Plasma's Journey from Donor to Patient

‘Arm to Arm’

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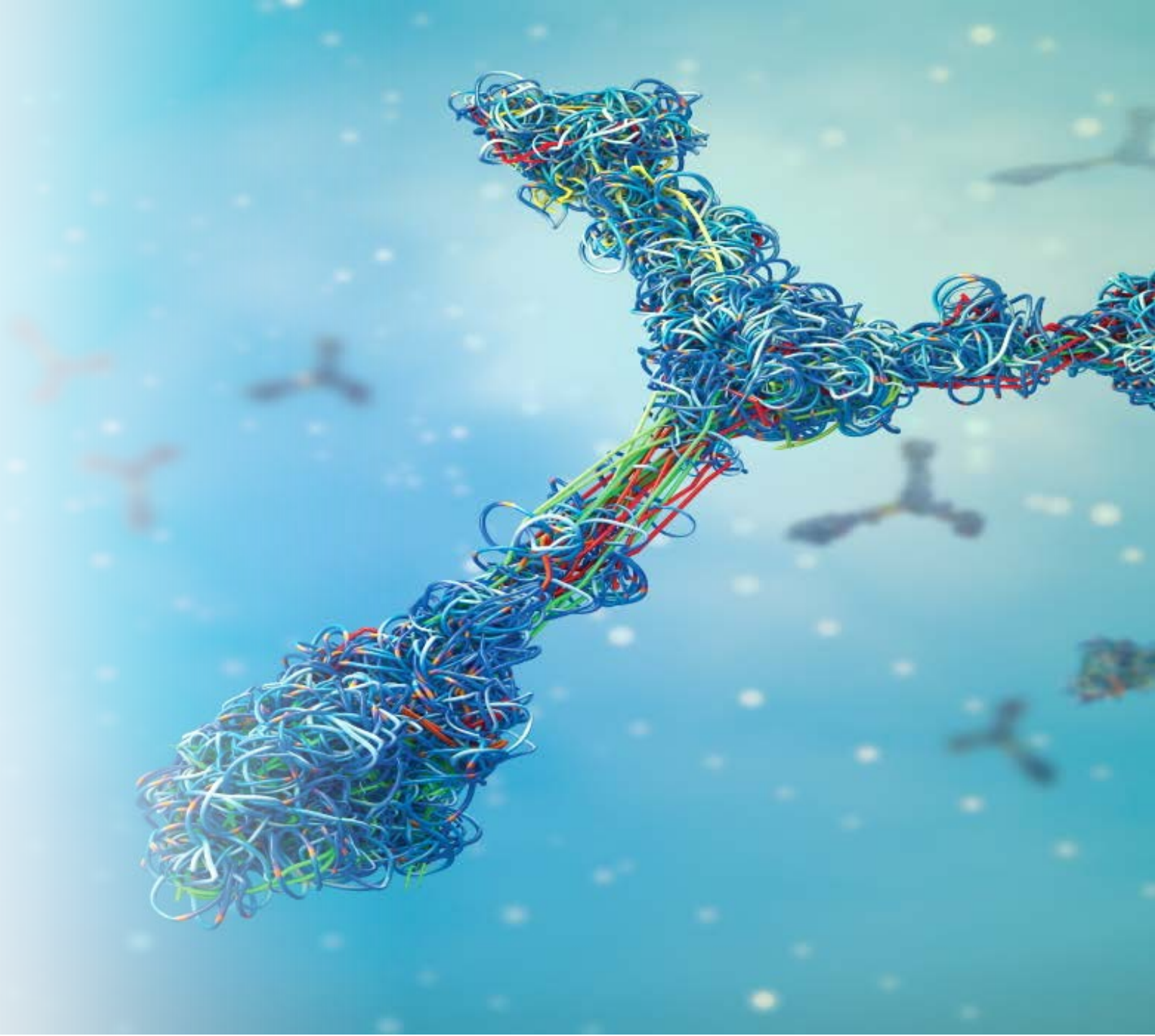
Introduction

- What is Plasma?
- History of Plasma
- Plasma Fractionation
- Steps from Plasma to Patient
- The economics of Plasma
- COVID-19
- UK Plasma

