

# TOPIC #3

Dr. Chiu

### TOPIC #3 Overview

This package contains background information for the issues that will be discussed during this portion of Advisory Committee meeting. The materials have been provided in order to show the history of the issues and discussions that have taken place concerning the safety of gelatin used in the manufacture of drug products marketed in the United States. The materials are as follows:

- Agendas and questions from the April 23 and 24, 1997 and April 15 and 16, 1998 TSE Advisory Committee meetings
- Unofficial Summaries of the April 23 and 24, 1997 and April 15 and 16, 1998 TSE Advisory Committee meetings
- 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 (September 1997)
- Opinion on the Safety of Gelatine – Adopted at the Scientific Steering Committee at its plenary meeting of March 26 and 27, 1998 (EU)

During this portion of the meeting, the Committee will hear updates on the interim validation study results on the inactivation of BSE through the gelatin manufacturing process, from the Gelatin Manufacturers of Europe (GME). Since this is an information sharing discussion, no questions are being posed to the Committee for this section. The intent of this topic discussion is to provide new information that is not completed for publication and provide what may be expected for future discussions.

**FOOD AND DRUG ADMINISTRATION  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

*Holiday Inn - Bethesda  
Versailles Ballroom  
8120 Wisconsin Avenue  
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**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE**

*April 23 and 24, 1997*

**AGENDA**

Day 1 (Wednesday, April 23, 1997)

- 9:00 a.m. Opening and Administrative Remarks
- 9:05 Welcome and Introductory Comments  
-- **Randy Wykoff, M.D., Associate Commissioner  
for Operations, FDA**
- 9:15 Open Public Hearing
- 10:15 Open Committee Discussion: The safety of both imported gelatin and gelatin byproducts with regard to the risk imposed by bovine spongiform encephalopathy.
- Background - Overview of the gelatin issue and uses of gelatin in FDA-regulated products  
-- **Kiki Hellman, Ph.D., CDRH, FDA**
- 10:45 Break
- 11:00 Sources of Materials for Gelatin Manufacture  
-- **John Vanderveen, Ph.D., CFSAN, FDA**  
-- **John Honstead, D.V.M., CVM, FDA**
- 11:45 Committee questions of previous speakers
- 12:15 p.m. Break for lunch
- 1:15 Reconvene
- Gelatin Processing  
-- **Donald Wrathall, Ph.D., Eastman Gelatine**  
-- **Michael Dunn, Ph.D., Kind & Knox Gelatine**
- 1:45 Exposure Estimates and Risk Assessment  
-- **Mike DiNovi, Ph.D., CFSAN, FDA**  
-- **Philip M. Bolger, Ph.D., CFSAN, FDA**

**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE**

**AGENDA (Page 2)**

Wednesday, April 23, 1997 (continued)

- 2:15 Risk Reduction--USDA Regulations on Importation of Gelatin  
-- John Gray, D.V.M., USDA
- 2:30 Committee questions of previous speakers
- 3:00 Break
- 3:15 Survivability of TSE Agents and Kinetics of Inactivation  
-- Robert Rohwer, Ph.D., VA Medical Center, Baltimore
- 3:45 Process Validation Studies: Review Issues  
--Carol Vincent, M.S., CDER, FDA
- 4:00 Validation Study on the Clearance of Scrapie During Gelatin Processing (The Inveresk Research International Study and gelatin processing in Europe)  
--Mr. Reinhard Schrieber, DGF Stoess AG, Eberbach, Germany
- 4:30 Committee questions of speakers
- 5:00 Recess for the day

Day 2 (Thursday, April 24, 1997)

- 8:00 Reconvene
- Charge and Questions for the Committee  
-- David Asher, M.D., CBER, FDA
- 8:15 Open Public Hearing (if needed)
- 8:45 Process Validation - Existing research on processing and validation of removal of infectious agents  
-- Robert Rohwer, Ph.D., VA Medical Center, Baltimore
- 9:30 Committee questions of previous speakers
- 9:45 Open Committee discussion and responses/recommendations to charge/questions
- 10:30 Break
- 10:45 Resume discussion  
Summary of Committee conclusions/recommendations
- 1:30 Adjourn

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**April 23-24, 1997**

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FAC Temporary Industry Liaisons, and Guest Speakers

