December 20, 2005

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No: 2002N-0273 (formerly Docket No. 02N-0273)

**Substances Prohibited From Use in Animal Food and Feed**

Dear Sir or Madame:

As scientists and recognized experts who have worked in the field of TSEs for decades, we are deeply concerned by the recent discoveries of indigenous BSE infected cattle in North America and appreciate the opportunity to submit comments to this very important proposed rule We strongly supported the measures that USDA and FDA implemented to protect public health after the discovery of the case of bovine spongiform encephalopathy (BSE) found in Washington State in 2003. We know of no event or discovery since then that could justify relaxing the existing specified risk material (SRM) and non-ambulatory bans and surveillance that were implemented at that time. Further, we strongly supported the codification of those changes, as well as additional measures to strengthen the entire feed and food system. The discovery of additional cases of indigenous BSE in North America since that time has validated our position and strengthened our convictions.

We caution against using the 18 month enhanced surveillance as a justification to relax or impede further actions. While this surveillance has not uncovered an epidemic, it does not clear the US cattle herd from infection. While it is highly likely that US and Canadian cattle were exposed to BSE prior to the 1997 feed ban, we do not know how many cattle were infected or how widely the infection was dispersed. BSE cases are most likely clustered in time and location, so while enhanced surveillance provides an 18 month snapshot, it does not negate the fact that US and Canadian cattle were exposed to BSE. We also do not know in any quantitative or controlled way how effective the feed ban has been, especially at the farm level. At this point we cannot even make a thorough assessment of the USDA surveillance as details such as age, risk category and regional distribution have not been released.



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A number of countries initially attempted to take partial steps in regard to feed controls only to face repeated disappointments in predicted downturns of the epidemic course. We in North America could do this experiment all over again, waiting for each new warning before adding more stringency to our control measures, or we can benefit from the experience of others and take decisive measures now to arrest any further development of underlying cases that is implicit in those already discovered to date.

The discovery of 5 indigenous North American cases, including one born after the implementation of the current feed ban, should provide the necessary incentive to implement, monitor and enforce a comprehensive and protective feed ban that is more congruent with the measures that have been proven to be effective throughout the world. In particular, we urge the FDA to act without further delay to strengthen the animal feed regulations by implementing the program proposed by the Canadian Food Inspection Agency (CFIA) in the December 11, 2004 Gazette. This includes removing all specified risk materials (SRMs) and deadstock from all animal feed. We also urge that the FDA discontinues the legal exemptions which allow ruminant protein to be fed back to ruminants (with the exception of milk). Many of these exemptions do not exist in other countries.

Bovine products and byproducts are used for both food and pharmaceuticals. These human uses require the highest level of safety. Because of the hardy nature of the BSE agent and its high potential for cross contamination, the most effective way to protect bovine products and bovine derived materials from contamination by BSE is to ensure that infected animals or carcasses never enter processing plants. The goal would be to discover and remove infected animals from production as early as possible in the infection and long before they would be sent to slaughter. Until we have diagnostic tools powerful enough to allow us to discover the disease early in its prolonged pre-clinical incubation, we have to rely on the next best strategy which is to prevent any exposure through feed. The exemptions in the current ban as well as in the newly proposed rule make this difficult if not impossible, as they still provide legal avenues for ruminants to consume potentially contaminated ruminant protein.

It is our opinion that the proposed rule falls woefully short in effective measures to minimize the potential for further transmissions of the disease. By the FDA's own analysis, exempted tissues (such as distal ileum, DRGs, etc) contain approximately 10% of the infectivity in affected animals. Thus the proposed rule still allows the possibility for cattle to be exposed to BSE through:

1. Feeding of materials currently subject to legal exemptions from the ban (*e.g.*, poultry litter, plate waste)
2. Cross feeding (the feeding of non-ruminant rations to ruminants) on farms; and
3. Cross contamination of ruminant and non-ruminant feed