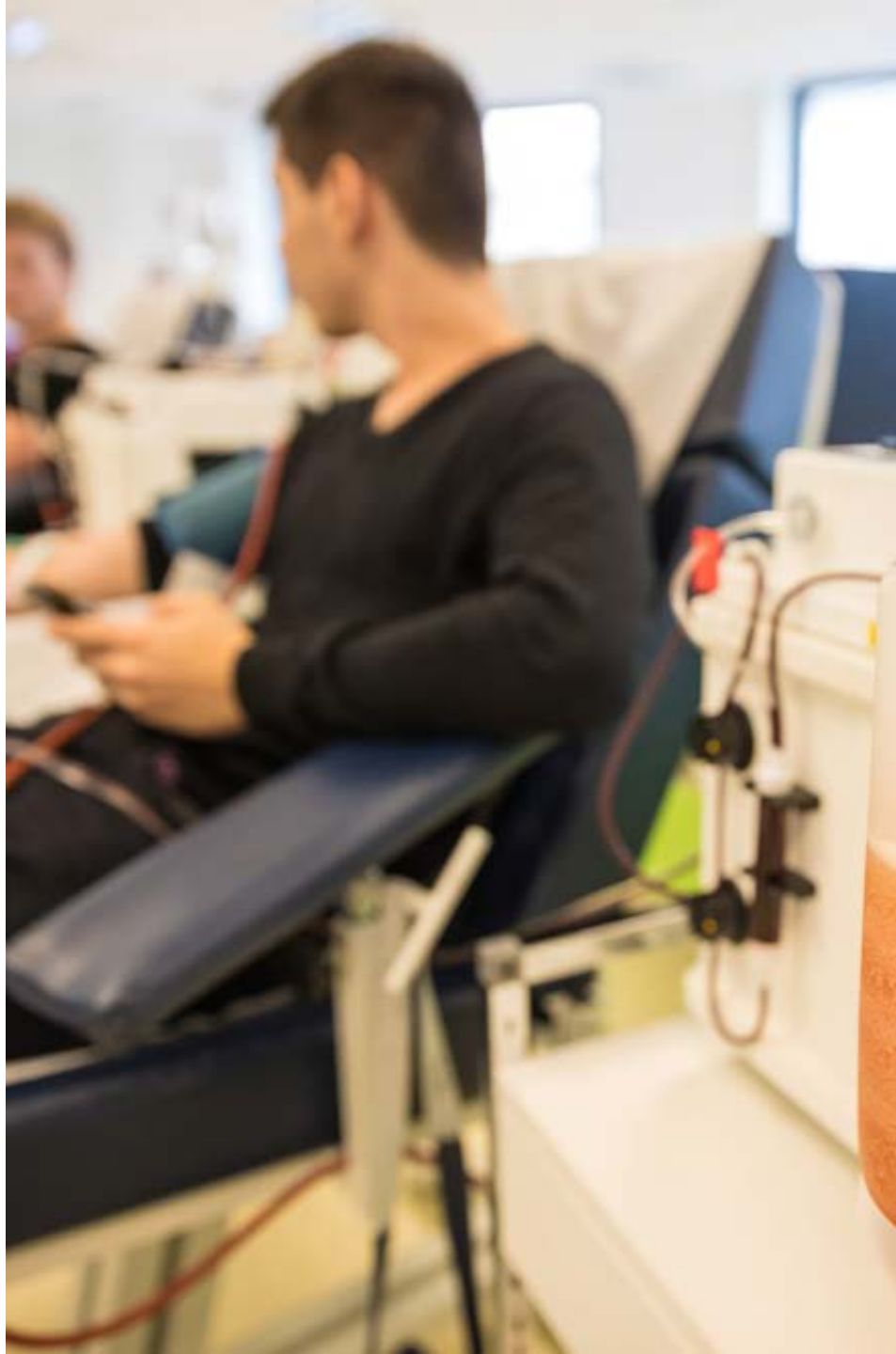


What is Plasma?

- Liquid part of blood
- Carries dissolved proteins and other chemicals around the body to where they are needed
- Various functions:
  - Maintain fluid pressure (albumin)
  - Protect against infection (immunoglobulin)
  - Stops bleeding/blood loss (clotting factors)

What is Plasma?

- Plasma can be donated by people in two ways:
  - Recovered Plasma - whole blood donation separated into cells and plasma
  - **Plasmapheresis** - returns solid cells to the donor (source plasma)



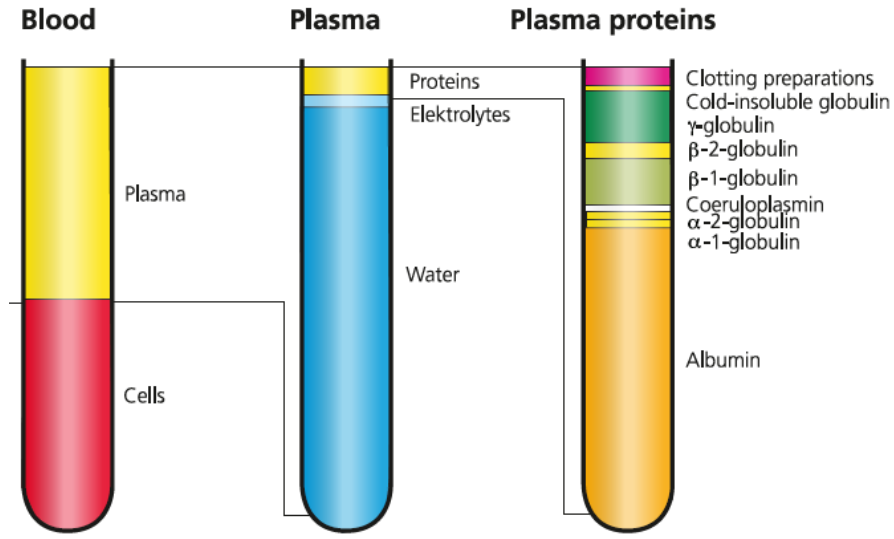
What is Plasma?

- 1990s: >100 known proteins
- 2002: 490 by LC-MS
- 2008: 695 by LC-MS/MS
- 2008: HIP^2 database: 12,787 proteins & 86,831 peptides by MS/MS

Serum Albumin Structure, Wladek Minor, University of Virginia

What is Plasma?

- Plasma itself represents about ½ the volume of blood
- Most of the plasma is actually water
- Proteins of interest in the remainder (per litre):
  - 40g Albumin
  - 12g Immunoglobulins
  - 300µg Factor VIII
  - +1000 other proteins



History of Plasma

- Late 17th Century, Europe
  - *The blood of a gentle calf*
  - Direct, whole blood transfusions from animal to human
  - Direct, whole blood transfusions from human to human – still to transfer personality traits
- Early 20th Century, USA
  - First ‘modern’ transfusion - Father to baby

1692. Transfusion of lamb’s blood for the treatment of insanity.
German medical textbook

History of Plasma

- WWI
  - Plasma suggested as a treatment but not followed up
- 1930s, USSR, America, Britain
  - Use of plasma on an experimental basis
  - Plasma more robust, but still difficult to work with – Specification by US Navy
- WWII
  - Whole blood couldn't survive the journey from USA
  - First use of ethanol-fractionated albumin – Pearl Harbor, 1941