J Michael Dunn, Ph.D.  
Manager, Pharmaceutical and Edible Technical  
Services  
Kind & Knox Gelatine, Inc.  
P.O. Box 927  
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Donald P. Wrathall, Ph.D.  
Sr. Technical Associate  
Eastman Gelatine Corp.  
227 Washington St.  
Peabody, Massachusetts 01960

Guest Speakers

Reinhard Schrieber, Executive Director  
Deutsche Gelatine-Fabriken Stoess AG  
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John Gray, D.V.M.  
U S. Department of Agriculture  
Animal and Plant Health Inspection Services  
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Robert Rohwer, Ph.D.  
Director, Molecular Neurovirology Unit  
VA Medical Center  
Medical Research Center 151  
10 N. Green Street  
Baltimore, MD 21201

Guest Expert

Mr. Gerald M. Wiseman  
9 Scott Drive  
Framingham, Massachusetts 01701  
(retired; formerly with Kraft Foods - Atlantic Gelatin)

### **Charge to the Committee:**

To assess the safety of imported and domestic gelatin and gelatin byproducts used in FDA-regulated products with regard to the risk posed by bovine spongiform encephalopathy.

### **Questions for the Committee:**

#### **Sourcing and controls:**

1. What steps are needed to identify and control the source of feed stocks for animals used to manufacture gelatin?
2. What specific slaughtering procedures should be discouraged or prohibited to reduce the risk from exposure to the BSE infectious agent?
3. What bovine-derived tissues, if any, should not be used in the production of gelatin?
4. What concerns, if any, are posed by tissues obtained from other animal species (e.g., pigs, goats, sheep, and such game animals as bison, deer, and elk)?
5. What criteria exist for distinguishing between the risks of bovine sources-derived ingredients from different countries?

#### **Exposure and Risk Assessment**

1. What are the risks of infection from gelatin or gelatin byproducts by different routes of exposure (i.e., injection, implants, oral consumption, ocular, topical)?
2. In general, when used in the formulation of products, gelatin is added in relatively small amounts. Does the amount used have an impact on the estimated risk?

#### **Processing and Process Validation**

1. What specific processing procedures are essential in assuring optimum inactivation?
2. What criteria should be considered in designing process validation studies and in analyzing the data?
3. Is there one gelatin manufacturing process that is superior for inactivating BSE's infectious agent?

Summary Questions:

1. Is there sufficient scientific justification to continue the exemption of gelatin from the restrictions FDA recommends for other bovine-derived materials from BSE countries (i.e., that these materials not come from BSE countries)?
  
2. If not, what level of restriction will appropriately reduce risk:
  - Restrict gelatin from all BSE countries?
  - Restrict gelatin only from those countries where BSE is prevalent?
  - Allow gelatin from all BSE-free herds?
  - Provide some other level of control?  
(e.g., a country's criteria for identifying suspect BSE cases and overall surveillance and testing systems, or use of specific inactivation methods)?

FOOD AND DRUG ADMINISTRATION  
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY  
COMMITTEE

Holiday Inn - Versailles Rooms I & II  
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April 15 & 16, 1998

*Agenda*

**Wednesday, April 15, 1998 - TSE Advisory Committee Meeting**

8:00 a.m. Opening and Administrative Remarks (COI, waivers, etc.)  
William Freas, Ph.D. Executive Secretary, TSEAC, FDA

8:15 a.m. Introductory Remarks-  
Sharon Smith Holston  
Deputy Commissioner for External Affairs, FDA

**TALLOW AND TALLOW DERIVATIVES**

8:30 a.m. Open Public Hearing

9:30 a.m. Background (FDA)  
John Bailey, Ph.D.  
Director, Office of Cosmetics and Colors  
Center for Food Safety and Applied Nutrition, FDA

