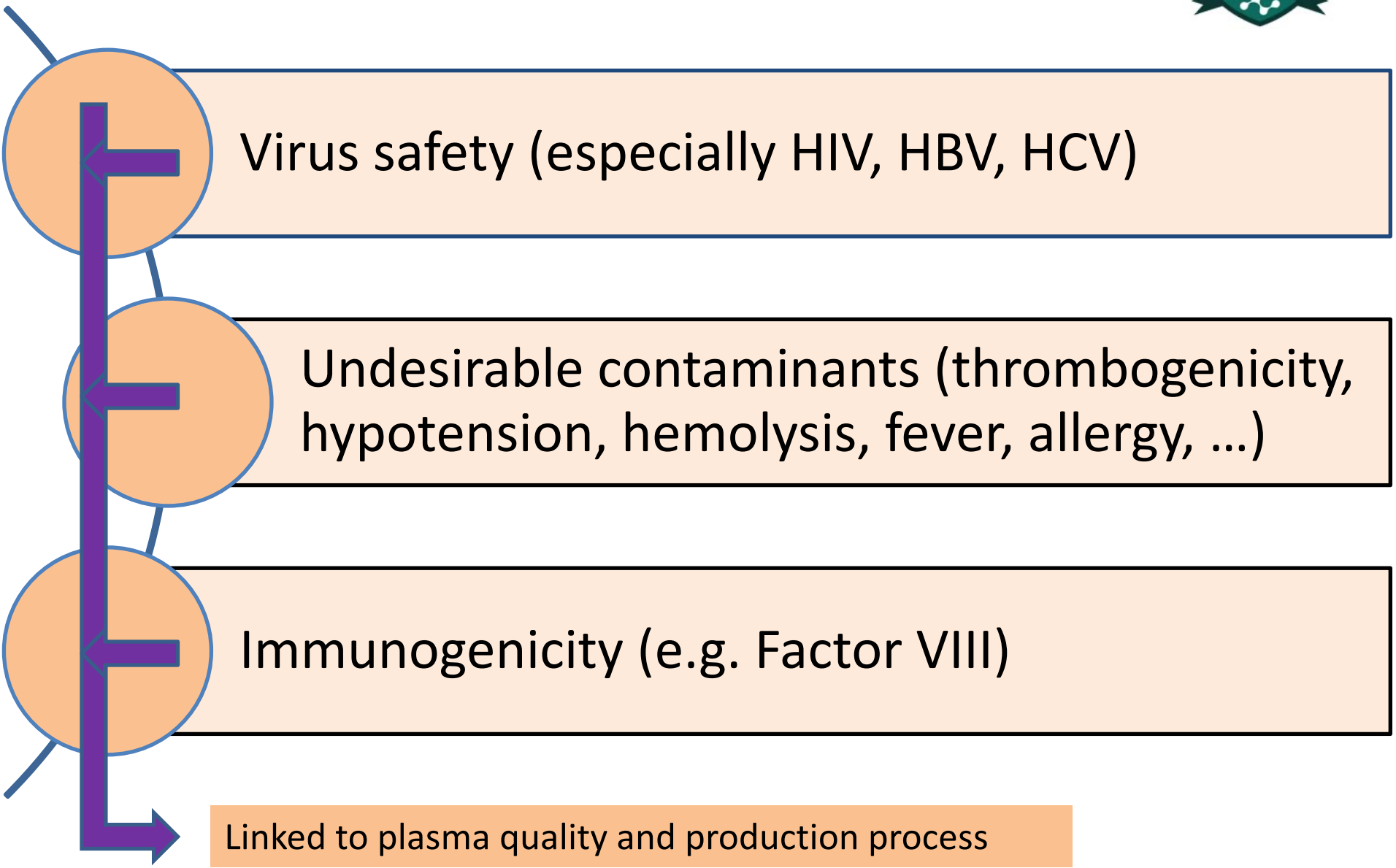
Clinical fields covered by main plasma products

