

LAW OFFICES

KLEINFELD, KAPLAN AND BECKER, LLP

1140 NINETEENTH STREET, N.W.
WASHINGTON, D. C. 20036-6606

TELEPHONE (202) 223-5120

FACSIMILE (202) 223-5619

www.kkblaw.com

WEST COAST OFFICE:
ONE MARKET STREET
STEUART TOWER, SUITE 1450
SAN FRANCISCO, CA 94105-1313
TELEPHONE (415) 538-0014
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD
1907-1993

ALAN H. KAPLAN
1930-2001

October 20, 2003

THOMAS O. HENTELEFF
RICHARD S. MOREY
KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
BONNIE A. BEAVERS
DANIEL R. DWYER
GLENN E. DAVIS
STACY L. EHRLICH
JENNIFER A. DAVIDSON
STACEY L. VALERIO
ROBERT O. WINTERS

OF COUNSEL
HARVEY A. SUSSMAN

2185 03 OCT 21 10:47

Via Hand Delivery

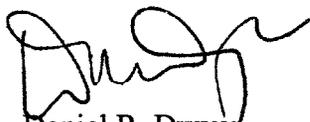
Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

To Whom It May Concern:

Pursuant to 21 CFR 10.30, please find enclosed for filing a Citizen Petition submitted by the Gelatin Manufacturers of Europe (GME) and the Gelatin Manufacturers Institute of America (GMIA), requesting modification of a guidance document entitled "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" (Docket No. 97D-0411, September 1997).

Thank you for your assistance with this matter.

Sincerely,


Daniel R. Dwyer

enclosure

1997D-0411

CPI

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

October 20, 2003

CITIZEN PETITION

The Gelatin Manufacturers of Europe (GME) and the Gelatin Manufacturers Institute of America (GMIA) submit this petition under the Federal Food, Drug, and Cosmetic Act (including section 402 thereof) to request that the Commissioner of Food and Drugs modify a guidance document entitled "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" (Docket No. 97D-0411, September 1997) (the "gelatin guidance").

A. Action Requested

FDA's gelatin guidance provides recommendations on the sourcing and processing of gelatin from countries reporting BSE and from countries that do not meet the BSE-related standards of the Office International des Epizooties (OIE). The guidance was developed by FDA based in part on the recommendations of the agency's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) in April 1997.

A key provision of the guidance is Recommendation 4, which addresses gelatin produced from bovine bones for consumption by humans through oral or topical administration. This recommendation provides as follows:

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.*

(Emphasis in original.)

1997D-0411

CP 1

For the reasons discussed in section B below, GME and GMIA request that the following modifications be made to Recommendation 4 of the gelatin guidance:

- Add a requirement that bovine bone gelatin be made using manufacturing processes that are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity that is sufficient to protect human health. (Examples of such manufacturing processes include those reviewed by the TSEAC at its July 17, 2003 meeting.)
- Delete the requirement that heads, spines, and spinal cords be removed at the slaughterhouse “directly after slaughter” and “as the first procedure following slaughter,” and clarify that heads, spines and spinal cords may be removed at any time or place after slaughter.
- Clarify that bones used in the manufacture of gelatin should come from cattle that meet generally accepted standards for BSE safety, that is: (1) cattle reside in and originate from countries where the feeding of cattle with feed that contains proteins derived from mammalian tissues is prohibited (except as permitted under 21 CFR 589.2000); (2) cattle have tested negative for BSE under any applicable BSE testing requirements in effect in the jurisdiction where the cattle are located; and (3) no cattle show signs of neurological disease. (NOTE: With respect to the issue of neurological disease, Recommendation 2 of FDA’s gelatin guidance states that “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.” Therefore, this issue need not be addressed in Recommendation 4.)

The proposed revised text of Recommendation 4 is as follows (deleted text is crossed out, new text is double-underlined, and italics reflect emphasis in original):

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, in such countries, the cattle come from BSE free herds feeding of cattle with feed that contains proteins derived from mammalian tissues is prohibited (except as permitted under 21 CFR 589.2000); if the cattle have tested negative for BSE under any applicable BSE testing requirements in effect in the jurisdiction where the cattle are located; and if the slaughterhouse removes the heads, spines and spinal cords directly after slaughter heads, spines and spinal cords are removed from gelatin raw materials; and if the gelatin manufacturing processes are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity that is sufficient to protect human health.** 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~~ heads, spines and spinal cords are removed from gelatin raw materials; and if the gelatin manufacturing processes are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity that is sufficient to protect human health.* *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.*

[Footnote to text] * The Transmissible Spongiform Encephalopathies Advisory Committee voted on July 17, 2003 that the results of studies of BSE inactivation by certain gelatin manufacturing processes demonstrate a reduction in infectivity that is sufficient to protect human health. (Transcript of meeting, pp. 150-158.)