1943. An American medic administers plasma to a wounded soldier in Sicily. NARA

Origins of Modern Plasma Fractionation

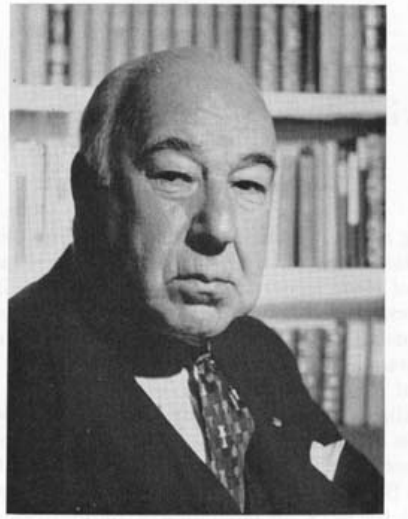
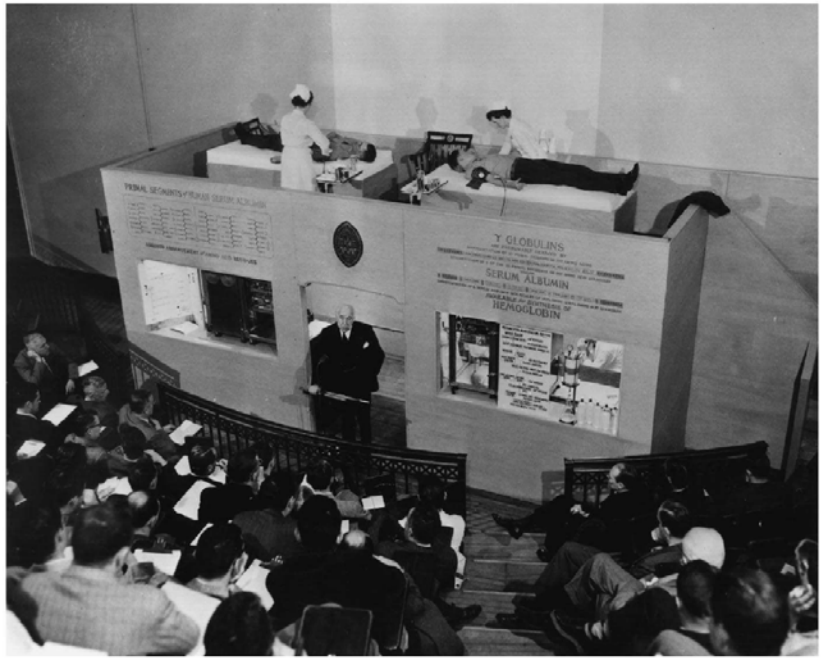


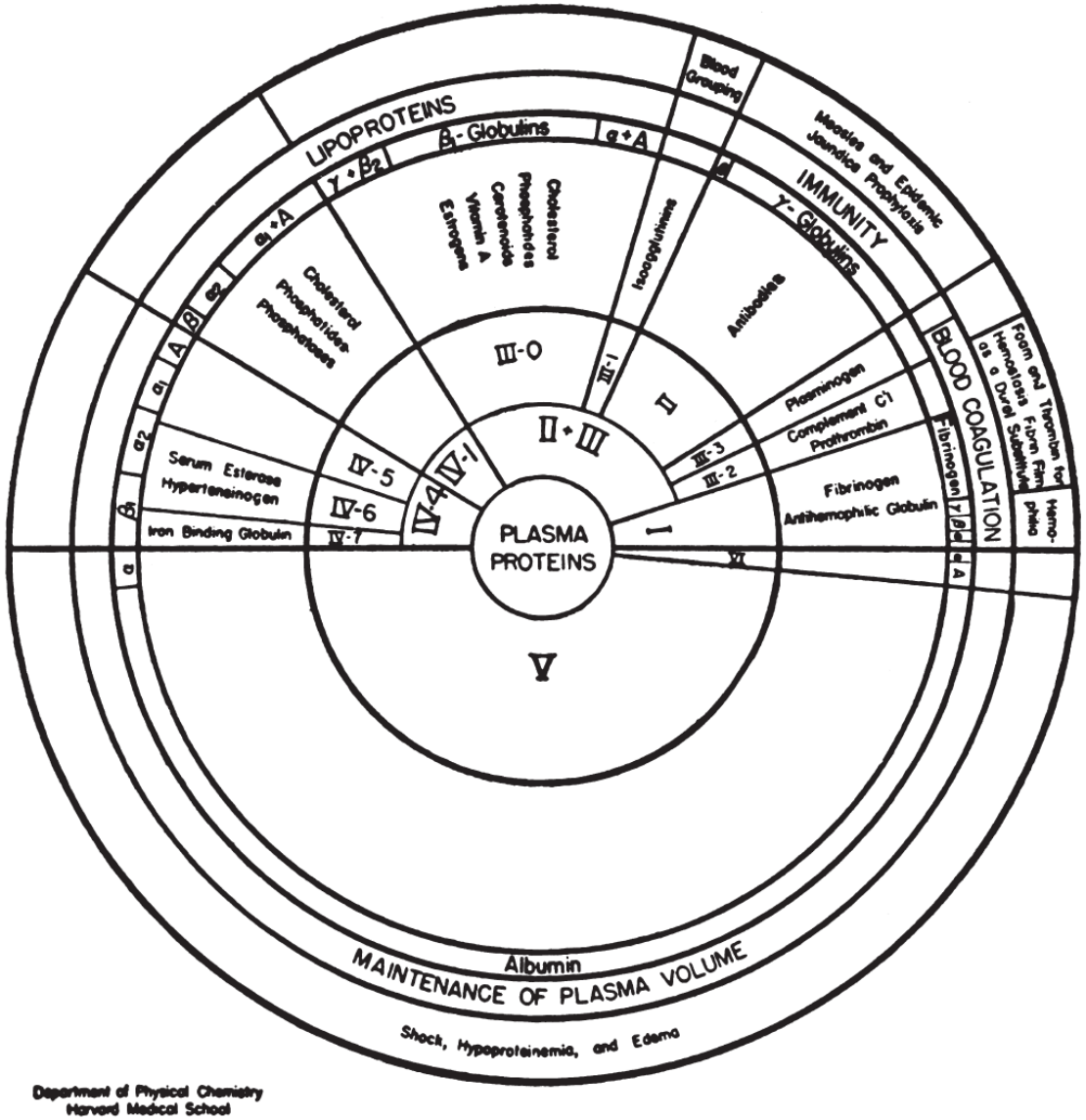
FIGURE 73.—Edwin J. Cohn, Ph. D.

- Methods for large scale separation of plasma proteins driven by need for “stable plasma protein fraction” (i.e. albumin) in WWII
- Edwin Cohn and co-workers published landmark paper in 1941
- Describes use of ethanol for fractional precipitation of proteins



