

Managing TSE Risk For Biotech Products In A Global Market

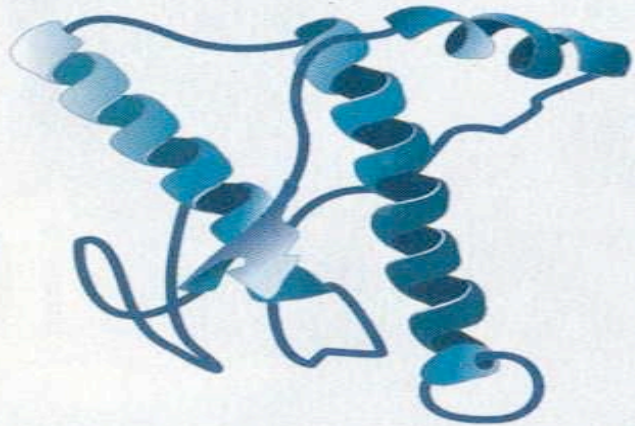
**Barbara Potts, Ph.D.
WCC – PDA Dinner Meeting
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Prions

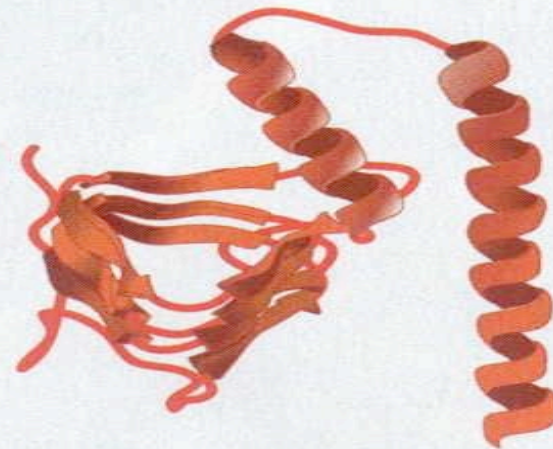
- Native form of mammalian prion protein (P_rP)
 - Causes no disease: amino acids form mainly alpha helices
- Isoform of mammalian prion protein (PrP^{sc})
 - Causes CNS destruction: amino acids form mainly beta-pleated sheet structure
 - Forces other normal proteins to adopt misfolded shape
- Prion like agents in yeast and fungus
 - Causes no disease
 - Forces other normal proteins to adopt misfolded shape

A BAD INFLUENCE

Prion proteins exist in at least two forms [*below*]*—*the normal, or cellular, version [PrP^{C}] and the disease-causing one [PrP^{Sc}]. In a process that is not well understood, PrP^{Sc} changes PrP^{C} into more PrP^{Sc} ; the newly altered prions, in turn, can corrupt other normal ones [*bottom*]. Usually the body eliminates PrP^{Sc} before too much of it accumulates. But if it does build up and is not successfully removed by the cell's machinery, illness can result.

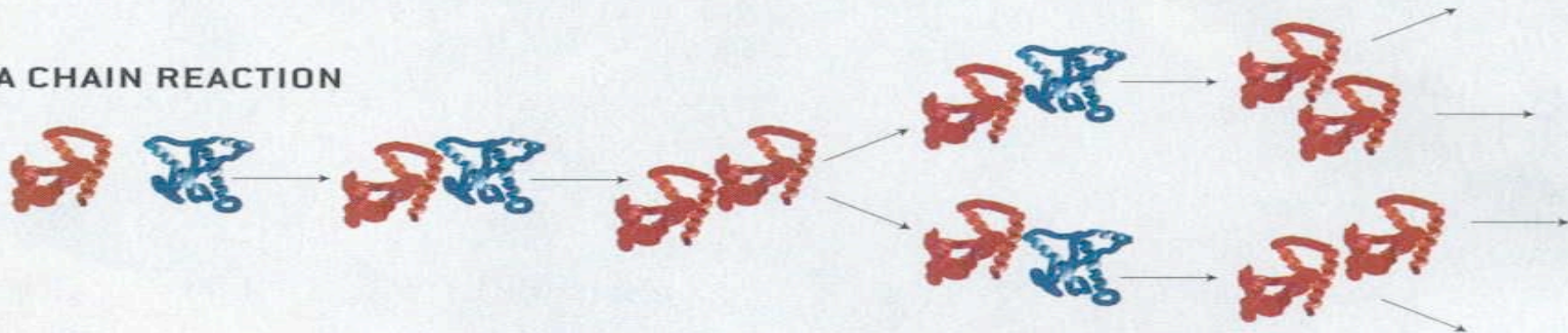


NORMAL PRION PROTEIN (PrP^{C})



DISEASE-CAUSING PRION (PrP^{Sc})