B. Statement of Grounds

At its recent meeting on April 17, 2003, the TSEAC reviewed new studies showing the effects on BSE and TSE infectivity of several different gelatin manufacturing processes and concluded that “the results of these new studies demonstrate a reduction in infectivity that is sufficient to protect human health.” (Transcript of meeting, pp. 150-158.)¹ However, as it is currently written, Recommendation 4 of the gelatin guidance does not rely on these validated manufacturing processes to assure safety. Rather, it imposes two safety conditions: first, that cattle come from “BSE-free herds,” and second, that the slaughterhouse remove the heads, spines, and spinal cords “directly after slaughter.”

These two conditions have only limited applicability to the gelatin manufacturing process for two principal reasons:

- First, the identification of “BSE-free herds” is imprecise because the long incubation period of the disease can create uncertainty as to whether a herd is BSE-free, and there are currently no available testing procedures for living cattle. (In this petition, we propose the use of more specific criteria, consistent with generally accepted BSE-prevention practices, in order to determine appropriate source animals. These criteria will provide a stronger assurance that source animals are BSE-free, recognizing that complete assurance is not an achievable goal at this time.)

¹ FDA website: <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3969t1.PDF>. See also questions for the committee at http://www.fda.gov/ohrms/dockets/ac/03/questions/3969Q1_1.pdf.

- Second, although heads and spinal cords are removed at the slaughterhouse as standard practice in Europe, spines (i.e., the vertebral column) are necessarily removed at a different location, later in time.

Because these two conditions have only limited applicability to the gelatin manufacturing process, the gelatin guidance would be strengthened if Recommendation 4 were to place greater reliance on the validated ability of gelatin manufacturing processes to reduce BSE infectivity in a manner sufficient to protect human health.

Accordingly, GME and GMIA request that Recommendation 4 be revised to expressly require the use of gelatin manufacturing processes that are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity sufficient to protect human health. When this is done, the protections provided by other criteria in the guidance (that is, the criteria for the selection of appropriate source animals and for the removal of heads, spines, and spinal cords from the raw material supply) become comparatively less important.

In addition, GME and GMIA request that Recommendation 4 be revised to describe the criteria for the selection of appropriate source animals and for the removal of heads, spines, and spinal cords from the raw material supply in terms that (1) provide a stronger assurance that source animals are BSE-free, and (2) more realistically reflect the extent to which these criteria can be achieved by European producers.

GME and GMIA are confident that, taken together, these modifications will result in a gelatin guidance that provides a stronger assurance of safety than does the current document.

The following sections review background information on the development and implementation of FDA's gelatin guidance, and discuss in more detail the requested modifications to the guidance.

1. Background.

- a. The 1997 gelatin guidance was developed in reaction to incomplete information on the ability of the gelatin manufacturing process to inactivate BSE infectivity.*

Beginning in 1992, FDA issued letters to members of the regulated industry to recommend that bovine-derived materials from cattle that have resided in, or originated from, BSE countries not be used in the manufacture of FDA-regulated products intended for humans or animals. Initially, FDA exempted gelatin from this guidance. For example, in 1993, FDA clarified that it did not object to the use of bovine-derived

materials from BSE countries in the manufacture of pharmaceutical grade gelatin. In 1994, FDA stated that it was not extending its recommendation regarding the use of bovine-derived materials from BSE countries “to dairy products or gelatin, because available evidence does not suggest transmission via these foods.” 59 Fed. Reg. 44591 (Aug. 29, 1994). In January 1997, in the context of a proposed rule on substances prohibited from use in animal food or feed, FDA stated:

Data available to the agency suggest that gelatin does not transmit the TSE agent. The WHO has concluded that gelatin in the food chain is considered to be safe, as the conventional manufacturing process for gelatin has been demonstrated to significantly inactivate any residual infective activity that may have been present in source tissues FDA concurs with this statement and the scientific information on which it is based.