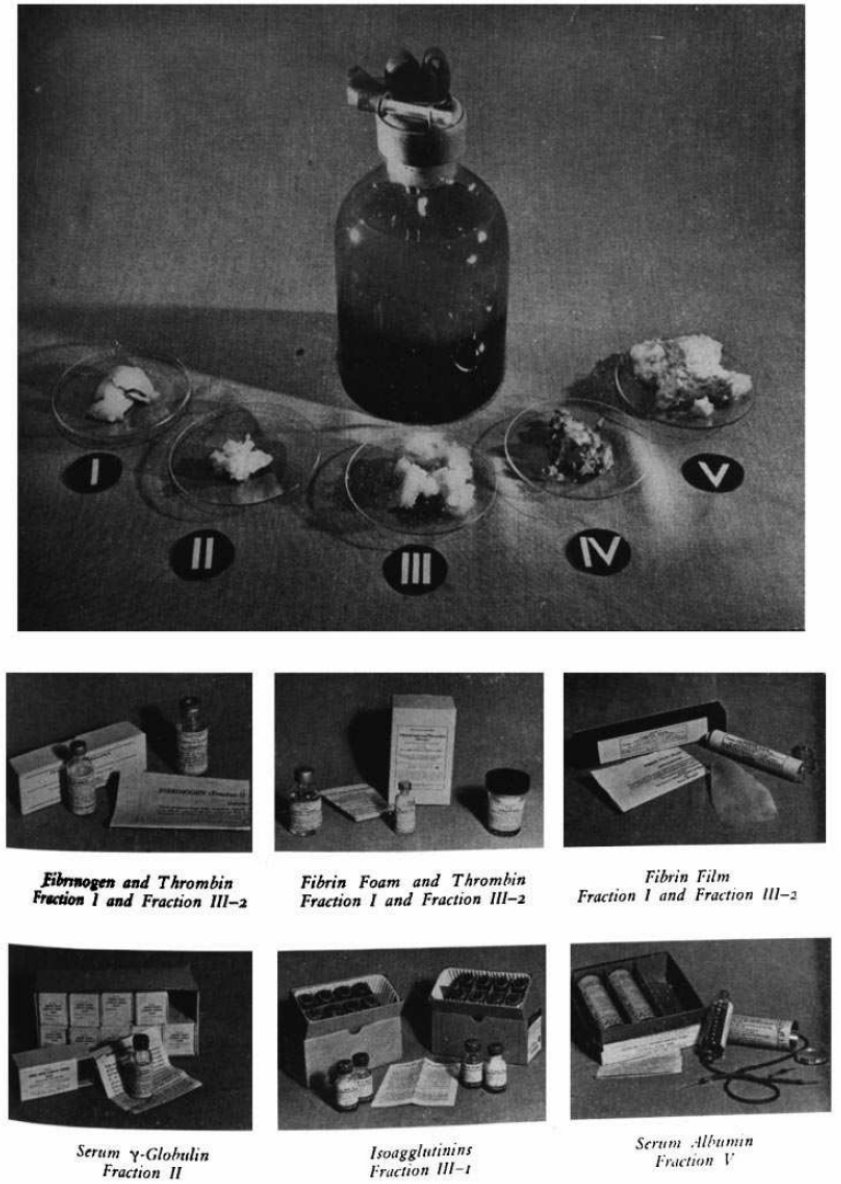
What is Plasma Fractionation?

- Separation of plasma proteins into definable fractions
- Based on manipulation of specific protein solubility under different conditions of
  - Temperature, ionic strength, conductivity, protein concentration and pH
- Widely known as ‘Cohn fractionation’ or ‘Cold Ethanol fractionation’

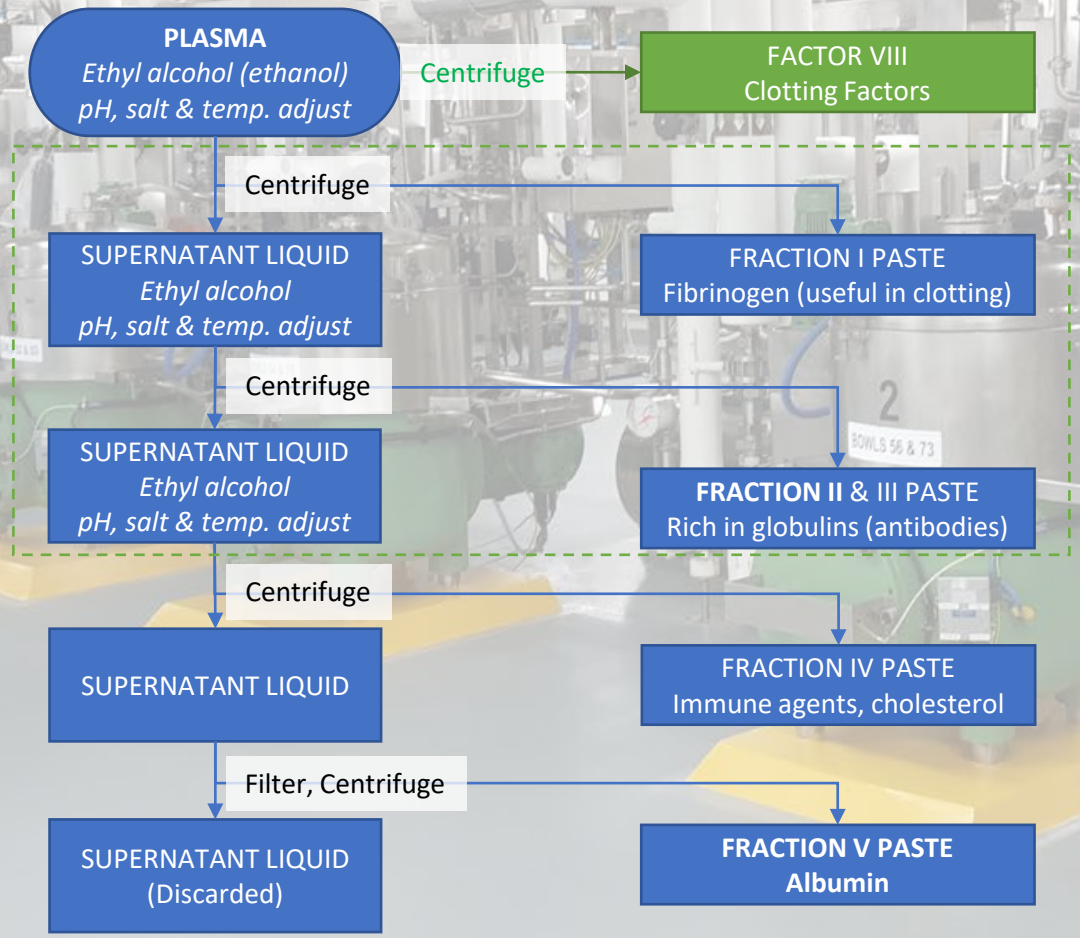


Cohn Fractionation

- Identified by Roman Numerals
- I Fibrinogen (Fibrin Foam) & Thrombin
- II Serum **γ-Globulin**
- III Other globulins
  - Including blood grouping isoagglutinins
- IV Complement components
- V Serum **Albumin**



