Attachment 4

U.S. Food and Drug Administration

Guidance for Industry

The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use

Comments and suggestions regarding this document should be submitted by December 22, 1997, to Docket No. 97D-0411, Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857.

U.S. Department of Health and Human Services

Food and Drug Administration

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Introduction - FDA has adopted Good Guidance Practices (GGPs), which set forth the agency's policies and procedures for the development, issuance, and use of guidance documents (62 FR 8961, February 27, 1997). This guidance is issued as Level 1 guidance consistent with GGPs. The agency is soliciting public comment but is implementing this guidance immediately because of public health concerns related to the use of gelatin. This guidance document represents the agency's current thinking on reducing the potential risk of transmission of BSE related to the use of gelatin in FDA-regulated products for human use. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

Purpose - This guidance document addresses the safety of gelatin as it relates to the potential risk posed by BSE in FDA-regulated products for human use. It is intended to provide guidance to industry concerning the sourcing and processing of gelatin used in FDA-regulated products. In developing this proposed guidance, FDA considered various information, including the conclusions of the Transmissible Spongiform Encephalopathies (TSEs) Advisory Committee in a meeting on April 23-24, 1997. The committee reviewed data on the sourcing and processing of materials used to make gelatin as well as data from an experimental study on the effect of gelatin processing on the infectivity of a spongiform agent.

Background - Over the last several years, FDA has provided guidance to manufacturers

and importers of FDA-regulated products regarding products containing or exposed to bovine-derived materials from countries reporting cases of BSE. The U.S. Department of Agricultures Animal and Plant Health Inspection Service (APHIS) identified these BSE countries beginning in December 1991 (9 CFR 94.18; see also recent USDA interim rule designating the Netherlands a BSE country: 62FR18623 on April 15, 1997). As a way to prevent the introduction of BSE infection in U.S. cattle, USDA has prohibited, since 1989, the importation of livestock from BSE countries, and has also banned, since 1991, bovine-derived products from BSE countries which are intended for animal use. USDA has conducted extensive monitoring and has diagnosed no cases of BSE in U.S. cattle to date.

The British BSE epidemic is thought to have resulted from the practice of adding rendered animal tissue to cattle feed. Early on, some evidence suggested the potential for cross-species transmission of TSEs (rare, fatal neurological diseases such as scrapie in sheep and Creutzfeldt-Jakob disease in humans). Although it was not known whether BSE could be transmitted from contaminated cattle to humans, FDA believed it prudent to alert manufacturers to this potential risk. Since 1992, FDA has sent a number of letters to manufacturers of FDA-regulated products providing guidance on the use of bovine materials from BSE countries (see Appendix A for a chronology of FDA's guidance to the industry).

Guidance on Gelatin - In 1994, representatives of the gelatin industry presented preliminary data to FDA staff concerning an experimental study of the infectivity of TSE-infected tissue that had undergone one of two processes (lime or acid) used to make gelatin. Based on these data, FDA decided not to include gelatin as part of its recommendations concerning other bovine ingredients in FDA-regulated products. A notice in the *Federal Register* of August 29, 1994, summarized FDA's recommendations to reduce any potential BSE risk and clarified that FDA's recommendations at that time did not extend to gelatin for human use produced from bovine materials from BSE countries.

Recent Review of Gelatin Guidance - In 1996, FDA decided to review its previous guidance on the use of gelatin because of new information suggesting that BSE may be transmissible to humans and because of updated data from the study on the effect of gelatin processing on infectivity.

During the April 1997 meeting of the TSE advisory committee, information on industry practices and the results of the research study were presented. The study involved mouse brain tissue that had been infected with scrapie (as a BSE model).[1] The tissue was treated with lime or with acid according to gelatin manufacturing conditions. Neither the acid nor the lime treatment completely inactivated the infectious agent. A second infectivity study is due to be completed in late 1997 or early 1998.

