



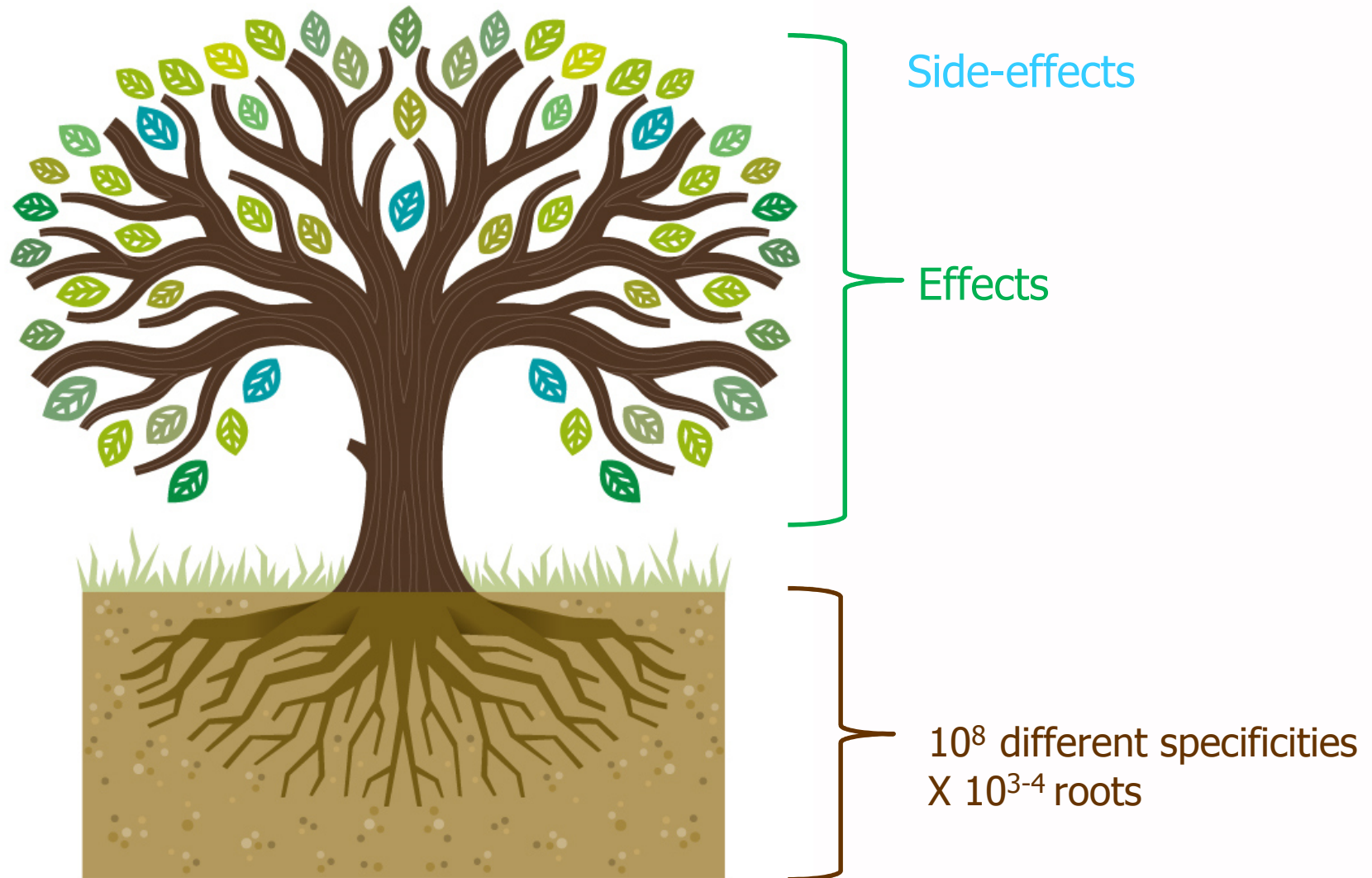
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# Quality and Clinical Safety of Immunoglobulin Therapies (Regulator's Perspective)