We are most concerned that the FDA has chosen to include a provision that would allow tissues from deadstock into the feed chain. We do not believe that down or dead stock

should be allowed into the food or feed chain whatever the age of the animal and whether or not the CNS tissues are removed. We do not support the provision to allow removal of brain and spinal cord from deadstock over 30 months for a number of reasons. This category of animals contains the highest level of infectivity and that infectivity is in other tissues besides just brain and spinal cord. Recent improvements in the BSE bioassay, have now made it possible to detect BSE infectivity 1000 time more efficiently than before. This assay has revealed the presence of BSE infectivity in some but not all peripheral nerves and in one muscle. (Buschmann and Groschup, 2005) This published and peer reviewed work is consistent with other publicly reported studies in Japan where, by western blot testing, prions were found in the peripheral nerves of a naturally infected 94-month-old cow. We feel that the studies as reported above have merit. The current studies not only re-enforce the risk of down and deadstock but also appear to provide additional information that these animals may be a potential source of greater levels of infectivity into the feed system. We also doubt that brain and spinal cord can be completely removed especially during warmer weather. Given the biological composition of these tissues, they are predisposed to rapid autolysis.

As world wide surveillance for BSE increases, several atypical cases of bovine TSE have been discovered. These cases either show no clinical signs, or present as 'downers', and have an atypical neuropathology with respect to lesion morphology and distribution, causing problems in both clinical and post-mortem diagnosis. The origin of the cases are unclear but they suggest that even should typical BSE be eliminated, there may be other TSE diseases of cattle that could result by "mutation" and selection. Refeeding of contaminated protein could potentially perpetuate transmission much like typical BSE. An effective feed ban could prevent the expansion of such strains. We also note that there are other species which are susceptible to BSE and the current regulations allow for SRMs to be included in feed for these animals.

For BSE to be perpetuated, the animal production system must have a source of agent and a means by which cattle or other susceptible species are exposed to this agent. We feel that in North America, the source and routes of exposure still exist, hence allowing for the continued recycling of BSE. We have detailed the scientific justifications for our position below.

**Source of the agent: SRMs (Specified Risk Materials)**

SRMs, as defined by the USDA, are tissues which, in a BSE infected animal, are known to either harbor BSE infectivity or to be closely associated with infectivity. If SRMs are not removed, they may introduce BSE infectivity and continue to provide a source of animal feed contamination. For example, the skull and vertebral column which encase the brain and spinal cord, respectively, can be assumed to have gross contamination. Rendering will reduce infectivity but it will not totally eliminate it. This is significant as research in the United Kingdom has shown that a calf may be infected with BSE by the ingestion of as little as .001 gram of untreated brain.

The tissue distribution of infectivity in BSE infected cattle has primarily been determined by 3 studies conducted in the United Kingdom all of which had limitations.

In two of the studies, bioassays were done in mice which are at least 1000 fold less sensitive to BSE infection than cattle themselves. Only higher titers of infectivity can be detected by this method. These investigations found infectivity in the brain, spinal cord, retina, trigeminal ganglia, dorsal root ganglia, distal ileum and bone marrow (the bone marrow finding was from one animal). Infectivity was found in distal ileum of experimentally infected calves beginning six months after challenge and continuing at other intervals throughout life. (Wells et. al., 1994; 1998). The bioassay study in calves has produced similar results and in addition infectivity has been found in tonsil. The study is still in progress. Another project has found infectivity in the lymphoid tissue of third eyelid from naturally infected animals. (Dr. Danny Matthews, UK DEFRA, personal communication).

While bioassay in cattle is far preferable to mice in terms of sensitivity, cattle nevertheless present their own limitations in terms of the long incubation time and the limited number of animals that can be used for assay compared to rodents. As a consequence the significance of the negative finding for many tissues is questionable. In fact, by the end of 2004 there was increasing evidence in species other than cattle that peripheral nerves and muscle have infectivity. (Bosque et al., 2002; Glatzel et al., 2003;Bartz et al., 2002; Androletti et al., 2004; Mulcahy et al., 2004; Thomzig et al., 2003; Thomzig et al., 2004)

In some of these species, studies indicate that the agent migrates to the brain and spinal cord, replicates to high levels in the CNS and then spreads centrifugally from the spinal cord back down through the spinal neurons to the junction of the nerves and muscle into the muscle cells themselves. A recent German study (Buschmann and Groschup, 2005) examined nerves and muscle from a cow naturally infected with BSE and found that infectivity was present in several peripheral nerves and one muscle. The method of detection was bioassay in bovinized transgenic mice that show the same or greater sensitivity to transmission of BSE as cattle. This research concurs with findings by Japanese scientists that BSE infectivity is present in peripheral nerves at least in the clinical stage of disease.

