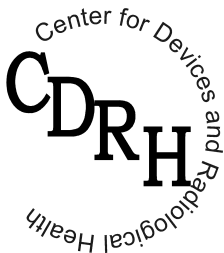


Guidance for FDA Reviewers and Industry

Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)

Document Issued on: November 6, 1998



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

CDRH BSE Working Group

Preface

Public Comment

Until February 4, 1999, comments and suggestions regarding this document should be submitted to Docket No. 98D-0924, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 12420 Parklawn Drive (HFA-305), Room 1-23, Rockville, MD 20857. Such comments will be considered when determining whether to amend the current guidance.

After February 4, 1999, comments and suggestions may be submitted at any time for Agency consideration to: Kiki B. Hellman, Ph. D., Office of Science and Technology (HFZ-113), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Kiki B. Hellman, Ph. D. at (301) 443-7158 or Karen F. Warburton, Office of Device Evaluation (HFZ-460)

Additional Copies

World Wide Web/CDRH home page at <http://www.fda.gov/cdrh> or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 2206 when prompted for the document shelf number.

Medical Devices Containing Materials Derived from Animal Sources (Except In Vitro Diagnostic Devices), Guidance for FDA Reviewers and Industry

Introduction and Background

Bovine Spongiform Encephalopathy (BSE) is a degenerative disease which affects the central nervous system of cattle. It is similar to other transmissible spongiform encephalopathies (TSEs) such as scrapie in sheep and Creutzfeldt-Jakob Disease (CJD) in humans. At this point in time the incubation period of BSE appears to be from 2 to 8 years. There is currently no treatment, nor is there a validated test to detect the disease in a live animal. Diagnosis is determined by microscopic examination of brain tissue. The nature of the BSE agent is widely theorized to be a prion, an abnormally folded version of a normal cellular protein. The abnormal protein then recruits additional molecules of normal protein and facilitates their conversion to the abnormal form. The agent is extremely resistant to traditional forms of disinfection and sterilization. As new information on the diagnosis, treatment and nature of the agent becomes available, this guidance will be modified as appropriate.

Epidemiologic data suggest that the BSE epidemic in Great Britain which began in 1986 occurred through feeding cattle contaminated meat and bone meal as a protein source. The BSE agent may have been present for a long time, but changes in rendering procedures in the late 70's and early 80's may have enabled the active agent to survive in the animal feeds. The agent is thought to be from scrapie-infected sheep, but cattle with a previously unidentified TSE have not been ruled out. An association between cases of variant CJD in Great Britain and BSE seems likely, although causality has not been proved. To date, there have been no cases of BSE in the United States.

The possibility of introducing the BSE agent through a medical device requires special attention on the part of manufacturers with regard to the sourcing and processing of bovine-derived material. At present this can most easily be accomplished by assuring that the source cattle are free of BSE. In 1993 and more recently, on May 9, 1996, the Food and Drug Administration (FDA) issued letters to manufacturers to request that bovine-derived materials from cattle which have resided in or originated from countries where BSE has been diagnosed not be used in the manufacture of FDA-regulated products. (Attachments 1, 2 and 3)

Since 1989, the USDA has restricted the importation of live ruminants from Great Britain. Currently the USDA restricts the importation of live ruminants from countries where BSE is known to exist, and from those countries that present a significant risk of introducing BSE into the United States. Also restricted (by USDA) from import from these countries are other ruminant-derived products such as bone meal, meat and bone meal, blood meal, offal, glands, and gelatin for animal consumption. FDA recently prohibited protein derived from mammalian tissues to be used in ruminant feed for animals in the US (Federal Register June 5, 1997; 21 CFR Part 589 "Substances Prohibited From Use in Animal Food or Feed; Animal

Proteins Prohibited in Ruminant Feed").

To track medical devices which either contain or are exposed to animal-derived materials during manufacturing (e.g., human cells grown in media containing fetal calf serum), CDRH has developed the CDRH Biomaterials Database which contains an inventory of these devices, including type of material, animal species and country of origin, and target organ or tissue for each device. Originally proposed in response to the BSE issue, the Database was expanded to include all animal-derived products (including human) in order to respond to other animal material-based sourcing concerns that may arise in the future.

Purpose of Guidance

The purpose of this document is to provide recommendations for information to be included in submissions (IDE, PMA, 510(k)) for medical devices which either contain or are exposed to animal-derived materials during manufacturing. This will reduce the likelihood of the transmission of BSE through medical devices and will provide a profile of the animal-derived materials which can be used in risk analysis of the devices.

