CSL Behring

Manufacturing of IgG Products

IPOPI 2018, Lisbon

Disclosures

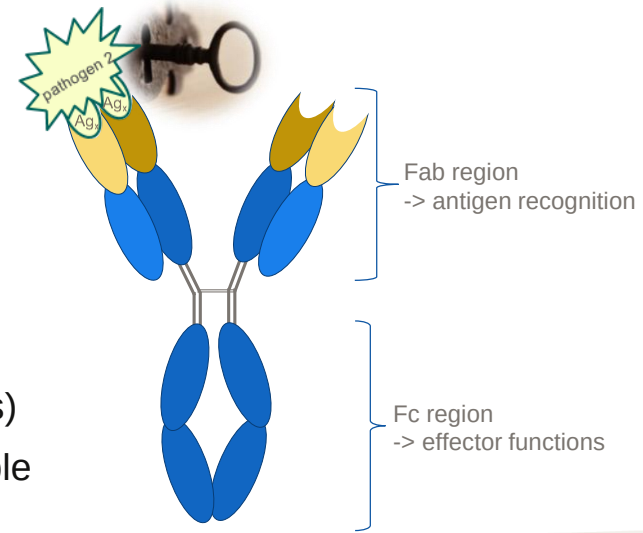
- Martin Imboden is an employee of CSL Behring

AGENDA

- IgGs: structure and therapeutical use
- Plasma Fractionation Industry: where it all began
- Today's IgG manufacturing processes
- Key characteristics of IgG products

IgGs in a Nut Shell

- IgGs (antibodies): plasma proteins produced by B-cells upon stimulation of the immune system by pathogens/antigens
- Y-shaped proteins: 2 heavy and 2 light chains
- Part of the body's defense arsenal to neutralize, destroy and remove foreign substances such as pathogens or toxins
- IgGs have a dual function:
  - Fab arms: specific recogniton and binding of antigens (microbes)
  - Fc stem: effector functions, i.e. making pathogenes/Ag accessible for destruction/removal by the immune system



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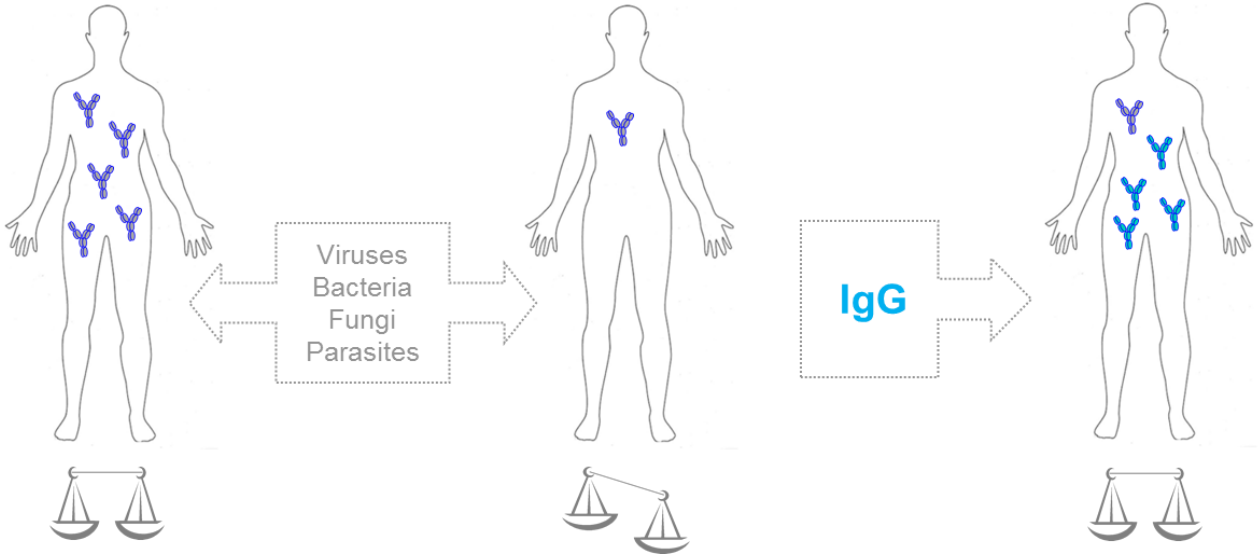
IgGs as Therapeutics

- 1952: first therapeutic use reportes for the treatment of PID.
- 2017: 187 metric tons of IgGs administered globally in various therapeutic areas.
- High pure IgG concentrates prepared from plasma of usually 10’000-50’000 healthy volunteers, i.e. broad spectrum of specificities against «the universe» of pathogens/Ag.
- Administration routes: intravenous infusion (IVIG) and subcutaneous injection (SCIG); [intramuscular injection (IMIG)]
- Therapeutic use:
  - Substitution therapy: low dose treatment
  - Immunomodulating therapy: high dose treatment

⇨Saves lives and improves the quality of life for people with rare and serious conditions.