It is our opinion that there is increasing evidence that the pathogenesis of BSE might not be entirely different from TSEs in other species at the point of clinical disease in that there is peripheral involvement. We feel that the studies as reported above have merit. The current studies not only re-enforce the risk of down and deadstock but also appear to provide additional information that these animals may be a potential source of greater levels of infectivity into the feed system.

In the event that FDA may confer with USDA about the risks associated with peripheral nerves we want to point out one issue. In the recent publication of the final rule on the

importation of whole cuts of boneless beef from Japan, 9 CFR Part 94 [Docket No. 05-004-2] RIN 0579-AB93, we disagree with the interpretation provided by USDA, APHIS.

APHIS seems to discount the studies conducted by Groschup et al. 2005. on the basis that the transgenic mouse bioassay that they used may be too sensitive. In taking this position they have failed to realize that the point of an assay is to reveal in which tissues the infectivity resides and its relative concentration to brain or spinal cord. For this purpose, no assay can be too sensitive. Of course, the probability of an actual infection will be affected by the efficiency of infection which will be a function of dose, route of exposure and any host barrier effects that are present.

We would also like to point out a factual error in the conclusion. APHIS states, "Given these factors, APHIS has determined that the finding of BSE infectivity in facial and sciatic nerves of the transgenic mice is not directly applicable to cattle naturally infected with BSE. Therefore, we do not consider it necessary to make any adjustments to the risk analysis for this rulemaking or to extend the comment period to solicit additional public comment on this issue." It is incorrect that the infectivity was found in the peripheral nerves of transgenic mice. The peripheral nerves were harvested from a cow naturally infected with BSE. Transgenic mice were used as a bioassay model.

From [Docket No. 05-004-2] RIN 0579-AB93:

"Peripheral Nerves

Issue: Two commenters stated that the underlying assumption of the proposed rule, that whole cuts of boneless beef from Japan will not contain tissues that may carry the BSE agent, is no longer valid because researchers have found peripheral nervous system tissues, including facial and sciatic nerves, that contain BSE infectivity.\2\ One of these commenters requested APHIS to explain whether and what additional mitigation measures are needed to reduce the risks that these tissues may be present in Japanese beef. This commenter further requested an additional comment period to obtain public comments to treat this new scientific finding.

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\2\ Bushmann, A., and Groschup, M.; Highly Bovine Spongiform Encephalopathy-Sensitive Transgenic Mice Confirm the Essential Restriction of Infectivity to the Nervous System in Clinically Diseased Cattle. The Journal of Infectious Diseases, 192: 934-42, September 1, 2005.

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Response: APHIS is familiar with the results of the study mentioned by the commenters in which mice, genetically engineered to be highly susceptible to BSE and to overexpress the bovine prion protein, were inoculated with tissues from a BSE-infected cow. This study demonstrated low levels of infectivity in the mouse assay in the facial and sciatic nerves of the peripheral nervous system. APHIS has evaluated these findings in the context of the potential occurrence of infectivity in the peripheral nerves of cattle and the corresponding risks of the presence of infectivity in such tissues resulting in cattle or human exposure to the BSE agent. The results from these experiments in genetically engineered mice should be interpreted with caution, as the findings may be influenced by the overexpression of prion proteins and may not accurately predict the natural distribution of BSE infectivity in cattle. Further, the overexpression of prion

proteins in transgenic mice may not accurately mimic the natural disease process because the transgenic overexpressing mice have been shown to develop spontaneous lethal neurological disease involving spongiform changes in the brain and muscle degeneration.\3\ In addition, the route of administration to the mice was both intraperitoneal and intracerebral, which are two very efficient routes of infection as compared to oral consumption. Given these factors, APHIS has determined that the finding of BSE infectivity in facial and sciatic nerves of the transgenic mice is not directly applicable to cattle naturally infected with BSE. Therefore, we do not consider it necessary to make any adjustments to the risk analysis for this rulemaking or to extend the comment period to solicit additional public comment on this issue."