Scope of Guidance

This guidance is applicable to all medical devices, except in vitro diagnostic devices, which either contain or are exposed to animal-derived materials during manufacturing. All animal species (e.g., human, bovine, ovine, porcine, avian (e.g., chicken), fish, etc.) are included.

Recommendations for Medical Devices Containing Materials Derived From BOVINE Sources

1. All materials in a device which are derived from a bovine source should be identified. Examples are: bovine pericardium used in heart valves, bovine viscera used in gut sutures, bovine bone used in dental implants, and bovine collagen used in lacrimal plugs. These also include devices which are exposed to materials of bovine origin during manufacture (e.g., human cells grown in media containing fetal calf serum, tissue culture cells exposed to bovine trypsin.)
2. The bovine material should come from cattle which have not originated from or resided in a country where BSE has been diagnosed or which presents a significant risk of introducing BSE. This list of countries is maintained by the USDA and codified in 9 CFR 94.18. The countries currently identified include all countries of Europe.

Countries in which BSE exists:

Great Britain (including Northern Ireland and the Falklands)
Switzerland
France

Republic of Ireland
Oman
Portugal
The Netherlands
Belgium
Luxembourg

Countries which present significant risk:

Albania
Austria
Bosnia-Herzegovina
Bulgaria
Croatia
Czech Republic
Denmark
Federal Republic of Yugoslavia
Finland
Germany
Greece
Hungary
Italy
the former Yugoslav Republic of Macedonia
Norway
Poland
Romania
the Slovak Republic
Slovenia
Spain
Sweden

3. Tractable records should be maintained by the device manufacturer for each lot of bovine material and each lot of FDA-regulated product. Records should indicate the country of origin and residence of the animals. The bovine tissue source (e.g. bone, heart valve, ligament/tendon) should also be indicated.
4. If the manufacturer certifies that the bovine-derived material is only available from a country where BSE is known to exist, then the manufacturer should provide evidence to indicate that the BSE agent is inactivated during the manufacturing process. A detailed description of the manufacturing process should be submitted. Evidence of inactivation may be derived from one or more of the following:
 - a. Validation study using an appropriate model (e.g., scrapie in mice.) If a validation study protocol and/or data are submitted the reviewer should

contact the Division BSE Focal Point (see below) for further guidance. Manufacturers are encouraged to consult with FDA during protocol development. Validation studies take at least 2 years to complete, are technically difficult, and may require review by experts in the TSE field. The TSE Advisory Committee will be consulted as appropriate.

- b. Other valid scientific evidence (e.g., scientific literature to support specific processing methods of specific tissues (e.g, hydroxyapatite obtained from bovine bone.))
5. The FDA has recently changed its position with regard to the use of **gelatin**. A guidance document has been issued regarding the use of gelatin in FDA-regulated products for human use (Attachment 4). The guidance pertinent to medical devices reads:

"Gelatin produced from bones and hides obtained from cattle residing in, or originating from, countries reporting BSE or from countries that do not meet the latest BSE-related standards of the Office International des Epizooties (OIE) should not be used either in injectable, ophthalmic, or implanted FDA regulated products, or in their manufacture."

The guidance also states:

"At this time there does not appear to be a basis for objection to the use of gelatin produced from bovine hides and bones in FDA products for human use if the gelatin is produced in the United States from US-derived raw materials or from cattle born, raised and slaughtered in other countries that have no reported BSE cases and that meet OIE BSE standards."

6. There are currently no restrictions on bovine milk and milk-derived products.

Note--Future Considerations: FDA is considering other changes in its policy concerning BSE and the safety of regulated products. Options to be considered in the future include evaluation of a country's compliance with BSE related standards of the Office International des Epizooties; and evaluating products with regard to the risk posed by the bovine tissue source and end use, in addition to the country of origin. For example, bovine neural tissue implanted in the central nervous system would pose a much greater risk than a few microliters of highly purified bovine pancreatic trypsin used in a manufacturing process to recover tissue culture cells which are further purified before use.

Experimental data with the mouse/scrapie model suggest that brain and spinal cord tissue from TSE-infected animals have high levels of infectivity; tissues such as lymph nodes and spleen are of medium infectivity; tissues such as bone marrow and liver may sometimes have low levels of infectivity. Experiments with TSE agents also indicate that the intracerebral

route of inoculation is the most efficient way of transmitting the disease, followed by parenteral inoculation; the oral route is the least efficient.

Another future option might be to encourage the use of closed herds for material sources. Animals of known lineage, husbandry and medical history should provide the safest sources. Should BSE be discovered in the United States, a closed herd would become a significantly more important source for bovine material. Because the incubation time for BSE is long (2-8 years) herds would have to be closed for at least 3 years for isolation to be meaningful.