Products	Clinical Indications
Polyvalent immunoglobulins (IV, IM, SC)	• Substitutive therapy in primary deficiency • Immunomodulation
Hyperimmune Immunoglobulins • HBV, tetanus, rabies, CMV IgG, etc., • RhD (anti-D) IgG	• Treatment and prophylaxis of infectious disease (hep B; tetanus; rabies; varicella-zoster, • Prevention of hemolytic disease of the new born (RhD IgG)
Purified coagulation factors (factor VIII, IX, XI, vWF, VII)	• Deficiency in one particular coagulation factor (hemophilia A, B, C, vWD..)
Fibrinogen	• Congenital or acquired deficiency
Prothrombin complex (FII, VII, IX, X, PC, PS, etc.); activated prothrombin complex	• Complex liver disease
Antithrombin; Protein C	• Congenital deficiency
Alpha 1-antitrypsin	• Lung panacinar emphysema due to congenital deficiency
Albumin	• Blood volume replacement / oncotic pressure

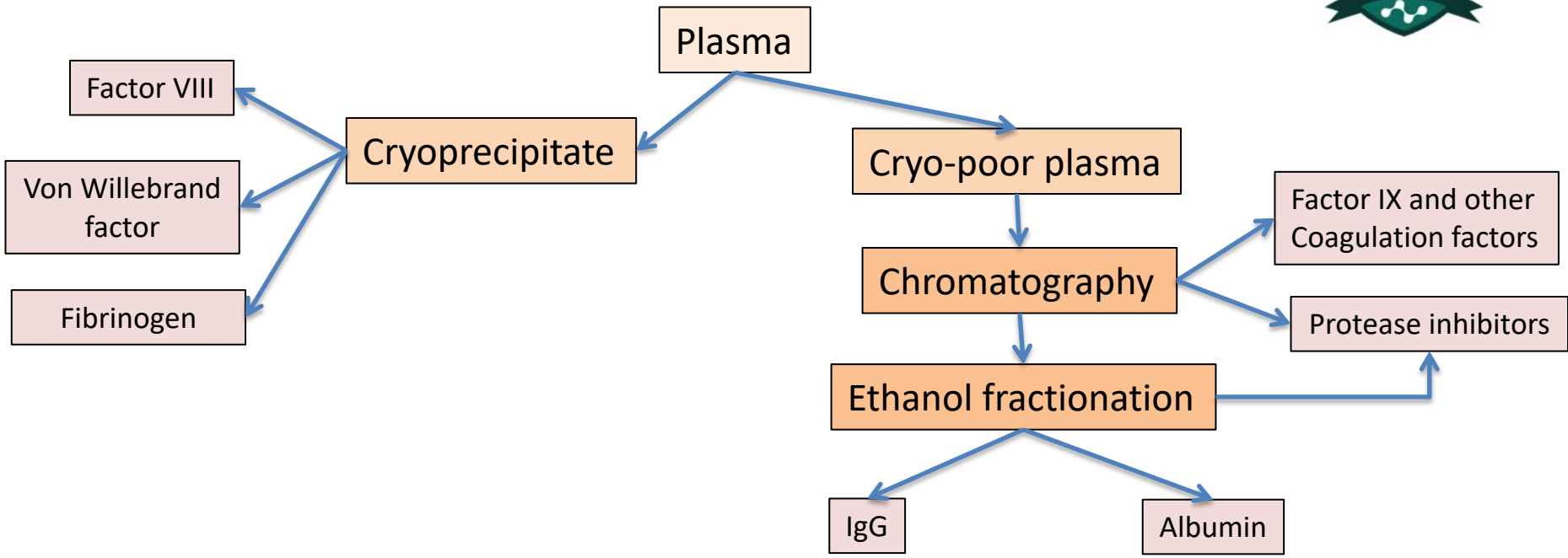
Clinical fields covered by main plasma protein product classes

Products	Clinical Indications
Polyvalent immunoglobulins (IV, IM, SC)	• Substitutive therapy in primary deficiency • Immunomodulation — Immunological disorders
Hyperimmune Immunoglobulins • HBV, tetanus, rabies, CMV IgG, etc., • RhD (anti-D) IgG	• Treatment and prophylaxis of infectious disease (hep B; tetanus; rabies; varicella-zoster, — Infectious diseases • Prevention of hemolytic disease of the new born (RhD IgG) — Hemolytic disease
Several coagulation factors (factor VIII, IX, XI, vWF, VII)	• Deficiency in one particular coagulation factor (hemophilia A, B, vWD,…)
Fibrinogen — Tissue hemostatic/sealing agent (fibrin glue/fibrin sealant)	• Congenital or acquired deficiency
Prothrombin complex (FII, VII, IX, X, PC, PS, etc.); activated prothrombin complex	• Complex liver disease — Coagulation & bleeding disorders
Antithrombin; Protein C	• Congenital deficiency
Alpha 1-antitrypsin	• Lung panacinar emphysema due to congenital deficiency — Other genetic diseases
Albumin — Traumas / liver diseases etc.	• Blood volume replacement / oncotic pressure

