



Human Vaccines and TSE Agents: a Case Study in Risk Evaluation and Risk Management

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Phase I-IV

Bioanalytical

Bioequivalence

Consulting

Staffing

Background: BSE and Biologics (I)

- ▶ FDA concern for the contamination of biological products by the agent of bovine spongiform encephalopathy
- ▶ Concern heightened by the appearance of new variant Creutzfeldt Jakob Disease (vCJD) in the UK in 1996 and its attribution to oral exposure to the infectious agent of BSE.
- ▶ FDA and CBER policy for sourcing of bovine materials; e.g.,
 - ▶ December, 1993, FDA Letter to Manufacturers
 - ▶ May, 1996, FDA Letter to Manufacturers
 - ▶ September, 1997, FDA Guidance for Industry on the Sourcing and Processing of Gelatin
 - ▶ April, 2000, CBER Letter to Manufacturers of Biological Products

Background: BSE and Biologics (II)

- ▶ “[T]hat bovine-derived materials from cattle which have resided in or originated from countries where Bovine Spongiform Encephalopathy (BSE) has been diagnosed not be used in the manufacture of FDA-regulated products intended for administration to humans. ... The list of countries where BSE is known to exist is maintained by the United States Department of Agriculture (USDA).”
 - December, 1993 Letter to Manufacturers of FDA-regulated products

- ▶ “[T]hat manufacturers ... assure that materials derived from all species of ruminant animals born, raised, or slaughtered in countries where BSE is known to exist, or countries where the USDA has been unable to assure FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans.”
 - April, 2000, CBER Letter to Manufacturers of Biological Products

Countries where BSE is known to exist: 9CFR 94.18 (a)(1)

Austria	Japan
Belgium	Lichtenstein
Czech Republic	Netherlands
Denmark	Oman
Finland	Poland
France	Portugal
Germany	Slovakia
Greece	Slovenia
Ireland (Republic of)	Spain
Israel	Switzerland
Italy	United Kingdom*

- Includes England, Scotland, Wales, Isle of Man, Northern Ireland and the Falkland Islands

Background: BSE and Biologics (III)

- ▶ In early 2000, through a product review, the Office of Vaccines learned that recommendations for sourcing of bovine-derived materials were not followed in at least one instance.
- ▶ This finding prompted the Office of Vaccines to request manufacturers to review the sources of all bovine-derived materials used in the production of their vaccines. This review identified additional vaccines that were manufactured with various bovine-derived materials that had been obtained from European countries on the USDA list.