Substitution Therapy: Low Dose Treatment



IgG deficiency

-> recurrent infections

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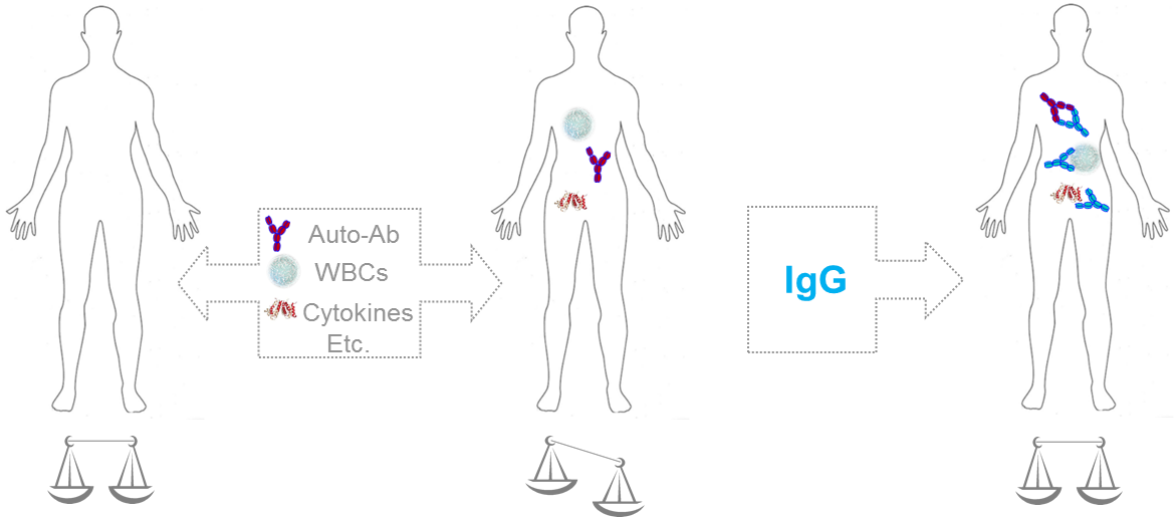
Immunomodulation: High Dose Treatment



Immune system misfire

-> Autoimmune and inflammatory diseases

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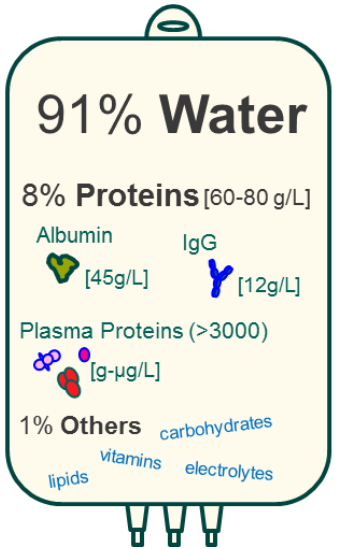
Plasma Industry: Where it all began….

- WW II created an **unmet medical need** for volume expanders:
  - 1940: US Department of Navy mandated Edwin Cohn at the Harvard University to develop an industrial process to isolate albumin out of human plasma
  - 1941: few bottles of **albumin** to treat some of those wounded in the attack on Pearl Harbor
  - 1942: **immunoglobuline** fraction as measles prophylaxis

- Cohn’s ethanol fractionation method: the basis for most current plasma fractionation processes:
  - Differential solubility of plasma proteins in alcoholic solutions