Quality and safety hallmarks of PDMPs (historical perspectives)



Plasma fractionation technology



Technology	Comments
Cryoprecipitation	• Still used to isolate cryoprecipitate for Factor VIII isolation
Chromatography	• Mostly ion-exchange and affinity • Used for most proteins
Ethanol fractionation	• Still used for albumin • Decreasing use for IgG

Plasma

Plasma thawing

Cryoprecipitate

Precipitation/adsorption

Chromatography

FVIII

vWF

Fibrinogen



+ viral reduction treatments integrated in the plasma fractionation cascade

Cryo-poor plasma



Fraction (I+) II+III

Chromatography

Chromatography

IgG

Chromatography

aFII

FVII

FIX

Chromatography

PCC

Chromatography

PC

Chromatography

AT

Fibrinogen

Ethanol fractionation

Alpha 1-AT

Albumin

Protein recovery in plasma fractionation

Protein	Recovery/L
Albumin, g	25 - 27
IgG, g	3.5 – 5.2
Factor VIII, IU	120 - 200
Factor IX, IU	200-300
Alpha 1-AT, g	0.2-0.6

IgG profile and yield influenced by regional characteristics (climate, vaccination, & pathogens)

Apheresis plasma > recovered plasma

Processing factors affecting plasma protein recovery

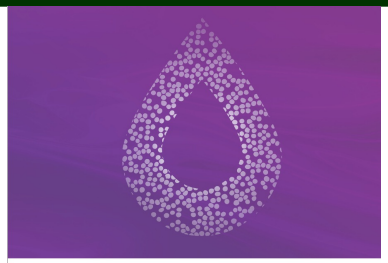
- Plasma processing (separation, freezing, cold storage conditions)
  → impact on coagulation factor VIII, proteolytic activity)
- Type of intermediate plasma fractions used as starting material, such as cryo-poor plasma versus ethanol fractionation paste (e.g. AT, or Alpha 1-antitrypsin)
- Virus reduction treatments (e.g. heat-treatments may affect functional activity; S/D treatment requires additional processing to remove the S/D agents)
- Batch size

PDMPs: Specific points to consider

- Typically produced from large pools of human plasma
  (= plasma from many donors)
- Used for life-long treatment (e.g. congenital bleeding or immunodeficiencies)…
- … or to treat chronic/critical patients
  (e.g. albumin)
- Clinical use (dose, frequency) is intimately linked to the specificities of the proteins: biological functions, half-life, risks of activation, etc.)

The principle of patient-centredness is

PDMPs: Optimal use



GUIDANCE ON INCREASING SUPPLIES OF PLASMA-DERIVED MEDICINAL PRODUCTS IN LOW- AND MIDDLE-INCOME COUNTRIES THROUGH FRACTIONATION OF DOMESTIC PLASMA

World Health Organization

1.7 Optimal use of PDMPs

In addition to generating sufficient supplies of plasma for manufacture into PDMPs, an economically viable programme for provision of PDMPs needs to ensure that the usage of these medicines is based on sound medical practice and evidence. In recent years, historical indications for several products have been shown to have a weak evidence base, warranting more restricted use. For example, some uses of albumin and immunoglobulins have been reconsidered as they are outside well established clinical indications. In particular, several applications of immunoglobulins in primary and some secondary immunodeficiencies and neurological, dermatological and haematological conditions are being debated because the usage is not supported by compelling evidence-based data. However, clinical guidelines provide useful recommendations on the supported indications of immunoglobulins. Updated guidelines for administration of coagulation factor concentrates need to be followed to decrease the risks of development of inhibitors. The principle of patient-centredness is crucial to ensure the optimal use of PDMPs.