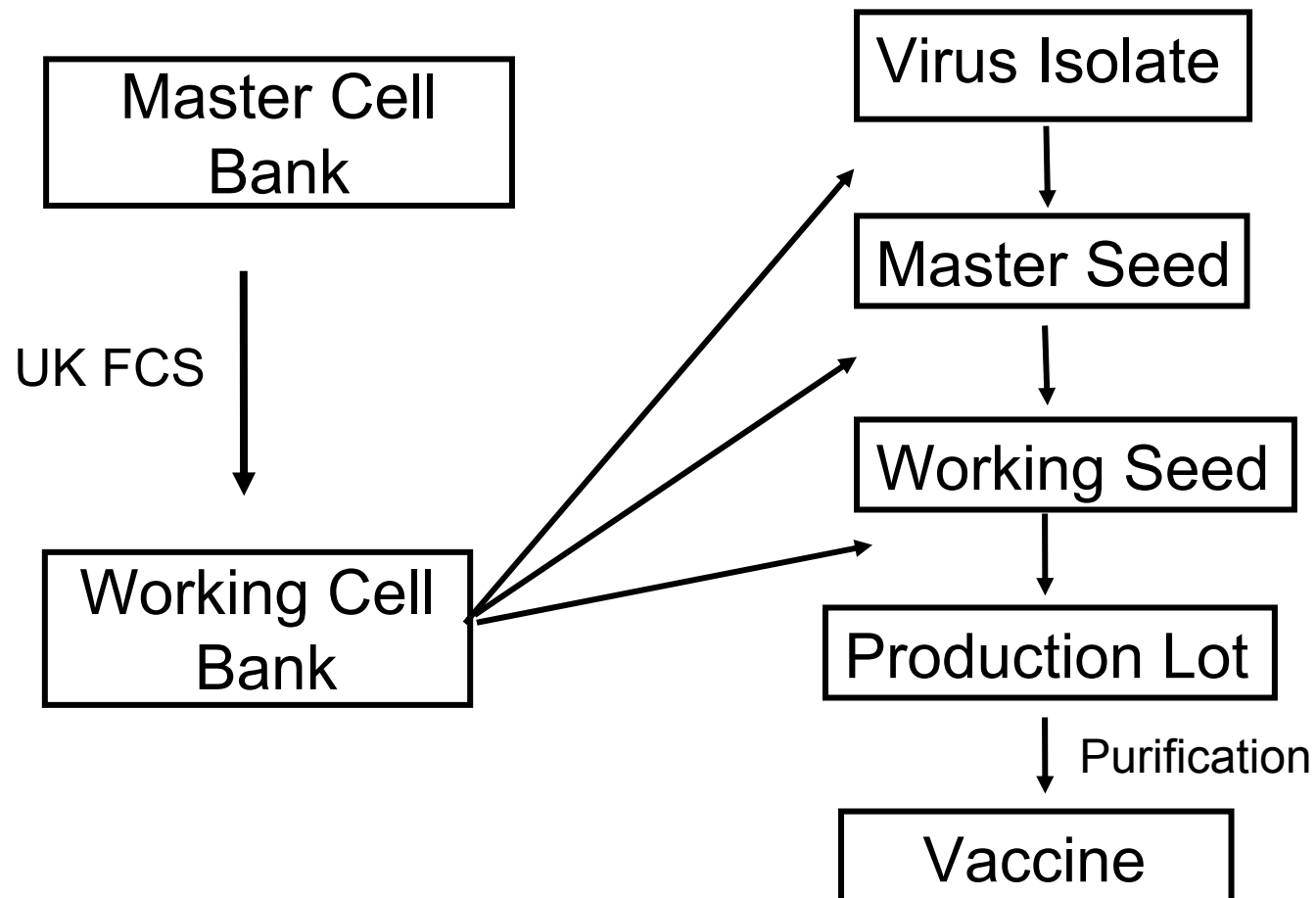
TSE-related Issues from Comprehensive Survey: Examples

- ▶ Use of fetal calf serum from the U.K., manufactured during the mid 1980s, in the establishment of cell and seed banks
- ▶ Use of European-sourced beef broth (skeletal muscle plus pancreatic extract) in bacterial fermentation
- ▶ Use of various European-sourced low molecular weight materials (other than milk derived), e.g., hemin for bacterial cultures
- ▶ Use of gelatin derivatives (prepared from bones sourced in Europe)

OVRP Response

- ▶ Following the general review of all vaccines for the use of bovine-derived materials
 - ▶ Risk assessment for cases wherein sourcing recommendations were not followed (worst-case assessment)
 - ▶ Recommendations provided to manufacturers
- ▶ Review of OVRP activities with the TSE and Vaccines Advisory Committees (joint session)
- ▶ Communication efforts

Risk Estimate: a Viral Vaccine Example



Risk Estimate: a Viral Vaccine Example

- ▶ Media Components
 - ▶ Fetal calf serum from the UK during early years of the epidemic when the incidence of disease was approximately 1 per 200 adult cows (USDA)
 - ▶ Maternal to fetal transmission rate of 10%
 - ▶ Fetal calf serum pooled in lots of ca. 1500
- ▶ Vaccine production
 - ▶ Multiple entry points for cells and FCS into production
 - ▶ Potential amplification during production
 - ▶ Limited purification or inactivation

