Implications of Animal Derived Products and Processes on Manufacturing and Regulatory Systems

Presented by Sue Sutton-Jones
Objectives

• Brief overview of Serologicals Corporation
• Explanation of prions and prion diseases
• Regulatory Considerations
  – FDA
  – USDA
  – EMEA
  – Rest of World
• Manufacturing Considerations
• Safety of Animal Derived Products
Serologicals Corporation

- Serologicals Corporation is now comprised of 3 main businesses: Celliance™, Chemicon™ and Upstate™. All 3 Companies provide animal derived products of different species in their product offerings.

- Animal Blood Proteins
  Celliance™ provides a wide range of approximately 90 distinct animal protein products. These products, such as BSA, are primarily supplied to life science companies for use in blood typing and other diagnostic reagents. One of the primary uses of bovine albumin is to enhance the detection of blood group antibodies, a characteristic essential for the safe transfusion of whole blood. The Company also provides a line of highly purified animal proteins known as tissue culture media components that are used by biotechnology and biopharmaceutical companies as nutrient additives in cell culture media. Examples of these media components are Bovine EX-CYTE®, produced through a patented manufacturing process, and transferrin.
Do I Look Angry?
• The cells misfire, work poorly, or don't work at all. In mad cow disease, for example, with their brain cells running amuck, the mad cows wobble and stagger and appear fearful--their "madness" is craziness, not anger.

• Sheep and goats with the disease **scrapie**, which is like mad cow disease, become so uncomfortable and itchy that they frantically rub up against anything they can, finally scraping off (hence, the name of the disease), most of their wool and hair.
Prion Diseases in General

- Infected prion-bloated brain cells die and release prions into the tissue. These prions can then enter, infect, and destroy other brain cells.
- As clusters of cells die, the brain stops looking like a brain and starts looking more like Swiss cheese.
- The medical term for the prion diseases is "spongiform encephalopathies," in acknowledgement that the sick brains (encephalo is Greek for brain; pathy is Greek for disease) are riddled with holes and have taken the form of sponges.
Where Do Prions Come From?

- Scientists now speculate that the “mad cow” prions started out in sheep suffering from scrapie and made their way into cows and then moved more recently into humans. Transmission is from feed. Cattle \textit{were} fed meal made from sheep "offal," the bones and other waste parts of sheep carcasses.

- Standard procedures for grinding up carcasses were altered in the 1970s, and the new processing methods seem not to have been adequate for destroying scrapie prions. The cattle were exposed, through the offal, to sheep prions, and the prions eventually established themselves in their cow hosts.

- Prions adapted further, infecting cells of people who had eaten beef, such as hamburgers, from prion-bearing cows.
What is the difference between the terms BSE and TSE?

• These diseases
  – are transmissible - from host to host of a single species and, sometimes, even from one species to another (such as bovine to human)
  – destroy brain tissue giving it a spongy appearance

• For these reasons, prion diseases are also called transmissible spongiform encephalopathies or TSEs.
Prion Diseases in General

Mad Cow is not the only prion disease!
Kuru

• Nickname is "laughing death."
• An exotic disease confined pretty much to the Fore tribe in northern regions of New Guinea.
• One custom of the Fore community was to eat the brains of dead relatives, a practice that promoted transmission of disease-causing prions.
• When cannibalism was banned, the incidence of Kuru was greatly reduced.
• When the kuru prion infects nerve cells, craziness and dementia, loss of coordination, and other symptoms develop.
Gerstmann-Straussler-Scheinker Syndrome (GSSS)

- This disease was linked to two mutations in the prion gene in 1989.
- PrPSC fragments accumulate in the brain in structures called plaques.
- In Alzheimer's disease, similar plaques develop, but they are composed of fragments of a different protein.
Fatal Familial Insomnia (FFI)

- This is a disease that was first associated with a prion in 1992.
- There is some evidence that this results from a deficiency of the normal prion protein, a deficiency that occurs because mutant prions are unable to fulfil their normal functions.
  - it runs in families,
  - prevents people from sleeping,
  - causes motor and emotional problems, and
  - is eventually a killer.
- Here, too, as in inherited cases of CJD, patients have a specific mutation in the prion gene.
Alpers Syndrome

- **Alpers syndrome** is the name given to prion diseases in infants.
CJD

• Due to publicity, we may think the current epidemic of CJD appears to be linked with mad cow disease and the transmission of sheep prions to cows and then to humans.

• Actually, most cases of CJD in the past 20 years arose from what doctors call "therapeutic misadventures" in which a patient who was being treated for some disease or condition developed CJD as a result of the treatment.
CJD Therapeutic Accidents

• In 1974, for example, a woman received a new cornea and developed CJD. The donor of the cornea had had a prion disease.

• In 1977, two patients with epilepsy developed CJD. Both had undergone tests during which electrodes were implanted deep in their brains. While the electrodes were recording electrical signals in the patients' brains, they were unexpectedly leaving behind deadly prions picked up from a previous patient.

• In the mid 1980s, a number of people receiving hormone treatments developed CJD. The hormones had been extracted from a pool of 20,000 pituitary glands, at least one of which had come from a patient who died of CJD.
• Some cases of CJD appear to be genetic, and when the disease is inherited it typically develops after age 55.
• When the gene that encodes PrPC has a specific mutation, the formation of PrPSC rather than PrPC is favored.
• A genetic predisposition for CJD may account for the high incidence of CJD in central Slovakia, where it is the fifth leading cause of death.
• In Chile and Israel, there are also clusters of people with CJD.
Sporadic Prion Diseases

- CJD and FFI occasionally occur in people who have no family history of the disease and no known exposure to infectious prions. The cause of their disease is uncertain.
- Perhaps their normal PrPC protein has spontaneously converted into the PrPSc form.
- Despite not knowing the mechanism, all the cases are found in people with a susceptibility polymorphism in their PRNP genes.
vCJD

• A new variant form of CJD (vCJD) was officially recognized in March 1996.
• This disease is clinically and physiologically different from classical CJD. Clinically, the average vCJD patient dies at 27.5 years of age in contrast to the CJD patient who dies at an average age of 68 years.
• Their symptoms include behavioral changes, loss of muscle coordination, and a loss of sensations, rather than changes in mental activity and thinking ability.
• Pathologically, the brain lesions more closely resembled those from a cow suffering from bovine spongiform encephalopathy (BSE) than brain lesions from a human with CJD.

www.arches.uga.edu/~steph116/causes.htm
Diagnosis is Difficult in the Living

• The most reliable means for diagnosing any TSE is the microscopic examination of brain tissue - a post-mortem procedure. Preliminary diagnoses of vCJD are based on patient history, clinical symptoms, electroencephalograms, and magnetic resonance imaging of the brain.
Chronic Wasting Disease in Elk and Deer in the United States

- The importance of having strong prion disease surveillance in the United States has been further underlined by recent reports that chronic wasting disease (CWD), an endemic prion disease affecting elk and deer which is found in an increasing number of states in the Midwest and Southwest, may be transmitted to humans generating a new prion disease.
- The World Health Organization (WHO) and the CDC agree that there currently is insufficient evidence to establish a link between human disease and handling or consuming CWD-infected deer.
- Although no human cases of CWD have been identified, laboratory research suggests that it is theoretically possible; however it is believed that the risk to humans is low.
VERONA - The white-tailed deer recently diagnosed with chronic wasting disease was one of the deer donated to the Verona Fire Department and served at its Annual Sportsmen's Feast on Sunday, March 13, an Oneida County Health Department spokesman said today.

People who consumed the venison need not worry about contracting the disease, spokesman Ken Fanelli said.

"There's no indication whatsoever that the disease has been linked to human illness of any kind," Fanelli.

The deer was donated before the health department knew it had the disease, according to the health department.
• A number of TSEs have been found in other animals.
• Cats are susceptible to Feline Spongiform Encephalopathy (FSE)
• Mink are also susceptible to a TSE.
• Chronic Wasting Disease (CWD): a similar disease is found in elk and mule deer in the Rocky Mountains of the U.S. and Canada and now New York State!
BSE In Goats

• BSE was found in one French goat that died in 2002.
• We have also been told by DEFRA that it is possible that one Scottish goat that died in 1990 may have had BSE, but it will take up to two years to confirm this.
• BSE has not been found in the current UK goat population, nor in 140,000 goats tested across Europe since 2002, apart from the French finding.
• On the basis of the current evidence, the Agency is not advising people against eating goat meat.
• BSE has not been found in the current UK goat population and the UK has not imported any goat meat from France since 1997.
Should I Eat Goat Cheese?

• The Agency is not advising against eating goat products such as cheeses. EFSA’s current advice is that, provided the milk is sourced from healthy animals, milk and milk products from goats are unlikely to present any risk of contamination, irrespective of country of origin.
Quick Quiz

• What state in the USA produces the largest share of GOATS?
How Did a Disease in Sheep Affect Cattle?

- Cattle and sheep are extremely close evolutionary relatives. They belong to the family Bovidae, and share a common ancestor that lived probably no more than 20 million years ago.