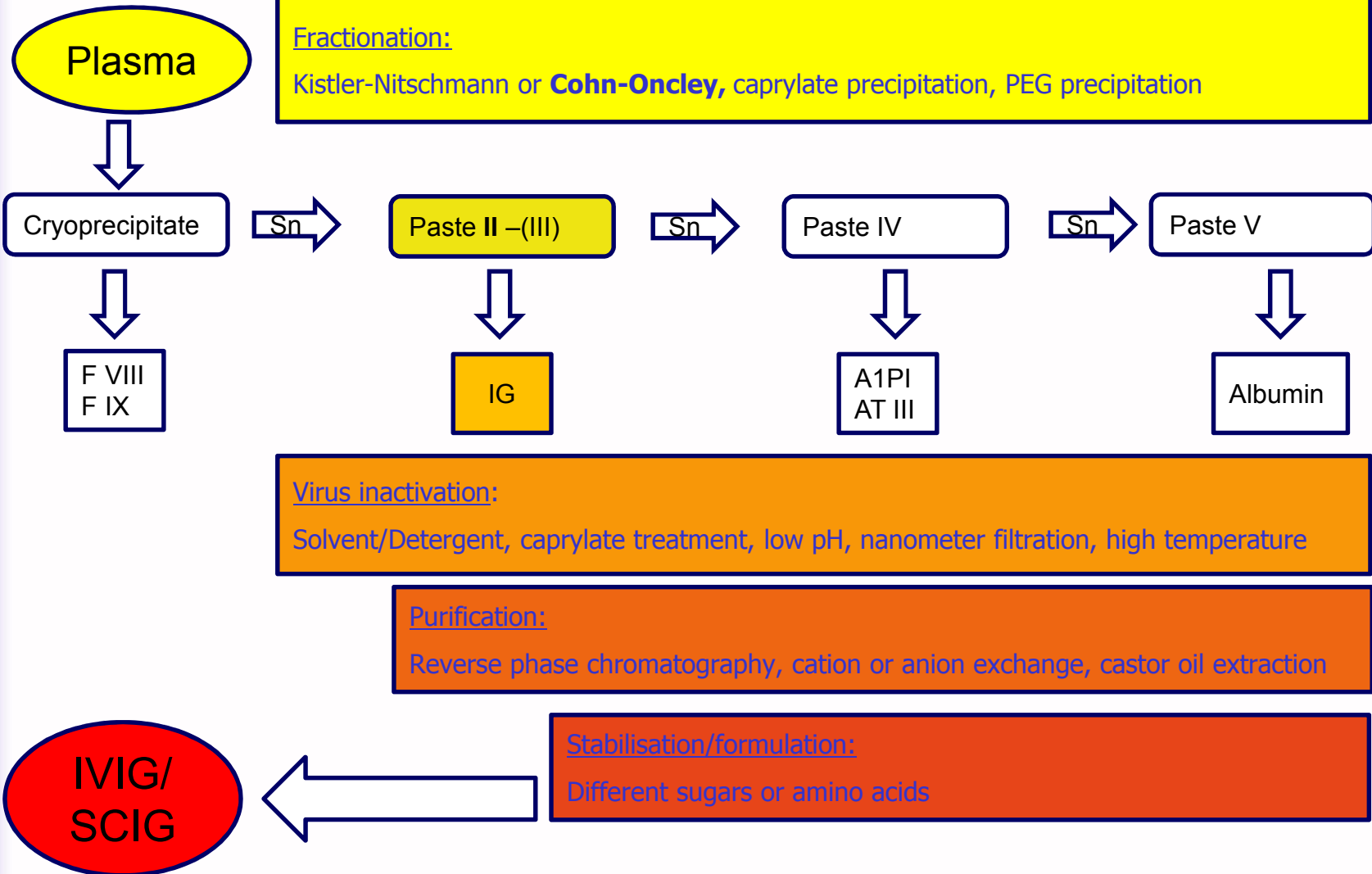
## DISCLAIMER

*Any opinions/recommendations presented  
here are my own and do not necessarily  
reflect those of any official body*