10:00 a.m. BREAK

**Tallow Presentations**

10:15 a.m. Opening Remarks  
Don Franco  
National Renderers Association

- 10:20 a.m. Feedstocks and Process Control (slaughterhouse/renderers)  
Domestic vs. Imports  
Edible vs. Inedible  
**Mike Langenhorst, President**  
**ANAMAX Corporation**
- 10:40 a.m. Manufacturing Process (Renderers)  
Domestic - Edible and Inedible  
Imports - Edible and Inedible  
**Mike Langenhorst, President**  
**ANAMAX Corporation**
- 11:10 a.m. Market Dynamics Data  
Domestic vs. Imports  
Edible Tallow vs. Inedible Tallow used in Cosmetics and other  
FDA Regulated products.  
**Mitch Kilanowski**  
**Darling International, Inc.**
- 11:30 a.m. Inactivation of BSE Agent by Rendering  
**David Taylor, Ph.D.**  
**Institute for Animal Health, BBSRC/MRC Neuropathogenesis Unit,**  
**Scotland**
- 12:00 p.m. Safety Data - BSE Update - Status of the Outbreak - New Tissues  
Distribution.  
**Raymond Bradley, FRCVS, FRC Path, Consultant on Bovine**  
**Spongiform Encephalopathy - Central Veterinary Laboratory,**  
**Ministry of Agriculture, Fisheries & Food, United Kingdom**
- 12:30 p.m. Committee Questions
- 1:00-2:00 LUNCH
- Tallow Derivatives Presentations**
- 2:05 p.m. Introduction to Soap and Detergent Association (SDA) and Presenters  
**Gerald Pflug, Ph.D.**  
**President, Soap and Detergent Association**

- 2:15 p.m.      Feedstocks  
                  Considerations for Feedstock Selections  
                  Types and Specifications  
                  Animal Fats (reasons for their prominence in U.S. and  
                  worldwide-consistent quality per grade, reliable and ample  
                  supply, economical, versatile)  
**Charles Green, Ph.D.**  
**Director, Regulations/Toxicology**  
**Oleochemicals/Surfactants Group**
- 2:25 p.m.      Overview of U.S. Oleochemical Industry  
                  Description, Value of Output, Size (number of plants), Imports  
                  Products and their Major End Uses  
                  Quality Assurance Measures  
**Charles Green, Ph.D.**  
**Director, Regulations/Toxicology**  
**Oleochemicals/Surfactants Group**
- 2:35 p.m.      Production Processes  
                  Production Processes and Operating Steps (e.g., saponification,  
                  hydrolysis, transesterification)  
                  The Initial Production Step for Downstream Fatty Acid  
                  Derivatization and Temperature/Pressure Conditions of  
                  Derivatization Processes  
                  Operating Conditions  
                  Routine In-Process and Quality Testing  
**Charles Green, Ph.D.**  
**Director, Regulations/Toxicology**  
**Oleochemicals/Surfactants Group**
- 3:15 p.m.      Questions for previous speakers
- 3:30 p.m.      **BREAK**
- 3:45 p.m.      Manufacturing Process for Mg Stearate  
**Philip Merrell, Mallinckrodt Chemical, Inc.**
- 4:00 p.m.      Manufacturing Processes for Polysorbates  
**Stan Gorak,**  
**ICI Americas**

- 4:15 p.m.      Oleochemical Safety in the U.S.  
                  Other or further quality assurance measures to enhance the safety of rendered animal fat feedstocks with respect to the inclusion of protein particles in tallow in the U.S.  
                  Research results which indicate tallow is not a source of BSE infectivity and other research that supports the safety of tallow.  
                  U.S. situation compared to Europe  
                  Conclusions and summary of why oleochemicals produced in the U.S. do not present a risk of BSE infectivity.  
                  **Dennis Walker**  
                  **Professional and Regulatory Services, Chemical Division**  
                  **The Proctor & Gamble Co.**
- 4:30 p.m.      Safety of Pharmaceuticals  
                  **Fred Bader, Ph.D., PhRMA**
- 4:45 p.m.      Committee Questions
- 6:00 p.m.      Adjourn

**Thursday (Day Two), April 16, 1998 - TSE Advisory Committee Meeting**

**Tallow and Tallow Derivatives, Contd.**

- 8:00 a.m.      Introductory Remarks  
                  **William Freas, Ph.D., Executive Secretary, TSE Advisory Committee**
- 8:05 a.m.      Continuing Perspective in Rendering  
                  **Doug Anderson**  
                  **Executive Vice President, Darling International, Inc.**