Cohn Fractionation



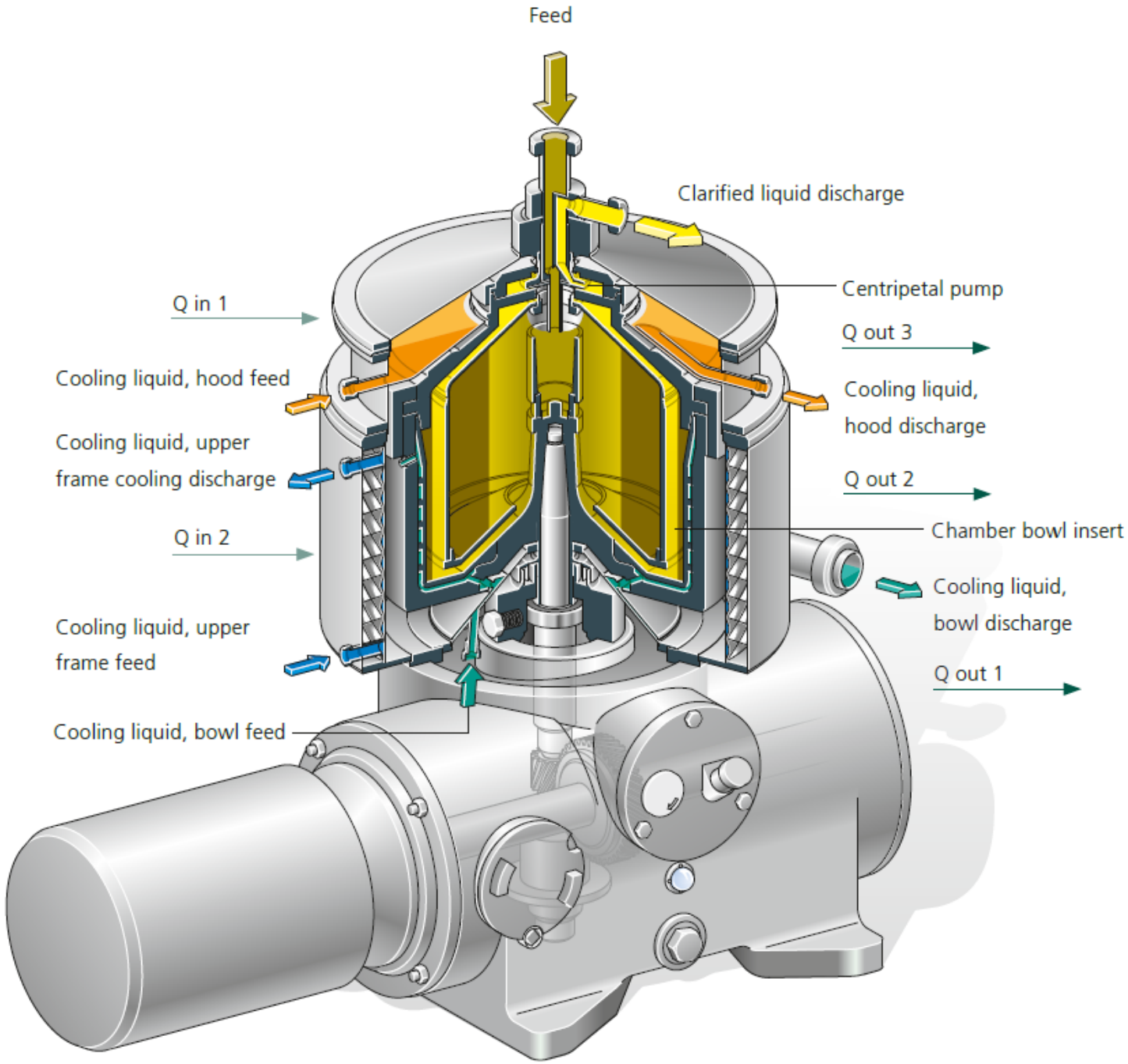
Kistler-Nitschmann - these steps combined

Step 1 - Donation

- Donation is exclusively from United States
  - Many markets require this restriction
  - Donor Screening
- Collected by Plasmapheresis
- Frozen at source
  - Held for min. 60 days
- Tested at source
- Shipped frozen
- Tested in-process

Step 2 – Pooling & Cryoprecipitate Separation

- Plasma arrives frozen from donation centers
- Thousands of donations are ‘pooled’ into a single batch
- Partially thawed
- Separated via centrifuge
  - ‘Cryoprecipitate’ to Factor VIII
  - ‘Cryoprecipitate Supernatant’ (Step 2)
  - Constantly cooled
    - Water/Ethanol