**Source of the agent: Deadstock**

The total amount of TSE infectivity in a TSE infected animal increases steadily throughout the infection and exponentially once the infectivity reaches the brain. Infected individuals only exhibit recognizable clinical signs once infectivity titers have reached high levels in the brain. Surveillance data collected throughout Europe indicates there is a much greater likelihood for BSE to be detected in dead or down cattle than from healthy normal animals. This has so far also been borne out by the experience in North America. Animals that die of BSE harbor the greatest amount of agent that can be produced by the disease. Leaving the tissues from the highest risk category of cattle in the animal feed chain will effectively nullify the purported intent of this regulation. This point is supported by the 2001 Harvard risk assessment model that demonstrated that eliminating dead and downer, 4D cattle, from the feed stream was a disproportionately effective means of reducing the risk of re-infection.

*"The disposition of cattle that die on the farm would also have a substantial influence on the spread of BSE if the disease were introduced." The base case scenario showed that the mean total number of ID50s (i.e., dosage sufficient to infect 50 percent of exposed cattle) from healthy animals at slaughter presented to the food/feed system was 1500. The mean total number of ID50s from adult cattle deadstock presented to the feed system was 37,000. This illustrates the risk of "4D cattle" (i.e., deadstock).*

From the Harvard Risk Assessment, 2001, Appendix 3A Base Case and Harvard Risk Assessment, 2001 Executive Summary

It is likely that these numbers would have to be adjusted upwards, if the UK attack rate and Groschup data were considered.

**Inflammation and TSEs**

There have been 3 recent peer reviewed publications which indicate that chronic inflammatory conditions in a host with a TSE may induce prion replication in, or distribution to organs previously thought to be low or no risk. They are as follows:

1. Chronic Lymphocytic Inflammation Specifies the Organ Tropism of Prions (Heikenwalder et. al. 2005 www.scienceexpress.org/20 January 2005/ Page 1/ 10.1126/science.1106460)

2. Coincident Scrapie Infection and Nephritis Lead to Urinary Prion Excretion (*Seeger et al., Science* 14 October 2005:Vol. 310. no. 5746, pp. 324 – 326 DOI: 10.1126/science.1118829)

3. $PrP^{sc}$ in mammary glands of sheep affected by scrapie and mastitis (Ligios C., *et al. Nature Medicine*, **11**. 1137 – 1138, 2005)

These studies from the Aguzzi laboratory warn that concurrent chronic inflammatory disease could dramatically alter the distribution of BSE infectivity in infected cattle. Down and dead stock are at higher risk for both BSE and other systemic conditions. If the results reported above are also applicable to cattle, the carcasses of dead and down stock affected by BSE might contain even higher levels of infectivity, or contribute infectivity via tissues that are not ordinarily at risk in normal animals.

**Exposure: Industry Practices or Exemptions which may pose a risk**

Poultry Litter

In the United States poultry litter can be fed to cattle. There are two potential sources of risk from poultry litter. Poultry litter not only consists of digested feed but also of feed which spills from the cages. As a consequence, the practice of feeding litter back to cattle is by its nature non-compliant with the current feed ban if the poultry themselves are being fed ruminant protein. Given that ruminant protein can no longer be fed to ruminants in the United States and that most, if not all, countries will no longer import North American ruminant MBM, an even larger part of poultry diets is now ruminant MBM. Spillage provides a direct link to back to cattle but feces are also likely to contain infectivity.

