

Pathogen Safety and BSE / variant CJD

Thomas R. Kreil, Global Pathogen Safety

Parenteral Drug Industry
Plasma Protein Industry Summit
September 7, 2017; Beijing

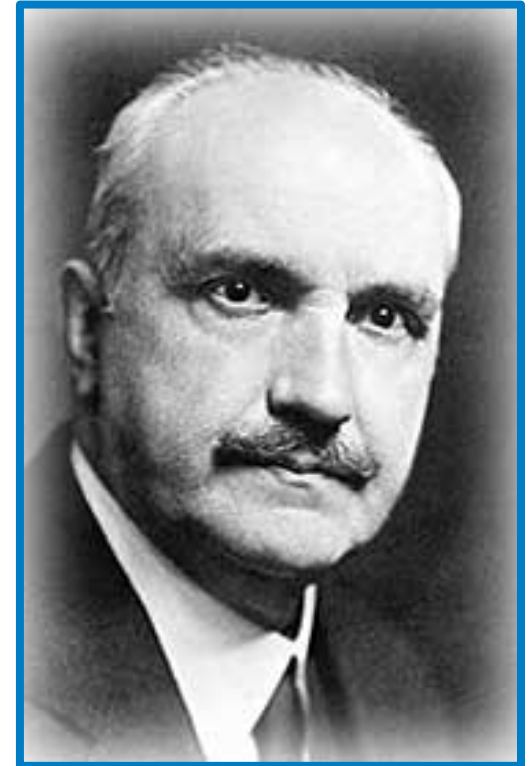


Pathogen Safety

Those who cannot remember the past are condemned to repeat it.

Jorge Agustín Nicolás Ruiz de Santayana, *The Life of Reason*

- BIO-technology: Great Successes, and Exposure
- Learnings, Concepts for Mitigation
 - Continuing Challenges → Verification
- Prion Diseases, and Safety Margins
- Predicting the Future !?



Medical Biotechnology → Plasma Derivatives

- Human Serum Albumin, HSA
 - Development driven by military needs during WW II
- Gamma-globulins
 - Initially immune replacement; increasingly immune modulation
- Hemophilia treatment

- Risk
Potential exposure,
to infectious disease agents from thousands of donors.

Plasma Derivatives – Learnings

Guideline on plasma-derived medicinal products

- Introduction
 - ... **transmission of viruses is of particular concern.**
- Measures taken to prevent infection ...
 - ... **selection** of donors ...
 - ... screening of individual donations ... (= **testing**)
 - ... inactivation or removal (= **reduction**) of viruses