Whenever FDA changes policy on BSE, this guidance document will be revised accordingly.

Recommendations for Medical Devices Containing Materials Derived From Animal Sources OTHER Than Bovine

All materials in a device derived from **any** animal source, including human, should be identified by tissue type and species of origin. Some examples of materials are: porcine heart valves, porcine collagen corneal shields, porcine blood vessels used in vascular grafts, porcine collagen used in wound dressings, and hyaluronic acid from rooster combs used in viscoelastic fluids. This also includes devices exposed to materials of animal origin during manufacture (e.g. porcine trypsin used in artificial skin.)

1. Country of origin/residence should be identified for all materials.
2. For products derived from human tissue, refer to 21 CFR 1270, Human Tissue Intended for Transplantation, for additional requirements.

CDRH Biomaterials Database

Reviewers will evaluate submissions to identify products which contain or are exposed to animal-derived materials. Information on these products will be entered into the CDRH Biomaterials Database (Attachment 5).

The acknowledgement letter issued to manufacturers upon receipt of the IDE, PMA or 510(k) submission will prompt them to notify the reviewing Division if the device contains an animal or human derived material and such information was not provided in the original submission.

BSE Working Group:

Chair: Kiki Hellman (OST)

ODE Division Focal Points:

DGRD: David Berkowitz

DCLD: Claudia Gaffey/Gus Gonzalez
DCRND: Lisa Kennell
DOD: Karen Warburton
DRAERD: Raju Kammula
DDIGD: Pandu Soprey

Database Contacts:

Stan Brown (OST)
Ken Krell (OMS)

Attachments:

1. FR notice (August 29, 1994) Bovine Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products
2. May 9, 1996 letter to Manufacturers of FDA-Regulated Drug/Biologic/Device Products
3. Background Information and Chronology of U.S. BSE-Related Actions
4. FDA Guidance, "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use" (September 1997)
5. Database Data Entry Form

[Federal Register: August 29, 1994]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing the texts of four letters it recently issued to manufacturers of FDA-regulated products requesting that bovine-derived materials from certain cattle not be used in the manufacture of FDA-regulated products intended for humans or animals. FDA believes that bovine spongiform encephalopathy (BSE), a neurological disease of bovine animals, is a concern in the manufacture of FDA-regulated products. FDA believes that precautionary measures will reduce potential risk of exposure to, or transmission of, the agents that cause BSE in cattle. FDA is publishing the texts of the four letters at the end of this document in addition to mailing them directly to manufacturers.

FOR FURTHER INFORMATION CONTACT:

For dietary supplements and cosmetics: Elisa L. Elliot, Center for Food Safety and Applied Nutrition (HFS-22), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5140.

For medical devices: Kiki B. Hellman, Center for Devices and Radiological Health (HFZ-113), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-7158.

For human drugs: Gayle R. Dolechek, Center for Drug Evaluation and Research (HFD-335), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301-594-0104.

For biological products: Timothy W. Beth, Center for Biologics Evaluation and Research (HFM-635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-594-3074.

For veterinary drugs: William C. Keller, Center for Veterinary Medicine (HFV-210), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1722.

For animal feeds: John P. Honstead, Center for Veterinary Medicine (HFV-222), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1728.

For information on countries with BSE: Harvey Kryder, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Federal Bldg., rm. 757, 6506 Belcrest Rd., Hyattsville, MD 20782, 301-436-7885.

SUPPLEMENTARY INFORMATION: FDA has recently issued four letters requesting that bovine-derived materials from cattle that have resided in, or originated from, countries designated by the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), as countries where BSE exists, not be used in the manufacture of FDA-regulated products intended for humans or animals. A letter dated

November 9, 1992, was issued to manufacturers of dietary supplements. A letter dated December 17, 1993, was issued to manufacturers of human drugs, biologics, and medical devices. (With respect to the December 17 letter, the agency has subsequently clarified that FDA does not object to the use of bovine-derived materials from BSE-countries in the manufacture of pharmaceutical grade gelatin at this time.) A letter dated August 17, 1994, was issued to manufacturers of FDA-regulated products for animals. A letter dated August 17, 1994, was issued to manufacturers and importers of dietary supplements and cosmetics.

BSE is a neurological disease of bovine animals. USDA has regulations that prohibit and restrict the importation of certain animal products and animal byproducts from ruminants that have been in countries where BSE exists. These countries are designated by USDA and listed in 9 CFR 94.18.

The BSE agent is extremely resistant to traditional forms of processing and sterilization. The disease was first identified in 1986. Since that time, over 100,000 cattle in Great Britain have either died or been destroyed as a result of BSE infection. At the present time, BSE is not known to exist in the United States. The disease is not known to be contagious by direct transmission.