Ethanol Fractionation of Plasma Proteins

Human Plasma

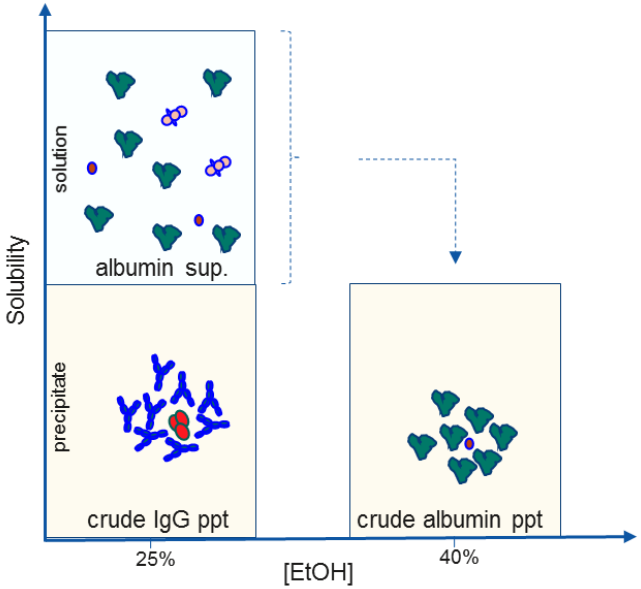


CSL Behring Fractionation Tanks

5 parameter system:

- EtOH conc.,
- pH,
- salt conc,
- temperature,
- protein conc.

EtOH Precipitation Principle



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Plasma Fractionation: Cohn's Method

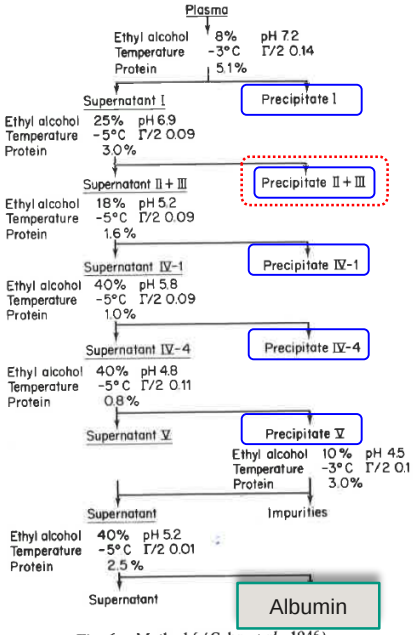

Fig. 6. Method 6 (Cohn *et al.*, 1946).

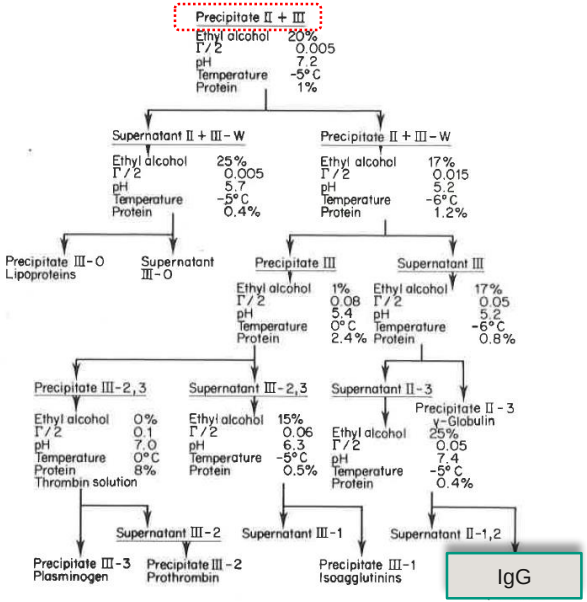

Fig. 7. Method 9 (Oncley *et al.*, 1949).

From: Methods of Plasma Fractionation, John M. Curling, Academic Press 1980

Downside of Cohn's initial process:

- Lenghty and labor intensive process
- Requires large volumes of EtOH
- Low yielding process (albumin 60%, IgG 55%)
- Only suitable for intramuscular injection due to process induced aggregates