- So it is no surprise that cattle could contract a prion disease when fed with offal from sheep contaminated with scrapie, a spongiform encephalopathy endemic to sheep.
Crossing the Species Barrier

• At the Compton Laboratory, Bill Gordon’s* first breakthrough came in 1950, when he discovered that scrapie could be transmitted from sheep to goats.

*Bill Gordon, a Scottish scientist who directed the Compton Laboratory of England’s Institute for Research on Animal Diseases. (1950)
What About Human Infections?

• Human beings are extremely distant relatives of bovids such as cattle and sheep.

• It is thought the most recent common ancestor was alive around 70 million years ago, when mammals all looked like rats, and dinosaurs still ruled the Earth.

• Because of this evolutionary separation, human prions are unlikely to be similar to those of either sheep or cattle.
The Prion “Family” Tree

• The evolutionary 'family tree' seems, at first glance, to support this view. Prions from cattle (*Bos taurus*) and sheep (*Ovis aries*) are similar to each other, and to prions from other ungulates such as goats (*Capra hircus*) and deer (*Odocoileus hemionus*). They are quite different from those found humans (*Homo*), gorillas (*Gorilla*), chimpanzees (*Pan*) and a wide range of monkeys.

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The study, published in the 25 April 1996 issue of *Nature* comes from a team of researchers based in Oxford, in the UK, including Professor T. R. E. Southwood, a former advisor to the British Government on BSE. Given the lack of similarity, it is not self evident why bovine prions would infect a human. So it is easy to understand why politicians and scientists thought this was a remote possibility. What we have not yet understood is the significance of similarities that do exist.
Characteristics of Normal Proteins

• The normal protein
  – is called PrPC (for cellular)
  – is a glycoprotein normally found at the cell surface inserted in the plasma membrane
  – has its secondary structure dominated by alpha helices (probably 3 of them)
  – is easily soluble
  – is easily digested by proteases
  – is encoded by a gene designated (in humans) PRNP located on our chromosome 20.
PrP gene

- PrP gene encodes the prion protein
- Japanese research suggests that it protects the brain against dementia and other degenerative problems associated with old age.
- Sometimes, 'rogue' prions are produced by genetic mutations. This explains why some cases of CJD in humans are inherited.
Prion Facts

- These particles are rod-shaped, about 165 nanometers long and about 11 nanometers in diameter, and they consist largely of a protein called PrPSc, having molecular weight 33,000-35,000.
- They are able to resist inactivation by boiling, acid (pH 3-7), ultraviolet radiation (254 nm), formaldehyde, and nucleases.
- They can be inactivated by boiling in detergents, alkali (pH > 10), autoclaving at 132 degrees centigrade for over 2 hours, and denaturing organic solvents such as phenol.
What Exactly is a Prion Anyway?

• Prions cause **both** infectious and **and** hereditary diseases
• Prions cause diseases, but they aren't viruses or bacteria or fungi or parasites.
• Prions are smaller than viruses.
• They are simply proteins, and proteins were never thought to be infectious on their own.
• Organisms are infectious, proteins are not.
• Prions are so small that they can’t be seen with the most powerful microscopes. It takes an electron microscope.
What Exactly is a Prion Anyway?

- Prions consist only of protein and do not have nucleic acid (genetic information).
- Prions exist normally in a harmless form.
- The normal cell proteins have all the same "parts" as the prions--specifically the same amino acid building blocks--but they fold differently.
- Think of them– Transformer Toys to understand “folding”.
What Exactly is a Prion Anyway?

- Prions are found in all mammals.
- There are large numbers of them in the brain, especially on the surface of membranes.
- Abnormally folded prion proteins cause normal proteins to re-fold into disease causing shapes.
- Newly re-folded prion proteins interact with other prion proteins causing them to refold too.
- Altered proteins are resistant to breakdown and may accumulate into plaques.
- The prion diseases of humans and animals are 100% fatal.
How Does a Prion Cause Damage?

- Prions on cell surfaces allow too much fluid to enter the cell, producing a spongy appearance when cross-sections of brain tissue are analyzed under a microscope.
- Prions enter brain cells and there convert the normal cell protein PrPC to the prion form of the protein, called PrPSC.
  - PrP stands for prion protein
  - Cellular prion proteins (PrPC).
  - Abnormal, pathogenic isoform (PrPSc)
How Does a Prion Cause Damage?

• When normal cell proteins transform into prions, amino acids that are folded tightly into alpha helical structures relax into looser beta sheets.

• More and more PrPC molecules transform into PrPSC molecules, until eventually prions completely clog the infected brain cells.
Prion Research

• Stanley Prusiner\(^1\) who
  – pioneered in the study of these proteins and
  – was awarded the Nobel Prize in 1997 for his efforts
  – has named them prion proteins (designated \textbf{PrP}) or simply \textit{prions}. He confirmed that prions are molecules of a normal body protein that have \textbf{changed their three-dimensional configuration}.  

\(^1\) Stanley Prusiner, M.D., a neurobiologist at the University of California at San Francisco, was awarded the 1997 Nobel Prize in Medicine for his groundbreaking discovery and definition of a new class of disease-causing agents called prions.
Fig. 1. Neuropathologic changes in Swiss mice after inoculation with RML scrapie prions

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- Fig. 1. Neuropathologic changes in Swiss mice after inoculation with RML scrapie prions. (a) Hematoxylin and eosin stain of a serial section of the hippocampus shows spongiform degeneration of the neuropil, with vacuoles 10-30 µm in diameter. Brain tissue was immersion fixed in 10% buffered formalin solution after the animals had been sacrificed and was then embedded in paraffin. Py, pyramidal cell layer; SR, stratum radiatum. (b) Glial fibrillary acidic protein (GFAP) immunohistochemistry of a serial section of the hippocampus shows numerous reactive astrocytes. (Bar in b = 50 µm and also applies to a.)

- Photomicrographs were prepared by Stephen J. DeArmond.

vCJD

**Fig. 4.** Histopathology of vCJD in Great Britain.  
(A) Section from frontal cortex stained by the periodic acid-Schiff (PAS) method, showing a field with aggregates of plaques surrounded by spongiform degeneration.  
(B) Multiple plaques and amorphous deposits are PrP-immunopositive.  
Scale bar, 50 μm.  
Photomicrographs prepared by S. J. DeArmond.
Fig. 5. Structures of prion proteins

Fig. 5. Structures of prion proteins. (A) NMR structure of SHa recombinant (r) PrP(90-231). Presumably, the structure of the -helical form of rPrP(90-231) resembles that of PrPC. rPrP(90-231) is viewed from the interface where PrPSc is thought to bind to PrPC. The color scheme is as follows: -helices A (residues 144-157), B (172-193), and C (200-227) in pink; disulfide between Cys-179 and Cys-214 in yellow; conserved hydrophobic region composed of residues 113-126 in red; loops in gray; residues 129-134 in green encompassing strand S1 and residues 159-165 in blue encompassing strand S2; the arrows span residues 129-131 and 161-163, as these show a closer resemblance to -sheet (155). (B) NMR structure of rPrP(90-231) is viewed from the interface where protein X is thought to bind to PrPC. Protein X appears to bind to the side chains of residues that form a discontinuous epitope: some amino acids are in the loop composed of residues 165-171 and at the end of helix B (Gln-168 and Gln-172 with a low-density van der Waals rendering), whereas others are on the surface of helix C (Thr-215 and Gln-219 with a high-density van der Waals rendering) (178). (C) PrP residues governing the transmission of prions (180). NMR structure of recombinant SHaPrP region 121-231 (155) shown with the putative epitope formed by residues 184, 186, 203, and 205 highlighted in red. Residue numbers correspond to SHaPrP. Additional residues (138, 139, 143, 145, 148, and 155) that might participate in controlling the transmission of prions across species are depicted in green. Residues 168, 172, 215, and 219 that form the epitope for the binding of protein X are shown in blue. The three helices (A, B, and C) are highlighted in pink. (D) Schematic diagram showing the flexibility of the polypeptide chain for PrP(29-231) (156). The structure of the portion of the protein representing residues 90-231 was taken from the coordinates of PrP(90-231) (155). The remainder of the sequence was hand-built for illustration purposes only. The color scale corresponds to the heteronuclear {1H}-15N nuclear Overhauser enhancement data: red for the lowest (most negative) values, where the polypeptide is most flexible, to blue for the highest (most positive) values in the most structured and rigid regions of the protein. (E) Plausible model for the tertiary structure of HuPrPSc (166). Color scheme is as follows: S1 -strands are 108-113 and 116-122 in red; S2 -strands are 128-135 and 138-144 in green; -helices H3 (residues 178-191) and H4 (residues 202-218) in gray; loop (residues 142-177) in yellow. Four residues implicated in the species barrier are shown in ball-and-stick form (Asn-108, Met-112, Met-129, Ala-133).
Fig. 6. Miniprions produced by deleting PrP residues 23-89 and 141-176

Fig. 6. Miniprions produced by deleting PrP residues 23-89 and 141-176. The deletion of residues 141-176 (green) containing helix A and the S2 -strand is shown. Side chains of residues 168, 172, 215, and 219, which are thought to bind protein X, are shown in cyan.
Fig. 8. Disappearance of the kuru and BSE epidemics

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- Fig. 8. Disappearance of the kuru and BSE epidemics. (A) Annual number of cases of BSE in cattle in Great Britain. (B) Biannual number of cases of kuru in Papua New Guinea.
- Data were compiled for BSE by John Wilesmith and for kuru by Michael Alpers.
BSE in Great Britain
The BSE epidemic in Great Britain was estimated to affect almost one million cattle were infected with prions,

The mean incubation time for BSE is about 5 years. Most cattle therefore did not manifest disease because they were slaughtered between 2 and 3 years of age.