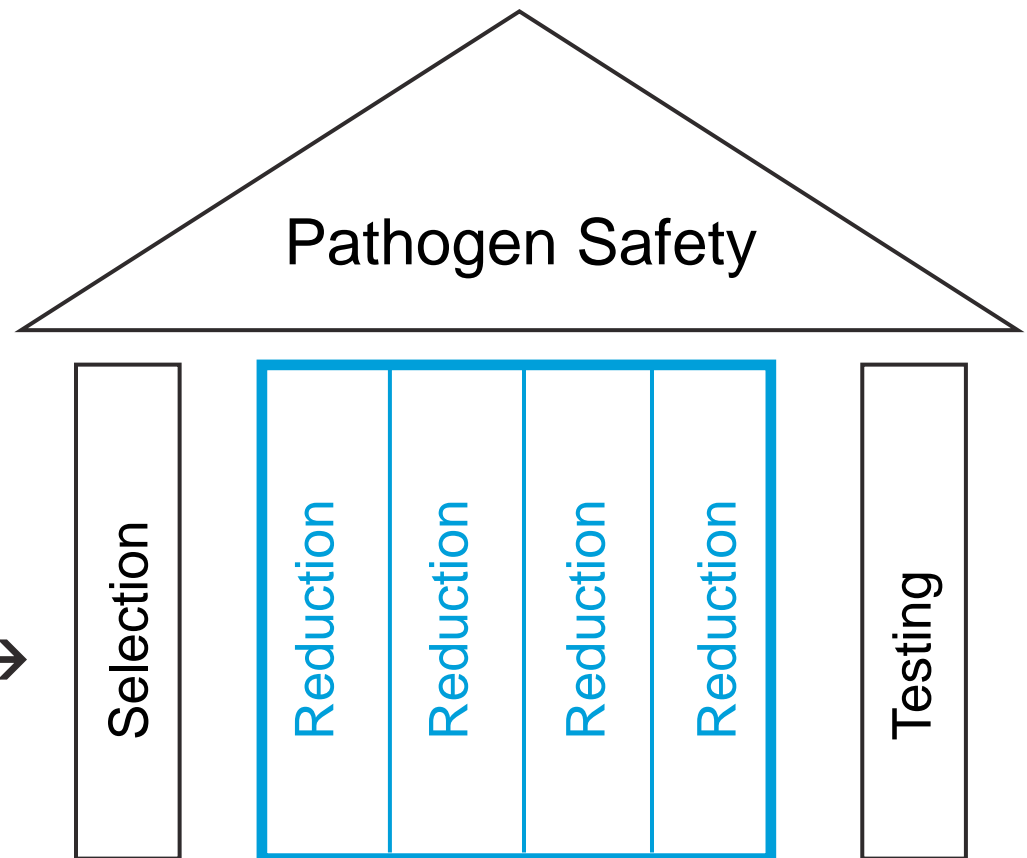
EMA/CHMP/BWP/706271/2010

„Safety Tripod“

- **Selection, Testing:**
limited by what is known

- **Reduction:**
more generic,
robustness can be tested

- **Quantitatively: Different** →



Safety Tripod, Quantitatively → WNV in the US

- **Selection**¹
 - 20% risk reduction, i.e. **0.1 log₁₀**
→ 81% of viremic donors are asymptomatic
- **Testing**¹
 - 93% risk reduction, i.e. **~1 log₁₀**
→ MP NAT identifies only
1/2 to 2/3 of viremic donations
- **Reduction**²
 - Several **orders of magnitude**,
at each dedicated step ...

1) LR Petersen, JS Epstein; N Engl J Med [2005] 353:516

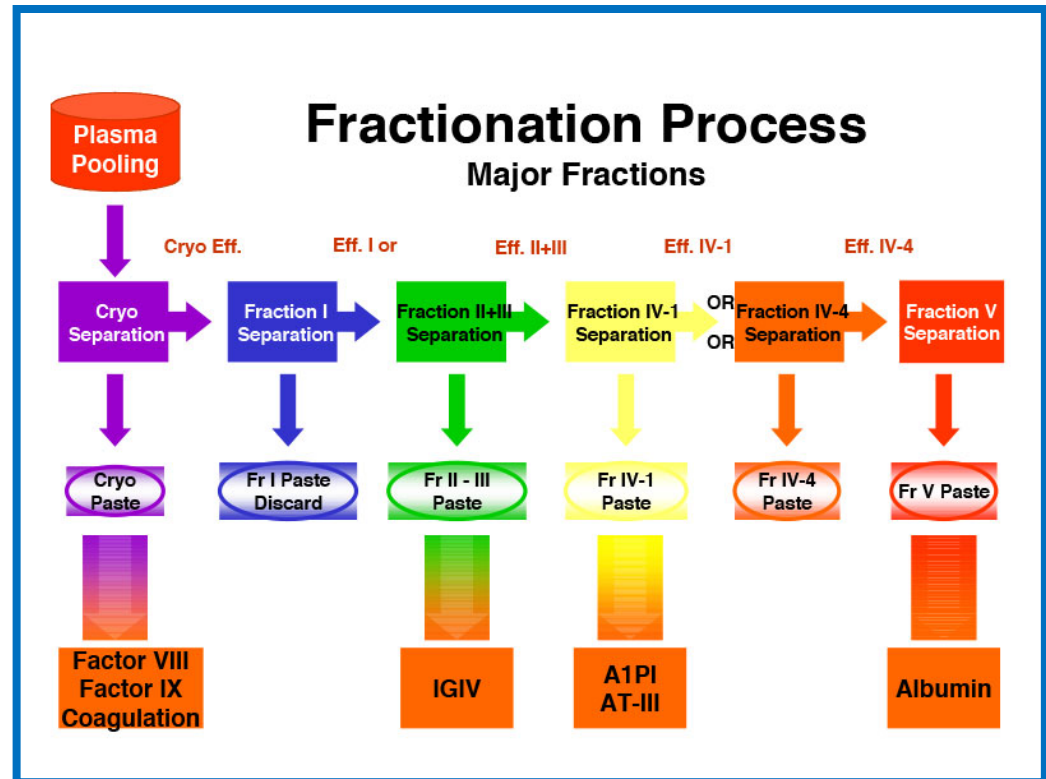
2) TR Kreil et al.; Transfusion [2003]43:1023