# Manufacturing



Sn = supernatant  
A1PI= Alpha-1 proteinase inhibitor (Prolastin-C)



# Guidance for Quality



Biological  
reference standards



ICH GLs: viral safety, impurities,  
comparability

COUNCIL OF EUROPE



CONSEIL DE L'EUROPE



Monographs:

- 0918 for IVIG
- 2788 for SCIG
- 0338 for IMIG

IG batch testing in OMCL



European Union

2002/98/EC ("Blood Directive"):  
standards of quality and safety for the collection,  
testing, processing, storage and distribution of  
blood + blood products



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

- GL on plasma derived medical  
products EMA/CHMP/BWP/706271/2010



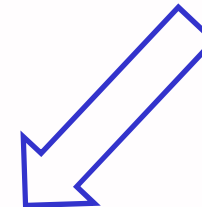
# Guidance for Clinic

Pre-authorisation:  
**IVIG GL**  
(EMA/CHMP/BPWP/94033/2007 rev.2)  
**Ongoing revision**

**SCIg/IMIg GL**  
(CHMP/BPWP/410415/2011 rev. 1)

Post-marketing:  
Pharmacovigilance Risk Assessment Committee (PRAC)

PSUR single assessment	Signals Eudra- Vigilance	PASS	Art. 31 + 20 urgent safety procedures
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**Product specific Summary of  
Product Characteristics (SPC)  
+  
CoreSPC (IVIG + SCIG)**

(CHMP/BPWP/94038/2007 rev. 4)  
(EMA/CHMP/BPWP/143744/2011 rev. 1 )



# Clinical Safety



## Pre-authorisation:

- Adverse events (AEs) :
  - AEs and serious adverse events (SAEs) from all subjects throughout all studies
  - Short term tolerance
  - Infusion rates
  - Children and adolescents vs. adults
  
- Separate safety evaluation of excipients
  
- Comprehensive risk management plan (RMP) including post-marketing safety data collection in children
  
- Adverse drug reactions (ADRs= related AEs) are listed in the SPC/PIL



# Causes of Side-effects



- Product related
  - Pathogens
  - **Impurities**
  - **Excipients**
  
- Administration related
  - 1st administration or Ig switch
  - Infusion rate
  - Administration route
  
- Patient related
  - Underlying disease
  - Co-morbidities
  - Concomitant medication
  - Age, gender, genetics

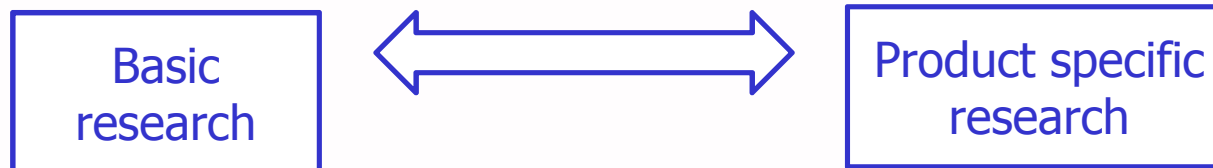




# Impurities

- Contaminants: (viruses, bioburden)
  - donor screening, plasma pool testing, validated virus removal
- Process related impurities: (caprylic acid, S/D related substances, ethanol,....)
  - are removed by the end of the process
- Product related impurities:
  - can be only controlled if known
    - IgG antibodies: Anti A / Anti B haemagglutinins, anti D
    - Polymers
    - IgA content
    - FXIa or other pro-coagulant proteins

## What is the impact of impurities not detected?







## Types of Side-effects

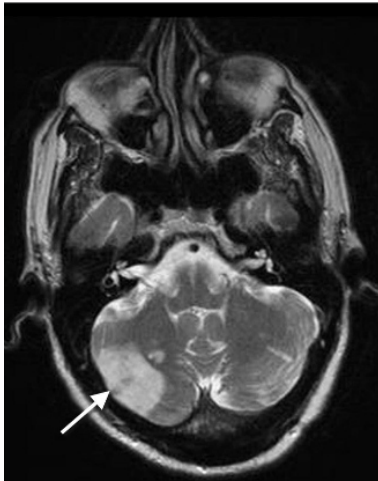
- Thromboembolic events (TEE)
- Haemolysis
- Hypersensitivity, anaphylactoid reactions
- Aseptic meningitis syndrome (AMS)

Can we map  to  ?