Nevertheless, more than 160,000 cattle, primarily dairy cows, have died of BSE over the past decade.

The BSE epidemic was a common-source epidemic caused by meat and bone meal (MBM) fed primarily to dairy cows.

The MBM was prepared from the offal of sheep, cattle, pigs, and chickens as a high-protein nutritional supplement.

In the late 1970s, the hydrocarbon-solvent extraction method used in the rendering of offal began to be abandoned, resulting in MBM with a much higher fat content.

It is now thought that this change in the rendering process allowed scrapie prions from sheep to survive rendering and to be passed into cattle.
Many plans have been offered for the culling of older cattle to minimize the spread of BSE but that has not been thought to be sufficient.

It seems more important to monitor the frequency of prion disease in cattle slaughtered for human consumption.

No reliable, specific test for prion disease in live animals is available, but immunoassays for PrPSc in the brainstems of cattle might provide a reasonable approach to establishing the incidence of subclinical BSE in cattle entering the human food chain.
Reaction to BSE in Cattle

- After the BSE scare and as a precautionary measure, Britain (alone in Europe) has banned sheep tissue from the food chain. Even though there has been no documented case of a BSE/TSE from sheep infecting a human.
- Scientists also checked for BSE in sheep, as distinct from the sheep version called scrapie, but found none.
- It was estimated that the risk of any Briton ever catching CJD from beef was put at between one in 50 million and one in a billion.
- The risk now of catching CJD from sheep which "might" have inherited BSE from some leakage into flocks years ago incredibly remote.
- Scientists advised the Government's Chief Medical Officer that there were "no grounds" for taking action on sheep.
Allaying the Public’s Fears

In an attempt to allay fears, Agriculture Minister John Gummer poses with his daughter and a pair of well-placed burgers. Note the extra hand helping Cordelia hold hers. (photo ©Jim James, PA News Ltd. Used with permission.)
• Public Panic

• Government takes conservative action without solid scientific proof to back up concerns.

• This seems to allay public fears but does not provide a cost effective and beneficial solution.
BSE Events in North America
Mad-cow Inquiry Shifts Its Focus to Canada

U.S. Examining Mad Cow Case; First for Nation

By MATTHEW L. WALD
and ERIC LICHTBLAU

WASHINGTON, Dec. 20 — A sick cow slaughtered about two weeks ago near Yalaha, Wis., has tested positive for mad cow disease in early

slaughtered beef out of the food supply. Only the brain, spinal cord and related parts can spread the disease to humans, Mr. Veneman

wrote.

Federal officials from the U.S. Department of Agriculture said they were tracing the beef to its processor in Wisconsin. The meat is currently in storage.

Agriculture Secretary Ann Veneman said a single U.S. cow in Washington state tested "presumptively" positive for mad cow disease this week. The cow was slaughtered on May 14, and its meat has not been distributed.

Discovery Expected to Jolt American Cattle Industry; Food Supply Called Safe

WASHINGTON—Federal officials announced they have found the first case of suspected mad cow disease in the U.S., a dead cow in Washington state tested "presumptively" positive for the disease.

The case of mad cow disease detected in the U.S. For First Time

Japan, S. Korea ban beef imports

of Jacinthe. USDA officials are inspecting the farm, the province of Quebec. At least two other infected processing plants where meat for a cow was found with mad cow disease, Dr. Levine said. The announcement was made by Agriculture Secretary Ann Veneman.

The U.S. government has been working with its international partners to develop strategies to address the threat.
USDA Communication regarding Canadian case of Mad Cow disease

- Borders Between Canada and US were closed
- Effective as of 1:30 p.m. E.S.T. May 20, 2003
- Included derivatives of processed animal proteins
Immediate Serologicals Actions

- Corporate BSE Committee established
  - Executive membership
- Communications to customers
- Contacts to USDA initiated
- Contacts with CFIA initiated
- Contacts to FDA initiated
- Monitor websites – CFIA, USDA – APHIS, FDA
- Identify exposure for material in Milford, MA and Toronto, Ontario
Immediate Serologicals Impact

- USDA stopped endorsement for export from the US for bovine material manufactured in Canada.
- USDA stopped import of product from Canada of bovine material regardless of raw material source.
- US and Canadian source material manufactured in Canada could ship within the US.
- US and Canadian source material manufactured in Canada could not ship internationally.
Next Steps

• Initiate 4 import license applications
  – 4 major product lines

• Contact key suppliers to initiate import permit applications
  – Lypholization
  – Testing

• Contact USDA in Washington for clarification of new import/export requirements

• Meeting with Sutton, MA USDA to determine requirements to resume export processes
Key Business Decisions

- Shutdown Toronto facility and clean
  - Hydrochloric Acid – 20 Be
  - Hypochlorite solution
  - Sulphuric Acid, CP
  - Sodium Hydroxide 50%
- Convert Toronto raw material to US source product
- Maintain contact with appropriate regulatory bodies to expedite permits
Barriers and Roadblocks

• Import permits – normal processing time 2-3 weeks
  – No guarantee from USDA for availability timing
  – Initial applications were lost within the USDA
  – Identifying appropriate contact at USDA to expedite

• Import permit requirements not clear
  – CFIA not sure what USDA would accept
  – CFIA inspection of Toronto performed, but not certain of next step
  – Identifying appropriate contacts at CFIA
Barriers and Roadblocks

- The rules continue to change
  - Import permits for porcine products
  - Canada import permits
  - Variation in understanding of the regulations border to border, agent to agent
  - Individual country requirements continue to change
- No notification of changes in advance
- No central point of information to confirm the rules for various countries
What Happens Now When BSE is found in US Source Animals?

• Raw Material from Australia and/or New Zealand
• Alternative Materials
  – Recombinant Proteins
• We are required to re-demonstrate Safety of Manufacturing Processes
Alternatives to Animal Derived Materials?

- Recombinant proteins
  - Not readily available
  - Long development time
  - Additional clinical trials
  - Expensive for Pharma and Bio customers to convert
  - We are negatively impacting worldwide economies by turning away from products proven to work in multiple product lines and applications
BSE Action Strategy – Drivers

USDA

“BIO”

FDA

Congress, Senate

Industry

Big Pharma, Biotech, Diagnostics

NCBA
Serologicals’ Approach to Minimizing Risk of BSE

- We use only US Sourced Material that is certified to comply with all regulations
  - We are now limiting the acceptance of plasma to only animals less than 30 months old
  - First shipment back into Canada was 06 Feb 2004
- We adhere to rigorous internal policies to control the use, location and disposal of materials.
- Our manufacturing processes include steps that have been demonstrated to reduce prion/viral loads
JUST WHEN YOU THOUGHT IT WAS GOING BACK TO BUSINESS AS USUAL

• CALGARY - Beef industry officials in Canada were cited as saying they don't expect the U.S. border to reopen until 2006, three years after a ban was put in place.

• Dennis Laycraft of the Canadian Cattlemen's Association was quoted as saying, "You could easily get into nine months to a year and a half ... in terms of the likely time frames around these court proceedings."
The Regulators
What is FDA’s Role?

• FDA is the Agency responsible for assuring that all FDA-regulated products remain safe and uncompromised from BSE and related diseases. Many FDA-regulated products contain bovine ingredients, for example, heart valves, ophthalmic devices, dental products, wound dressings, injectable drugs, vaccines, soups, gravies, sausage casings, and animal feeds.
Expanded "Mad Cow" Safeguards Announced
To Strengthen Existing Firewalls Against BSE Transmission

• The first firewall is based on import controls started in 1989.
• A second firewall is surveillance of the U.S. cattle population for the presence of BSE, a USDA firewall that led to the finding of the BSE cow in December.
• The third firewall is FDA's 1997 animal feed ban, which is the critical safeguard to help prevent the spread of BSE through cattle herds by prohibiting the feeding of most mammalian protein to ruminant animals, including cattle.
• The fourth firewall, recently announced by USDA, makes sure that no bovine tissues known to be at high risk for carrying the agent of BSE enter the human food supply regulated by USDA.
• The fifth firewall is effective response planning to contain the potential for any damage from a BSE positive animal, if one is discovered. This contingency response plan, which had been developed over the past several years, was initiated immediately upon the discovery of a BSE positive cow in Washington State December 23.
Our first firewall is formed through regulations and enforcement to protect U.S. borders from potentially infective materials utilizing a regime of import controls. USDA, beginning in 1989, enacted major restrictions on imports, and more restrictive import controls have been introduced as we have learned more about the science of BSE and as the worldwide epidemiology has changed. FDA remains a committed partner with USDA and CBP in protecting our borders.

