

NNFA BSE GUIDANCE

**Developed by NNFA's
Committee for Product and Label Integrity**

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Background

First diagnosed in 1986 in Great Britain, bovine spongiform encephalopathy (BSE), widely known as “mad cow disease,” is a neurological disease affecting the central nervous system of cattle. BSE is classified as a transmissible spongiform encephalopathy (TSE). Other TSE’s include scrapie in sheep and goats, chronic wasting disease of deer and elk, and Creutzfeldt-Jacob disease (CJD) in humans. Prions are aberrant proteins believed to cause the TSE’s. Prions are not viruses, bacteria, fungi or other known pathogen and are resistant to enzymatic breakdown within the body. In humans, for categorization purposes, it is important to distinguish between classical CJD and new variant CJD (nvCJD). Classical CJD occurs in about one person per million per year and was around long before the emergence of BSE in cattle, occurring spontaneously via inheritance or accidentally as a result of medical procedures.^{1,2,3} There is strong scientific evidence linking the new variant CJD to the consumption of food products from BSE-infected cattle.²

Though about 95 percent of all BSE cases have occurred in the United Kingdom, the disease also has been confirmed in native-born cattle in many other European countries as well as in Canada and Japan. A complete list of countries/areas affected by BSE can be found at <http://www.aphis.usda.gov/NCIE/country.html>. New cases of BSE in the U.K. peaked at 36,680 in 1992 and with active feed security measures, fewer than 1,500 cases were confirmed in 2000. In December 2003, one case of BSE was confirmed in the United States in a dairy cow from the state of Washington. Following this incident, the FDA and USDA instituted additional safeguards to protect US food and feed supply.

The US has had BSE-surveillance programs for over a decade to prevent BSE in cattle or nvCJD in humans from occurring in this country. Working together, agencies within the federal government have taken numerous steps to prevent BSE in this country. The USDA’s Animal and Plant Health Inspection Service (APHIS) enforces explicit regulations preventing importation of animal protein products, regardless of species, from BSE countries. New USDA policies were put into place in December 2003 to further strengthen protections against BSE by removing certain animals and specified risk material 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 tested for BSE until the test has confirmed negative; and prohibiting the air-injection stunning of cattle. Additionally, USDA will begin immediate implementation of a verifiable system of national animal identification.

As of May 2003, the total worldwide number of known nvCJD cases among humans was approximately 139.² FDA has reported one case of the new variant CJD (nvCJD) in a woman who contracted the disease while residing in the UK, whose symptoms appeared years later after she moved to the US.² NNFA has no knowledge of evidence linking these cases to dietary supplements.^{2,4}

The Centers for Disease Control and Prevention (CDC) conducts surveillance for CJD through examination of death certificate data for US residents. This information is shared with the Food and Drug Administration (FDA), Food Safety and Inspection Service (FSIS), the National Institutes of Health (NIH), and stakeholders.^{2,4} In addition, the American Association of Neuropathologists has established a National Prion Disease Pathology Surveillance Center at Case Western Reserve University and has actively been looking for nvCJD since 1994.

¹ Prusiner, SB. The prion diseases. *Scientific American* 1995; 272: 48-57

² “FDA: Consumer Questions and Answers About BSE” available at their Web site:

<http://www.cfsan.fda.gov/~comm/bsefaq.html>

³ Trying to Keep “Mad Cow Disease” Out of U.S. Herds, *FDA Consumer magazine* (March-April 2001) available at their Web site at http://www.fda.gov/fdac/features/2001/201_cow.html

⁴ HHS Fact Sheet *from* U.S. Department of Health and Human Service (August 23, 2001) available at their Web site: <http://www.hhs.gov/news/press/2001pres/01fsbse.html>

FDA has stated that the BSE issue is a food issue, not specific to dietary supplements. However, manufacturers of dietary supplements that include bovine-derived materials must ensure they follow appropriate quality-control measures. Currently, there are no tests to identify prions in foods, raw materials or finished products, thus prevention is the necessary approach to minimizing risk.³ FDA has identified three priorities in its approach to surveillance; 1) ensuring the sources of bovine-derived raw materials/products are from BSE-free countries, 2) ensuring manufacturers and importers are maintaining adequate documentation/paper trail that bovine-derived materials/products did not originate from a BSE-infected country or herd, and 3) prevention of contamination/adulteration and co-mingling of raw materials.

