Pathogen Safety and BSE / variant CJD

Thomas R. Kreil, Global Pathogen Safety

Parenteral Drug Industry
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Pathogen Safety

Those who cannot remember the past are condemned to repeat it.
Jorge Augustín 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 !?
• 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.
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
 Selection, Testing: limited by what is known

 Reduction: more generic, robustness can be tested

 Quantitatively: Different →
Safety Tripod, Quantitatively → WNV in the US

• **Selection**
  - 20% risk reduction, i.e. $0.1 \log_{10}$
  → 81% of viremic donors are asymptomatic

• **Testing**
  - 93% risk reduction, i.e. $\sim 1 \log_{10}$
  → MP NAT identifies only 1/2 to 2/3 of viremic donations

• **Reduction**
  - Several *orders of magnitude*, at each dedicated step …

2) TR Kreil et al.; Transfusion [2003]43:1023
• **Fractionation** ¹

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

¹) PPTA Pathogen Safety Steering Committee
Reduction → Manufacturing Process Improvements

• Heat Treatments

• Solvent Detergent ¹
  – universally effective against lipid-enveloped viruses

• Nanofiltration ²
  – generically effective against all viruses, based on size

→ dedicated & robust !

1) PPTA Pathogen Safety Steering Committee

2) PPTA Pathogen Safety Steering Committee
   Manuscript under construction
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)

Emerging Agents

Verification
of manufacturing process reduction capacity
→ published & discussed with stakeholders

- WNV
- H5N1
- CHIKV
- HEV
- ZIKV

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 CASES BY YEAR AND COUNTRY
1994-2016 (n=230)
• 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

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

- **Learnings**
  Ample opportunity (!)

- **Concepts**
  Mature; “just” need implementation

- **Promises**
  Huge (!)

→ the patients are waiting