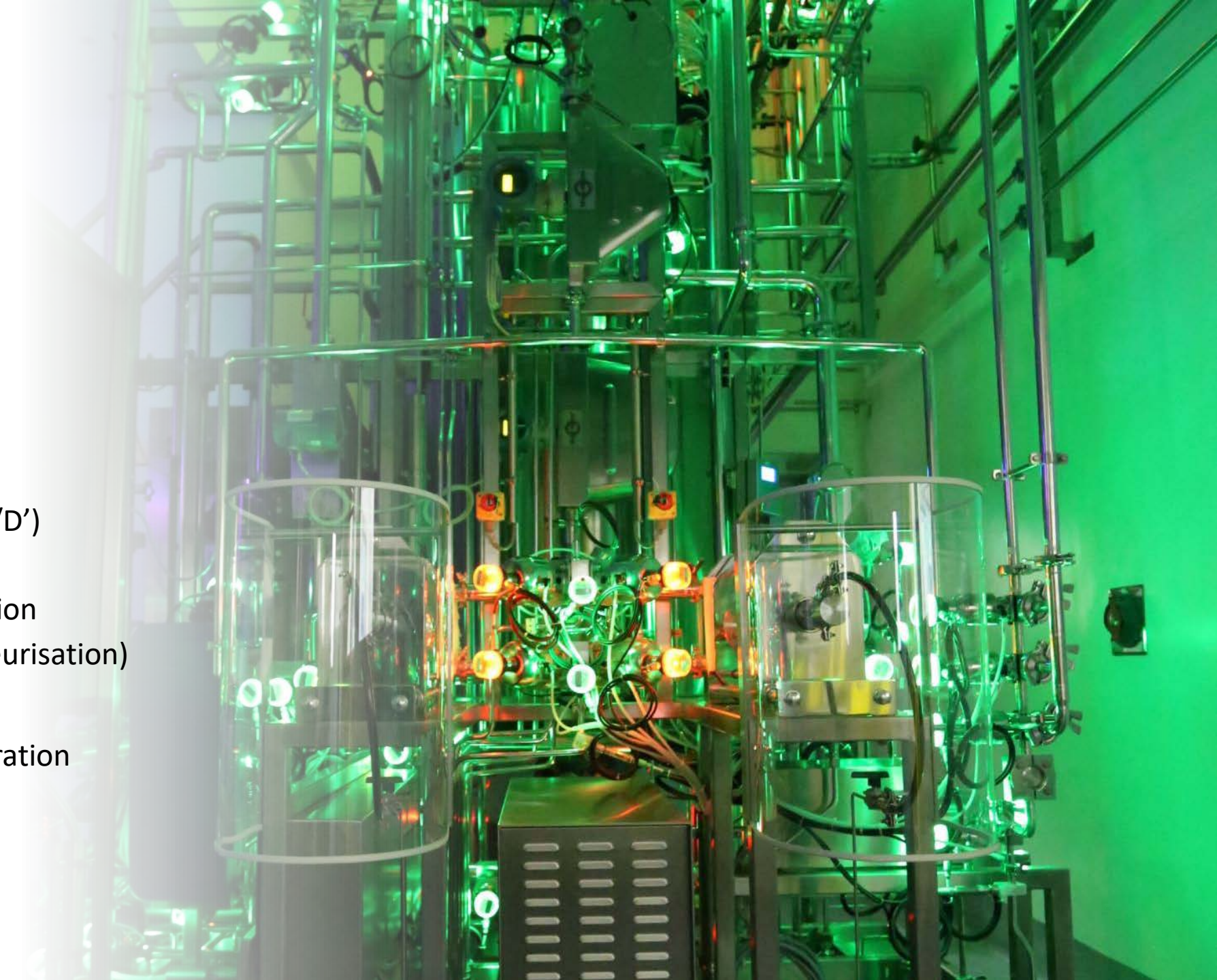


Step 3 - Fractionation

- Various stages of precipitation & separation
  - Various intermediates produced as ‘pastes’ & can be held frozen
- Factors IX and X Coagulation Factors
  - 0.2-5 mg/L (with FVIII)
- **Fraction V for Albumin**
  - 30 g/L
- **Fraction II for Immunoglobulins**
  - 5-10 g/L

Step 4 – Purification / Formulation

- Removal of impurities
  - Chromatography
- Virus reduction
  - Solvent/Detergent (‘S/D’)
  - Filtration
  - Filled Product Incubation
  - Heat Treatment (Pasteurisation)
- Concentration
  - Ultrafiltration / Diafiltration
- Formulation
  - Stabilizers
  - Excipients

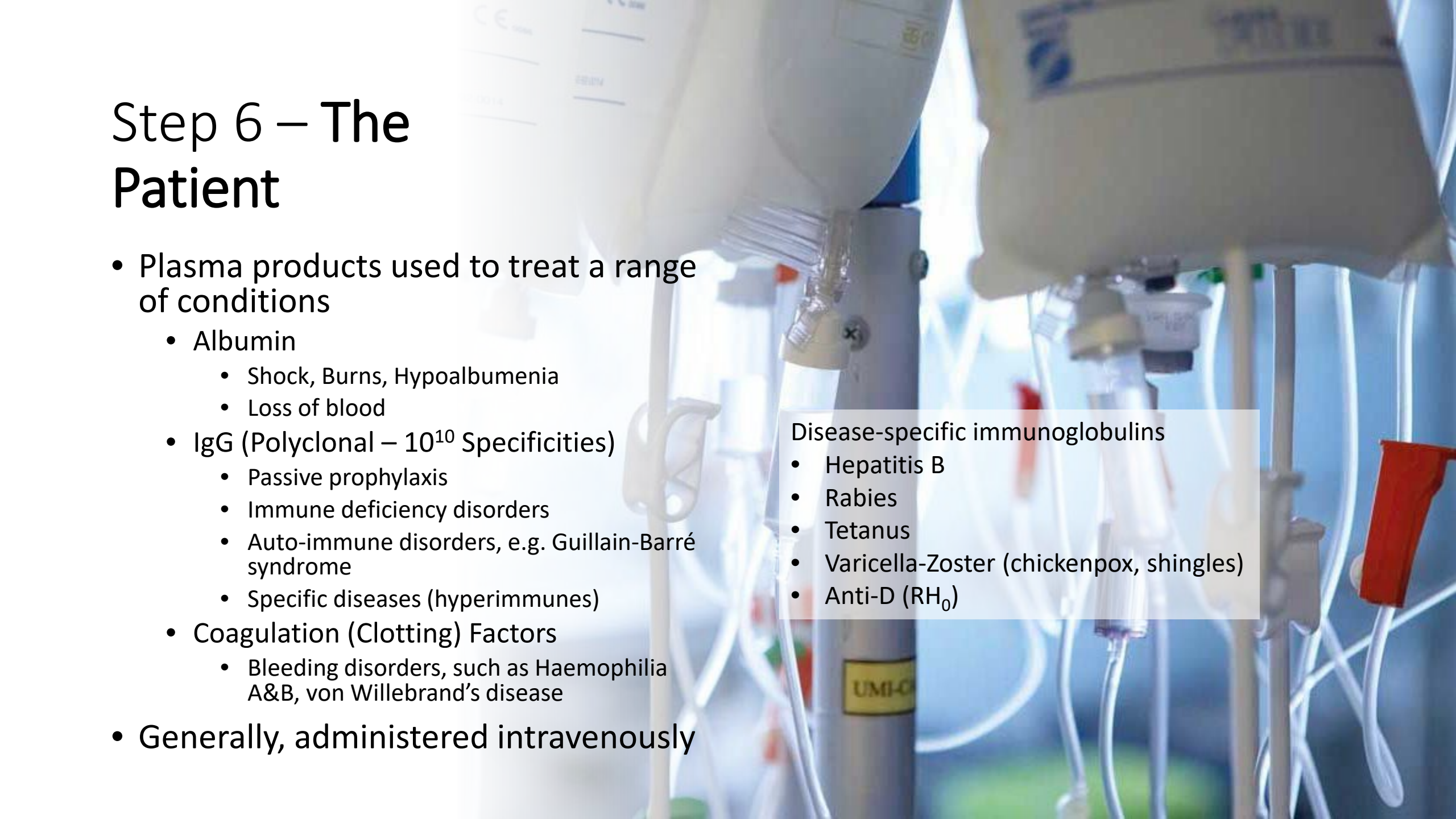


Step 5 – Freeze Drying

- Otherwise known as *Lyophilization*
- Removes liquids from the products
- Stabilises for longer-term storage
- Coagulation factors only
  - Proteases, not suitable for storage in liquid form
- Freeze-dried product good for hostile environments
  - But requires reconstitution, e.g. with Water for Injections (WFI)