- Side-effects/warnings for excipients



# Thromboembolic events (TEE)



	Period	TEE / 1000 kg Ig
IVIG Octagam	8/2010	9
	2008	1.8
	2006	0.3
3 other IVIGs	2006 - 2011	< 1

8/2010

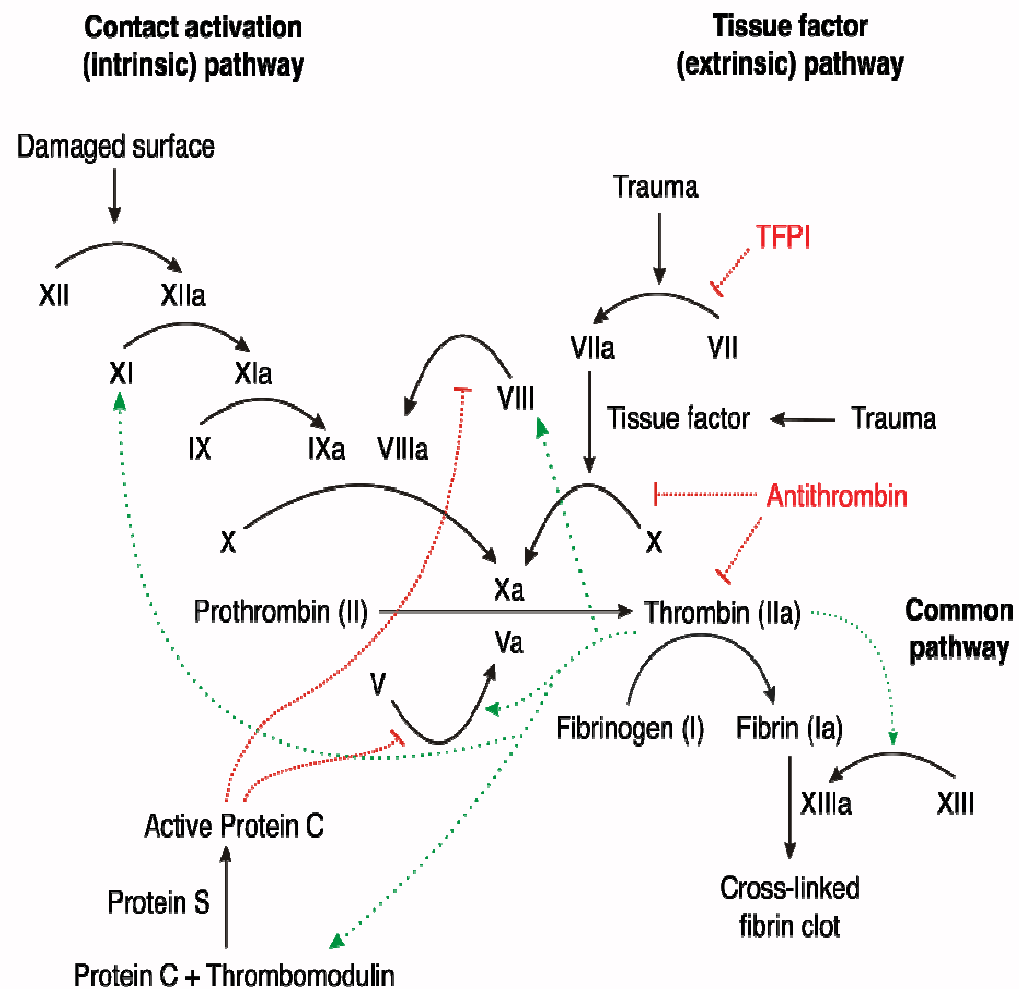
1. Cerebellar infarction
2. Multiple cerebral infarctions, splenic and hepatic infarctions
3. Multiple cerebral infarctions
4. Multiple emboli