62 Fed. Reg. 552 at 572 (Jan. 3, 1997).

Subsequently, FDA modified its policy toward gelatin based on advice from the TSEAC. On April 23 and 24, 1997, the TSEAC reviewed the available data on the ability of the gelatin manufacturing process to inactivate BSE infectivity. A majority of the TSEAC members concluded that then-current scientific evidence did not justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine-derived materials from BSE countries. However, most of the members who reached this conclusion indicated that they did so based on a lack of data, and that it would be important to develop data to support a conclusion that the gelatin manufacturing process significantly reduces BSE infectivity. (Transcript of meeting, April 24, 1997.²)

Based on the TSEAC’s deliberations, FDA revised its prior advice to industry on gelatin by issuing the gelatin guidance in September 1997. 62 Fed. Reg. 52345 (October 7, 1997).³ The guidance includes several recommendations for reducing the potential risk of transmission of BSE via the use of gelatin in FDA-regulated products for human use, including Recommendation 4 quoted above.

b. Certain provisions in the 1997 gelatin guidance make it impossible for safe European gelatin to comply with the guidance.

The gelatin guidance was issued under FDA’s “Good Guidance Practices” under which FDA provides advice without binding either FDA or the public. Nevertheless, although the guidance has no legal effect, it had and continues to have a significant effect on the marketplace because most customers of the gelatin industry (such as gelatin capsule

² FDA website: <http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3283t2.rtf>.

³ A copy of the gelatin guidance is enclosed, and can also be found at <http://www.fda.gov/opacom/morechoices/industry/guidance/gelguide.htm>.

manufacturers) require the terms of the guidance to be met as contractual conditions. Thus, as a practical matter, the guidance has a legal effect. This has resulted in two significant problems for the European gelatin industry.

The first problem arises from the language in Recommendation 4 of the guidance requiring that slaughterhouses remove heads, spines, and spinal cords “directly after slaughter” and “as the first procedure following slaughter.” In Europe, the removal of heads and spinal cords is consistent with this recommendation, but the removal of spines (i.e., the vertebral column) is not. The vertebral column holds the carcass together while it is processed by the slaughterhouse, shipped, and further processed by downstream producers. As a result, the vertebral column can only be removed from gelatin raw materials at a step later than the first procedure following slaughter. In Europe, it is standard practice that the vertebral column be removed under the supervision of a public veterinarian at a time after slaughter and at a location other than the slaughterhouse. Because of this, there is a risk that European gelatin would be considered non-compliant with the requirement in FDA’s guidance that the spine be removed “directly after slaughter” and “as the first procedure following slaughter.”

The second problem caused by the gelatin guidance arises from the language in Recommendation 4 requiring that gelatin raw materials from BSE countries come from “BSE-free herds.” The definition of “BSE-free herd” is unclear. In Europe, it is mandatory that animals over 30 months of age be tested for BSE, whereas animals under that age normally are not tested because they have not been determined to pose a risk to human health. If “BSE-free herd” is defined in a manner inconsistent with this practice, or in a manner that includes additional requirements that are not expressly stated in the guidance, there is a risk that European gelatin would be considered non-compliant with FDA’s guidance.

On April 16, 1998, the TSEAC considered the first problem, that is, the question of whether spines should be removed from gelatin raw materials as the first procedure following slaughter. The TSEAC recommended to FDA that healthy cattle from BSE countries may be considered a safe source of bones to produce gelatin intended for oral consumption by humans or for topical application to humans if the cattle are from BSE-free herds and the heads, spines, and spinal cords are removed from carcasses – without requiring that such removal occur “directly after slaughter.” *See* Transcript of TSEAC meeting, April 16, 1998, pp. 257-259.⁴

On November 9, 1998, GME requested by letter that FDA implement this TSEAC advice by revising Recommendation 4 of the guidance to provide that heads, spines and spinal cords must be removed, but without specifying a required time or place for such removal. FDA has not responded to this request.

⁴ FDA website: <http://www.fda.gov/ohrms/dockets/ac/98/transcript/3406t2.rtf>.

c. New information is now available on the ability of the gelatin manufacturing process to reduce BSE infectivity in a manner sufficient to protect human health.