The advisory committee members stated opinions on questions raised by FDA and were polled on their answers to the final question, "Does current scientific evidence justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine-derived materials from BSE countries?" Ten of the 14 members responded "no"or a "qualified no"to this question (see Appendix B for a summary of the advisory committee meeting).

Recommendations - FDA has been reviewing the currently available scientific information, including information provided on behalf of the Gelatin Manufacturers of Europe and the Gelatin Manufacturers Institute of America. FDA also considered the advisory committee's recommendations and other available information. Based on this review, FDA proposes the following recommendations concerning the acceptability of gelatin for use in FDA-regulated products intended for human use:

1. In order to ensure that all parties in the distribution chain take appropriate responsibility,

importers, manufacturers, and suppliers should determine the tissue, species, and country source of all materials to be used in processing gelatin for human use.

2. Bones and hides from cattle that shows signs of neurological disease, from any source country, should not be used as raw material for the manufacture of gelatin.

3. 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)[2] (see Appendix C) should not be used either in injectable, ophthalmic, or implanted FDA-regulated products, or in their manufacture.

4. At this time, there does not appear to be a basis for objection to the use of gelatin in FDA-regulated products for oral consumption and cosmetic use by humans when the gelatin is produced from bones obtained from cattle residing in, or originating from, BSE countries, if the cattle come from BSE-free herds and if the slaughterhouse removes the heads, spines, and spinal cords directly after slaughter. Nor does there appear to be a basis for objection to gelatin for oral consumption and cosmetic use which is produced from bones from countries which have not reported BSE but which fail to meet OIE standards if the slaughterhouse removes the heads, spine, and spinal cords after slaughter. Gelatin processors should ensure that slaughterhouses that supply bovine bones for gelatin production remove heads, spines, and spinal cords as the first procedure following slaughter.

5. At this time, there does not appear to be a basis for objection to the use of gelatin produced from bovine hides, from any source country, in FDA-regulated products for oral consumption and cosmetic use by humans use if processors ensure that the bovine hides have not been contaminated with brain, spinal cord, or ocular tissues of cattle residing in, or originating from, BSE countries and if they exclude hides from cattle that have signs of neurological disease (see #2).

6. 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-regulated products for human use if the gelatin is produced from U.S.-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.

7. At this time, there does not appear to be a basis for objection to the use of gelatin produced from porcine skins, from any source country, in FDA-regulated products for human use. Processors should ensure that gelatin made from porcine skins is not cross-contaminated with bovine materials originating from BSE countries or from countries that do not meet OIE standards.

APPENDIX A
CHRONOLOGY OF FDA'S BSE-RELATED GUIDANCE/REGULATION

- In November 1992, FDA wrote to manufacturers of dietary supplements, alerting them to the developing concern about transmissible spongiform encephalopathies (TSEs) in animals and Creutzfeldt-Jakob Disease in humans. In that letter, the agency recommended that manufacturers investigate the geographic source(s) of any bovine or ovine material (generally neural or glandular) used in their products. FDA 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 the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, or from scrapie-infected sheep flocks, either foreign or domestic (9 CFR 94.18) .

- In a December 17, 1993, letter to manufacturers of drugs, biologics, and medical devices, FDA recommended against the use of bovine-derived materials from cattle which have resided in, or originated from, BSE countries (59 FR 44592) . FDA recommended that manufacturers: a) identify bovine-derived materials in the product and identify all countries where the animals used to produce the material have lived; b) maintain traceable records for each lot of bovine material and for each lot of FDA-regulated product using these materials; c) document the country of origin of the live animal source of any bovine-derived materials used in the manufacture of the regulated product; and d) maintain copies of the record identified above for FDA-regulated products manufactured using bovine-derived materials at foreign sites or by the foreign manufacturers.