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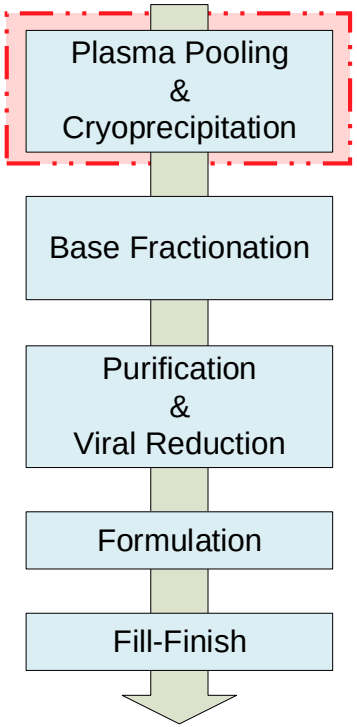
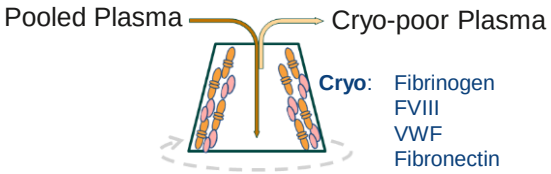
IgG Manufacturing: a Typical Process Scheme



CSL Behring Plasma Pooling

Pool size: >1000 donors



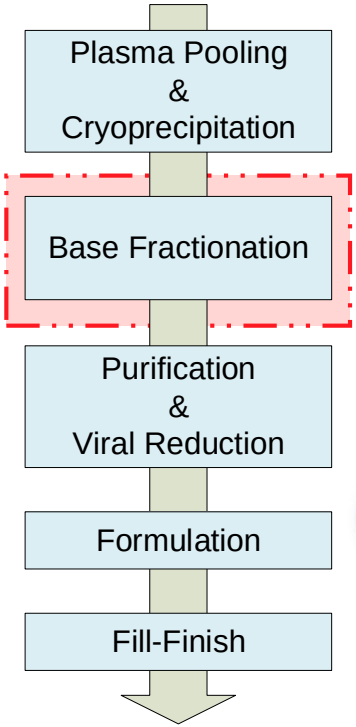
Cryo-Centrifuge

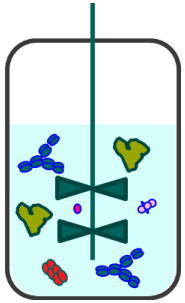
CSL Behring Cryo-Centrifuges

Temperature sensitive step:

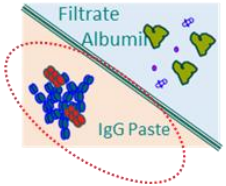
- Thawing of plasma: yield and quality of cryo-precipitate
- Prevent cryo-precipitate dissolution, i.e. keep at 1-6°C
- Impact on product quality (e.g. FVIII)

IgG Manufacturing: a Typical Process Scheme





Cryo-poor plasma
Buffer
EtOH



Harvest of crude IgG paste

CSL Behring Filterpress

CSL Behring Fractionation Tanks

<u>Base Fractionation</u>:

- Majority of fractionators: EtOH fractionation to obtain a crude IgG fraction (paste)
- Fractionator propriatary process conditions
- Harvest of crude IgG paste: filtration or centrifugation

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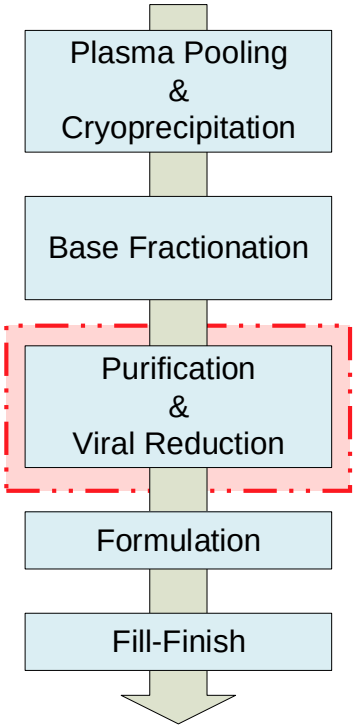
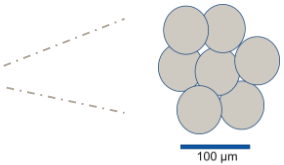
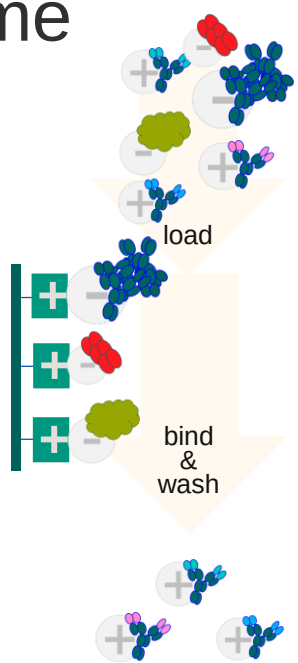
IgG Manufacturing: a Typical Process Scheme