There is no reason to expect that TSE infectivity would be inactivated by passage through the poultry gut, and only a slim possibility that composting would reduce infectivity at all. Thus poultry feces are another potential route of transmission back to cattle. Evidence for this comes from rodent experiments where infectivity was demonstrated in the feces after being fed: "Laboratory experiments show that mice orally challenged with scrapie have detectable infectivity that passes through the gut. Gut contents and fecal matter may therefore contain infectivity, and it is noted that in experimental oral challenges in cattle conducted in the UK, feces must be treated as medical waste for one month following the challenge. It is concluded that digestive contents and fecal material from livestock or poultry currently being fed with MBM potentially contaminated with BSE should not be used as a feed ingredient for animal feed." **[Proceedings: Joint WHO/FAO/OIE/ Technical Consultation on BSE: public health, animal health and trade. Paris, 10-14 June 2001; and Alan Dickinson, personal communication].**

It may be possible to remove the risk from poultry litter by sterilization. However, unless or until a method can be developed and validated, poultry litter should be banned from ruminant feed.

Ruminant Blood

In contrast with humans, sheep, monkeys, mice and hamsters, including sheep and mice infected with BSE and humans infected with vCJD considered identical to BSE, no infectivity has so far been demonstrated in the blood of BSE infected cattle. However, we consider it unlikely that cattle are the sole outlier to what has been a consistent finding in all other TSE diseases where the measurement has been made with sufficient sensitivity to detect the low levels of infectivity that are present in blood. Rather, this failure is more likely the result of the very small volumes of blood that were used for the inoculations (less than 1 ml), whereas whole transfusions were administered to assay animals in the published sheep scrapie/BSE experiments. If blood is infected then all vascularized tissues can be expected to contain some infectivity in proportion to the content of residual blood.

Micro emboli are a possible source of blood-borne agent that could be at much higher titer than blood itself, in slaughtered cattle carrying BSE infection. Stunning can release micro emboli of brain tissue into the circulatory system from where they can be distributed to other tissues in the few moments before the exsanguination and death. (Anil, et al, 2001a & b; Anil et al, 2002; Love, et al, 2000). This source of infection could extend a higher infectivity risk to tissues that would otherwise be at low risk, thereby allowing exposure of cattle through any of the legal exemptions and potentially producing a feed and food risk. Blood-borne contamination may be a special problem where spray-dried blood is being used as a milk replacer for calves, as it is thought that young animals are especially susceptible to infection.

Certainly, blood and blood proteins should not be used as feed without conclusive evidence that they are safe.

Unfiltered Tallow

Ruminant tallow is exempted from the current feed ban. Tallow contains protein impurities (i.e. MBM) that could be a source of TSE infectivity. There are no impurity level requirements for this tallow. It has been reported that it is standard practice to produce tallow which has an impurity level of .15% or below, but it is not clear that this is fully adequate to remove the risk of transmission and there is no requirement to meet even this standard. We urge that protein contaminants be excluded from tallow and that SRMs also be removed.

Plate Waste

Plate waste is not limited to meat (muscle tissue). For example, cuts that include a portion of the spinal cord or that are contaminated by cord or ganglia during preparation could contain high levels of infectivity if derived from a TSE infected animal late in the preclinical stage of infection. At best this material would only be exposed to normal cooking temperatures. USDA, APHIS experience with the Swine Health Protection Act has revealed that plate waste also includes uncooked trimmings and bones. Although the current FDA regulation requires the plate waste be treated again, there are no specifications which would render a TSE agent inactive. Of greatest risk would be any bovine source of infectivity but also sheep scrapie, although not known to be a risk for human consumption, is one of the possible origins of BSE. The sheep scrapie agent is known to be widely dispersed including relatively high titers in lymphoid as well as nervous tissue. We support the USDA's opposition to the exemption of "plate waste" as stated in written comments since 1997.

**Exposure: Cross Feeding and Cross Contamination**

The UK epidemiology has clearly shown that BSE contaminated feed is the primary if not sole vehicle for the transmission of BSE between cattle. Moreover, results from the United Kingdom's attack rate study indicate that it does not take much exposure to transmit BSE to cattle. Recent results from the attack rate study which is still in progress have found that .1 g of brain transmitted BSE by the oral route to 3 cows out of 15 thus far, and .01 and .001gr of brain have transmitted BSE (1 cow out of 15). (Danny Matthews, DEFRA presentation at TAFS meeting, Washington, DC April 2004).