To assist manufacturers and importers of bovine-derived materials in developing their quality control plans, FDA has provided the following guidance in its Import Alert IA1704⁵:

- a. *To ensure that bovine-derived materials (listed in IA1704 appendix A) used in the product(s) are from non-BSE-countries, identify all countries where the animals used were born, raised or slaughtered. The supplier of the bovine-derived materials should provide the necessary records.*
- b. *Maintain traceable records for each lot of bovine-derived material and records of products containing the materials.*
- c. *Maintain records for those products manufactured at foreign sites or by foreign manufacturers which contain bovine-derived materials.*

Manufacturing

Because there is no developed detection method of the causative agent of spongiform encephalopathy, it becomes of paramount importance for manufacturers to choose raw materials in a manner that will minimize the risk of transmission. These guidelines are provided to assist manufacturers in developing and documenting systems for minimizing that risk.

Where manufacturers have a choice to use ruminant or non-ruminant material, the use of non-ruminant material is preferred. Therefore, manufacturers must collect as much information as possible about the source material. The manufacturer should audit the supplier of these materials to ensure that they are sourced and handled in conformity with this guidance and appropriate quality control systems.

In gathering information, manufacturers should be cognizant of the parameters that are useful in determining the risk of contamination of source materials. The risk of transmission of infectious agents can be greatly reduced, then, by controlling a number of these parameters. These parameters include,

- Source of animals
- Nature of animal tissue used in manufacture
- Production process (es)

No single approach will necessarily establish the safety of a product and therefore the three approaches cited above may need to be complementary to each other for minimizing the risk of contamination.

The European Union has been a leader in developing resource materials that can aid a manufacturer in assessing the relevant parameters used to control contamination of source material.⁶ A number of these publications and their availability are listed in the footnote.

⁵ Import Alert IA1704 from FDA available at their Web site at http://www.fda.gov/ora/fiars/ora_import_ia1704.html

⁶ Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products from the Committee on Proprietary Medicinal Products (EMEA/410/01 – FINAL) available at their website: <http://www.emea.eu.int/pdfs/vet/regaffair/041001en.pdf>. Also, the Office International Des Epizooties (OIE) most recent version of the OIE International Animal Health Code, Chapter 2.3.13 on *Bovine Spongiform Encephalopathy* contains information on assessing BSE-free herds.

Another guide to developing the appropriate investigation scheme comes from Health Canada in a request to Canadian Establishment License Holders in which questions were asked regarding actions taken to minimize risks of transmission of spongiform encephalopathy including an assessment of how the material is used by the manufacturer. The following is a list of those questions:

- Type of animal-derived materials used in production;
- Origin of the material (e.g., bovine, ovine, cervine);
- Country of original source of material (country from where the animals originated);
- Source of the material (primary manufacturer of the material);
- Supplier of the material (if different from the manufacturer);
- Brief description of how the material is used in the manufacturing process or added to the final formulation (e.g. fermentation reagent, stabilizer);
- The level at which the material is present in the final product.

To assist in evaluating animal-derived source materials, the organs used by the manufacturers of source materials have been classified as to the level of infection that might be expected in each, were the animal diseased. (e.g., FDA Category I, high infectivity: brain, spinal cord.⁷) Both the European Union and the US FDA have developed classification schemes.⁸

In addition to the publications and above listed points to consider, the FDA recommends that information regarding animal origin, source material manufacturing, and use in dietary supplements be documented and that manufacturers retain those documents for possible review by the agency.

For those manufacturers who may also rely on processing to inactivate the agents responsible for the spongiform encephalopathy infection those processes should be appropriately and adequately validated. There are several publications generated by the European Union that can provide guidance on adequate process validations.⁹ Again, all of the validation studies should be carried out under a well-defined protocol and all results documented.

In summary, this guidance offers only an introduction to development of individual procedures manufacturers will use for minimizing risks of spongiform encephalopathy transmission. Because there are many more details associated with a thorough evaluation of source materials, NNFA encourages its members at a minimum to very carefully consider and completely review all materials cited in this guidance before writing the standard procedure. After the procedure is established, then very carefully begin the assessment and documentation of each point.

Ingredient Sourcing

In order to comply with the FDA's recommendation to control the use of bovine-derived ingredients, including excipients and processing aids that are sourced from animals born, raised, or slaughtered in specific BSE countries, manufacturers must develop quality controls throughout the company to eliminate such ingredients from being used in dietary supplements.

The Purchasing Department plays an essential role in assuring that the requirements established by the Quality Department are strictly followed. Standard Operating Procedures (SOP), supplier surveys, supplier audits, and a supplier certification program should be used to minimize the potential risk of BSE exposure in humans.