As discussed above, FDA's gelatin guidance was developed in 1997 after the TSEAC concluded that then-current scientific evidence did not justify continuing to exempt gelatin from restrictions that had been put in place for other bovine-derived materials from BSE countries. The TSEAC's conclusion was based primarily on a lack of data that the gelatin manufacturing process significantly reduces BSE infectivity.

Now, however, such data are available. At its meeting on July 17, 2003, the TSEAC reviewed data from studies commissioned by the European Commission and GME. These data validate that the processes used to manufacture gelatin (in both Europe and the United States) are effective at inactivating BSE infectivity. As TSEAC Member R. Nick Hogan, M.D., Ph.D., stated during the meeting, "... I think that all the questions that the original Committee in 1997 had regarding the data, in my mind, have been answered." (Transcript of meeting, p. 151.) After reviewing these data, the TSEAC as a whole concluded that the data "demonstrate a reduction in infectivity that is sufficient to protect human health."⁵ *Id.* at 150, 158.

d. This new information provides a stronger basis for assuring safety than the conditions currently included in the guidance, and the guidance should be revised to reflect the relative importance of this new information.

These new data indicate that the most effective way for the gelatin guidance to assure safety is to require the use of manufacturing processes that are the same as, or equivalent to, those that have been validated as effective at inactivating BSE infectivity in a manner sufficient to protect human health. Accordingly, GME and GMIA request that Recommendation 4 be revised to expressly require the use of such manufacturing processes. When this is done, the protections provided by the existing criteria in the guidance (relating to selection of appropriate source animals and to removal of heads, spines, and spinal cords from the raw material supply) become comparatively less important.

GME and GMIA further request that Recommendation 4 be revised to describe the criteria for the selection of appropriate source animals and for the removal of heads, spines, and spinal cords from the raw material supply in terms that (1) provide a stronger

⁵ The vote was 7 in favor, 1 abstain, and 1 against.

assurance that source animals are BSE-free, and (2) more realistically reflect the extent to which these criteria can be achieved by European producers. The availability of data demonstrating that gelatin manufacturing processes reduce infectivity in a manner sufficient to protect human health provides assurance that these revisions to the guidance will in no way compromise the public health.

Indeed, because the original impetus for FDA's gelatin guidance was a lack of definitive data to establish that the gelatin manufacturing process significantly reduces BSE infectivity, and because these data are now available, GME and GMIA believe that the guidance is now no longer necessary in order to assure a safe supply of gelatin. Rather, the safety of gelatin can be regulated under FDA's existing authorities, including applicable good manufacturing practice regulations governing different categories of FDA-regulated products.

However, assuming that the guidance will remain in effect, the following section describes in more detail the necessary modifications to the guidance.

2. Requested Modifications to the Gelatin Guidance.

The following are the requested modifications to the gelatin guidance:

- a. Add a requirement that bovine bone gelatin be made using manufacturing processes that are the same as, or equivalent to, those that have been validated as effective at inactivating BSE infectivity in a manner sufficient to protect human health.*

The strongest contribution to the safety of bovine bone gelatin is provided by the processes used to manufacture the product. Gelatin made using different manufacturing processes was tested to assess the ability of these processes to reduce BSE and TSE infectivity. The TSEAC considered these tests in detail and concluded that the manufacturing processes demonstrate a reduction in infectivity that is sufficient to protect human health. In order to assure that this conclusion continues to be valid for future batches of gelatin, such gelatin should be fundamentally the same as, or equivalent to, the product tested (in terms of the processing conditions to which the gelatin is subjected).

Accordingly, GME and GMIA request that the gelatin guidance be modified to add a requirement that bovine bone gelatin be made using manufacturing processes that are the same as, or equivalent to, those that have been validated as effective at inactivating BSE infectivity.

- b. Delete the requirement that heads, spines, and spinal cords be removed at the slaughterhouse “directly after slaughter” and “as the first procedure following slaughter,” and clarify that heads, spines and spinal cords may be removed at any time or place after slaughter.***

The gelatin guidance currently requires that heads, spines and spinal cords be removed at the slaughterhouse “directly after slaughter” and “as the first procedure following slaughter.” In Europe, the removal of heads and spinal cords is accomplished at the slaughterhouse shortly after slaughter. However, as discussed in section 1.b. above, the removal of spines (the vertebral column) is not. Because the data on BSE inactivation presented to the TSEAC validated that the gelatin manufacturing process can inactivate BSE infectivity even when extremely high levels of infectivity are added to the bones, there is a reasonable basis for concluding that the time and/or place of removal of spines (and heads and spinal cords) is not material to protection of the public health.