- On July 1, 1994, Ms. Linda Suydam, then Interim Deputy Commissioner for Operations, sent letters to counsel representing the Gelatin Manufacturers Association (GMA) and the Gelatin Manufacturers of America (GMIA) which stated that, after reviewing available scientific information, "FDA does not object to the use of bovine-derived materials from BSE-countries in the manufacture of pharmaceutical grade gelatin at this time."The agency also stated that, "We continue to consider it prudent, however, to obtain such materials from non BSE-countries whenever practical, and to maintain records as to the sources of the bovine materials used to manufacture pharmaceutical grade gelatin."

- FDA published a notice in the *Federal Register* of August 29, 1994, entitled, "Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-regulated Products"(59 FR 44592). The notice published letters to Manufacturers of Dietary Supplements (November 9, 1992), Manufacturers of FDA-Regulated Products (December 17, 1993), Manufacturers of FDA-regulated Products for Animals (August 17, 1994), and to Manufacturers and Importers of Dietary Supplements and of Cosmetics (August 17, 1994). The letter to manufacturers and importers of dietary supplements and cosmetics stated, "The FDA is recommending that firms that manufacture or import dietary supplements and cosmetics containing specific bovine tissues...ensure that such tissues do not come from cattle born, raised, or slaughtered in countries where bovine spongiform encephalopathy (BSE) exists (BSE-countries)."The Agency also stated, "At this time, FDA is not extending the recommendation in this letter to dairy products and gelatin, because available evidence does not suggest transmission via these foods."

- In October 19, 1995, FDA issued Import Alert 17-04 (replacing the 1992 Import Bulletin and revising an alert issued July 18, 1995) calling for the detention, without examination, of bulk shipments of high-risk bovine tissues and tissue-derived ingredients from the United Kingdom, France, Ireland, Oman, Switzerland, and Portugal.

- In March 1996, the British government announced that new information from the Spongiform Encephalopathy Advisory Committee (SEAC) suggested a possible relationship between BSE and 10 cases of a newly identified form of CJD.[4] On May 9, 1996, FDA sent letters to inform the industry of the announcement by the British government and to reiterate the Agency's concerns on this issue. In these letters, FDA strongly reiterated its recommendations that firms that manufacture or import FDA-regulated products take whatever steps necessary to assure themselves and the public that bovine-derived ingredients do not come from cattle, born, raised, or slaughtered in countries that have reported BSE.

- In May 21, 1996, letters to counsel to the GMA and GMIA, Dr. Michael A. Friedman, Deputy Commissioner for Operations stated that, "Although we continue to review

scientific information on animal and human transmissible spongiform encephalopathies related to FDA-regulated products, we have no new knowledge, at this time, to cause us to change our position on gelatin as stated in those letters." However, FDA staff began review of final data from the mouse study whose preliminary data FDA had reviewed in deciding that gelatin from BSE countries was acceptable in FDA-regulated products.

- On June 5, 1997, FDA published in the *Federal Register* a document entitled, "Substances Prohibited From Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed; Final Rule (62 FR 30936). This final rule excludes domestic gelatin from the definition of animal proteins prohibited in ruminant feed. In fact, U.S. manufacturers do not add gelatin--a poor source of protein--as a protein supplement to animal feed. (Imported gelatin and other bovine-derived products from BSE countries intended for animal use are banned by USDA/APHIS).

APPENDIX B
SUMMARY OF TSE ADVISORY COMMITTEE MEETING

On April 23-24, 1997, FDA held a public meeting of the Transmissible Spongiform Encephalopathies Advisory Committee to help FDA assess the safety of imported and domestic gelatin and gelatin by-products in FDA-regulated products with regard to the risk posed by bovine spongiform encephalopathy (BSE). Following presentations on gelatin sourcing and processing, risk assessment, process validation, and BSE's infectivity, panel members were asked the following:

1. Which, if any, specific gelatin-processing procedure is preferred or essential to assure optimal inactivation of any contaminating TSE agent?