Withdrawal of all  
batches and  
Marketing  
Authorisation

1000 kg = 33.333 single administration IVIG



# Coagulation cascade

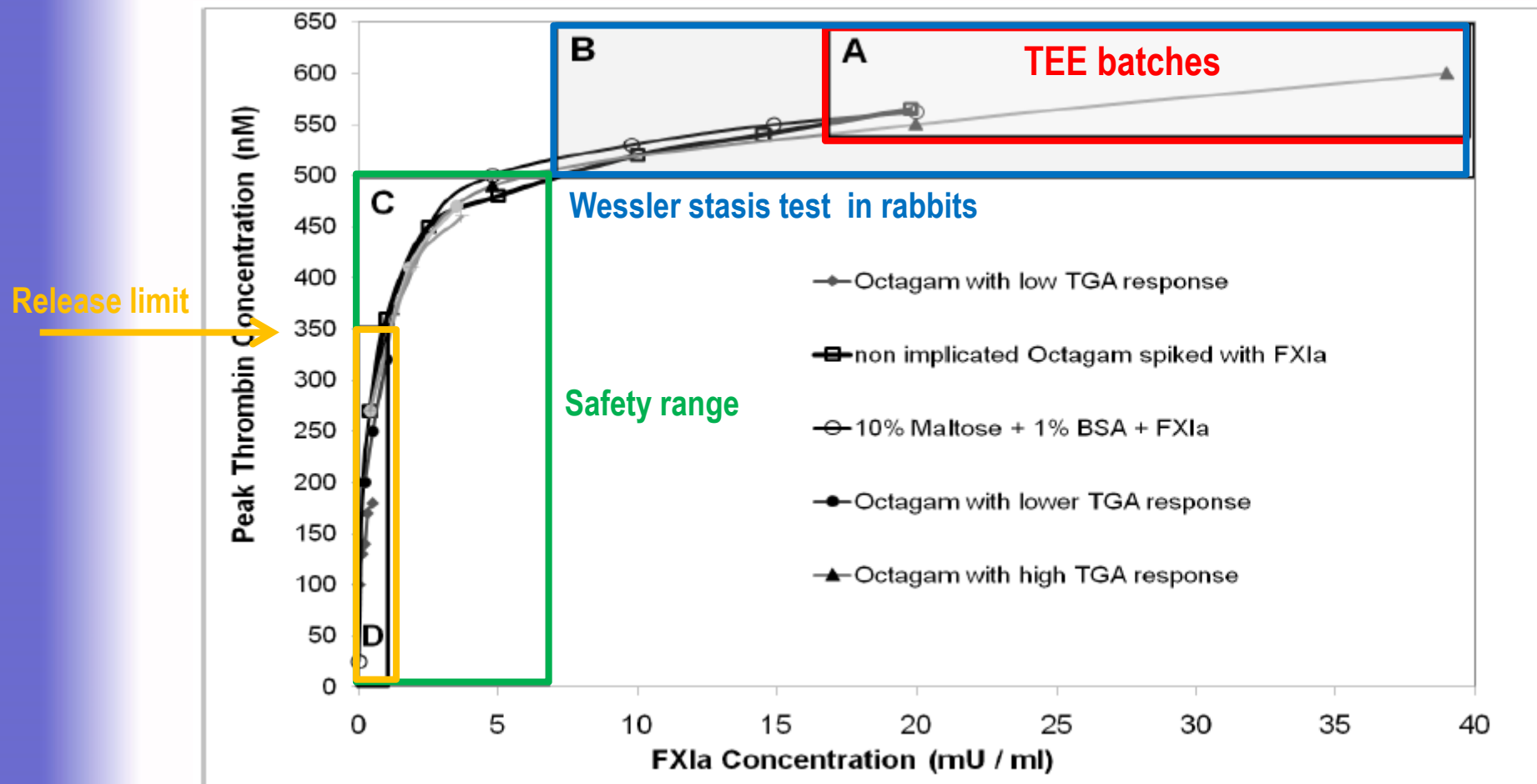




# TEE root



## Unexpected presence of FXIa in the final product





## TEE lessons learned

- **Change of Eur. Pharm. Monographs for IVIGs and SCIGs**
  - *Product does not exhibit thrombogenic activity*
- **All** manufacturers submitted variations that demonstrated compliance with this monograph
- Development of FXIa reference preparation (NIBCS) which is now WHO Reference Reagent
- **Strengthened warning statement in IVIG and SCIG core SPC**  
Patient with risk factors → minimum rate of infusion and dose practicable



