News from the microbiology bench…

The Human Skin Double-Stranded DNA Virome: Topographical and Temporal Diversity, Genetic Enrichment, and Dynamic Associations with the Host Microbiome

Then…

Source: CDC/ Barbara Jenkins, NIOSH

and Now…

Source: Baxter Healthcare
Adventitious Agents in Pharmaceutical Manufacturing

- How do Pharmaceutical Manufacturers provide strategic risk mitigation and assessment of adventitious agents in the manufacture of pharmaceuticals and medical devices derived from and/or manufactured with animal components/derivatives?

- What are Adventitious Agents?
  - And specifically, what are TSEs?

- Where could they enter pharmaceutical manufacturing?

- Why does Pharma need experts in Adventitious Agents?

- Is there regulatory guidance?

- ... And What Do These have in Common?
What are Adventitious Agents?

- Adventitious agents are microorganisms that have been unintentionally introduced into the manufacturing process.

- Include bacteria, fungi, mold, yeast, mycoplasmas, rickettsia, protozoa, parasites, TSE agents (prions), and viruses.

A little more on prions…. 

Prion diseases or transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that affect both humans and animals.

Examples include vCJD, BSE, Scrapie, Kuru, CWD, and inherited FFI, GSS.

The causative agents of TSEs are believed to be prions. The term "prions" refers to abnormal, pathogenic agents that are transmissible and are able to induce abnormal folding of specific normal cellular proteins called prion proteins that are found most abundantly in the brain.

...and why do we care so much about them?

- BSE in 1986 and vCJD in 1996
- Transmission via medical devices (EEG electrodes), blood transfusions, blood products, animal-derived medical products, contaminated animal feed
- No diagnostic tests
- Very difficult to inactivate

**vCJD deaths: UK and non-UK**

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Source: Diack *et. al.*; Prion [2014] 8; 286–295

Caption
This magnified image of the small intestine shows specialized structures called Peyer’s patches -- which are part of the body’s immune system. Researchers have shown how deadly proteins called prions -- which cause variant CJD in people and BSE in cows -- invade the body through Peyer’s patches before infecting the brain.

Credit
Prof Neil Mabbott & Dr David Donaldson, The Roslin Institute, University of Edinburgh

Usage Restrictions
Image may only be used with appropriate caption and credit.
BSE Cases Reported to the OIE in 2013, 2014 and 2015.  

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1. Data as of 30 June 2015.  
2. Data as of 18 February 2015.  
3. Data as of 30 June 2015.  
4. Data as of 26 June 2015.  
5. Data as of 30 June 2015.  
8. Includes 1 atypical BSE case (H-type). Data as of 13 October 2015.
Raw Materials…to People…to Process…to Finished Product

- **Obviously of Animal Origin**
  - Blood/plasma – serum, albumin
  - Proteins
  - Wool
  - Tendons, Tissue
  - Charcoal
  - Amino Acids
- **Actives/Additives**
  - gelatin, collagen, elastin

- **Not Obviously of Animal Origin**
  - Manufacturing Aids – tallow derivatives (glycerol, fatty acids)
  - Detergents – Tween-80
  - Tubing
  - Product Contact (storage bags)
  - Device Components with “fluid path”

Any Materials that Enter the Manufacturing Stream Should be Evaluated
Inactivation of Adventitious Agents

**Little reduction:**
- Autoclaving at 121°C, UV, proteolytic enzymes, aldehydes, gamma irradiation, alcohols, dry heat, chlorine dioxide, iodine, microwave

**Significant reduction:**
- 1 or 2 M NaOH soak, hot 1M HCl, dry heat >200°C, Autoclave 18 min at 134-138°C, chaotropic agents (guanidinium thiocyanate, sodium dichloroisocyanurate (16,500 ppm free chlorine)

**No detectable infectivity:**
- Sodium hypochloride (16,500 ppm), autoclaving 121°C after 1M NaOH soak or autoclaving in 1M NaOH, boiling in 1M NaOH

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Adapted from: Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance, Author: Gerald E. McDonnell

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A Critical role for Sterility Assurance in Product and Process Development
Why do Pharmaceutical, Medical Device and Biologics Manufacturers need Subject Matter Experts in Adventitious Agents?

Ensuring Patient Safety for All Products

Regulatory Requirements:
- EMA/410/01 rev.3 “Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”
- ISO 22442-1-4:2015 “Medical Devices utilizing animal tissues and their derivatives”

Internal Procedures and Processes:
- Corporate SOPs
- Medical Information for Customers
- Product and Process Development
- Risk Evaluation and Review
Are There Other Adventitious Agents of Concern?

Zika Virus as One Example of an Emerging Infectious Disease

**US States Statistics as of 20Apr2016:**

- Travel-associated Zika virus disease cases reported: 358
- Locally acquired vector-borne cases reported: 0
- Total: 358
  - Pregnant: 31
  - Sexually transmitted: 7
  - Guillain-Barré syndrome: 1

Estimated range of *Aedes aegypti* (left) and *Aedes albopictus* (right) in the United States, 2016

http://www.cdc.gov/chikungunya/resources/vector-control.html
The Reason Why...