The committee agreed with the FDA that the alkali treatment step in gelatin production was a key step in the inactivation of BSE infectious agent. It stated that steps such as heat, alkaline treatment, and filtration could be effective in reducing the level of contaminating TSE agents; however, scientific evidence is insufficient at this time to demonstrate that these treatments would effectively remove the BSE infectious agent if present in the source material.

2. What criteria should be considered in designing gelatin process validation studies and analyzing the results of such studies?

The committee agreed with FDA that there is a need for well-designed process validation protocols to verify that a specific manufacturing process would inactivate BSE's infectious agent. It recommended that FDA use the help of outside experts to review industry submissions. The committee also offered to provide input. The committee stated the need for assurance that manufacturers would follow the specified manufacturing processes.

3. If gelatin and gelatin by-products are no longer to be exempted from FDA BSE restrictions, what level of restriction is sufficient to reduce risk appropriately?

The committee expressed some concern over the current list of USDA-designated BSE countries because ineffective BSE surveillance by some countries may fail to detect BSE cases. It indicated the need for developing criteria for BSE designation/classification. USDA is addressing the issue of effective surveillance and revising its current list. However, it may be some time before this is completed. The committee stated that sourcing for gelatin should be as safe as possible and that countries which had no reported cases, but had an established BSE risk, or lacked an appropriate surveillance system would be of concern.

The committee stated that criteria for gelatin should be established relative to the risk posed by the use of that gelatin . The risk would differ for oral consumption, parenteral, and cosmetic uses. Other factors, such as processing and the type of material processed (bovine/porcine, bones/hides), should be considered in this risk assessment.

4. Does current scientific evidence justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine-derived materials from BSE countries (i.e., that these materials NOT come from BSE countries)?

Ten members said NO or a qualified no; three said YES or a qualified yes; one abstained.

APPENDIX C
International Animal Health Code
Special Edition 1997
Chapter 3.2.13.

Bovine Spongiform Encephalopathy
(BSE)

Article 3.2.13.1.

Bovine spongiform encephalopathy (BSE) is a progressive nervous disease of adult cattle. BSE has a long *incubation period* measured in years, and arose from feeding contaminated ruminant protein.

The BSE status of a country can only be determined by continuous surveillance and monitoring. The minimum requirements for effective surveillance are:

1) compulsory notification and clinical investigation of suspect *cases*;

2) a risk assessment identifying the potential hazards for BSE occurrence:

a) risk arising by:

i) importation of animals or *embryos/*ova which are potentially infected with a transmissible spongiform encephalopathy (TSE);

ii) importation and feeding of potentially contaminated animal feedstuff to cattle;

b) indigenous risks:

i) consumption, by cattle, of contaminated, animal-derived proteins arising from transmissible spongiform encephalopathy-infected animals and rendering processes which do not inactivate the agent;

ii) potential vertical transmission of BSE from cows originating from infected countries;

3) a continuous BSE surveillance and monitoring system with emphasis on risks identified in point 2) above; and

4) examination in an approved laboratory of brain material from cattle older than 20 months displaying signs of progressive neurologic disease in accordance with the diagnostic techniques set out in the *Manual*. A sufficient number of investigations as indicated in Table I of the Guidelines for Continuous Surveillance and Monitoring of BSE (Appendix VIII of document 65 SG/12/CS.) should be carried out annually;

in countries where progressive neurologic disease incidence is low, surveillance

should be targeted at cattle older than four years of age displaying other progressive disease conditions;

5) records of the number and results of investigations should be maintained for at least seven years.

Each confirmed case should be reported as a separate *outbreak.*

Article 3.2.13.2.