A CHAIN REACTION

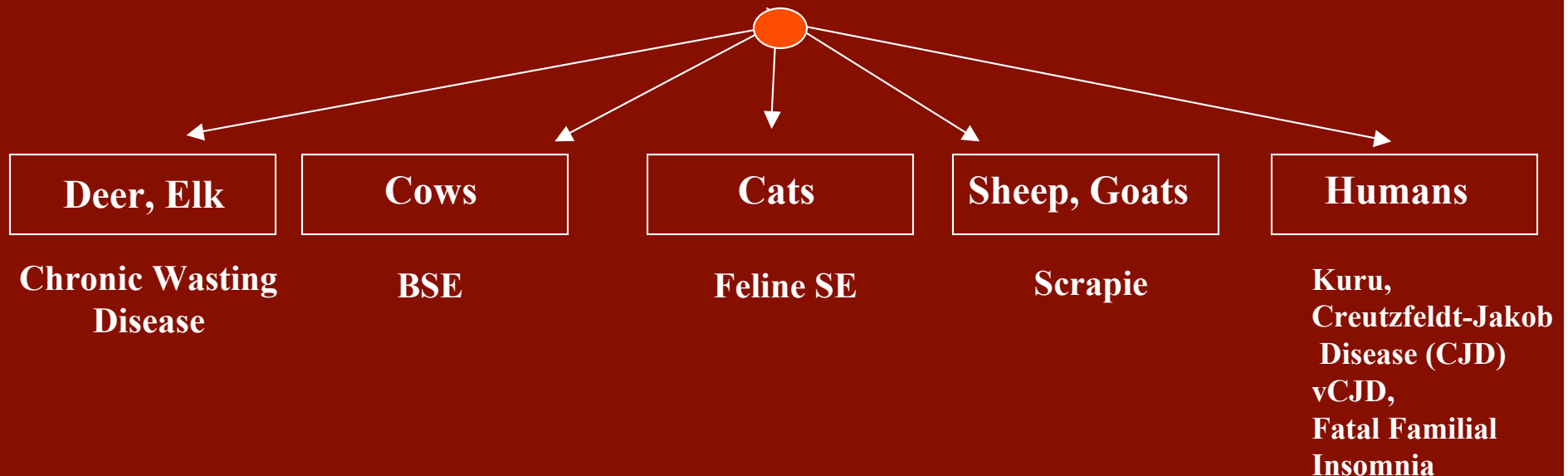


Disease Causing Prion (PrP^{sc})

Builds up, and if not removed by cell's machinery, illness can result.

TSE

(Transmissible Spongiform Encephalopathy)



BSE/TSE Background

- **Transmission**
 - experimental/accidental
 - Inoculation, contaminated instruments in brain surgery, transplantation of human meninges and cornea
- **Natural**
 - Genetic, congenital??
 - Unknown
 - _ VCJD – via blood transfusion
 - _ Milk from scrapie infected sheep
 - _ BSE - oral route (food born infection)

(First recognized in the UK in 1986)

BSE/TSE Background

- **Diagnosis is based on clinical signs with post mortem confirmation of brain lesions**
 - Histopathology to detect spongiform changes in CNS
 - Detection of the fibrillary protein in CNS
 - Immunocytochemical detection PrP^{Sc} (Gold Standard Test)
 - BioRad ELISA that detects PrP^{Sc}

Key BSE/TSE Events in 2003-2005

2003: One BSE positive animal detected in Canada

One BSE positive animal detected in USA (originally from Canada)

2004: One BSE positive animal detected in USA (domestic animal)

2005: Two BSE positive animals detected in Canada

2003: A recipient of RBCs from a vCJD case died of vCJD

2004: A preclinical vCJD case was diagnosed in a second person who had received RBCs from a vCJD case

-Abnormal prion protein typical of vCJD was detected at autopsy in the spleen and cervical lymph node

NOTE: Improbable that two cases of vCJD due to food-borne transmission in the TMER Cohort studied

Conclusion: vCJD is transmitted in the blood and possibly in blood products (e.g. plasma)

TMER Cohort: 50 recipients of blood components from 16 donors later found to have vCJD

Risk Assessment for Adventitious Agent Control Identify and Assess

| Agent | Likelihood of Contamination | Consequences | Impact |
|-------------------|-----------------------------|---|--|
| Prions | Very Low | Recall of products Long term shut down of manufacturing Reduced inventory of drugs for patients Reduced public trust | Very high |
| Viruses | Medium | Short term shutdown of manufacturing | High |
| Mycoplasma | Low - Medium | Rejection of impacted lots | Medium – low (depends on frequency) |
| Bacteria | Medium - high | Depending on level - may lead to rejection of impacted lots | Medium – low (depends on frequency) |
| Mold-Yeast | Low | Depending on level – may lead to rejection of impacted lots | Medium |