Reduction → Manufacturing Process Improvements

- **Fractionation** ¹

→ purification process, i.e. removal of (any) impurities from product-containing fractions



1) PPTA Pathogen Safety Steering Committee
Dichtelmüller HO et al, Transfusion [2011] 51(7):1412-30

Reduction → Manufacturing Process Improvements

- **Heat Treatments**
- **Solvent Detergent** ¹
 - universally effective againsts lipid-enveloped viruses
- **Nanofiltration** ²
 - generically effective againsts all viruses, based on size

→ **dedicated & robust !**

1) PPTA Pathogen Safety Steering Committee
Dichtelmüller HO et al, Transfusion [2009] 49(9):1931-43

2) PPTA Pathogen Safety Steering Committee
Manuscript under construction

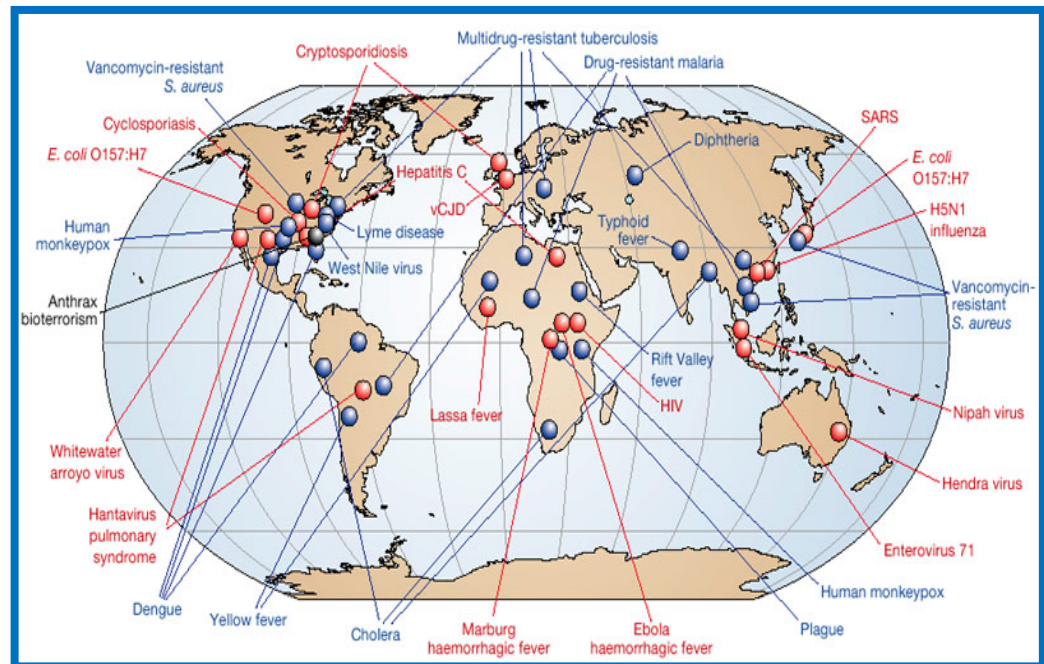
Reduction is Critical – of WHAT ?

Emerging Agents of potential relevance for blood product safety,

→ *Virus de jour*

- West Nile Virus (WNV)
- Influenza, “bird flu” (H5N1)
- Chikungunya virus (CHIKV)
- Hepatitis E virus (HEV)
- Zika virus (ZIKV)

Morens D.M. et al., Nature [2004] 430: 242-9



Emerging Agents

Verification

of manufacturing process
reduction capacity

→ published & discussed
with stakeholders

- WNV
- H5N1
- CHIKV
- HEV
- ZIKV

Transfusion 2003 / 2007 / 2012 / 2016 / 2017

**West Nile virus and the safety of plasma derivatives:
verification of high safety margins, and the validity of
predictions based on model virus data**