Countries may be considered free of BSE if:

1) they have implemented a risk management strategy to address any risk, as identified in Article 3.2.13.1. point 2); and

2) The feeding of *meat-and-bone meal* to cattle derived from ruminants originating from animal TSE infected countries, or countries which do not have an effective and continuous surveillance and monitoring system as described in Article 3.2.13.1 points 3) and 4), has been banned and is effectively enforced;

AND

3) a) there has been no clinical case of BSE, the disease is notifiable, and an effective and continuous surveillance and monitoring system is practised, as described in Article 3.2.13.1. point 3) and 4); or

b)all *cases* of BSE have been clearly demonstrated to originate directly from importation of live cattle originating from BSE infected countries, provided that the disease is made notifiable and suspect animals are slaughtered, investigated and, if disease is confirmed, completely destroyed and an effective and continuous surveillance and monitoring system is practised, as described in Article 3.2.13.1. points 3) and 4); or

c) BSE has been eradicated (under study).

Article 3.2.13.3.

Veterinary Administrations can authorise without restriction the import or transit through their territory, directly or indirectly, of milk, milk products, tallow, hides and skins originating from healthy animals from countries where BSE has been reported. There is also no scientific evidence of a risk associated with the trade in semen from healthy animals. By-products, such as gelatin and collagen, are considered to be safe if produced by processes (under study) which inactivate any residual BSE infectivity.

Article 3.2.13.4.

When importing from countries with low incidence of BSE, *Veterinary Administrations* should require:

<u>for cattle</u>

the presentation of an *international animal health certificate* attesting that:

1) the disease is compulsorily notifiable;

2) affected cattle are slaughtered and completely destroyed;

3) suspect heifers or cows close to calving are isolated;

4) an effective and continuous surveillance and monitoring system is practised in accordance with Article 3.2.13.1.;

5) the feeding of *meat-and-bone meal* derived from ruminants to ruminants has been banned and effectively enforced;

6) cattle selected for export:

a) are identified by a permanent mark enabling them to be traced back to the dam and herd of origin;

b) are not the calves of BSE suspect or confirmed females.

Article 3.2.13.5.

When importing from countries with a high incidence of BSE, *Veterinary Administrations* should require:

for cattle

the presentation of an *international animal health certificate* attesting, in addition to the requirements set forth in Article 3.2.13.4. that animals for export:

1) either were born after the date on which an effective ban on the use of ruminant *meat-and-bone meal* in feed for ruminants has been effectively enforced; or

2) were born, raised and had remained in a herd in which no *case* of BSE had ever been confirmed, and which contains only cattle born on the farm or coming from a herd of equal status; and

3) have never been fed ruminant meat-and-bone meal.

Article 3.2.13.6.

When importing from countries with a low incidence of BSE, *Veterinary Administrations* should require:

for *fresh meat* (bone-in or deboned) and *meat products* from cattle

–

the presentation of an *international sanitary certificate* attesting that:

1) the disease is compulsorily notifiable;

2) affected cattle are slaughtered and completely destroyed;

3) *ante mortem* inspection is carried out on all bovines;

4) an effective and continuous surveillance and monitoring system is practised in accordance with Article 3.2.13.1.;

5) the meat products do not contain brain, eyes, spinal cord or distal ileum from cattle over six months of age which were born before the date on which the feed ban referred to in paragraph 5) of Article 3.2.13.4. was effectively enforced.

Article 3.2.13.7.

When importing from countries with high incidence of BSE, *Veterinary Administration* should require:

for *fresh* bone-in *meat* from cattle

–

the presentation of an *international sanitary certificate* attesting, in addition to the requirements set forth in Article 3.2.13.6., that:

1) the tissues listed in Article 3.2.13.12. are removed from all cattle at slaughter and destroyed;

2) the cattle from which the *meat* originates:

a) were born after the date on which a ban on the use of ruminant *meat-and-bone meal* in feed for ruminants has been effectively enforced; or

b) were born and had only been kept in herds in which no *case* of BSE had been recorded; and

c) have never been fed ruminant meat-and-bone meal.

Article 3.2.13.8.