When developing purchasing procedures, supplier surveys and supplier audit checklists, the following should be considered and/or included:

⁷ Import Alert IA1704 from FDA available at their Web site at http://www.fda.gov/ora/fiars/ora_import_ia1704.html

⁸ The European Union classification scheme is found in the EMEA/410/01 Note For Guidance, and the US FDA classification scheme comes from WHO Consultation on Public Health Issues Related to Animal and Human Spongiform Encephalopathies, World Health Organization, Office of International Epizootics, Geneva, Switzerland, November 12-14, 1991.

⁹ The EMEA/410/of Note For Guidance

- The name, the complete address and telephone number of the supplier.
- The name, title and phone number of the supplier contact person.
- The materials, including part numbers, considered for purchase.
- Bovine materials are to be obtained from countries which have a surveillance system for bovine spongiform encephalopathy (BSE) in place and which report zero cases of BSE.
- A certificate stating bovine materials are from as BSE-free country must accompany the material.
- No neurological bovine materials should be purchased or accepted.
- Reference to the specifications and other pertinent documents applicable to the materials considered for purchase.
- A request for a statement from the supplier regarding his ability to comply with applicable regulatory requirements, such as GMP or ISO-9000 requirements.
- A request for a statement from the supplier regarding his manufacturing and quality control capabilities pertinent to the materials to be purchased.
- The signature and date that a responsible supplier company officer certifies that all statements made on the Supplier Survey form are accurate and complete.
- Purchasing is responsible for assuring, by means of complete documentation, that every supplier is currently certified to provide all materials, being purchased from that supplier.

Prior to qualifying vendors, companies should establish internal control parameters for setting raw material specifications. The following should be considered when developing specifications for any new raw materials:

- Does the product originate from animal sources or is any materials from animal origin used in the manufacture of the product?
- If “Yes,” companies should list the relevant substances, detailing which animal species and which organ/tissues are involved for each substance.
- If “Yes,” is the raw material bovine derived?
- If “Yes,” companies should consider the internal quality control measures and documentation, such as those addressed in this QA guidance, required to minimize the risk of exposure to BSE diseases through contaminated materials.

NOTICE

By furnishing this guidance, NNFA does not provide any opinion as to:

- The safety of any product containing any ingredient;
- The efficacy of any product containing any ingredient;
- The use of any specific brand of product; or
- The level of substantiation for either the safety or efficacy of any such product.

Neither this guidance, nor any portion of this guidance, may be used in advertising or promotional materials. In addition, this guidance does not constitute, and is not to be used as, “third party literature” as that term is used in connection with section 5 of the Dietary Supplement Health and Education Act (DSHEA).

As with any health-related product, consumers should discuss the use of any products with a health care practitioner.

Sample Standard Operating Procedure

Title: Documentation for Ruminant Derived Products Effective Date:	Supersedes:	Page ___ of ___
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1. **PURPOSE:** To insure the safety of all ruminant sourced ingredients* through lot specific documentation. Transmittable Spongiform encephalopathy (TSE) found in bovine, cervine and ovine species is closely related to a new variant Creutzfeld-Jakob disease found in humans. This procedure establishes a paper trail to insure that ingredients of this type are from approved FDA/USDA countries and have been documented to be disease free.
* Cosmetics are exempt.
2. **SCOPE:** All raw materials and finished bulk products derived solely or in part from ruminant derived sources.
3. **RESPONSIBILITY:** Quality Control
4. **DEFINITIONS:**
 - A. Bovine: Cow
 - B. Ovine: Sheep
 - C. Cervine: Deer
 - D. Creutzfeldt-Jakob disease: A brain wasting disease in humans similar to encephalopathies found in sheep, cows and deer.
 - E. BSE (Bovine Spongiform Encephalopathy): A brain disease found in cows.
 - F. encephalopathy: A disease of the brain
5. **FREQUENCY:** All incoming materials
6. **PROCEDURE:**
 - A. Quality Control will maintain a current list of all non-exempt ruminant sourced materials used by (Company Name) and countries known to be affected by BSE and other related diseases
 - B. Upon receipt of incoming goods, Quality Control will identify those raw materials and bulk finished products either solely or in part derived from non-exempt animal sources.
 - C. During the inspection process, Quality Control will verify that the origin of these materials are from approved countries and substantiate they are from disease free sources through the certificate of analysis and/or other related documentation.
 - D. Any material that falls into this category and whose origin is unknown or lacks the appropriate substantiation will be quarantined until such verification can be established.
 - E. Materials failing to meet these criteria will be rejected.
7. **SAFETY:**
8. **ATTACHMENTS:**
9. **REFERENCES:**