Thomas R. Kreil, Andreas Berting, Otfried Kistner, and Johanna Kindermann

H5N1 influenza virus and the safety of plasma products

T.R. Kreil, U. Unger, S.M. Orth, G. Petutschnig, O. Kistner, G. Poelsler, and A. Berting

Chikungunya virus and the safety of plasma products

Sandra M. Leydold, Maria R. Farcet,* Johanna Kindermann, Jens Modrof, Gerhard Pölsler,
Andreas Berting, M. Keith Howard, P. Noel Barrett, and Thomas R. Kreil*

**Hepatitis E virus and the safety of plasma products:
investigations into the reduction capacity of manufacturing
processes**

*Maria R. Farcet, Cornelia Lackner, Gerhard Antoine, Philip O. Rabel, Andreas Wieser,
Andreas Flicker, Ulrike Unger, Jens Modrof, and Thomas R. Kreil*

**Zika virus is not thermostable: very effective virus
inactivation during heat treatment (pasteurization)
of human serum albumin**

Maria R. Farcet and Thomas R. Kreil

Emerging Agents – Prion Diseases

- **Bovine Spongiform Encephalopathy (BSE)**

- Fatal degeneration of the brain and spinal cord, incubation period of 2.5 to 5 years
- Caused by a misfolded protein, i.e. a prion
- 1986–1998 UK epidemic: more than 180,000 cattle infected, 4.4 million slaughtered during the eradication program

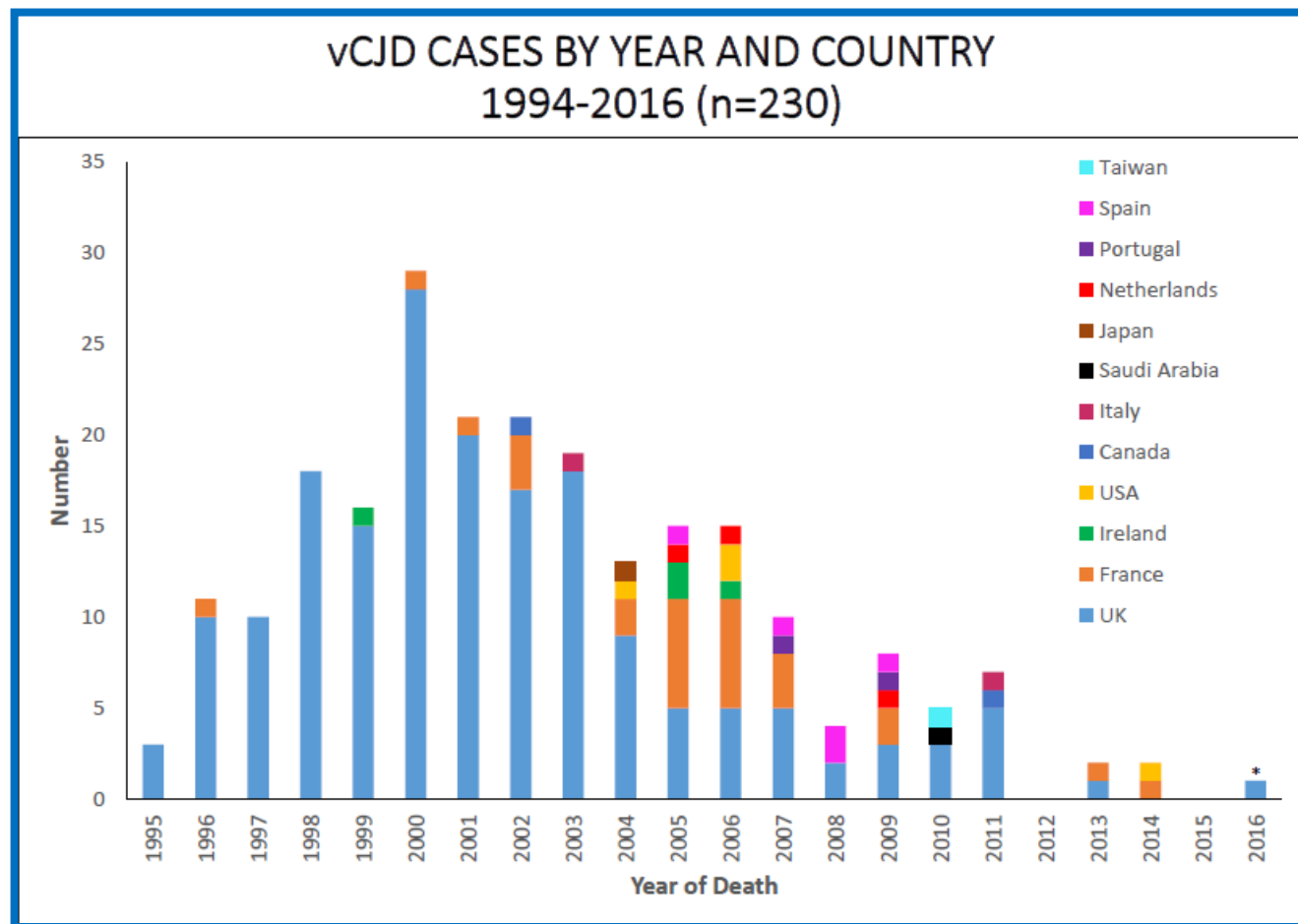
- **Variant Creutzfeldt-Jakob Disease (vCJD)**