BSE is a neurological disease classified as a transmissible spongiform encephalopathy (TSE), and is similar to other TSE's such as scrapie in sheep and Creutzfeldt-Jakob disease (CJD) in humans. Its continued spread within countries where BSE exists appears to be through the use of feed containing protein and other products from ruminants infected with BSE. In the United Kingdom, scrapie in sheep has been epidemiologically associated with the occurrence of BSE in cattle. Scrapie in sheep is known to have existed in Britain, Ireland, France, and Germany for over 200 years and has been observed in the United States and Canada for about 50 years. Because FDA cannot positively rule out a direct association between scrapie and BSE, FDA is proposing elsewhere in this issue of the Federal Register to prohibit the use in ruminant feed of specified offal from adult sheep and goats.

CJD is a rare neurological disease of humans that has similarities to BSE in cattle. The cause of CJD is unknown except in a few cases of specific genetic mutations and iatrogenic CJD in the case of CJD-contaminated growth hormone injections, dura mater grafts, and corneal transplants. Even though there is no direct evidence supporting an association between BSE and human disease, FDA believes that it is prudent to reduce any potential risk of human exposure to the BSE agent.

The purpose in issuing these four letters is to request that bovine-derived materials from cattle that have resided in or originated from USDA-designated BSE countries not be used in the manufacture of FDA-regulated products intended for humans or animals. Meat (i.e., skeletal muscle) is not covered by these letters. For guidance on importation of meat and other USDA-regulated products, refer to Title 9 of the Code of Federal Regulations.

The text of the November 9, 1992, letter to manufacturers of dietary supplements follows:

November 9, 1992

Dear Manufacturer of Dietary Supplements:

In a series of recent meetings, representatives of the dietary supplement industry have suggested that if FDA has concerns involving dietary supplement products, it should communicate its concerns directly to the industry. We agree that this is a reasonable and appropriate suggestion. Therefore, I wish to bring a matter of some importance to FDA to your attention. I would like to share with you FDA's concerns regarding the marketing of certain nutritional supplements. We have become aware that some supplements contain brain, nervous tissue, or glandular materials from a variety of animal species, including bovine (oxen, beef) and ovine (sheep) species. We are concerned that some amount of these materials may

have come from countries experiencing Bovine Spongiform Encephalopathy (BSE) in the case of bovine tissues, or scrapie in the case of ovine tissues.

As you may know, BSE is an infectious neurologic disorder of cattle, and is prevalent in certain parts of the world (''BSE countries''). Scrapie is a spongiform encephalopathy of sheep, and is a disease that is endemic in many parts of the world, including the United States. It is believed that the rapid spread of BSE among animals in Great Britain was caused by inadequately rendered, scrapie agent-containing material being fed to cattle. Thus, it is suggested that BSE is the clinical manifestation of scrapie in cattle. It is further suggested that cattle became infected by the orogastric route. Both scrapie and BSE are classified as transmissible spongiform encephalopathies. The causal agent is unknown, but suspected to be an agent known variously as ''prion,'' ''virino,'' ''unconventional virus,'' or ''slow virus.'' That these agents can infect across species, and infect primates, has been demonstrated repeatedly in laboratory studies.

Although cases are rare, spongiform encephalopathies can affect humans, most notably, Creutzfeldt-Jakob Disease (CJD). CJD is a rare disease, its incidence being about 1 case per million population. It is 100% fatal. Human-to-human transmission by iatrogenic means (e.g., contaminated neurosurgical instruments, corneal and dura mater implants, human growth hormone injections) has been documented. The possibility of transmission of animal spongiform encephalopathy agents to humans from consumption of animal brains from a variety of species, such as squirrel, goat, sheep, and hogs, and from consumption of sheep's eyeballs has been examined in the past. Although proof of such dietary transmission is lacking, some suspicions remain. The rarity of the disease, coupled with what is believed to be a long onset time (median - 13 years), make more precise epidemiological studies extremely difficult. Additionally, there may be a genetic or other susceptibility in some individuals.

FDA has recently been involved in investigating a consumer complaint involving a confirmed case of CJD. It is standard procedure for FDA to follow-up on all consumer complaints involving death or serious injury. In the course of this investigation, FDA learned that the woman had taken a bovine tissue-containing dietary supplement. Although, at the present there is no basis to conclude that this supplement played any role in causing this disease, FDA and NIH have decided that it is prudent to further investigate this matter. Therefore, both agencies have begun to conduct cooperative studies to determine whether nutritional supplements containing brain, nervous tissue or glandular materials from bovine and ovine species might be linked to human spongiform encephalopathies.