This conclusion is supported by the discussion of TSEAC members at the April 17, 2003 meeting. For example, as the Chair, Suzette A. Priola, Ph.D., observed:

... [G]iven all the data we have seen showing inactivation of infectivity following the gelatin extraction process, the issue of ... cross-contamination by a spinal cord being removed at a different part of the slaughter process may not be as major an issue given the fact that now there are these five individual studies, all of which saying that the gelatin process itself, as you get to the end, can remove extremely high levels of infectivity under worst case conditions. So it's possible that this discussion as to when things are removed ... may not, given that data, be as critical as it might have been before we had access to this data.

(Transcript of meeting, p. 175.)

TSEAC Member Lisa A. Ferguson, D.V.M., commented that “... [I]t's important to essentially limit the use of vertebral column in the production of gelatin or ... not us[e] vertebral column in the production of gelatin. I don't think it makes any difference where or when that is removed” Chair Priola agreed, saying, “... [I]t's important that it is being removed given the data [we] heard. Where exactly it's removed may not be that big of an issue since you can [in]activate, apparently, quite effectively quite a bit of infectivity that might be residual on the bone surface after removal of the spinal cord.” (*Id.* at 188-189.)

Similarly, TSEAC Member Hogan observed that, because the data on BSE inactivation show that, even with high titer material, infectivity is eliminated “virtually totally,” the “real-world” starting level of infectivity is, as a practical matter, “irrelevant, because it's never going to be as high as what they are starting with in these validation studies.” (*Id.* at 178.)

Accordingly, GME and GMIA request that the gelatin guidance be modified to:

- delete the requirement that heads, spines, and spinal cords be removed at the slaughterhouse “directly after slaughter” and “as the first procedure following slaughter,” and
- provide for the removal of heads, spines and spinal cords at any time or place after slaughter.

c. Clarify that appropriate source animals consist of those residing in and originating from countries where the feeding of cattle with feed that contains proteins derived from mammalian tissues is prohibited (except as permitted under 21 CFR 589.2000); and those that have tested negative for BSE under any applicable BSE testing requirements in effect in the jurisdiction where the cattle are located.

At this time, the gelatin guidance provides for the use of bovine bone gelatin from BSE countries “if the cattle come from BSE-free herds.” However, it is unclear what the guidance means by “BSE-free herds.” It is important that the guidance identify clearly the appropriate source animals for gelatin raw materials, so as to avoid misinterpretation that could result in gelatin being inadvertently non-compliant with FDA’s guidance.⁶

There is no regulatory definition of “BSE-free herd.” According to an FDA representative at the April 17, 2003 TSEAC meeting, the term “BSE-free herd” was used in the guidance not as a term of art, but as a general indicator of the type of herd that could provide acceptable source animals. This term was “specified but not defined ... just to put the industry on notice that under no circumstances did we consider material from a herd recognized to have BSE as being an acceptable source for any kind of gelatin entering the United States.” (Transcript of meeting, p. 173.)

Rather than rely on the vague term “BSE-free herd,” GME and GMIA recommend that the guidance rely on established criteria for prevention and detection of BSE in cattle. In Europe, these established criteria include (but are not limited to): (1) a ban on the feeding of processed animal protein to animals which are kept, fattened or bred for the production of food; (2) BSE testing for all cattle over 30 months of age; and (3) surveillance for all animals to detect clinical symptoms suggestive of BSE. (*See Regulation (EC) No. 999/2001, as amended.*)

⁶ In particular, it is important to clarify that, even though USDA might not consider any herd in a BSE country to be BSE-free for purposes of its regulations governing importation of products for animal use (*see* statement of Dr. Ferguson, Transcript of meeting, April 17, 2003, p. 161), it is possible to identify appropriate source animals from BSE countries for purposes of FDA regulations.