Rendering may reduce infectivity but it does not eliminate it. (Taylor et al, 1995; Taylor et al, 1997; Schreuder et al, 1998). Given that BSE can be transmitted to cattle via an oral route with just .001 gram of infected tissue, it may not take much infectivity to contaminate feed and keep the disease recycling. This is especially true in countries like the US and Canada which do not have dedicated lines and equipment to manufacture and process feed for ruminants and non-ruminants.

In addition, epidemiological investigations in European countries have shown that cross feeding and cross contamination on farm can be a significant vehicle for continued BSE transmission even after feed bans are well established. Cross feeding is the practice of feeding meal for poultry or pigs or pet food (which can legally contain ruminant MBM) to cattle on the same farm. This is usually due to simple human error or negligence. (Hoinville, 1994; Hoinville et al, 1995; Doherr et al, 2002a; Stevenson et al, 2000)

FDA, CVM reports that compliance with the existing feed ban is high. For the most part this does not include the compliance level on the farm. There are hundreds of thousands of farms in the US. Many of these have multiple species. That is, they raise cattle, pigs, chickens etc., on the same premises. The sheer numbers of farms make it very difficult to

assure compliance on farm and to adequately cover all farms by inspection. Even if the rendering industry and feed industry can maintain 100% compliance at their facilities, if a producer inadvertently feeds chicken feed containing bovine MBM to their cattle, they negate a perfect compliance rate higher in the chain. Recent data from the Harvard BSE risk assessment suggest that the level of misfeeding on farms plays a significant role in the ability of the agent to recycle. In fact George Gray, principal investigator for the study, stated that if, in the United States, misfeeding were to occur at a level of 15%, the R0 would be over 1, indicating that the BSE level would not be declining. (George Gray presentation at the Meeting on BSE Prevention in North America: An Analysis of the Science and Risk; January 27, 2005, Washington, DC.)

The May 2003 Canadian BSE case illustrates the difficulty of on farm enforcement and its serious ramifications. The BSE positive cow was rendered and the MBM distributed to various locations. Two of these locations were poultry farms which mixed their own feed. The farms also had cattle. The subsequent investigation could not eliminate the possibility that the cattle had been fed the same feed as the poultry. The cattle on these farms were completely depopulated.

Human error is extremely difficult to prevent, and managing the risk through enforcement is problematical when confronted with the extreme logistical challenges of on farm monitoring. By eliminating the highest risk materials (SRMs and deadstock) which could introduce infectivity into the feed stream, the MBM resulting from processing becomes inherently safer. If mistakes are then made on farm, they no longer contribute to the recycling of BSE.

**Exposure: Susceptibility of other Species**

**Felines**

A transmissible spongiform encephalopathy has been diagnosed in eight species of captive wild ruminants as well as exotic felines (cheetahs, pumas, a tiger and an ocelot) and domestic cats (Wyatt 1991). There have been over 80 domestic cat cases of Feline Spongiform Encephalopathy (FSE) in Great Britain, and cats in Norway, Northern Ireland, Lichtenstein and Switzerland. The agent isolated from several of these cases is indistinguishable from BSE in cattle using strain typing in mice, suggesting that FSE is actually BSE in exotic and domestic cats. Epidemiological evidence suggests BSE contaminated feed to be the probable source of infection in these species. (MAFF Progress Report, June 1997), thus providing additional supporting evidence for the

dangers of BSE contaminated feed and reinforcing the necessity of removing all sources of potential contamination from the feed stream.

**Other species**

Studies conducted at the National Institutes of Health Rocky Mountain Laboratory caution against assuming that animals which do not become clinically ill are not infected. It is unknown if certain animals may become carriers, i.e., become infected, shed agent but do not progress to clinical disease. Infection of certain rodent species with different TSE strains suggests the possibility of a carrier state (Race and Chesebro, 1998; Race et. al, 2001, Race et al., 2002). In the more recent studies, mice were inoculated with 263K hamster scrapie. There was a prolonged period (approximately one year) where there was no evidence of replication of infectivity. Furthermore, there was no evidence of PrPres during this phase of inactive persistence, which was followed by a period of active replication of infectivity and agent adaptation. In most cases, PrPres was not detected in the active phase as well. It is important to determine if this persistence and adaptation occurs in other species exposed to TSEs as it may have significance in feeding programs which continually expose other species to BSE infectivity. For example, if BSE infected brain and spinal cord are continually fed to certain species, it may be possible for the agent to persist and adapt in these new species. Over time, the 'resistant' species may become a source of agent. The results of Race and colleagues, warns that an inactive persistent phase might not produce detectable PrPres, yet there would be infectivity (Race et. al., 2001).