In 1991, the United States Department of Agriculture published a rule (9 CFR 95.4) which prohibits imports of various tissues and organs from ruminants in countries where BSE exists. Similar prohibitions have been in place for scrapie for many years. The concern addressed by the rules was that BSE - or scrapie-containing materials may find their way into cattle or sheep in the U.S. Nevertheless, FDA feels that the principle embodied in the USDA rule is an appropriate standard for tissues, organs, glands, and processed extracts from these articles insofar as they may be used for human food, including in supplement form.

FDA is requesting that you investigate the source of your neural and glandular tissue(s) or tissue extracts of bovine or ovine species to determine if they are being produced in known BSE countries or from flocks in which scrapie may be present. We would recommend that you reformulate your products using neural or glandular tissues that you are assured are BSE or scrapie free. We suggest within the next two months, that you gather information and determine the source of bovine or ovine materials used in your product(s). If you use bovine-derived materials in your product(s),

we suggest that you develop a plan to assure, with a high degree of certainty, that there is no possibility that materials of bovine origin are being supplied by BSE countries, either directly or indirectly. If you use ovine materials in your product(s), we suggest that you also develop a similar plan for assuring that these tissues are from scrapie-free animals. We fully recognize that there is no proven link between BSE or scrapie, and human disease, but given the devastating consequences of human spongiform encephalopathies such as CJD, we believe that our request is a prudent step at this time.

FDA requests that you communicate your plan(s) to us once you have developed them. We recognize that the steps you take to secure the assurances you need from exporting countries may be difficult, but we are certain you will agree with us that they are desirable.

If you need any additional information or guidance, please contact Dr. Douglas L. Archer, Deputy director, Center for Food Safety and Applied Nutrition at 202-205-4057. We appreciate your cooperation and attention to this matter.

Sincerely,

Fred R. Shank, Ph.D.

Director

Center for Food Safety and Applied Nutrition

The text of the December 17, 1993, letter to manufacturers of drugs, biological drugs, medical devices, and biological device products follows:

December 17, 1993

TO: Manufacturers of FDA-regulated Products

The Food and Drug Administration (FDA, the Agency) is issuing this letter to request that bovine-derived materials from cattle which have resided in or originated from countries where Bovine Spongiform Encephalopathy (BSE) has been diagnosed not be used in the manufacture of FDA-regulated products intended for administration to humans. We are advising you of our current recommendations pertaining to the use of such bovine-derived products.

FDA is providing the following information to explain why the Agency thinks that an animal disease (such as BSE) may potentially be a concern in the manufacture of FDA-regulated products intended for administration to humans. BSE has been reported for more than 109,000 cattle in the United Kingdom [Fall, 1993 quarterly report of the Ministry of Agriculture, Fisheries, and Food (MAFF)], and to a much lesser extent in other European countries. This neurological disease is a transmissible spongiform encephalopathy (TSE), and is similar to other TSEs such as scrapie in sheep and Creutzfeldt-Jakob Disease (CJD) in humans. The spongiform encephalopathies are uniformly fatal, and no rapid diagnostic test for infection in living animals (or humans) is currently available. Iatrogenic transmissions of CJD from both pituitary-derived human growth hormone (somatotropin) and dura mater\1\ have been reported. Research projects into the exact nature of both the BSE agent and other spongiform encephalopathy agents, host range, patterns of pathogenicity, and development of rapid antemortem diagnostic tests are ongoing. Available scientific information indicates that these agents are extremely resistant to inactivation by normal disinfection or sterilization procedures. The list of countries where BSE is known to exist (BSE-countries) is maintained by the United States Department of Agriculture (USDA). Countries listed in the Federal Register on December 6, 1991 (56 FR 63865 through 63870) include France, Great Britain (includes the Falkland Islands), Northern Ireland, the Republic of Ireland, Oman, and Switzerland.

\\1\Brown P, Preece MA, Will RG. ``Friendly fire in medicine:

hormones, homografts, and Creutzfeldt-Jakob disease''. Lancet 1992:340:24-27.

While transmission of the causative agent of BSE to humans has not been reported to date, FDA considers the recommendations below to be prudent at this time to further reduce any potential risk of exposure or transmission of a BSE-agent to humans by FDA-regulated products.

The Agency notes that regulated products intended for administration to humans and manufactured with bovine-derived materials derived from cattle that have at any time been in BSE-countries may be adulterated under Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), for drugs and biological drug products; or Section 501(h) of the Act, for medical devices and biological device products. The Agency is considering rulemaking to restrict the use of bovine-derived materials from BSE-countries. At this time, FDA recommends that bovine-derived materials from BSE-countries not be used in the manufacture of FDA-regulated products.