# Steps reducing pro-coagulant activity



Plasma

Fractionation:

Kistler-Nitschmann or Cohn-Oncley, **caprylate precipitation, PEG precipitation**

**Adsorption of FXI**

Virus inactivation:

Solvent/Detergent, **caprylate treatment, low pH**, nanometer filtration, **high temperature**

Purification:

Reverse phase chromatography, **cation exchange** or anion exchange, castor oil extraction

IVIG/  
SCIG


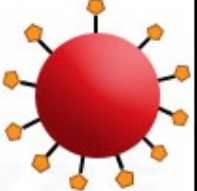
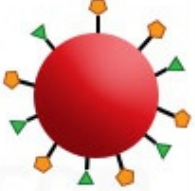









Stabilisation/formulation:

Different sugars or amino acids



# Blood and antibodies

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-B and Anti-A
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

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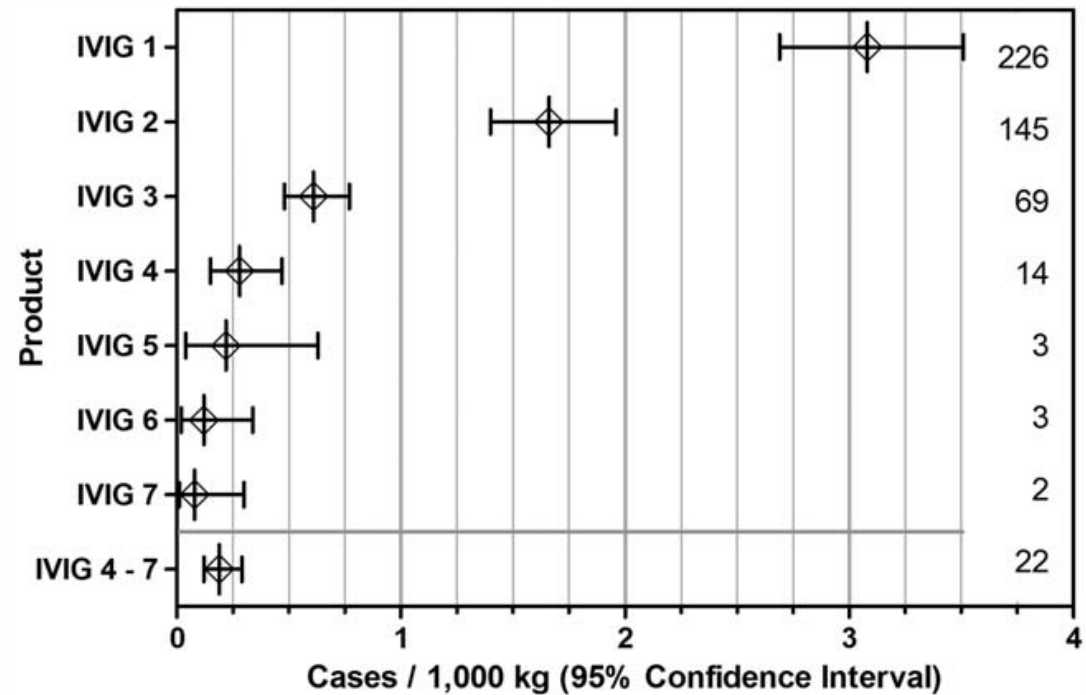
# Haemolysis



## Hemolytic anemia

- Haemoglobin  $\downarrow > 1$  g/dL  
(severe  $> 2$  g/dL)
- $\uparrow$  bilirubin
- $\uparrow$  reticulocyte count