CSL Behring Chromatography Column



Chromatography Resin



Principle of Anion Exchange Chromatography

Purification: proprietary steps

- Removal of residual impurities:
  - Precipitation: PEG or OA
  - Chromatography (final polishing)

⇨ Substantially improve adverse event profile

⇨ High-yielding process

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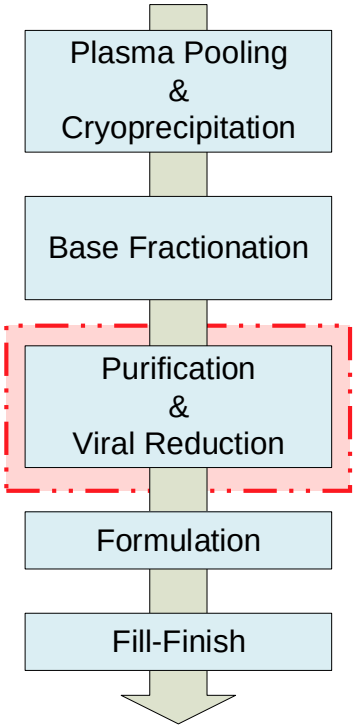
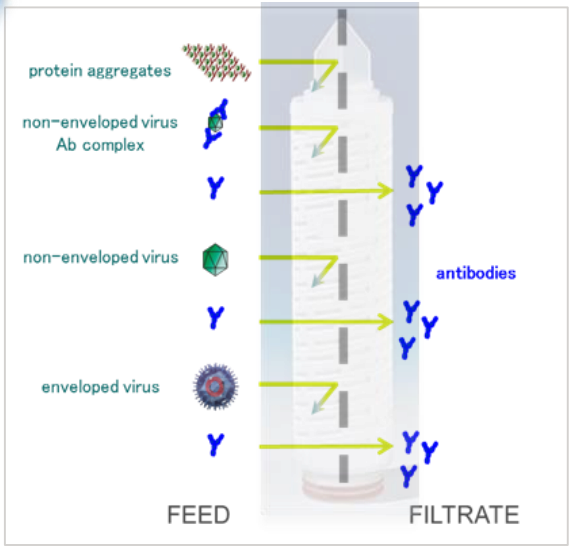
IgG Manufacturing: a Typical Process Scheme



CSL Behring Virus Filtration

Viral Reduction:

- Robust and dedicated process steps
- Virus reduction methods:
  - Inactivation: chemical/thermal treatments
  - Removal: partitioning/virus filtration
- At least 2 different steps with ≥ 99.99% reduction per step
- Proven effectiveness in down scale studies



Principle of Virus Filtration

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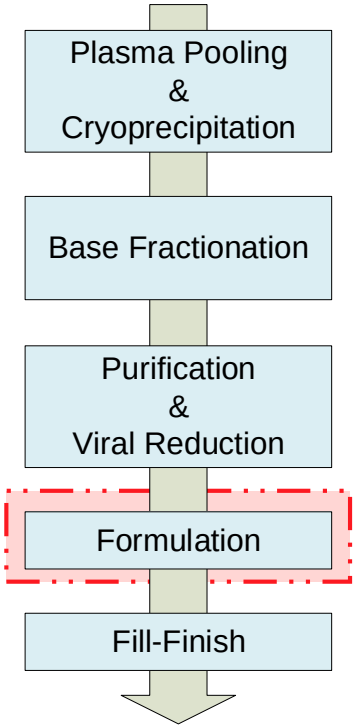
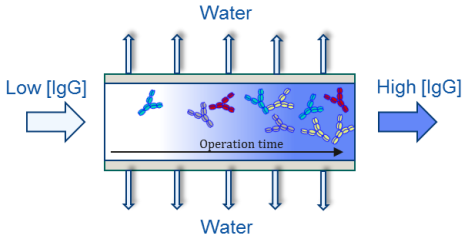
IgG Manufacturing: a Typical Process Scheme





Ultrafiltration Principle


CSL Behring Bulk Formulation

Bulk Formulation:

- IgG formulations: lyophilized powders or liquid solutions (IVIG: 5% or 10%; SCIG: 20%)

  ⇨ adjustment of protein concentration
  ⇨ pH and salt adjustment
  ⇨ addition of stabilizers: sugars/amino acids
  - stability
  - tolerability