The Agency is providing the following suggestions to prevent the use of bovine-derived materials from cattle which have resided in or originated from BSE-countries. FDA recommends that manufacturers:

- a. identify bovine-derived materials used in the regulated product and identify all countries where the animals used for the material have lived. This information may be provided to the regulated-product manufacturer by the supplier of the bovine product. The supplier may also provide the manufacturer with appropriate veterinary regulatory inspection certification of slaughter, as required by the country of origin of live animals.
- b. maintain traceable records for each lot of bovine material and each lot of FDA-regulated product using these materials. These records should be part of the batch records, and available for FDA inspection.
- c. document the country of origin of the live animal source of any bovine-derived materials used in the manufacture of the regulated product. Documentation should be maintained for any new or in-process lots of licensed, cleared, or approved products; products pending clearance or approval; and investigational products intended to be administered to humans. Such documentation should be a part of the traceable records maintained in conjunction with batch production records, and such information should be available for review during FDA inspections.
- d. maintain copies of the records identified above for FDA-regulated products that are manufactured with bovine-derived materials at foreign sites, or by the foreign manufacturers. The U.S. firms responsible for marketing these products should be responsible for these records. Manufacturers of products subject to licensure should maintain records at the site of manufacture.

The Agency recommends that the information identified above be obtained for all currently approved, cleared, or licensed products, pending or approvable products, and investigational products.

Some manufacturers of FDA-regulated products may have already provided some of this information in applications to the USDA for permits to import certain animal products into the United States. In some instances, copies of these applications and permits may contain some of the information that the FDA is requesting. FDA suggests that this information be documented, recorded, and maintained for all bovine-derived products currently manufactured or marketed in the U.S. This information should be available for FDA inspection.

If you have any questions regarding the above items please contact the appropriate center as follows:

Center for Devices and Radiological Health: 301-594-4692 ext.

Center for Drug Evaluation and Research: 301-594-0054
Center for Biologics Evaluation and Research--contact the
Application Division in the CBER Office responsible for the
regulation of your product. These Offices are:
Office of Vaccines Research and Review 301-594-2090
Office of Therapeutics Research and Review 301-594-5109
Office of Blood Research and Review 301-594-2012
Regulated-product manufacturers are referred to the USDA for
current information and countries on the "BSE-list". Additional
information and regulations concerning bovine spongiform
encephalopathy (BSE) and affected animals may be obtained from the
open veterinary literature and the United States Department of
Agriculture (see 9 CFR 94.18).

Sincerely yours,

Jane E. Henney, M.D.

Deputy Commissioner for Operations

The text of the August 17, 1994, letter to manufacturers of FDA-
regulated products for animals follows:

August 17, 1994

To: Manufacturers of FDA-regulated products for animals

The Food and Drug Administration is issuing this letter to
request that bovine-derived materials from cattle which have resided
in, or originated from, countries designated as bovine spongiform
encephalopathy (BSE) countries by United States Department of
Agriculture (USDA), Animal and Plant Health Inspection Service, not
be used in the manufacture of FDA-regulated products (drugs and
feed) intended for animals. FDA believes that this action is
necessary to prevent the occurrence of BSE in U.S. cattle. Meat
(i.e., skeletal muscle) is not covered by this letter. For guidance
on importation of meat and other USDA-regulated products, refer to
Title 9 of the Code of Federal Regulations.

FDA is providing the following information to explain why the
Agency thinks that BSE may potentially be a concern in the
manufacture of FDA-regulated products intended for administration to
animals. BSE has been identified in more than 100,000 cattle in the
United Kingdom and to a much lesser extent in other European
countries. BSE has not been diagnosed in the U.S. This neurological
disease is a transmissible spongiform encephalopathy (TSE), and is
similar to other TSE's such as scrapie in sheep and Creutzfeldt-
Jakob Disease (CJD) in humans. The spongiform encephalopathies are
uniformly fatal and no rapid diagnostic test for infection in living
animals is currently available. A range of research projects into
the exact nature of both the BSE agent and other TSE agents, host
range, patterns of pathogenicity, and development of rapid ante
mortem diagnostic tests is ongoing. Available scientific information
indicates that these agents are extremely resistant to inactivation
by normal disinfection or sterilization procedures. The list of
countries where BSE is known to exist is maintained by the USDA and
codified in Title 9, Code of Federal Regulations, Part 94.18.