**Current Regulatory Policies on Tallow & Tallow Derivatives**

- 8:15 a.m.      European Union/ Commission  
                  **David Taylor, Ph.D.**  
                  **Institute for Animal Health, BBSRC/MRC Neuropathogenesis Unit,**  
                  **Scotland**
- 8:45 a.m.      USDA and FDA  
                  **USDA : Dr. Bob Brewer**  
                  **FDA: Yuan-yuan Chiu, Ph.D.**

9:15 a.m. FDA Questions on Tallow and Tallow Derivatives  
Yuan-yuan Chiu, Ph.D.  
Center for Drug Evaluation and Research

9:25 a.m. Committee Discussion and Deliberation/Vote  
Paul Brown, MD, Committee Chair

10:45 a.m. BREAK

### **GELATIN PRESENTATIONS**

11:00 a.m. Open Public Hearing - Gelatin

11:30 a.m. Opening and Introductory Remarks  
FDA Guidance Document on Gelatin Safety  
David Asher, MD  
Center for Biologics Evaluation and Research, FDA

12:00 a.m. Implication of New BSE Data on Gelatin and UK Action  
Raymond Bradley, FRCVS, FRC Path - Consultant on Bovine  
Spongiform Encephalopathy - Central Veterinary Laboratory,  
Ministry of Agriculture, Fisheries & Food, United Kingdom

12:15 p.m. Safety assessment of gelatin, including a discussion of completed and  
ongoing research; and discussion of FDA's gelatin guidance.  
William Stringer (Coalition of Gelatin Capsule Manufacturers),  
Thierry Salmona and Reinhard Schrieber (Gelatin Manufacturers of  
Europe)

12:55 p.m. LUNCH

### **Current Regulatory Policies on Gelatin**

2:00 p.m. European Union/Commission  
David Taylor, Ph.D.  
Institute for Animal Health, BBSRC/MRC Neuropathogenesis Unit,  
Scotland

2:20 a.m. FDA Questions on Gelatin  
Carol Vincent  
Center for Drug Evaluation and Research, FDA

2:30 p.m. Committee Discussion and Deliberation/Vote  
Paul Brown, MD, Committee Chair

3:30 p.m. BREAK

## **DURA MATER**

3:45 p.m. Open Public Hearing

4:00 p.m. Human Dura Mater Issue: Update and FDA Proposed Course of Action  
Kiki Hellman, MD  
Center for Devices and Radiological Health, FDA

4:15 p.m. FDA Charge to the Committee  
Kiki Hellman, MD  
Center for Devices and Radiological Health, FDA

4:30 p.m. Committee Discussion and Deliberation  
Paul Brown, MD - Committee Chair

5:00 p.m. Summary and Conclusions

5:30 p.m. Closed Session

6:00 p.m. Adjourn

## FDA Questions on Tallow

- 1. Does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the rendering of tallow should not come from BSE countries as designated by USDA?

## FDA Questions on Tallow Derivatives

- 3. Does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the manufacturing of tallow derivatives should not come from BSE countries as designated by USDA?

## FDA Questions on Tallow and Tallow Derivatives

- 2. If yes, should FDA consider changes to the guidelines for tallow used in food and cosmetics?
  - a) On sourcing countries
  - b) On slaughtering procedures
  - c) On rendering processes

## FDA Questions on Tallow Derivatives

- 4. If yes, should FDA consider changes to the guidelines FDA for tallow derivatives used in food, cosmetics, nutritional and dietary supplements, and drugs administered via various routes?
  - a) On sourcing countries
  - b) On slaughtering procedures
  - c) On tallow quality controls
  - d) On manufacturing processes and process controls for various tallow derivatives

**Charge to the FDA TSEAC  
Concerning the Safety of Gelatin  
Prepared from Bovine Raw Materials**

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Consider whether the safeguards recommended in the most recent FDA Guidance Document are appropriate and adequate to protect the public from exposure to the BSE agent in gelatin for oral consumption or for topical application when the gelatin was prepared from bones and hides of animals born or residing in BSE countries or bovines from BSE-status-unknown countries.

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**Questions for the FDA TSEAC**

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**1. Concerning the Safety  
of Bovine-bone Gelatin:**

Can healthy cattle from BSE countries or from BSE-status-unknown countries be considered a safe source of bones to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE-free herds and the heads, spines and spinal cords are removed from carcasses immediately after slaughter?