EudraVigilance database 2008 – 2013; 7 IVIGs\*



- 466 cases: 93 mild to moderate, 373 severe (thereof 80% blood group A)

\*Bellac et al Transfusion July 2015  
<http://www.ncbi.nlm.nih.gov/pubmed/26174892>





# Haemolysis roots



- **Antibodies against A and B antigens co-purified** with other Igs
  - Blood group distribution of donors and their anti-A and anti-B titers
  - European Pharmacopeia: anti A/B titers of  $\leq 1:64$  and  $<$  limit reference preparation
  - High cumulative IVIG doses ( $> 2$  g/kg) with anti-A/anti-B titers  $\geq 1: 32$
- **Is the current limit in the Ph. Eur. still adequate ?**
- This limit was defined at a time when much lower cumulative IgG doses were administered than are currently used in immunomodulatory indications



# Haemolysis lessons learned



## ➤ **Product**

- Use of low titre plasma
- Reduction of anti-A and anti-B haemagglutinins through immunoaffinity chromatography (introduced in two products)

## ➤ **Strengthened warning statement in IVIG coreSPC**



- Patients with non-0 blood group
- Underlying inflammatory state
- High cumulative doses



# Hypersensitivity



HS describes a pathological immune response to repeated exposure to an antigen

<b>Product-related</b> 	<b>Patient-related</b> 
Aggregated IgG activates...	complement system
IgA content <small>(max: 4800µg/ml, min: 25 µg/ml)</small>	IgA deficient patient + IgG antibodies to IgA <small>(contraindication in the coreSPC)</small>
Naturally occurring anti-neutrophil cytoplasmic antibodies (ANCA)	dependent on autoimmune condition of patient (neutrophil priming e.g. by TNFα)
Dimers	(+) immunomodulatory effects  (-) TNF alpha within first hours of infusion



# Aseptic meningitis syndrome (AMS)



- ASM is rare
- ASM usually begins within 2 days following Ig with headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting
- Cerebrospinal fluid (CSF) shows increase in neutrophils, ↑protein, negative bacterial cultures
- AMS occurs more frequently with high-dose (2 g/kg) Ig



## **Product-related (?)**

- activation of TNF- $\alpha$ -primed neutrophils by ANCAs in IVIG might contribute to aseptic meningitis (Jarius et al.)

**Further investigation needed**



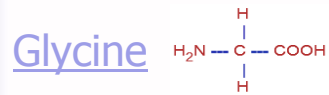
More frequent in patients with a history of migraine



# Excipients

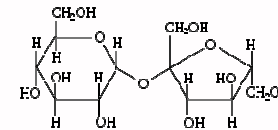


**Excipients are important for structural integrity + stability of IG**



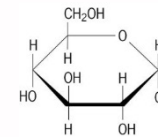
## Sucrose

Reports of renal dysfunction and acute renal failure

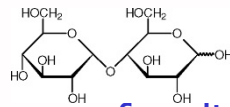


## Glucose

Should be taken into account in the case of diabetes

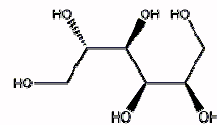


## Maltose



Interference of maltose in blood glucose assays → falsely elevated glucose readings → inappropriate administration of insulin, → life-threatening hypoglycaemia and death. True hypoglycaemia may go untreated, if hypoglycaemic state is masked by falsely elevated glucose readings