The Agency notes that products intended for animals and
manufactured with bovine-origin materials derived from cattle that
have, at any time, been in BSE countries may be adulterated under
Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.
The Agency is considering rulemaking to restrict the use of bovine-
derived materials from BSE countries in the manufacture of FDA-
regulated products for animals. At this time, we request that
bovine-derived materials from BSE countries not be used in the
manufacture of FDA-regulated products intended for animals.

FDA considers the recommendations below to be prudent at this
time to further reduce any potential risk of exposure to, or
transmission of, a BSE agent to animals by FDA-regulated products.

We recommend that manufacturers:

- a. Identify bovine-origin materials used in regulated products
for animals and identify all countries where the cattle used for the

material have lived. This information may be provided to the regulated product manufacturer by the supplier of the bovine material. The supplier may also provide the manufacturer with appropriate veterinary regulatory inspection certification of slaughter if already required by USDA for import from BSE countries which verify the country of origin.

b. Maintain traceable records for each lot of bovine-derived material and each lot of FDA-regulated products intended for animals that are manufactured using these materials. These records should be part of the batch records and available for FDA inspection.

c. Document the country of origin of the live animals for bovine-origin materials used in the manufacture of any new or in-process lots of FDA-regulated products intended for animals. Such documentation should be a part of the traceable records maintained in conjunction with batch production records and such information should be available for FDA inspection.

d. Maintain copies of the appropriate records identified above for FDA-regulated products intended for animals that are manufactured with bovine-derived materials at foreign sites, or by the foreign manufacturers. The U.S. firms responsible for marketing these animal products should be responsible for these records. Registered product manufacturers should maintain records at the site of manufacture.

The Agency recommends that the information identified above be obtained and maintained for all FDA-regulated products intended for animals.

Some manufacturers of FDA-regulated products intended for animals may have already provided some of this information in applications to the USDA for permits to import certain bovine materials into the U.S. In some instances, copies of these applications and permits may contain some of the information requested. We request that this information be documented, recorded, and maintained for all bovine-origin materials for use in FDA-regulated products intended for animals currently manufactured or marketed in the U.S. This information should be available for FDA inspection.

If you have any questions regarding the above items, please contact the Center for Veterinary Medicine:

For Veterinary Drugs: Dr. William Keller, Director, Division of Surveillance, HFV-210, 7500 Standish Place, Rockville, Maryland 20855, 301-594-1722

For Animal Feeds: Dr. John Honstead, Division of Animal Feeds, HFV-222, 7500 Standish Place, Rockville, Maryland 20855, 301-594-1728

Regulated product manufacturers are referred to the USDA for current information and countries on its list of countries with BSE in native animals. Additional information and regulations concerning BSE and affected animals may be obtained from the USDA, Animal and Plant Health Inspection Service (301-436-7830).

Sincerely yours,

Linda A. Suydam

Interim Deputy Commissioner for Operations

The text of the August 17, 1994, letter to manufacturers and importers of dietary supplements and cosmetics follows:

August 17, 1994

To Manufacturers and Importers of Dietary Supplements:

To Manufacturers and Importers of Cosmetics:

The Food and Drug Administration (FDA) is recommending that firms that manufacture or import dietary supplements and cosmetics containing specific bovine tissues (see Appendix A) ensure that such tissues do not come from cattle born, raised, or slaughtered in countries where bovine spongiform encephalopathy (BSE) exists (BSE-countries). Extracts of these tissues and ingredients derived from these tissues are also of concern. The recommended actions are

precautionary measures to reduce potential risk of human exposure to, or transmission of, the agent which causes BSE in cattle.

At this time, FDA is not extending the recommendation in this letter to dairy products or gelatin, because available evidence does not suggest transmission via these foods. Furthermore, meat (i.e., skeletal muscle) is not covered by this letter. For guidance on importation of meat and other products regulated by the United States Department of Agriculture (USDA), refer to Title 9 of the Code of Federal Regulations.

The Agency is providing the following information to explain why it believes that BSE may potentially be a concern with certain dietary supplements and cosmetic products. BSE has been identified in more than 100,000 cattle in the United Kingdom and, to a much lesser extent, in several other countries. BSE has not been diagnosed in the United States. This neurological disease is a transmissible spongiform encephalopathy (TSE) and is similar to other TSEs such as scrapie in sheep and Creutzfeldt-Jakob Disease (CJD) in humans. The spongiform encephalopathies are uniformly fatal and no rapid diagnostic test for infection in living animals or humans is presently available. Current scientific information indicates that the causative agent is extremely resistant to inactivation by normal disinfection or sterilization procedures. A range of research projects into the exact nature of both the BSE agent and other TSE agents, host range, patterns of pathogenicity, and development of rapid ante mortem diagnostic tests is ongoing.