Pigs displayed evidence of TSE infection after exposure to BSE by 3 distinct parenteral routes. Evidence of infectivity was found in the CNS, stomach, intestine and pancreas (Dawson et. al., 1990). Oral transmission has also been attempted in swine, but after an observation period of 84 months there was neither clinical nor pathological evidence of infection (Dawson et. al., 1990). Parenteral and oral transmission has also been attempted in chickens with no evidence of disease. Tissues from the BSE-challenged pigs and chickens were inoculated into susceptible mice to look for residual infectivity, but to date none has been found. In both instances the detection sensitivity was limited by the use of mice for bioassay instead of same species transmissions into cattle (or pigs and chickens).

If any of these scenarios played out and inapparent infections became established in commercial species, those species could become reservoirs for reinfection of cattle and perpetuation or reintroduction of the epidemic. We also do not know if atypical cases of BSE are more pathogenic for other species and if chronic inflammation may influence the susceptibility of other species. We offer these possibilities to reinforce the need to eliminate all possible sources of infectivity from the feed stream.

In January 2005, the European Union announced that BSE had been confirmed in a goat in France illustrating that the disease can be naturally transmitted to one of the small ruminants. The potential ramifications of this and the logistical challenges associated

with controlling BSE in sheep or goats also provides a justification for removing SRMs from all animal feed. Although these species are covered under the current regulations the cross contamination and cross feeding aspects stated for cattle are applicable.

The need to remove high risk material from all animal feed is also supported by other bodies with expertise in the field of TSEs:

Recommendations of the World Health Organization (WHO)

The World Health Organization (WHO) has issued the following recommendations for countries with BSE or those where a known exposure exists:

- No part or product of any animal which has shown signs of a TSE should enter any food chain (human or animal). In particular:
    - All countries must ensure the killing and safe disposal of all parts or products of such animals so that TSE infectivity cannot enter any food chain.
    - Countries should not permit tissues that are likely to contain the BSE agent to enter any food chain (human or animal).

From the report of a WHO Consultation on Public Health Issues related to Human and Animal Transmissible Spongiform Encephalopathies WHO/EMC/DIS 96.147, Geneva, 2-3 April 1996.

Office of International Epizooties (OIE)

The OIE is recommending that a list of SRMs which include brain, spinal cord, eyes, skull and vertebral column be removed from preparations used for food, feed, fertilizer, etc. If these tissues should not be traded we feel that they should not be used in domestic products either.

BSE Code Article 2.3.13.18

"From cattle, originating from a country or zone with a minimal BSE risk, that were at the time of slaughter over 30 months of age, the following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilizers, cosmetics, pharmaceuticals including biologicals, or medical devices: brains, eyes and spinal cord, skull, vertebral column and derived protein products. Food, feed, fertilizers, cosmetics, pharmaceuticals or medical devices prepared using these commodities should also not be traded."

**Conclusion**

In conclusion we urge the FDA to implement, monitor and enforce a comprehensive and protective feed ban that is more congruent with the measures that have been proven to be effective in other countries that have experienced BSE. We do not feel that we can

overstate the dangers from the insidious threat from these diseases and the need to control and arrest them to prevent any possibility of spread.

We also wish to emphasize that as scientists who have dedicated substantive portions of our careers to defining the risks from TSEs as well as developing strategies for managing those risks, we are confident that technical solutions will be found for many of the challenges posed by these diseases. Thus, we urge the FDA to frame its regulations in terms that allow for the future use of any banned material if it can be proven safe for a given application.

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