10. APPROVALS

Prepared By:	Dept/Title:	Date:
Approved By:	Dept/Title:	Date:
Approved By:	Dept/Title:	Date:

Dietary Supplements and Mad Cow Disease

Q. Are there strict import regulations that are designed to prevent the import of ingredients contaminated with BSE that may be used in pharmaceuticals, foods, and dietary supplements?

A. Yes. Dietary supplements are a subcategory of foods, and the import alerts and guidance documents on BSE apply equally to bovine ingredients used in conventional foods or in dietary supplements, as well as to bovine ingredients used in pharmaceuticals. For example, gelatin, is usually made from beef bones and is commonly used as an ingredient in conventional foods, dietary supplements, cosmetics and pharmaceuticals.

Q. What about gelatin?

A. The Food and Drug Administration issued a guidance document in 1997 describing appropriate source materials for gelatin products and gelatin manufacturers are required to comply with those guidelines. Gelatin is obtained from the bones and hides of beef and/or pork. The source materials are extracted under severe acid conditions for a period of days or under strong alkaline conditions for a period of weeks, and are then flash-sterilized with high heat.

Q. What are supplement manufacturers doing to be certain they are not receiving raw or finished materials that could be contaminated with BSE?

A. Currently, the only way that BSE can be diagnosed is through the brain autopsy of cattle; testing of glandular or other bovine-derived products is not yet possible. This is why it is critical for manufacturers to know and verify the sources of product ingredients derived from cows. In surveying our members, here's what we've found: Suppliers are getting their glandular products from only one source who is well-known to them; they are using only domestic cattle as sources; they require certificates indicating that the product is BSE-free.

Q. Should there be concern about glucosamine or chondroitin being contaminated with BSE?

A. Chondroitin does not come from neurological or glandular tissue, but is obtained from cartilage – specifically the trachea, which does not appear on the FDA's list of bovine tissues that may present a risk. There are domestic (U.S.) suppliers of chondroitin. There are also importers of this ingredient, who are required by the import alert to obtain their ingredients only from non-BSE countries, with appropriate documentation of the health of the animals as well as the country of origin. The processing of cartilage to extract chondroitin involves rigorous heat and chemical treatments. Chondroitin is frequently combined with Glucosamine, which is obtained entirely from shellfish and not from a bovine source.

Q. What countries do these ingredients come from?

A. In surveys of our membership, we are finding that most manufacturers are using only domestic (U.S.) sources. Those that do import bovine derived ingredients, do so from countries not identified as at-risk for BSE.

Q. What procedures are in place by FDA?

A. The FDA has kept the dietary supplement industry informed about BSE and advised through letters and guidance documents of appropriate precautionary measures to ensure dietary supplements are BSE-free. Since 1992, manufacturers of FDA-regulated products have not been allowed to use materials that originate in BSE-countries. Since then, the FDA has issued three additional advisories, including the latest as recent as November of last year.

Q. One expert was quoted as saying that more than 50 percent of dietary supplements contain ingredients that could be contaminated with BSE. Is that true?

A. Contrary to some reports that suggest a large number of dietary supplements contain ingredients derived from animal glands or organs, such products – sometimes called “glandulars” – actually account for less than 0.4

percent of the market. More than 99 percent of sales are of vitamins, minerals, herbs or botanicals, sports nutrition products, meal supplements and specialty products that do not contain glandular ingredients.

Q. Is it true that you can find raw, ground-up brains and other organs in dietary supplement products?

A. First of all, organ products used in dietary supplements are not “raw,” but are extensively processed. These ingredients are typically ground, heated, dried, defatted and powdered to remove water content, kill microorganisms and permit tableting of the material.

Organ meats, such as liver, are commonly consumed as conventional foods, and liver may also be used as a dietary supplement ingredient. Other organs, such as the pancreas provide the source of pharmaceutical enzymes such as pancreatin and may also be used as dietary supplement ingredients. Animal tissue such as brain, thymus (sweetbreads) and testicles (Rocky Mountain oysters) are consumed as foods and sometimes in glandular dietary supplements. USDA has issued no guidance against the use of such tissues, provided they are derived from health animals from non-BSE countries.