## Fructose/sorbitol



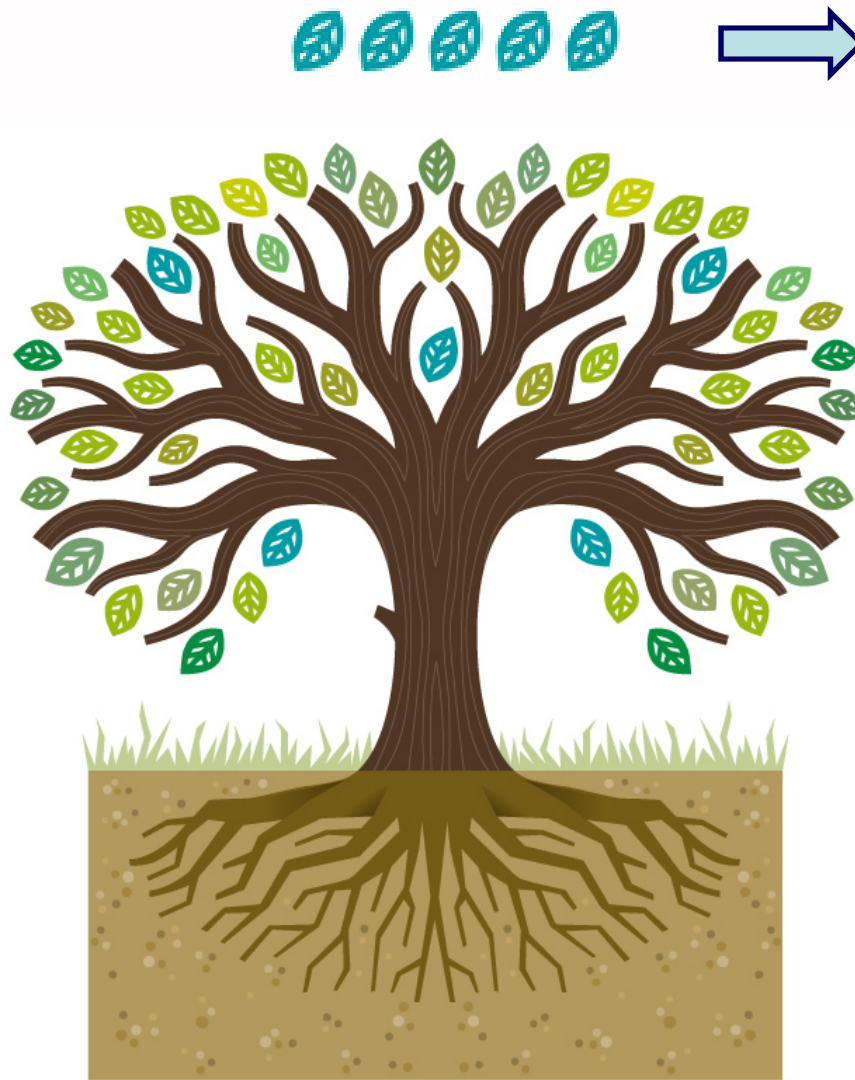
Patients with hereditary fructose intolerance (HFI) should not take this medicine. In babies and young children HFI may not yet be diagnosed and may be fatal



# Safety Summary



- Thorough research by industry into any planned production changes
- Company  $\leftrightarrow$  agency interaction
- Agency  $\leftrightarrow$  agency interaction
  
- Report cases to EudraVigilance databank  
<https://eudravigilance.ema.europa.eu/human/index.asp>
- Report side-effects directly to national authority
  
- Continuous updating of guidance on Quality and Clinic/ EU Monographs



Reporting side-effects



Basic research



Improvement of analytical methods



Biochemical root cause analysis



Improvement of the manufacturing process









# Monograph requirements



Tests	IVIG
Appearance *	Clear or slightly opalescent and colorless or pale yellow
pH	4.0 – 7.4
Osmolality	Min 240 mosmol/kg
Protein content *	≥ 30g/l
Protein composition *	≥ 95% immunoglobulin G
Molecular size distribution *	Mono/Dimer: ≥90% Polymer: ≤3%
Antibody to HBsAg	≥ 0,5 IU/g IgG
Anti-Complementary Activity	≤ 1 CH <sub>50</sub> /mg IgG (Hemolytic complement)
Pre-Kallikrein Activity (PKA)	≤ 35 IU/ml
Anti-A/B haemagglutinins *	≤ 1/64
Anti D antibodies *	≤ Biological reference preparation (BRP)
Pyrogen or	0,5g/Kg rabbit
Bacterial endotoxin	50g/l: 0,5 IU/ml or 100g/l: 1.0 IU/ml
Sterility	sterile
IgA	Content ≤ Label