Based on these criteria, GME and GMIA recommend that the guidance be revised to provide that bones used in the manufacture of gelatin come from cattle that meet generally accepted standards for BSE safety, that is: (1) cattle reside in and originate from countries where the feeding of cattle with feed that contains proteins derived from mammalian tissues is prohibited (except as permitted under 21 CFR 589.2000); (2) cattle have tested negative for BSE under any applicable BSE testing requirements in effect in the jurisdiction where the cattle are located; and (3) no cattle show signs of neurological disease. (NOTE: With respect to the issue of neurological disease, Recommendation 2 of FDA's gelatin guidance states that "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." Therefore, this issue need not be addressed in Recommendation 4.)

Indeed, at the April 17, 2003 meeting, TSEAC Member Ferguson commented that the term "BSE-free herd" is "very difficult to define" and "in some ways it is sort of meaningless." Dr. Ferguson went on to note, "... I'm not quite sure exactly what level of risk mitigation it's necessarily adding in this guidance. Probably more of the risk mitigation is coming from removing those tissues that are at highest risk and also just through the inactivation of the process itself. So perhaps what we should consider is[, is] that specific point even necessary in there or does it just cause more confusion than it is really worth?" (Transcript of meeting, p. 168.)

As Dr. Ferguson suggests, because other controls are available, a specification for appropriate source animals in the guidance could be eliminated without compromising the public health. However, if the guidance continues to provide such a specification, GME and GMIA request that, instead of referring to a "BSE-free herd," the guidance be revised to refer to established criteria for prevention and detection of BSE in cattle, as outlined above.

3. Conclusion.

For the reasons discussed in this petition, GME and GMIA request that Recommendation 4 of the gelatin guidance be revised as follows (deleted text is crossed out, new text is double-underlined, and italics reflect emphasis in the original):

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, in such countries, ~~the cattle come from BSE free herds~~ feeding of cattle with feed that contains proteins derived from mammalian tissues is prohibited (except as permitted under 21 CFR 589.2000); if*

the cattle have tested negative for BSE under any applicable BSE testing requirements in effect in the jurisdiction where the cattle are located; and if the slaughterhouse removes the heads, spines and spinal cords directly after slaughter heads, spines and spinal cords are removed from gelatin raw materials; and if the gelatin manufacturing processes are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity that is sufficient to protect human health.* 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 heads, spines and spinal cords are removed from gelatin raw materials; and if the gelatin manufacturing processes are the same as, or equivalent to, those that have been the subject of studies that demonstrate a reduction in infectivity that is sufficient to protect human health.** *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.*

[Footnote to text] * The Transmissible Spongiform Encephalopathies Advisory Committee voted on July 17, 2003 that the results of studies of BSE inactivation by certain gelatin manufacturing processes demonstrate a reduction in infectivity that is sufficient to protect human health. (Transcript of meeting, pp. 150-158.)

GME and GMIA are confident that, taken together, these modifications will result in a gelatin guidance that provides a stronger assurance of safety than does the current document.

C. Environmental Impact

This action has no environmental impact and therefore a claim for categorical exclusion is submitted pursuant to 21 CFR Part 25, Subpart C, including section 25.30(h).

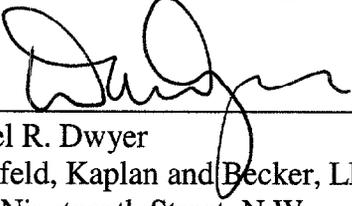
D. Economic Impact

Information will be submitted upon request.

E. Certification

The undersigned certify, that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

GELATIN MANUFACTURERS OF EUROPE

By: 
Daniel R. Dwyer
Kleinfeld, Kaplan and Becker, LLP
1140 Nineteenth Street, N.W.
Washington, DC 20036
(202) 223-5120
e-mail: ddwyer@kkblaw.com

Counsel to the Gelatin Manufacturers of Europe

GELATIN MANUFACTURERS INSTITUTE OF AMERICA

By:  /del
Mario Diaz-Cruz, III
David A. Biegging
Dorsey & Whitney LLP
Suite 400 South
1001 Pennsylvania Avenue, N.W.
Washington, DC 20004-2533
(202) 442-3565
e-mail: Diaz.Cruz.Mario@dorsey.com
Biegging.Dave@dorsey.com

Counsel to the Gelatin Manufacturers Institute of America

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

September 1997

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 Agriculture's 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:

for cattle

-

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

- 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

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;

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.

¹Shrieber, 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.

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

* * * * *

Reprinted by permission from the Office International des Epizooties.

FDA HOME PAGE

September 1997