The second firewall is surveillance of the U.S. cattle population for the presence of BSE. Surveillance of the cattle population is the primary responsibility of USDA, and USDA has recently announced steps to increase surveillance.
The third firewall is prevention of the amplification of BSE through feed provided to cattle and other ruminants, and this responsibility falls primarily on FDA. FDA’s animal feed ban regulations form the basis of this third firewall and have been cited as one of the most significant elements needed to prevent the spread of BSE in the U.S. We have taken intensive steps to get an extremely high level of compliance with this feed ban. As a result, we have been able to work with the animal feed industry to achieve more than a 99% compliance rate – and we intend to continue to work for full compliance.

FDA’s 4th Firewall Strategy

• The fourth firewall is making sure that no bovine materials that can transmit BSE be consumed by people.

• So even if a BSE-positive cow made it through all of the previous firewalls, which is extremely unlikely, it would not pose any risk to people. USDA and FDA have long had steps in place to help prevent any possible exposure to BSE in bovine products, and recently USDA announced additional major steps to prevent any of the tissues known to carry BSE from entering the beef supply, as well as to restrict use of certain “downer” cows that might be at higher risk of carrying BSE. FDA will be taking comparable measures to prevent human exposure to the FDA-regulated bovine products that might potentially harbor BSE.

FDA’s 5th Firewall

- A fifth firewall is effective response planning to contain the potential for any damage from a BSE positive animal, if one is discovered at some point in the system.

- This urgent response plan went into place immediately upon the discovery of a BSE-positive cow in Washington State on December 23, 2003. We have inspected and traced products at 22 facilities, including feed mills, farms, dairy farms, calf feeder lots, slaughterhouses, meat processors, transfer stations, and shipping terminals. We have accounted for all the products related to the BSE-positive cow that FDA regulates, and none have gone into human or animal consumption. Moreover, FDA has conducted inspections at all the rendering facilities involved, and found they were fully in compliance with the feed rule.

FDA Actions

• HHS intends to ban from human food (including dietary supplements), and cosmetics a wide range of bovine-derived material so that the same safeguards that protect Americans from exposure to the agent of BSE through meat products regulated by USDA also apply to food products that FDA regulates.

• FDA will also prohibit certain currently allowed feeding and manufacturing practices involving feed for cattle and other ruminant animals. These additional measures will further strengthen FDA's 1997 "animal feed" rule.
More FDA Action

- FDA is increasing its inspections of feed mills and renderers in 2004.
- Their 2001 base funding for BSE-related activities was $3.8 million.
- They shifted resources internally in 2001 and received a substantial increase from Congress in 2002.
- Their funded level for 2004 is currently approximately $21.5 million, almost a five-fold increase over the 2001 base.
- FDA will itself conduct 2,800 inspections and will make its resources go even further by working with state agencies to fund 3,100 contract inspections of feed mills and renderers and other firms that handle animal feed and feed ingredients.
- Through partnerships with states, FDA will also receive data on 700 additional inspections, for a total of 3,800 state contract and partnership inspections in 2004. These inspections would include 100 percent of all known renderers and feed mills that process products containing prohibited materials.
• The first interim final rule will ban the following materials from FDA-regulated human food, (including dietary supplements) and cosmetics:
  – Any material from "downer" cattle. ("Downer" cattle are animals that cannot walk.)
  – Any material from "dead" cattle. ("Dead" cattle are cattle that die on the farm (i.e. before reaching the slaughter plant);
  – Specified Risk Materials (SRMs) that are known to harbor the highest concentrations of the infectious agent for BSE, such as the brain, skull, eyes, and spinal cord of cattle 30 months or older, and a portion of the small intestine and tonsils from all cattle, regardless of their age or health; and
• The product known as mechanically separated beef, a product which may contain SRMs. Meat obtained by Advanced Meat Recovery (an automated system for cutting meat from bones), may be used since USDA regulations do not allow the presence of SRMs in this product.
The second interim final rule is designed to lower even further the risk that cattle will be purposefully or inadvertently fed prohibited protein. It was the feeding of such protein to cattle that was the route of disease transmission that led to the BSE epidemic in United Kingdom cattle in the 1980's and 1990's.
This interim final rule will implement four specific changes in FDA's present animal feed rule.

First, the rule will eliminate the present exemption in the feed rule that allows mammalian blood and blood products to be fed to other ruminants as a protein source. Recent scientific evidence suggests that blood can carry some infectivity for BSE.

Second, the rule will also ban the use of "poultry litter" as a feed ingredient for ruminant animals. Poultry litter consists of bedding, spilled feed, feathers, and fecal matter that are collected from living quarters where poultry is raised. This material is then used in cattle feed in some areas of the country where cattle and large poultry raising operations are located near each other. Poultry feed may legally contain protein that is prohibited in ruminant feed, such as bovine meat and bone meal. The concern is that spillage of poultry feed in the chicken house occurs and that poultry feed (which may contain protein prohibited in ruminant feed) is then collected as part of the "poultry litter" and added to ruminant feed.
• Third, the rule will ban the use of "plate waste" as a feed ingredient for ruminants. Plate waste consists of uneaten meat and other meat scraps that are currently collected from some large restaurant operations and rendered into meat and bone meal for animal feed. The use of "plate waste" confounds FDA's ability to analyze ruminant feeds for the presence of prohibited proteins, compromising the Agency's ability to fully enforce the animal feed rule.

• Fourth, the rule will further minimize the possibility of cross-contamination of ruminant and non-ruminant animal feed by requiring equipment, facilities or production lines to be dedicated to non-ruminant animal feeds if they use protein that is prohibited in ruminant feed. Currently, some equipment, facilities and production lines process or handle prohibited and non-prohibited materials and make both ruminant and non-ruminant feed -- a practice which could lead to cross-contamination.
FDA is prohibiting the use of certain materials that carry a risk of bovine spongiform encephalopathy (prohibited cattle materials) in food for humans, including dietary supplements, and cosmetics. Prohibited cattle materials include:

- specified risk materials
- small intestine of all cattle
- material from non-ambulatory disabled cattle
- material from cattle not inspected and passed for human consumption
- mechanically separated (MS) beef
What are Specified Risk Materials (SRMs)?

- Specified risk materials, from cattle 30 months and older, are the:
  - brain
  - skull
  - eyes
  - trigeminal ganglia
  - spinal cord
  - vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum)
  - dorsal root ganglia.
- Specified risk materials from cattle of any age are the
  - tonsils and
  - distal ileum of the small intestine.
- Prohibited cattle materials do **not** include tallow that contains no more than 0.15 percent hexane-insoluble impurities and tallow derivatives.
What products are covered by the interim final rule?

- All FDA-regulated human food and cosmetics, including:
  - Dietary supplements and dietary ingredients
  - Infant formula
  - Canned and frozen foods
  - Bakery goods, snack food, and candy (including chewing gum)
  - Food ingredients, including GRAS substances
  - Food additives, including food-contact substances
  - Cosmetics and cosmetic ingredients.
How can food manufacturers and processors comply?

- Manufacturers and processors who currently use prohibited cattle materials will need to switch to alternative ingredients. In addition, the rule requires that manufacturers and processors make existing records related to compliance with the rule available to FDA for inspection and copying.
When does the rule take effect?

- This rule is in effect as of July 14, 2004, the date of its publication in the *Federal Register*, however, FDA is providing a 90-day comment period on this interim final rule. The rule applies to human food and cosmetics manufactured from, processed with, or that otherwise contain material from cattle slaughtered on or after the interim final rule's effective date.
What would be required in the companion recordkeeping proposal?

- Manufacturers and processors of FDA-regulated human food and cosmetics that use cattle material in their products would be required to keep records demonstrating that these materials do not contain prohibited cattle materials. The proposal also would require that manufacturers and processors make these records available to FDA for inspection and copying.
What types of records would be required?

- Generally, FDA would expect a manufacturer or processor to have a signed and dated affirmation, including contact information, from the slaughter establishment stating that cattle material supplied by the establishment in a particular shipment does not contain prohibited cattle materials. For human food and cosmetics containing tallow, a manufacturer or processor would need to maintain records (signed, and dated, with contact information) either from the slaughter establishment affirming that the tallow was produced from material containing no prohibited cattle materials, or from the tallow supplier affirming that the tallow contains no more than 0.15 percent insoluble impurities.
How long would the records have to be retained?

• FDA is proposing that these records be retained for two years.
Where would the records have to be maintained?

- Records would have to be maintained at the manufacturing or processing establishment or at a reasonably accessible location. Electronic records would be acceptable and are considered to be reasonably accessible if they are accessible from an onsite location.
What about imported human food and cosmetic products containing cattle materials?