Indications of Factor VIII concentrate

Treatment and prophylaxis of bleeding in patients with haemophilia A

Most current PD-Factor VIII concentrates are **not** suitable for treatment of Von Willebrand Disease

FVIII: Dosage/duration of treatment

- Prophylaxis (high dose/low dose depending upon product type and availability) to prevent bleeding
- Severity of the disease
- Location and extent of bleeding
- Patient's clinical status



Refer to Recommendations/Guidelines (e.g. WFH)

Distinctive features of PD-Factor VIII concentrates

- **Level of purity (specific activity expressed in IU/mg)**
- Methods of purification (precipitations; anion-exchange chromatography; immunoaffinity
- Addition of albumin (as stabilizer)
- Level of co-purification of Von Willebrand factor

Distinctive features of PD-Factor VIII concentrates

- **Presence of Von Willebrand factor**
- Concentration sufficient for treating VWD
- Concentration insufficient for VWD treatment but beneficial to FVIII stability and potential decrease of the risk of inhibitors
- Absent (due to mode of purification)

Distinctive features of PD-Factor VIII concentrates

- **Type of virus inactivation & removal procedures**
  - Solvent-detergent + Dry-heat treatment
  - Pasteurisation (liquid heat-treatment)
  - Solvent-detergent + nanofiltration (20 nm or 15nm)

Indications of Factor IX concentrates

Treatment and prophylaxis of bleeding in patients with haemophilia B

Dosage and duration depends on severity of deficiency, location and extent of bleeding, and patient's clinical condition



Distinctive features of PD-Factor IX concentrates

- **Level of purity (specific activity)**
- Type of chromatography: anion-exchange; anion-exchange + affinity; immunoaffinity
- Formulation with albumin or not

Distinctive features of PD-Factor IX concentrates

Type of virus inactivation & removal procedures

- Solvent-detergent + Nanofiltration (15nm)
- Solvent-detergent + dry-heat
- Detergent + Vapour heat treatment
- Sodium thiocyanate + ultrafiltration

Use of Immunoglobulins in replacement therapy

Primary immunodeficiency syndromes: Congenital a/hypo/gammaglobulinaemia; Common variable immunodeficiency; Severe combined immunodeficiency

Myeloma or chronic lymphocytic leukaemia; secondary hypogammaglobulinemia; severe infections

Children with congenital AIDS or recurrent infections

Use of immunoglobulins in immunomodulation

- ITP
- Guillain-Barré syndrome
- Kawasaki disease
- Allogeneic bone marrow transplantation
- Others: autoimmune/inflammatory diseases

Clinical guidelines: recommendations on supported indications of IgG

Distinctive features of IgG concentrates

- **Type and combination of virus inactivation & removal procedures**
  - Solvent/detergent + nanofiltration 35nm + acid pH incubation
  - Solvent/detergent + nanofiltration 20nm
  - Caprylic acid treatment +/- acid pH incubation + nanofiltration
  - Pasteurisation + acid pH incubation

IgG pools can contain neutralizing antibodies against e.g. HAV, B19V

Distinctive features of IgG concentrates

Biochemical and formulation

- Liquid versus freeze-dried
- Intravenous vs subcutaneous vs intramuscular
- Concentration: 5%, 10%, 15%, 20%
- Residual level of IgA, pro-thrombotic factors (FXIa), isoagglutinins

Refined dedicated purification steps can remove unwanted proteins

Clinical use of albumin

4-5%: plasma exchange

20%: extra-vascular fluid mobilization

Typical PDMP consumptions in HIC and corresponding plasma volume

	Usage per 1000 inhabitants	Equivalent plasma volume (L)/per million inhabitants
Factor VIII (IU)	3000 - 8000 IU	20’000 - 55’000L*
Immunoglobulins (g)	50 - 200 g	10’000 - 40’000
Albumin (g)	150 - 600 g	6’000 – 24’000

Yield used:
Factor VIII: 150 IU/L
IgG: 5 g/L
Albumin: 25g/L

* Partly covered by recombinant molecules (“normal” rec FVIII; long-lasting FVIII; mAb)

IgG has become the protein driver of the plasma fractionation industry

Conclusions

- Some PDPMs are “essential” WHO medicines and all are vital in human therapy
- Plasma fractionation remains important to ensure sufficient supply of all PDMPs at global level
- Plasma generated in LMIC should not be wasted as demand for plasma products remains unmet worldwide

Thank you for your attention

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