Risk Estimate: a Viral Vaccine Example

- ▶ Basis for the calculation of BSE risk
 - ▶ 1 in 2000 calves is infected
 - ▶ BSE agent at a level of ca. 1 infectious unit per mL (based on largest volume tested for infectivity)
 - ▶ No increase in infectious doses due to propagation and no decrease in infectious doses due to purification
 - ▶ Dilution effects:
 - > Number of infectious units spread over the number of doses (= risk per dose)
 - ▶ No species barrier
 - ▶ Route of administration: IM < intra-cranial

Risk Estimate: a Viral Vaccine Example

<u>For FCS</u>	<u>Risk Factor</u>
Assuming 1 infectious unit /mL FCS	<1
Dilution of each infected FCS with FCS with FCS from 2000 normal calves	0.5×10^{-3}
Cells grown in 1 mL FCS used to make 10^3 doses of vaccine	1.0×10^{-5}
Route of administration	0.5×10^{-2}
Risk of infection per dose	$< 2.5 \times 10^{-11}$

Risk is less than one BSE infectious dose per 4×10^{10} vaccine doses for this viral vaccine manufactured with UK-sourced fetal calf serum

Risk Estimate: Some Uncertainties

- ▶ Incidence of BSE in cows in the early years of the epidemic
- ▶ Transmission to fetal calves may be < 10%
- ▶ Actual infectivity of FCS may be significantly less than 1 infectious unit per mL
- ▶ Further reductions in risk may be due to:
 - > Species barrier
 - > Route of administration
 - > Purification
- ▶ Error brackets about estimates

Immediate Responses

- ▶ Agreement by manufacturers to changing beef sources for bacterial fermentation broths and other affected components
- ▶ Agreement to re-derive working cell and seed banks, as necessary
- ▶ Existing vaccines remained on the market

Advisory Committees Meeting

- ▶ Joint meeting of the TSE and the Vaccines and Related Products Advisory Committees (July, 2000)
- ▶ Open public meeting
- ▶ Joint Committee convened to:
 - > Review the risk evaluations (FDA and manufacturers) and consider country, time, and animal husbandry
 - > Seek input on the corrective actions that have been taken and the decision to leave existing vaccines on the market until new lots of vaccines have been manufactured (ca. 1 year time lag)
 - > Input from the Committees on the need to re-derive master cell and seed banks
 - > The need for additional regulatory actions (recall, modification of the package insert, “Dear Health Care Provider” letters, etc.)

Advisory Committees Meeting: Conclusions and Recommendations

- ▶ The risk of vCJD posed by vaccines in the scenarios that were presented was remote and theoretical
- ▶ The benefits of vaccination far outweigh any remote risk of vCJD
- ▶ The Joint Committee had several recommendations
 - > Bovine-derived materials used in the routine production of vaccines that are sourced from countries on the USDA list should be replaced with bovine-derived materials from countries not on the USDA list
 - > Working bacterial and viral seed banks and WCBs that were established with bovine-derived material from countries on the USDA list should be re-derived with bovine-derived materials from countries not on the USDA list

Advisory Committees Meeting: Conclusions and Recommendations (cont'd)

- ▶ Master viral and bacterial seed banks that were established with bovine-derived material from countries on the USDA list need not be re-derived with bovine-derived materials from countries not on the USDA list. The risk of altering the vaccine through re-derivation of the master seed or cell bank far outweighs any risk for vCJD.
- ▶ These issues are of public interest and the public should be informed about the safety of vaccines that used materials from countries on the USDA list and the assessment of the nature of any risk for vCJD from such vaccines.