When importing from countries with a high incidence of BSE, *Veterinary Administrations* should require:

for *fresh* deboned *meat* and *meat products* from cattle

–

the presentation of an *international sanitary certificate* attesting that the conditions in Article 3.2.13.7. apply or alternatively that:

1) the disease is compulsorily notifiable;

2) affected cattle are slaughtered and completely destroyed;

3) *ante mortem* inspection is carried out on all bovines;

4) an effective and continuous surveillance and monitoring system is practised in accordance with Article 3.2.13.1.;

5) the tissues listed in Article 3.2.13.12. are removed from all cattle at slaughter and destroyed;

6) nervous and lymphatic tissues exposed during the cutting process have been removed and destroyed.

Article 3.2.13.9.

When importing from countries with a low incidence of BSE, *Veterinary Administrations* should require:

for bovine *embryos/ova*

the presentation of an *international animal health certificate* attesting that:

1) the disease is compulsorily notifiable;

2) affected cattle are slaughtered and completely destroyed;

3) suspect heifers or cows close to calving are isolated;

4) an effective and continuous surveillance and monitoring system is practised in accordance with Article 3.2.13.1.;

5) the feeding of *meat-and-bone meal* derived from ruminants to ruminants has been banned and effectively enforced;

6) embryos/ova for export are derived from females which:

a) are not affected with BSE;

b) are not the daughters of BSE affected females; and

c) were not suspected of being so affected at the time of embryo collection.

Article 3.2.13.10.

When importing from countries with a high incidence of BSE, *Veterinary Administrations* should require:

for bovine *embryos/ova*

–

the presentation of an *international animal health certificate* attesting that embryos/ova for export are derived from females which comply with the conditions in Article 3.2.13.5. and paragraph 6) of Article 3.2.13.9.

Article 3.2.13.11.

Meat-and-bone meal containing any ruminant protein which originates from countries with a high incidence of BSE, should not be traded between countries.

Meat-and-bone meal containing any ruminant protein which originates from countries with a low incidence of BSE, should not be traded between countries for use in ruminant feed. For other uses, it should have been processed in plants which are approved and regularly controlled by the *Veterinary Administration* following validation that each plant can achieve the processing parameters described in Appendix 4.3.3.1.

Article 3.2.13.12.

Bovine brains, eyes, spinal cord, tonsils, thymus, spleen and distal ileum (tissues under study) and protein products derived from them from cattle over six months of age originating from countries with a high incidence of BSE should not be traded between countries.

Bovine brains, eyes, spinal cord and distal ileum (tissues under study) and protein products derived from them from cattle over six months of age which originate from countries with a low incidence of BSE and were born before the date on which the feed ban referred to in point 5) of Article 3.2.13.4. was effectively enforced, should not be traded between countries, unless they comply with the provisions of Article 3.2.13.11.

Article 3.2.13.13.

Careful selection of source materials is the best way to ensure maximum safety of ingredients or reagents of bovine origin used in the manufacture of medicinal products.

Countries wishing to import bovine materials for such purposes should therefore consider the following factors:

1) the BSE status of the country and herd(s) where the animals have been kept, as determined under the provisions of Article 3.2.13.1. and Article 3.2.13.2.;

2) the age of the donor animals;

3) the tissues required and whether or not they will be pooled samples or derived from a single animal.

Additional factors may be considered in assessing the risk from BSE, i.e.:

1) precautions to avoid contamination during collection of tissues;

2) the process to which the material will be subjected during manufacture;

3) the amount of material to be administered;

4) the route of administration.

[1]Shrieber, R. 1997. Presentation to the FDA Transmissible Spongiform Encephalopathy Advisory Committee, April 23, 1997. Transcript is available in hard copy or on disk from Freedom of Information, HFI-35, Food and Drug Administration, Rockville, MD 20857.

[2]Office International des Epizooties. 1997. *International Animal Health Code,* Special Edition, Chapter 3.2.13. pp. 267-274, Paris.

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