• Importers would be required to electronically affirm their compliance with these recordkeeping requirements at the time the products enter the U.S. and would have to provide the required records to FDA within a reasonable time, if requested.
## FDA Results of Warning Letters Search

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Date Warning Letter Issued</th>
<th>Issuing Office</th>
<th>Subject</th>
<th>File</th>
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Our investigation found the following violations of 21 C.F.R. 589.2000:

1. Failure to separate the receipt, processing, and storage of products containing prohibited material from products not containing prohibited material [21 C.F.R. 589.2000(e)(1)(iv)];

2. Failure to establish written procedures, including clean-out and flushing procedures, to avoid commingling and cross-contamination of common equipment [21 C.F.R. 589.2000(e)(1)(iii)(B)];

3. Failure to maintain records sufficient to track prohibited materials throughout the receipt, processing, and distribution of your products [21 C.F.R. 589.2000(c)(1)(ii)];

4. Failure to provide for measures to avoid commingling or cross-contamination of feeds intended for ruminants and feeds intended for non-ruminants that may contain prohibited materials [21 C.F.R. 589.2000(c)(1)(ii)]. Specifically, our investigation found that the ruminant product “10% Beef Conditioned” was formulated primarily with screenings and fines derived from previously manufactured non-ruminant products, “Premium Rooster Kicker” in particular, that contain or may contain prohibited material. Such deviations cause the ruminant product “10% Beef Conditioner” being manufactured at this facility to be adulterated within the meaning of Sections 402(a)(2)(C) and 402(a)(4) of the Act;

5. Failure to label your non-ruminant products with the required cautionary statement “Do not Feed to Cattle or Other Ruminants” [21 C.F.R. 589.2000(c)(1)(ii)]. Our investigation specifically found that dog food containing prohibited material was added as an ingredient to your product “Premium Rooster Kicker.” The failure of these feeds to bear the required BSE warning statement causes them to be misbranded within the meaning of Section 403(f) of the Act.
USDA Actions

- **November 1989**
  - USDA/APHIS enacts emergency ban on the importation of high-risk ruminant products (including meat-and-bone-meal) from countries with confirmed cases of BSE.

- **December 6, 1991**
  - USDA/APHIS enacts formal regulation to restrict the importation of ruminant meat and edible products, and bans high risk by-products of ruminant origin from countries known to have BSE.

- **1993**
  - USDA/APHIS expands BSE surveillance program to include examination of brain tissue from non-ambulatory or “downer” cows.

- **1994**
  - USDA/APHIS implements immunohistochemistry testing method for BSE.
USDA Actions

- December 12, 1997
  - USDA/APHIS bans imports of all live ruminants and high-risk ruminant products from Europe.
- April 24, 1998
  - USDA/APHIS enters into a cooperative agreement with Harvard University’s School of Public Health to analyze and evaluate the USDA’s BSE prevention measures.
- December 7, 2000
  - APHIS prohibits all imports of rendered animal protein products from Europe, regardless of species.
- FY 2000
  - U.S. surveillance is increased to testing 19,990 cattle brains.
- November 2001
  - Harvard Center for Risk Analysis releases its BSE risk assessment study commissioned by the federal government. The report finds the risk of BSE ever occurring in the U.S. is very low.
USDA Actions

• May 20 2003
  – Canada confirms first indigenous case of BSE in a single 6-year old Alberta beef cow. The U.S. closes the border to live cattle and beef imports. (Canadian Food Inspection Agency (www.inspection.gc.ca)

• August 2003
  – USDA announces it will allow certain Canadian ruminant products to enter the U.S. under permit. These include boneless beef from cattle under 30 months of age and boneless veal from calves under the age of 37 weeks.

• October 2003
  – USDA announces a proposed rule to amend its BSE regulations to allow the importation of certain low-risk live ruminants and ruminant products from minimal BSE risk regions under specified conditions. The proposed rule places Canada on a list of countries considered minimal risk for BSE.
USDA Actions

• December 23, 2003
  – Recall initiated of meat distributed

• 2003
  – Fifty-three countries ban imports of US beef and beef products.

• December 25, 2003
  – The OIE International Reference Laboratory in Weybridge, England confirms the BSE diagnosis.
USDA Actions

- December 30, 2003
  - USDA/FSIS announces new rules banning all “downer” cattle from the human food chain, removing certain animals and specified risk material (SRM) and tissues from the human food chain, requiring additional process controls for establishments using advanced meat recovery (AMR), holding meat from cattle that have been targeted for BSE surveillance testing until the test has confirmed negative and prohibiting air-injection stunning of cattle.
• Pier Gambetti, whose mission is to hunt down human mad cow disease claims there's not enough testing for BSE in cattle here (US). "Thirty-seven million animals are slaughtered a year for consumption and less than a 1,000 are tested a year - it's too low," he said. "If you don't look, you don't find it," Gambetti said. "Our testing is not on the cutting edge."
• Let’s do the math: $2 + 2 = 5$!

• The US has 101 million cows where as France has 5.7 million. This being 17.7 as many cows, the US would need to test $17.7 \times 20,000 = 354,386$ cows a week to be testing proportionately.

• This compares to about 50 cows a week tested now. In other words, the US needs to test 7,000 cows where it is now testing 1 to keep up with international norms.

• The US will also have to develop or accept a test method as the “gold” standard to use
And if you were wondering:
Objectives

- **Transparency**
  - To ensure transparency in the global animal disease and zoonosis situation

- **Scientific Information**
  - To collect, analyse and disseminate scientific veterinary information

- **International Solidarity**
  - To provide expertise and encourage international solidarity in the control of animal diseases

- **Sanitary Safety**
  - Within its mandate under the WTO SPS Agreement, to safeguard world trade by publishing health standards for international trade in animals and animal products
  - To improve the legal framework and resources of national Veterinary Services
  - New mandates for animal production food safety and animal welfare
  - To provide a better guarantee of the safety of food of animal origin and to promote animal welfare through a science-based approach

http://www.oie.int/eng/en_index.htm
OIE Categories

• Category A
  – High infectivity tissues
• Category B
  – Lower infectivity tissues
• Category C
  – Tissues with no detected infectivity

http://www.oie.int/eng/en_index.htm
Diseases Notifiable to the OIE

Multiple species diseases
Anthrax
Aujeszky's disease
Echinococcosis/hydatidosis
Heartwater
Leptospirosis
Q fever
Rabies
Paratuberculosis
New world screwworm (Cochliomyia hominivorax)
Old world screwworm (Chrysomya bezziana)
Trichinellosis
Foot and mouth disease
Vesicular stomatitis
Lumpy skin disease
Bluetongue
Rift Valley fever

Cattle diseases
Bovine anaplasmosis
Bovine babesiosis
Bovine brucellosis
Bovine genital campylobacteriosis
Bovine tuberculosis
Bovine cysticercosis
Dermatophilosis
Enzootic bovine leukosis
Haemorrhagic septicaemia
Infectious bovine rhinotracheitis/infectious pustular vulvovaginitis
Theileriosis
Trichomonosis
Trypanosomosis (tsetse-transmitted)
Malignant catarrhal fever
Bovine spongiform encephalopathy
Rinderpest
Contagious bovinepleuropneumonia

Sheep and goat diseases
Ovine epididymitis (Brucella ovis)
Caprine and ovine brucellosis (excluding B. ovis)
Caprine arthritis/encephalitis
Contagious agalactia
Contagious caprine pleuropneumonia
Foot and mouth disease of ovine species (ovine chlamydiosis)
Haemorrhagic septicaemia
Infectious bovine rhinotracheitis
Rinderpest

http://www.oie.int/eng/en_index.htm
European Commission SSC Classification for Geographical

- BSE Risk (GBR)
- GBR level: Presence of one or more cattle clinically or pre-clinically infected with BSE in a geographical region/country
  - GBR I Highly unlikely
  - GBR II Unlikely but not excluded
  - GBR III Likely but not confirmed or confirmed at a lower level
  - GBR IV Confirmed at a higher level (> 100 cases/1 million adult cattle per year)

USA and Canada Are GBR III

- Canada and the United States have been re-classified from a GBR category II to GBR III in view of the first confirmed cases in 2003.
- EMEA/CHMP/BWP/27/04, 21 July 2004 states “From a public health perspective the reclassification of Canada and USA (to GBR III) does not change significantly the BSE risk of bovine blood and blood derivatives, gelatin or other ruminant materials.”
• On January 2 and 11, 2005, the Canadian Food Inspection Agency (CFIA) announced the confirmation of bovine spongiform encephalopathy (BSE, also known as "mad cow" disease) in two cows from the province of Alberta. One of the cows was born in October 1996 and the second cow was born in March 1998, after the Canadian government instituted a ruminant feed ban in 1997. No part of these animals has entered the human food supply, according to CFIA.

• These two BSE-positive cows bring the total number of BSE-infected cows identified in or linked to Canada to four, including a BSE-positive cow identified in Washington State that was later determined to have originated from Alberta.

The EMEA BWP published on 23 August 2004 a document entitled First Cases of BSE in USA and Canada: Risk assessment of Ruminant Materials Originating from USA and Canada.

This risk assessment is regarding the use of ruminant origin materials from the USA or Canada for use in human or animal medicinal products or the manufacture thereof. There is a public health conclusion and a regulatory conclusion.
From a **public health perspective** they concluded that the reclassification of Canada and the USA (to GBR III) does not change the level of BSE risk of bovine serum and blood derivatives significantly. The risk assessment for bovine serum and blood derivatives as performed previously is still valid.