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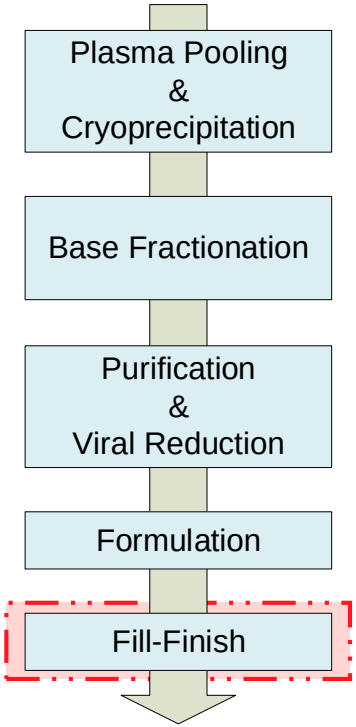
IgG Manufacturing: a Typical Process Scheme



CSL Behring Filling

CSL Behring Crimp Capping

CSL Behring Visual Inspection

CSL Behring Manual Packaging

Fill-Finish:

- Aseptic filling, stoppering & crimp capping
- Visual inspection
- Labeling & packaging
- QA release
- Shipping

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IgG Manufacturing: Quality Considerations

- Manufacturer's commitment:
  - Consistently produce and distribute products that are safe and efficacious
  - ⇨ Implement and use a Quality Management System that complies with the GMP regulations

Good
Manufacturing
Practices

e.g. FDA-cGMP Regulations

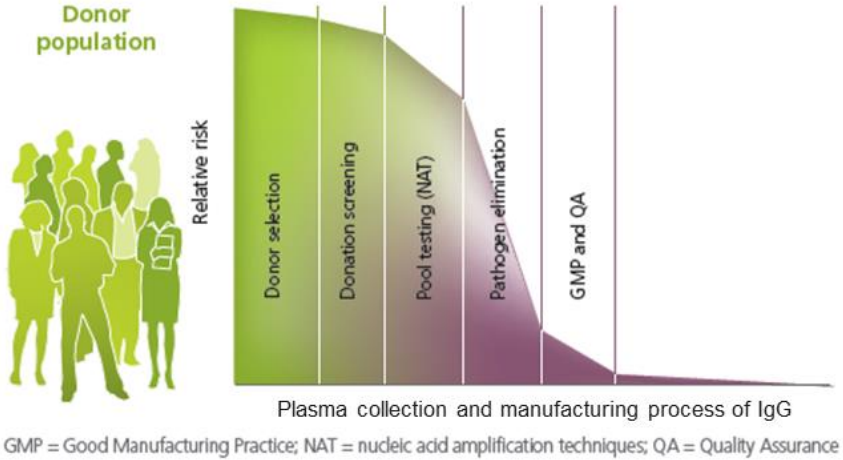
e.g. *EU-GMP Guide*

- GMP
  - Sets principles and guidelines that must be adhered to when manufacturing and importing medicinal products for clinical use.
  - Covers all aspects of production: plasma collection to product distribution.
  - Define minimum requirements.
  - Is enforced by the relevant Health Authorities.

IgG Manufacturing: Safety Considerations

The virus safety is based on:

- Careful selection of donors
- Screening of donations
- Testing of plasma pools
- Elimination or inactivation of pathogens potentially present in the starting material
- Strict adherence to current Good Manufacturing Practice and Quality Assurance measures
  - ⇨ IgG products reach highest levels on virus safety



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Key Characteristics of IgG Products

- Impact of plasma source, processing and product formulation on IgG product characteristics:

	Clinical Efficacy	Pathogen Safety	Tolerability	Stability/Shelf-life	Dosage & Administration
Plasma source	✓	✓	×	×	×
Processing	✓	✓	✓	✓	✓
Formulation	✓	×	✓	✓	✓

impact ✓
no impact ×

- Products conform to monographs on immunoglobulin products (e.g. Ph. Eu.)
- Product characteristics are conveyed in appropriate product labels (e.g. SmPC)
- Products have **comparable efficacies** in the approved indications
- Products are **different** with respect to **stability/shelf-life, dosage & administration** and **tolerability** (IgG products are generally **well tolerated**!)

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Thank You

Dr. M.A. Imboden

Breakthrough Technologies

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