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Long Range BSE/TSE Response Plan For Commercial Products

- Remove all bovine sourced raw materials from production with exception of exempt materials*
 - Milk derived
 - Tallow derived
- Remove all human sourced raw materials from production.
- Reference: Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products EMEA/410/01 Rev.2, July 1,2004

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BSE/TSE Response Plan For New Clinical Products

- No bovine sourced raw materials used with exception of exempt materials
- No human source raw materials used

Risk Management

Short Term Risk Reduction

- Source non exempt bovine raw materials from New Zealand and Australia
- Eliminate human raw materials from production

Long Term Risk Reduction

- Eliminate non exempt bovine raw materials from production

Steps In CHO And E.coli Production Where Raw Materials Must Be Monitored

Research and Process Development

Transfection/Transformation

↓
Selection

Prebanks

↓
Master Cell Bank

↓
Working Cell Bank

Process Development

Seed Train

↓
Unprocessed Bulk

↓
Recovery Steps

↓
Bulk/Drug Substance

↓
Drug Product

Manufacturing

Internal Customers

- Genentech Board of Directors
- Executive Committee made up of CEO, Presidents and Senior Vice Presidents
- GMP Core Team: Vice Presidents from Manufacturing, Quality, Process Development, Engineering, Compliance, Regulatory Affairs
- Regulatory Affairs**
- Legal Department
- Product Safety Committee
- Medical Communications*
- Chief Medical Officer
- Corporate Compliance*

** Members make up TSE Task Force Core Team

* Members make up TSE Task Force

Internal Customers

- Procurement*
- Engineering
- Materials Management*
- Manufacturing (3 locations)*
- External Quality *
- Quality Control **
- Quality Assurance *
- Process Development **
- CMC Teams*
- Research

** Members make up TSE Task Force Core Team

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External Customers

- Partners*
- Contract Manufacturing Organizations*
- FDA*
- Ex USA Regulatory Agencies*
- Patients**
- Raw Materials Vendors***

* All communication is managed through GNE Regulatory Affairs

** All communication is managed through GNE Medical Communications

*** All communication is managed through GNE Quality Control

- Note: GNE Quality Control collects all information and funnels it through the appropriate channels

Document Hierarchy

**Level 1:
(Global)**

Quality Manual

**Level 2:
(Global)**

Quality Policies and Guidance Documents

- TSE Emergency Response Plan
- Guidance document on sourcing of animal-derived raw materials with respect to TSE
- Guidance document on sourcing of animal-derived raw materials with respect to adventitious agents other than TSE agents

Level 3:

SOPs

- Testing program for GMP raw materials
- Deroughing and passivation of stainless steel parts, equipment and manufacturing support utilities
- Raw material review board responsibilities

Document Hierarchy

Level 4: Proof That SOPs Are Followed

Raw Material Specifications

- Certificate of Origin (all animal RM)
- Certificate of Analysis (all animal RM)
- EDQM Certificate of Suitability* (bovine RM)
- Specified risk statements (bovine RM)

*EDQM-European Directorate for the Quality of Medicines Certification Unit

Document Hierarchy

Level 4: Proof That SOPs Are Followed

- Raw material purchasing specification
- Vendor audit document
- Vendor initiated change control
- Quality agreements with contract manufacturing organizations
- Quality audits of raw material vendors
 - Every 2 years for bovine raw materials
- Procurement audits of raw material vendors

* EDQM-European Directorate for the Quality of Medicines Certification Unit

Communication To Internal Customers

- **Consultant (former USDA employee) provides daily updates on BSE/TSE topics.**
- **These updates are distributed to the TSE Task Force**

Risk Assessments of Product

- **Based on benefit/risk evaluation**
 - Route of administration of the medicinal product
 - Quantity of animal material used in product
 - Maximum therapeutic dosage (daily dose and duration of treatment)
 - Intended use of the medicinal product and its clinical benefit

Methods Used at Genentech To Prevent Adventitious Agent Contamination

| Adventitious Agent | Sourcing | Testing | Validated Viral Clearance Steps in Recovery | Cleaning with Validated Disinfectants | Heat Sterilization (autoclave, Steam In Place) | HTST* | Sterilizing Grade Filtration | |
|---|----------|---------|---|---------------------------------------|--|-------|------------------------------|--------------|
| | | | | | | | Validated | Study Report |
| | | | | | | | 0.1 | 0.22 |
| Prions | ✓ | | | | | | | |
| Viruses | | ✓ | ✓ (CHO) | ✓ | ✓ | ✓ | | |
| Mycoplasma | | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| Bacteria | | ✓ | | ✓ | ✓ | | ✓ | ✓** |
| Mold | | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| *High Temperature/Short Time ** Not all Bacteria | | | | | | | | |