From a **regulatory perspective**, proposed revision 2 of the TSE Note for Guidance requires the use of non-penetrative stunning if sourcing is performed in GBR III countries. Manufacturers of bovine serum (other than fetal bovine serum, calf serum, and donor bovine serum according to this risk assessment) and blood derivatives of Canadian or US origin will be asked to investigate and confirm that this requirement (non-penetrative stunning) is complied with.
• From a **public health perspective** they concluded that the reclassification of Canada and the USA (to GBR III) does not change the level of BSE risk of any gelatin (acid or alkaline) made from bones.

• From a **regulatory perspective**, an amendment to the TSE Note for Guidance is being proposed to allow the use of acid bone gelatin from GBR III sourced bones, providing the starting materials are free of skulls, spinal cord and vertebrae.

• For all other ruminant materials of Canadian/US Origin (other than blood derivatives and gelatin), the change in GBR rating does not cause concern with regard to TSE safety for Category C tissues and does not significantly change the risk for Category B tissues.
Over Thirty Months Rule Review

• The Over Thirty Months (OTM) Rule is the BSE control set up in 1996 that automatically bans older cattle from entering the human food chain. It is one of the two main food safety controls in relation to BSE used in the UK – the other being Specified Risk Material (SRM) controls.

• On 1 December 2004 Ministers announced the start of a managed transition towards the lifting of the OTM Rule following advice from the Food Standards Agency that the current control measures are no longer proportionate to the risk.

• The primary BSE control, the removal of Specified Risk Material (SRM), which removes more than 99% of any infectivity that may be present, will remain in place.
Geographical Distribution of Countries that Reported at least one BSE Confirmed Case from 1989 to 9 January 2004

- Countries having reported BSE in indigenous animals
- Countries/territories having reported BSE in imported animal(s) only

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World Organisation for Animal Health
PAL (Pharmaceutical Affairs Law) in Japan
effective 1 April 2005.
Japan Has First Death From Human Mad Cow Disease

• 7/2/2005, Reuters News:
  – TOKYO - Japan confirmed on Friday its first case of the human variant of mad cow disease after the death of a man believed to have contracted the fatal brain-wasting illness from eating infected beef in Britain.
  – The man died last December from variant Creutzfeldt-Jakob disease (vCJD), the Health Ministry said. He probably contracted the fatal illness during a month-long stay in Britain in 1989, it said.
• Biggest impact on finished products (pharmaceuticals, IVD, and medical devices). It doesn’t matter if the product was manufactured in the US, Europe, or any other part of the world.

• The manufacturer will have to be compliant with this new regulation in order to sell the product in Japan.

• In brief, any company that currently has a shonin (license for products) will have to submit an updated application to meet the new requirements at the time the kyoko (business license) is due for renewal. A kyoko is good for 5 years. Each company will probably have different dates for the kyoko expiration.
What does it mean to a manufacturer?

• Any customers that have licensed product in Japan will be subject to complying with this new regulation.
• The new regulation requires more detailed information be provided about the raw materials used in the product.
• For example: in the past one of your pharmaceutical customers that uses an animal derived raw material in the manufacturing of their product would refer to the drug master file currently on file with the FDA. They would not have been required to provide any additional detail.
• Now the customer will have to provide more detailed manufacturing information on the raw material. This might include manufacturing processes and formulation. There was great concern expressed about having to provide such proprietary information as part of the dossier. This is just one example of some of the changes your customers will be facing.
BSE and Viral Clearance Studies
BSE & Virus Clearance Studies - Why?

- BSE infectious agents - no practical detection method or RMs/Finished Products
- Addresses theoretical risk of BSE & viral contamination
- Possibility of unknown viral contaminants not detected by current protocols
- Satisfies biopharmaceutical customers
- Assists with regulatory requirements - exportation into Europe
- We need to deal with public perceptions
Why Do We Need to Require Studies for Removal of Adventitious Agents?

• Not just for BSE/Viral concerns:
  - Compete for nutrients in cell culture
  - Disrupt cellular processes, cell division - log growth phase
  - Infect cells, possible cytopathic effects
  - byproducts reduce cell productivity, digest secreted proteins
  - prions are not well understood
  - Unknown agents - not yet identified
  - biopharmaceuticals: agents ending up in human population?
• Scrapie used as a model: 263K
• Emulate production using lab scale process - BHL3
• Production - key points identified believed to impact infectivity: heating, filtration & ion-exchange
• Known titers of infectivity spiked at key process steps - downstream measurement
• Inoculate hamsters with 10-fold serial dilutions
• Compare infectivity recovered vs. spike
BSE Clearance Study

- Detection of Infectivity:
- Clinical signs - examine hamsters for scrapie ~ 1 year
- Examine brain by Western Blot for presence of PrP
- Proteinase K - transformed PrP (amyloid) is resistant
BSA: Viral Clearance

- Production - key points identified believed to impact viral infectivity: pH, heat, solvent fractionation
- Emulate production using lab scale process - dedicated virus facility
- Introduce challenge viruses prior to key process steps - select wide range of viruses
- Check infectivity downstream to process steps
Results:
2 heating & filtration steps plus 2 ion-exchange & charcoal filtration steps achieve a 16 Log total reduction in infectivity

Conclusion:
The manufacturing steps are very effective in eliminating a theoretical TSE contamination - applies to part numbers 3301, 3305 & 3310

Study Reprint is available online at www.Serologicals.com and Technical Support
Aprotinin: BSE Clearance

Results:
MeOH extraction, low pH, heating, AMS precipitation & ion-exchange chromatography: 17 Log total reduction in infectivity

Conclusion:
The manufacturing steps are very effective in eliminating a theoretical TSE contamination - applies to part numbers 7105 & 7107

Study Reprint is available online at www.Serologicals.com and Technical Support
### Challenge Viruses

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### BSA: Viral Clearance

#### Results: Cohn BSA

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# BSA: Viral Clearance

## Results: HS BSA

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**BSA: Viral Clearance**

- Results:
  - BVD, IBR & BTV: 6-7 Total Log reduction, regardless of the process
  - PPV: 3.5-3.8 Total Log reduction, regardless of process
  - Albumin yields for the fractionation process were within expected levels for the 2 processes
Manufacturing and Regulatory Considerations
Sometimes It Feels Like the Weight of the World is on the Manufacturer
Manufacturing

• Efforts to improve pathogen safety margins for these biological products are directed towards several areas within the manufacturing processes including:
  – (a) sourcing and screening of raw materials
  – (b) determining the potential for manufacturing processes to reduce pathogen titers, and
  – (c) incorporating methods designed specifically to remove or inactivate contaminating pathogens.

• Methods that could potentially reduce pathogen titers are a major focus for many manufacturers.

• In general, these methods are grouped into two categories, pathogen clearance and pathogen inactivation.
• Researchers have demonstrated that blood could potentially transmit prion infections in experimental animals.

• While every effort is being made to move away from ruminant-sourced products such as enzymes, media additives and serum during biopharmaceuticals manufacturing, these products cannot be totally excluded from many manufacturing processes.

• As BSE continues to be a pandemic problem, in the interests of protecting public health and safety, the potential risks of exposure to these agents must be minimized.
There is no evidence to date that BSE has been transmitted by the use of ruminant-derived raw materials during the manufacture of biopharmaceuticals.

**If** the current cases of vCJD are caused by bovine prions, then the exposure must have occurred before the specified bovine offals ban of November 1989 that prohibited human consumption of CNS and lymphoid tissues from cattle older than 6 months of age. This legislation was based on studies showing that the highest titers of scrapie prions are found in these tissues in sheep. Because the bioassay for bovine prions in mice is so insensitive, the abundance of prions in bovine muscle remains unknown. If the distribution of bovine prions proves to be different from that presumed for sheep, then assumptions about the efficacy of the offal ban will need to be reassessed. *

Raw Material Control

- RM supplier should maintain records related to the name/address of the facility in which the raw material is manufactured and/or the name and address of the supplier/distributor.
- Supplier should have a record of the species of animal from which the raw material is derived.
- The purchaser should have a record of the country(s) of origin of the animal(s) and the country/countries in which the animal has resided. Preferably animals should be sourced from countries that are free or provisionally free of BSE in accordance with OIE.
- **Animals from which the raw material is derived must fulfill the health requirements for human consumption.**
- Appropriate certificates should be available to support this.
- Animals should be sourced from countries that ban feeding of meat and bone meal to ruminants.

Source: D&MD Publications.
• If available, a record of the measures in place to prevent cross-contamination of the raw material with Category I-III risk ruminant materials will add confidence to the TSE risk assessment.
• Ideally, sourcing should be from countries that have not reported cases of BSE, and, require:
  • compulsory notification;
    - compulsory clinical and laboratory verification of suspected cases; and
    - preventative measures to exclude introduction of BSE, via: importation of cattle from ‘high-incidence’ BSE countries; ruminant feed (meat and bone meal) either from countries where BSE incidence is considered high/low or of unknown origin.
• To date, there is no validated test for detection of the BSE agent in raw materials.