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**2. Concerning the Safety  
of Bovine-hide Gelatin:**

Can healthy cattle from BSE countries or from BSE-status-unknown countries be considered a safe source of hides to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE-free herds and contamination of the hides with CNS tissues and eyes is avoided?

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## **CHARGE TO THE COMMITTEE for TOPIC III**

To comment on the FDA proposed course of action concerning the safe sourcing, processing and use of dura mater allograft that is intended to provide additional safeguards for dura mater allograft while maintaining the clinical utility and availability of the product.

Prepared: Kiki B. Hellman  
4/13/98

**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE  
HOLIDAY INN-BETHESDA, VERSAILLES BALLROOMS I & II, APRIL 15-16, 1998**

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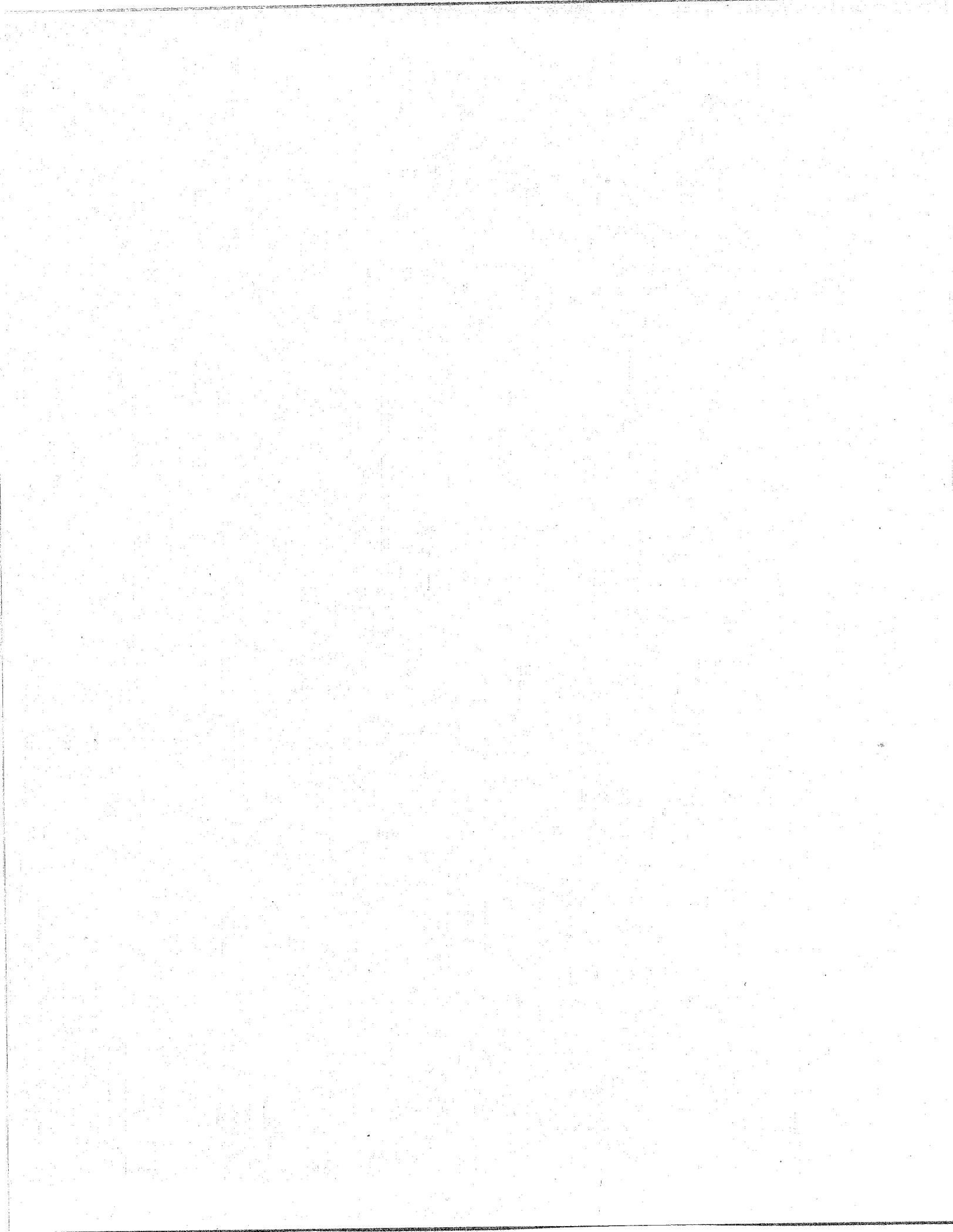
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UNOFFICIAL SUMMARY

On April 23 & 24, 1997 the Transmissible Spongiform Encephalopathies Advisory Committee met to discuss the safety of imported and domestic gelatin and gelatin by-products used in FDA-regulated products with regard to the risk posed by bovine spongiform encephalopathy (BSE).