Step 6 – The Patient

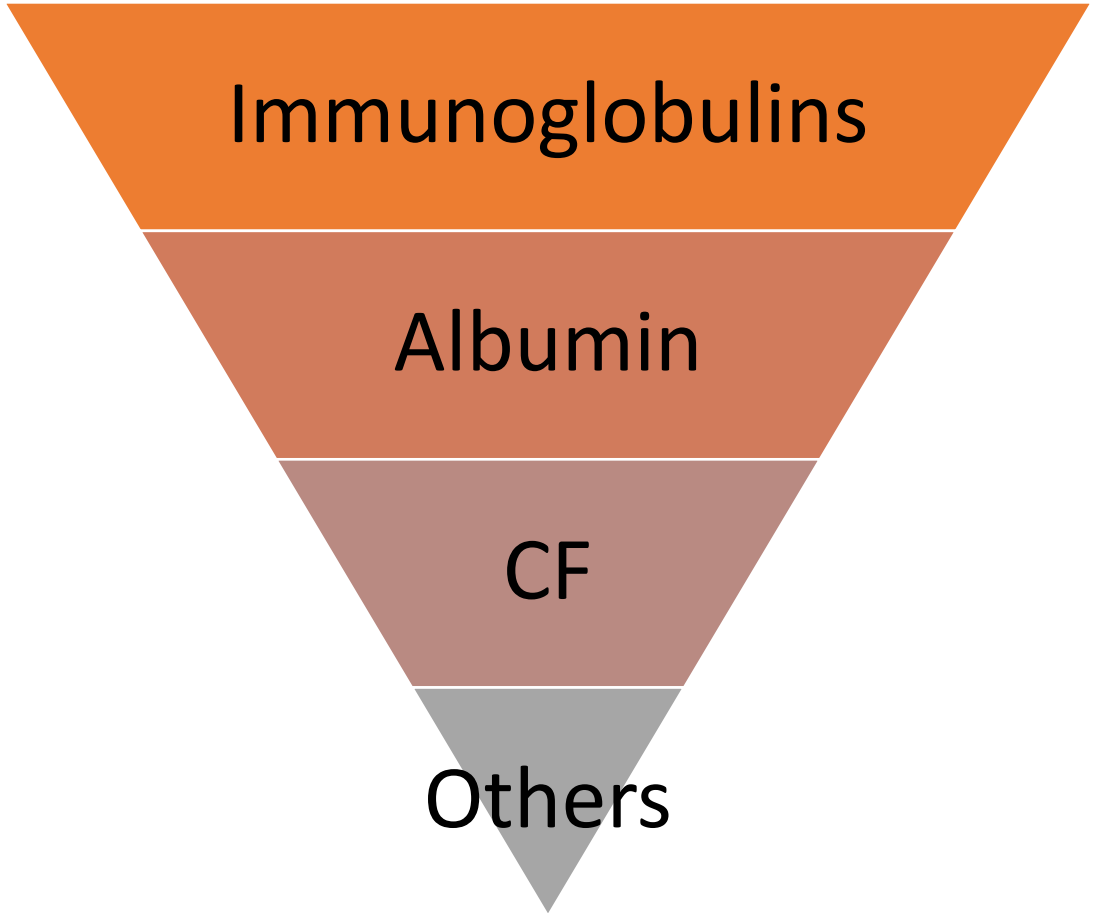
- Plasma products used to treat a range of conditions
  - Albumin
    - Shock, Burns, Hypoalbumenia
    - Loss of blood
  - IgG (Polyclonal – 10^{10} Specificities)
    - Passive prophylaxis
    - Immune deficiency disorders
    - Auto-immune disorders, e.g. Guillain-Barré syndrome
    - Specific diseases (hyperimmunes)
  - Coagulation (Clotting) Factors
    - Bleeding disorders, such as Haemophilia A&B, von Willebrand's disease
- Generally, administered intravenously



Disease-specific immunoglobulins
- Hepatitis B
- Rabies
- Tetanus
- Varicella-Zoster (chickenpox, shingles)
- Anti-D (RH_0)