Source: D&MD Publications
Cell Lines As Raw Materials

- Continuous cell cultures undergo numerous cell doublings, and consequently, they pose special theoretical risks: potentially harmful mutations might appear and be selected.
- Master seeds and master cell banks are commonly used for vaccine production and recombinant DNA technology-derived products.
- One regulatory and manufacturing concern is the status of these banks that may have been established decades ago. Must they be re-cloned if the country in which bovine materials were sourced becomes a GBR III or GBR IV?
- In general, with banked eukaryotic or bacterial cells and viral vaccine seeds, the overall risk-benefit assessment to date favors the continued use of the banked cells and the seed lot system. The benefits outweigh the risks.
Cell Banks

- Master seeds and master cell banks for vaccine antigens, biotechnology-derived medicinal products or other medicinal products that use seed lots or cell banking, that have already been approved for the manufacture of a constituent of an authorized medicinal product will be considered in compliance with EMEA/310/01 Rev2, even if they are incorporated in marketing authorization applications lodged after 1 July 2000 (for human products) or 1 October 2000 (for veterinary medicinal products). Master cell banks and master seeds established before the abovementioned dates but not yet approved as a constituent of an authorized medicinal product are required to demonstrate compliance with EMEA/310/01 Rev2.
Cell Culture Media - Bovine Blood Derivatives

- Bovine serum supplementation of cell culture processes has been a routine and necessary practice for biotechnology. In cases where use of bovine serum cannot be avoided specific guidance as regards sourcing and other considerations are stipulated.
- Regulations require that bovine serum should be tested for potential virus contaminants, such as bovine viral diarrhea virus (BVDV), infectious bovine rhinotracheitis (IBR) virus, and parainfluenza-3 (PI-3) virus. Bluetongue virus (BTV) may be an occasional contaminant of bovine serum. Both PI-3 and BTV are classified as viruses with pathogenic potential for humans (CPMP/BWP/3353/99).
• In addition to the presence of potential viral contaminants, a very significant concern is the potential for contamination of the serum with the bovine spongiform encephalopathy (BSE) agent. However, to date, there is no validated test for detection of the BSE agent in raw materials.

• Just as with human plasma pools, a batch of bovine serum may be derived from large numbers of animals. Serum suppliers must, therefore, take appropriate steps to ensure homogeneity of the harvested material, intermediate pools/bulk, and the production and processing of the final batch of serum.
Bovine Sera Used in Medicinal Products

- **Adult Bovine Serum**
  - Bovine serum derived from adult blood collected post-mortem from cattle that are declared fit for slaughter and for human consumption

- **Calf Serum**
  - Sourced from animals under the age of 12 months and produced in a similar way to adult bovine serum

- **Newborn calf serum (NCS)**
  - Obtained from calves under 20 days old

- **Fetal bovine serum (FBS)**
  - Obtained from fetuses from cattle declared fit for slaughter and for human
  - consumption

- **Donor bovine serum**
  - Derived from animals less than 30 months old; this is produced by repeated bleeding of donor animals from controlled standing herds.

Source: D&MD Publications.
The Quality System is Your Defense

• GMP requires manufacturers to document both the safety and efficacy of the product as well as provide information to demonstrate compliance with the principles of GMP including the existence of an adequate quality system.

• In the case of animal derived raw materials, these controls must be documented and maintained by the quality system.
Check List For Purchasers of Animal Derived Products

- Supplier certification
- Your supplier is obligated to provide details re their manufacturing process, and their QA program
- Agree up front with your supplier on release specs and on the contents of the batch documentation file that will be sent to you
- Audit the supplier—serum collection, processing and filling sites and QA
- Be sure that the supplier provides documentation that demonstrates the use of bovine-derived ingredients that are sourced from animals born, raised, or slaughtered in specific BSE countries and there is an adequate quality systems.
- ISO 9000 and HACCP (Hazard Analysis and Critical Control Points) can be used for documentation.
- A quality system is critical in preventing the potential for cross contamination of materials sourced in BSE-free countries with materials sourced from countries that have reported BSE,
- In common manufacturing or storage equipment must be validated to demonstrate the removal of, and prevention of cross-contamination
- Again, a quality system that can trace materials of ruminant origin used in manufacture is a necessity. Be sure that you will be able to obtain and archive information related to the manufacturing facilities and processes of your supplier.
- Biological raw materials employed in pharmaceutical/device manufacture should be sourced from animals that fulfill the health requirements for human consumption.
- Your purchasing group must be responsible for assuring, by means of complete documentation, that every supplier is currently certified to provide all materials being purchased from that supplier.
Regulatory Considerations

- Regulators Perspective
- Risk Assessment: General Considerations
- Risk Evaluation: Factors for Consideration
- Risk-Benefit Analysis
Use in Cell Culture

- Manufacturers are advised by regulators to make significant efforts to develop serum-free or reduced serum alternatives.
- Guidelines indicate that whenever feasible serum from non-ruminant animals should be used in product manufacture.
From The Regulatory Perspective

- The recommended approach is to replace the working cell banks as a precautionary measure, taking into account the need to maintain adequate supplies of the medicinal product with public health benefits during the replacement.
- Ruminant-derived materials used in fermentation/routine production and in the establishment of working seeds and working cell banks should be in full compliance with the TSE guideline.
- Existing WS and WCBs should be replaced if information is not available on all materials used in their establishment. A risk assessment can only be used to define the timeframe of the replacement.
- The origin of newly developed products should be documented as completely as possible
Considerations: Manufacturing Processes

• Potential of the manufacturing process to inactivate/remove the TSE agent

• Manufacturers should consider including procedures known to possess potential for prion clearance in their manufacturing processes

• Processes validated to remove/reduce or eliminate adventitious agents and avoid concentrating the TSE agent should be used
Considerations: Manufacturing Processes

- Prion clearance can include removal steps such as chromatography and filtration as well as inactivation methods (gamma-irradiation).
- Use of alcohols, or cryoprecipitation, so that each successive step precipitates out a few logs of infectivity
- Category A (high risk) materials are used in the manufacture of a product, dedicated equipment should be used.
- If materials from different risk categories are handled in the same plant, adequate control measures should be in place to minimize the risk of cross contamination
- Well-planned barriers and personnel and materials flow can reduce the likelihood of carrying infectivity past the removal steps
Prion Clearance

• Process characterization assists in determining whether the existing manufacturing steps could potentially clear prions (serendipitous clearance) or whether any additional clearance steps should be incorporated (based on assessment of level of risk associated with the product).

• CPMP (Committee for Proprietary Medicinal Products) guidance documents acknowledge that several routine processing steps such as precipitation, chromatography, and nanofiltration can contribute to TSE agent removal (CPMP/BWP/1244/00) and require that whenever TSE clearance claims are made for a particular step, the process should be validated (CPMP/BWP/877/96).
Prion Clearance Studies

- Dedicated laboratory, not manufacturing area
- Spiking studies*
  - Regulatory guidelines do not mandate a particular type of spike but require that an appropriate justification be provided for both the TSE strain used in the clearance studies as well as the nature of the spike.
  - Reduction factors of less than 1 log should not be used in calculation of the overall prion clearance capacity of the manufacturing process.
- Validated scale down of manufacturing process
- Identification of Critical Parameters
  - each process step is evaluated for its clearance abilit
- Critical process parameters should be controlled and monitored.

*Recommendations and guidance for design of virus clearance evaluation studies have been described in regulatory documents (CPMP/BWP/268/95, 1996)
Cleaning Procedures

- Validated methods for decontamination of equipment potentially exposed to TSE agents have not been established in part due to the lack of relevant scientific information.
- The removal of all adsorbed protein by the use of sodium hydroxide (NaOH) or chlorine-releasing disinfectants (e.g., 20,000 ppm chlorine for 1 hour) have been considered acceptable approaches where equipment that cannot be replaced has been exposed to potentially contaminated material
- Replace as many parts as humanly possible
- Elevated temperatures are often used in conjunction with NaOH.
- Cleaning effectiveness can be demonstrated by testing for residual protein or total organic carbon and/or by checking ionic strength of rinsing solutions (EMEA410/)
A prion has been defined as "small proteinaceous infectious particles which resist inactivation by procedures that modify nucleic acids".

Remember: Disinfection is not Business As Usual
Prions are hard to kill!

- **Ineffective**
  - Alcohol, Ammonia, β-propiolactone, Formalin, Hydrochloric acid, Hydrogen peroxide,
  - Peracetic acid, Phenolics, Sodium dodecyl sulfate (5%)
  - Gaseous Disinfectants
    - Ethylene oxide, formaldehyde
  - Physical processes
    - Boiling, Dry heat (< 300°C), radiation (microwave, UV, ionizing)

- **Variable or Partially Effective Methods**
  - Chlorine dioxide, glutaraldehyde, Guanidinium Thiocyanate (4M), Iodophores, Sodium dichloro-isocyanurate, Sodium metaperiodate, Urea (6 M)
  - Physical processes
    - Autoclaving, 121°C for 15 min, Boiling in 3% Sodium dodecyl sulfate

- These methods are capable of reducing prion titer but infectivity is still detectable following exposure to these treatments.

Source: D&MD Publications.
It is recommended that dry waste be autoclaved at 132°C for 4.5 h or incinerated. Large volumes of infectious liquid waste containing high titers of prions can be completely sterilized by treatment with 1N NaOH (final concentration) or autoclaving at 132°C for 4.5 h. Disposable plastic ware, which can be discarded as a dry waste, is highly recommended.
• Gordon* stabilized the vaccine using formalin, a potent disinfectant made from formaldehyde and alcohol. Normally this treatment would be expected to kill foreign infections, but the scrapie agent survived and went on to kill several hundred of the sheep treated with Gordon’s vaccine. Gordon realized that he had accidentally performed a massive experimental transmission, with disastrous results.