Since 1991, USDA has prohibited the importation into the U.S. of certain tissues and organs from ruminants from countries where BSE exists (BSE-countries; see 9 CFR 94.18). USDA's regulations are intended to protect livestock in the United States from contracting TSEs and address known or strongly suspected modes of transmission. For the up-to-date listing of BSE-countries please contact USDA, Animal and Plant Health Inspection Service (APHIS) at (301) 436-7830.

The USDA regulations permit, under certain conditions, the importation of some cosmetic ingredients (i.e., collagen, collagen products, amniotic liquids or extracts, placental liquids or extracts, serum albumin, and serocolostrum) derived from ruminants from BSE-countries; see 9 CFR 95.4.

The USDA regulations do not apply to imports of:

- * cosmetic products that are packaged and ready for sale;
- * bovine-derived materials intended for human consumption as either finished dietary supplement products or for use as ingredients in dietary supplements; or
- * human food (except meat, i.e., skeletal muscle).

While documented transmission of the causative agents of BSE or scrapie to humans has not been reported to date, the FDA wrote to manufacturers of dietary supplements in November 1992, alerting them to the developing concern about TSEs in animals and CJD in man. That letter recommended that manufacturers voluntarily investigate the geographic source(s) of any bovine or ovine material used in their products (generally neural or glandular tissue or tissue extracts). The Agency also suggested that each manufacturer develop a plan "to assure, with a high degree of certainty," that such materials are not from BSE-countries, as identified by USDA's APHIS, or from scrapie-infected sheep flocks, either foreign or domestic.

FDA now considers further protective steps to be reasonable and is restating and expanding its recommendation to manufacturers and importers of dietary supplements and their ingredients, to develop plans for ensuring, with a high degree of certainty, that specific bovine-derived materials (see Appendix A) from BSE-countries are not being used. The Agency is also recommending that manufacturers and importers of cosmetic products and their ingredients develop the same type of plans. FDA is not, at this time, recommending restrictions on the use of ovine-derived materials in the

manufacture of dietary supplement and cosmetic products and ingredients, as the epidemiological evidence now appears convincing that scrapie is not related to TSEs in humans.

FDA believes it is prudent to expand its recommendation to cosmetics and cosmetic ingredients because extracts of listed tissues, e.g. sphingolipids isolated from brain tissue and extracts of bovine placenta, are used in cosmetics. Additionally, FDA is unaware of data demonstrating that processing techniques used in the manufacture of cosmetics will inactivate TSE agents. Further, little is known about the potential human risk of transmission from topical application of cosmetics containing TSE agents to intact, broken or abraded skin.

To assist manufacturers and importers whose products are within the scope of this recommendation in developing their plans, the following guidance is provided:

a. To ensure that bovine-derived materials (listed in 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.

The Agency recommends that manufacturers and importers of dietary supplements and cosmetic products and ingredients used in the manufacture of these products develop their plans within the next two months and notify the Agency, in writing, that their plans have been developed. The designated contact is Dr. Elisa Elliot, Science Policy Analyst, Executive Operations Staff, HFS-22, Center for Food Safety and Applied Nutrition, FDA, 200 C Street, S.W., Washington, DC, 20204 or FAX (202) 205-5025. FDA recommends that the plans be implemented as soon after development as possible, and be available for review by the Agency during inspections.

The Agency is continuing to examine all available information about TSEs and will provide additional guidance as necessary. If you need more information please contact Dr. Elliot by telephone at (202) 205-5140.

We appreciate your attention to and cooperation in this matter.

Sincerely,

Linda A. Suydam

Interim Deputy Commissioner for Operations

Attachment

Appendix A

List of Tissues With Suspected Infectivity

Category I (High infectivity)

- <bullet> Brain
- <bullet> Spinal cord

Category II (Medium infectivity)

- <bullet> Ileum
- <bullet> Lymph nodes
- <bullet> Proximal colon
- <bullet> Spleen
- <bullet> Tonsil
- <bullet> Dura mater
- <bullet> Pineal gland
- <bullet> Placenta
- <bullet> Cerebrospinal fluid
- <bullet> Pituitary gland
- <bullet> Adrenal gland

Category III (Low infectivity)

- <bullet> Distal colon
- <bullet> Nasal mucosa
- <bullet> Sciatic nerve
- <bullet> Bone marrow
- <bullet> Liver
- <bullet> Lung
- <bullet> Pancreas
- <bullet> Thymus gland

List taken from "Report of a 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.

Dated: August 19, 1994.

Linda A. Suydam,
Interim Deputy Commissioner for Operations.
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