Following the Advisory Committees Meeting

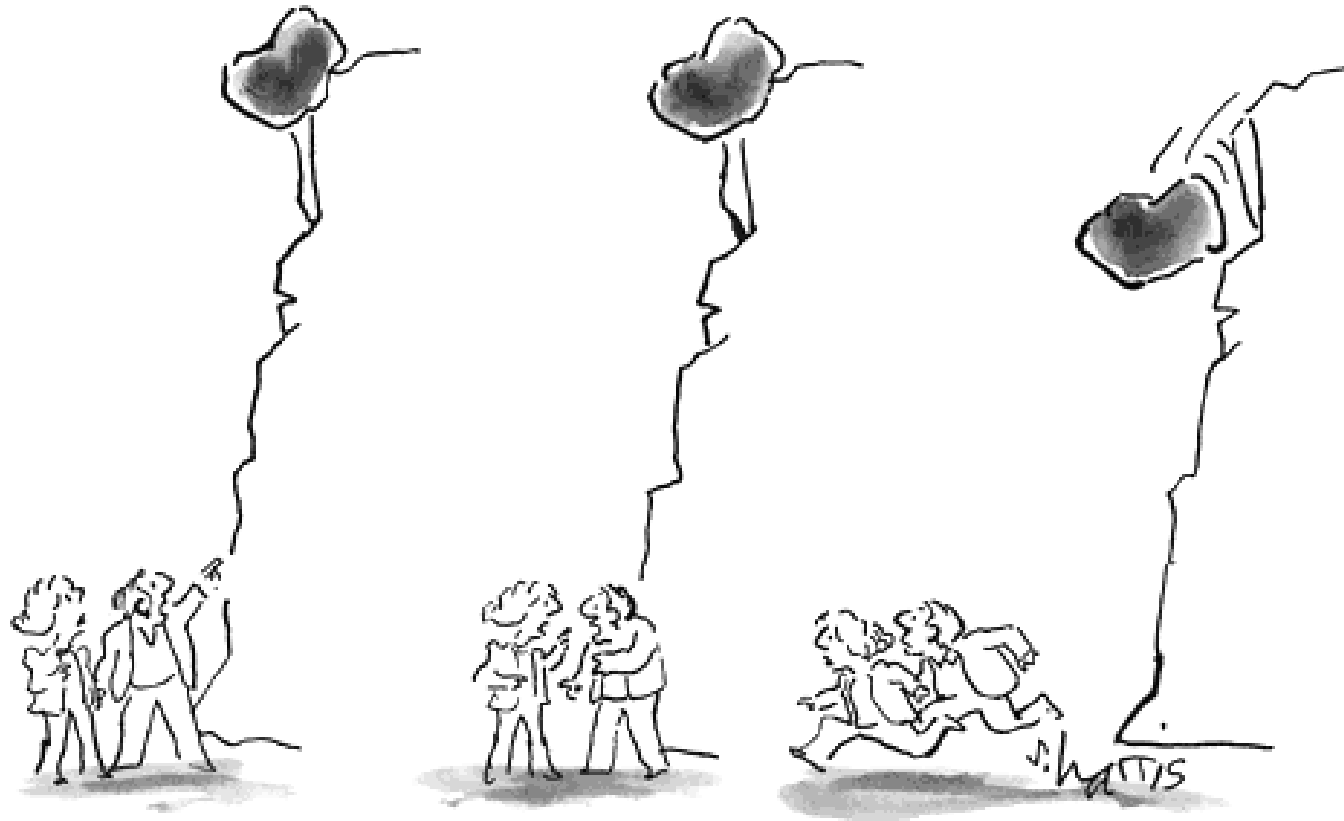
- ▶ A web site was created containing transcript of AC meeting, risk assessments, and listing of affected vaccines with periodic updates (www.fda.gov/cber/bse/bse.htm) .
- ▶ Issues published in the MMWR
- ▶ New sources of bovine materials were found and subsequently used in manufacturing.
- ▶ Working cell and seed banks were re-derived, qualified, and placed into production.
- ▶ The affected vaccines were replaced and the majority of affected vaccines were out of date by 2004.

Summary

RISK PERCEPTION

RISK ASSESSMENT

RISK MANAGEMENT





Thank you!

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