*Bill Gordon, a Scottish scientist who directed the Compton Laboratory of England’s Institute for Research on Animal Diseases. (1950)
Submitting to a Regulatory Body

- From a regulatory standpoint, TSE compliance is evaluated on a case-by-case basis.
- As with other raw materials used in EU pharmaceutical production, a “certificate of suitability to a monograph of the EP” (CEP), also sometimes referred to as a “certificate of suitability” should be available for ruminant-sourced materials.
Risk Evaluation: Factors for Consideration

- Donor Species and Animal
  - The potential risks associated with the use of a particular product should be evaluated in view of the species of origin of the donor as well as the recipient. While products of human origin may be preferable from an immunological standpoint, human-sourced agents carry the potential risk for intra-species amplification of any adventitious disease agent associated with the medicinal product.
Risk Assessment

• The first determination to be made is whether the donor animal is a TSE-relevant species
• The most satisfactory source of materials is from countries that have not reported cases of BSE and require compulsory notification, and compulsory clinical and laboratory verification of suspected cases (high risk / low risk)
• Sourced from animals that fulfill the health requirements for human consumption
• Fetal material carries less risk as compared with newborn, adolescent, or adult animals
• Source animals should be born after the ban on feeding MBM was imposed
• Source from well-monitored herds:
  – no cases of TSE
  – never been fed mammalian-derived protein
  – fully documented breeding history
  – new genetic material only from herds with the same BSE-free status
  – Readily identifiable animals
• Age of Animal
• Raw material sourced: blood, lung, pancreas, etc.
• Collection Methods:
  – No penetrative stunning
  – SOPs and prevention of cross contamination with SRMs at time of slaughter
  – Well trained personnel
Risk-Benefit Analysis

• Usage dictates the level of concern for animal-derived products
  – Bovine CNS tissue implanted in a human carries far greater risk than a biologic drug grown in cell culture media with BSA added

• Parenterals are generally of greatest concern
  – pose greater risks as compared with topical exposure or incidental contact from non-biological uses.
  – For biological products, such as vaccines or proteins produced in cell culture, all regulatory authorities make a clear distinction between one-time risks and recurrent additive risks.
Risk-Benefit Analysis

- Multiple exposures increase the opportunity for infection (hemophiliacs are an example)
- Implants and medical devices where the "exposure time" may be extended.
- Higher risk will also be more tolerable for essential/critical applications affecting small, high-need populations
- Cosmetic and luxury treatments are not generally tolerable for higher risk applications
- Population: Adult, Young, Old, Children
Detecting Prions in Our Food

- No practical detection methods exist, at present.
- The abnormally shaped prions are resistant to most heat and chemical treatments, however certain food manufacturing processes (e.g. gelatin production) do result in significant decrease in prion infectivity through exclusion.
- There are no known means of reconditioning contaminated foods. The key to food protection is obtaining bovine meat and meat byproducts from animals not infected with BSE and protecting against contamination of food with high risk tissues, especially brain and spinal cord tissue.
Dealing With Public Perceptions of Your Product
Public Perception
Balancing Panic and Protection

• What regulators and industry fear most deeply is “consumer panic.”

• The issues surrounding mad cow disease are difficult even for scientific specialists to grasp, and policymakers fear that any airing of these issues will trigger misunderstandings, media sensationalism, and consumer boycotts of beef, milk and other products.
Horror Stories Fuel Public Perceptions

- According to his friends, the beef scare had “tipped him over the edge.” Since it began, he had been unable to sell any of his 200 cattle and was facing financial ruin.

- Maynard Potter was not the only farmer to discover that reporting a case of scrapie had in practice become an offense punishable by bankruptcy.
• If you drive a car, there’s a certain statistical probability that you will die in a traffic accident.

• Do you still drive anyway?

• What are your odds?

http://www.nsc.org/lrs/statinfo/odds.htm
Acceptable Risks

• If you stay at home, you might die by gunshot from a burglar.
• Do you go home every night anyway?
• What are the odds of dying by firearm assault in the US?

http://www.nsc.org/lrs/statinfo/odds.htm
Acceptable Risks

• The odds of dying from an injury in 1999 were 1 in 1,805.¹
• The lifetime odds of dying from an injury for a person born in 1999 were 1 in 24.¹
• A fatal injury occurs every 6 minutes and a disabling injury occurs every 2 seconds.²

¹ http://www.nsc.org/lrs/statinfo/odds.htm
² http://www.crossroads.nsc.org/injury.cfm
Another Quick Guess!!!

• What are your chances of eating a hamburger in the UK that is contaminated with prions?

• Write it down!
Death Rate in the US from CJD

- The average annual CJD death rate in the United States has remained relatively stable at about one case per million population per year.

- In addition, CJD deaths in persons aged <30 years in the United States remain extremely rare (<1 case per 100 million per year).

http://www.cdc.gov/ncidod/diseases/cjd/bse_cjd_qa.htm
Heart Valves

• A British company preparing 40,000 heart valves a year from bovine pericardium, primarily for export, and they are not required to source this material from BSE-free herds even in peak epidemic years. It is amazing to watch health "authorities" groveling on their bellies to wring petty concessions from middle management at obscure little companies.

• The main worry is not the practice of using 800 potentially infected cows a week for human heart transplant material but that the press or recipients will get wind of it, hurting business.

Sun, 3 Sep 2000. Unpublished Inquiry documents obtained by CJD activist Terry S. Singeltary Sr. of Bacliff, Texas
• Just imagine. You have read about the Swissair disaster and are about to fly in a plane of the same make. As you leave for the airport, you read a report from a government scientist. He says that, in his opinion, there is "a very real risk" of the same fault occurring in other planes of the type. "If this distinct possibility is true," he goes on, "it would be an emergency."

• What on earth do you do? Do you fly anyway, change your flight, or wait for the Government to ground every plane? After all, the man is an official scientist. He has gone public. He purports to know.

Twenty-seven deaths have been attributed to CJD, many fewer than to such food poisons as *E. coli* or salmonella which we seem to take in our stride. Yet as a result of the resulting hysteria, and with continental farmers eagerly in the van, the beef industry was devastated. Tens of thousands of cattle were fed to power stations and some £5 billion of public money was squandered. The root cause was a group of scientists changing an "inconceivable risk" of contracting CJD from eating beef (in 1995) to a "very small" one (in 1996).

There is a human surveillance effort in the US

- **Protocols:** [Autopsy Protocol](#)
  [Biopsy Protocol](#)
  [CSF Protocol](#)
  [Urine Protocol](#)
  [Blood Protocol](#)

- **IMPORTANT NOTICE:** The Surveillance Center now requires that a genetic consent form be signed before we can sequence the prion protein gene. Please have the patient or next of kin sign a genetic consent form when submitting blood, brain biopsy tissue, or brain autopsy tissue. Please notify us in writing that a consent has been signed, or send us a copy of the signed consent. We cannot perform genetic testing without a signed consent. If your facility does not have a genetic consent form, please call us to request a copy of our form. These forms will soon be available on our new website.

- Does this help or scare us even more?
Sign The Petition!

• Join tens of thousands of citizens and sign the Mad Cow USA-Stop the Madness petition, demanding that the US Government adopt and enforce the same strict standards required by the European Union and Japan:
  – Mandatory testing for all cattle brought to slaughter, before they enter the food chain.
  – Ban the feeding of blood, manure, and slaughterhouse waste to animals.
  – Stop harassing farmers and food processors who are interested in independently testing their own beef.
What is an Acceptable Risk to Government Officials?

• Our puritan backgrounds lead us to:
  – “better safe than sorry” or “look before you leap.”

• What we need is to convince our government politicians world-wide to implement a risk-assessment policy based on sound science, not perceived danger.
Recommendaions for BSE Risk Mitigation

• We should not require the medical device and pharmaceutical industry to move to animal free media solely due to BSE concerns:
  – We should aggressively pursue requiring that animals are identified and tracked from birth herd to slaughter
  – Require studies that demonstrate the removal of viruses and prions during the manufacturing processes
  – Support/encourage the continued efforts of all agencies to have a consistent and immediately executionable plan for the NEXT occurrence of BSE in any country
MAD ABOUT PRIONS?

• Search the Web:
  – CDC
    http://www.cdc.gov/ncidod/diseases/cjd/cjd.htm
  – An FDA website describing the ruminant feedban introduced in the US as a result of the BSE outbreak in Europe:
    http://vm.cfsan.fda.gov/~lrd/tpprotei.html
  – The United Kingdom's Ministry of Agriculture website with regularly updated information on the BSE outbreak:
  – The United Kingdom's ministry of health website with monthly updated number of new variant CJD cases:
    http://www.doh.gov.uk/cjd/cjd_stat.htm
  – APHIS
And the Answer IS………

• Chances are 1 per 10 billion servings of beef in the UK

• According to: http://www.cdc.gov/travel/diseases/madcow.htm
Conclusion: Bovine Products Are Safe!
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