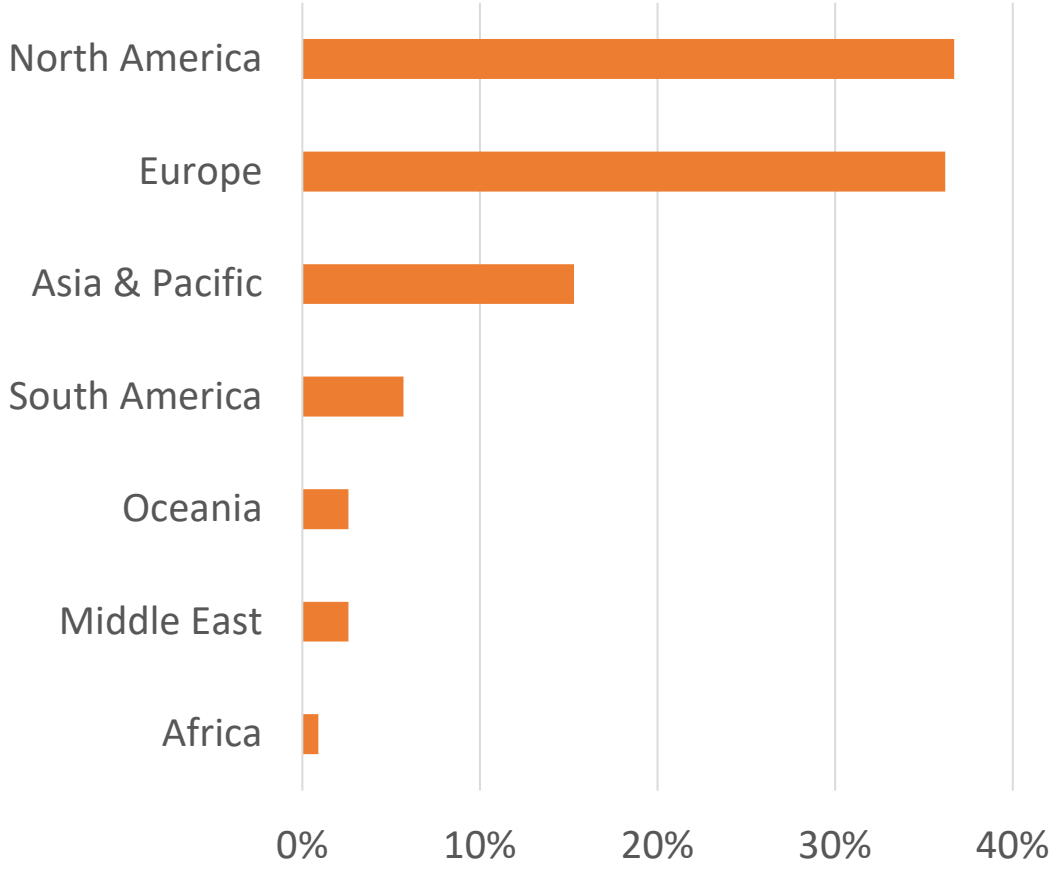
The Economics of Plasma

- Albumin used to be the primary driver
- Then a shift to Coagulation Factors (CF)
  - Factors VIII & IX
- Now, Immunoglobulins are the largest market (~50%), and growing



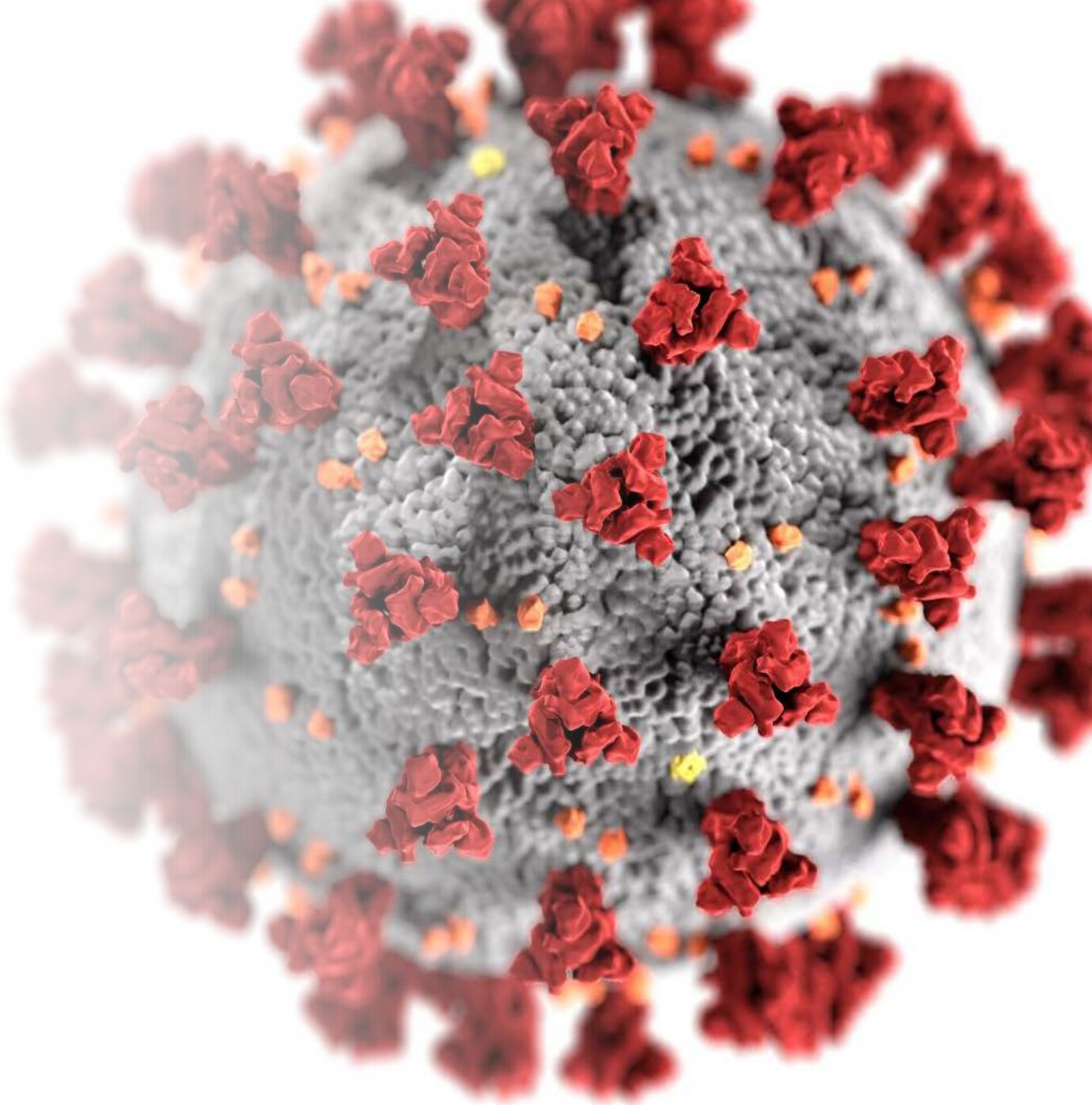
The Economics of Plasma

- Worldwide demand for plasma products
- North America largest market
- Asia & Pacific growing demand



COVID-19

- CoVIg-19 Plasma Alliance
- Ten plasma companies together to develop anti-SARS-CoV-2 polyclonal hyperimmune globulin
- Used convalescent plasma
- Unfortunately, did not meet its endpoints



UK blood plasma for medicines

- First blood plasma for medicines donations begin - NHS Blood and Transplant (nhsbt.nhs.uk)
- The restriction on using plasma from UK donors was introduced in 1998 as a precautionary measure against vCJD.
- The restriction was lifted by the Department of Health and Social Care in February 2021

Acknowledgements

- With thanks to Dr Mark Bulmer & Dr John More

- Starr, Douglas P. *Blood : an Epic History of Medicine and Commerce.* New York: Alfred
- Surgenor, Douglas M. *Edwin J. Cohn and the Development of Protein Chemistry*. Center for Blood Research and Harvard University Press.