- Fatal human neurodegenerative condition
- Consumption of BSE food strongly linked to vCJD in humans
- After containment of BSE in cattle, the number of vCJD cases in the UK has declined since 2000

vCJD – a VERY Rare Disease

- Courtesy: Prof. Robert Will

- Practically limited to
 - UK
 - France
 - Ireland



vCJD – Donor Selection (Testing: NOT Available)

- *The United Kingdom, Ireland, and France had the greatest vCJD risk, contributing approximately 95% of the total risk.*
- *Deferring US donors who spent extended periods of time in these three countries, combined with currently voluntary LR (leucoreduction) ... would reduce the vCJD risk ... similar to that achieved under the current policy.*

→ Summary

Deferral for UK, France, Ireland residency would result in **acceptable blood / plasma donors**

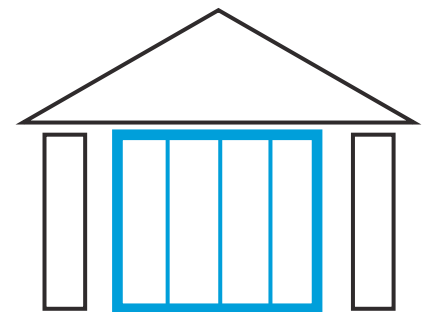
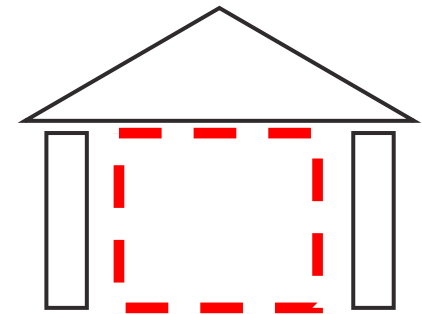
Yang H, Huang Y, Gregori L, Asher DM, Bui T, Forshee RA, Anderson SA (→ US FDA).
Transfusion. [2017] 57(4):924-932

vCJD & Blood / Plasma Product Safety

Blood products

Secondary cases of transfusion transmission

- CJD and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study ... 3 cases of vCJD ... in 67 recipients ... ;... no new cases of transfusion-associated vCJD since 2007
 - Urwin et al., Vox Sang [2016] 110(4)310



Plasma products

No confirmed transmissions

- Robust prion reduction

PPTA Pathogen Safety Steering Committee
Transfusion [2013] 53: 1894

**Prion removal capacity of plasma protein
manufacturing processes**

A data collection from PPTA member companies

*Kang Cai, Albrecht Gröner, Herbert O. Dichtelmüller, Fabrizio Fabbrizzi, Eckhard Flechsig,
Rodrigo Gajardo, Ilka von Hoegen, Juan I. Jorquera, Christoph Kempf, Thomas R. Kreil,
Douglas C. Lee, Mila Moscardini, Gerhard Pölsler, and Nathan J. Roth*

Pathogen Safety Concepts: Plasma, as well as Recombinants, and ATMPs

- **Learnings**

Ample opportunity (!)

- **Concepts**

Mature; “just” need implementation

- **Promises**

Huge (!)

→ the patients are waiting