They were asked:

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

The Committee stated 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 effectively remove the BSE infectious agent.

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

The Committee indicated that there is a need for well-designed process validation studies for verification of the gelatin process and, that FDA use the assistance of experts in the field to review these protocols that industry would submit. The Committee indicated that they would like to provide input to the review of these studies. The Committee stated there must also be assurance that specific manufacturing processes would be followed.

**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. The 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.

Two members said YES or a qualified yes.

One member abstained (uncertain).

**PLEASE REFER TO THE MEETING TRANSCRIPTS FOR A COMPLETE ANSWER TO THE QUESTIONS ADDRESSED DURING THIS ADVISORY COMMITTEE MEETING.**

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY  
COMMITTEE

April 15 & 16, 1998

*DRAFT Unofficial Meeting Notes (pretranscript receipt)*

The meeting was opened and conducted by the Chair Dr. Paul Brown. The committee was introduced and the conflict or interest statement was read into the public record. Following presentations by FDA, and industry, the committee discussed their charge for this topic which was to "Assess the safety of both imported and domestic tallow and tallow derivatives with regard to the risk posed by TSEs (specifically, BSE).

Four questions were discussed by the committee.

**1. Does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the rendering of tallow should not come from BSE countries as designated by USDA?** (The committee modified the question to include" BSE positive countries and countries with BSE of unknown status). The vote was 6 "NO" votes and 5 "YES" votes. Therefore, they recommended that FDA NOT change the current guidelines.

Question 2 was skipped because it was only to be answered if the answer to question 1 was "yes". Question 2 read "If yes, should FDA consider changes to the guidelines for tallow used in food and cosmetics? - a) On sourcing countries - b) On slaughtering procedures, - c) On rendering processes?"

**Question 3.- Does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the manufacturing of tallow derivatives should not come from BSE countries as designated by USDA?** The vote was 3 "NO" Votes and 8 "YES" votes. Therefore the committee proposed a change in the current FDA guidelines regarding tallow derivatives.

**Question 4. If yes, should FDA consider changes to the guidelines for tallow derivatives used in food, cosmetics, nutritional and dietary supplements, and drugs administered via various routes? - a) On sourcing countries - b) On slaughtering procedures, - c) On tallow quality controls,- d) On manufacturing processes and process controls for various tallow derivatives?** The committee voted 6 "YES to 5 "NO" that the tallow derivatives (excluding glycerin) may be sourced from "any" country.

Later in the day the committee voted on question #4 only as it applied to glycerin or glycerol. They voted 10 "YES" votes to 0 "NO" that glycerol could be sourced from "any" country.

## GELATIN PRESENTATIONS

Following presentations by FDA, industry and guest speakers The committee discussed the following two questions:

**Question 1.** The committee modified the first question drafted by FDA to read "**Can healthy cattle from BSE countries or from BSE-status unknown countries be considered a safe source of bones to produce gelatin intended for oral consumption by humans (or for topical application to humans) if, as previously recommended, the cattle are from BSE-free herds and the heads, spines and spinal cords are removed from carcasses?**" The committee deleted the words "immediately after slaughter" from the original question. The committee vote was 3 "NO" votes and 8 "YES" votes for this question (i.e. bones from healthy cattle can be considered safe provided they are from BSE-free herds and the heads, spines and spinal cords are removed from carcasses). Dr. Brown expressed the willingness of the committee to revisit the safety of bone gelatin next year when additional data on the infectivity of bone marrow becomes available.

**Question 2.** **Can healthy cattle from BSE countries or from BSE-status unknown countries be considered a safe source of hides to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE-free herds and contamination of the hides with CNS tissue and eyes is avoided?** The committee vote was 0 "NO" votes, 1 "Abstain" and 10 "Yes" votes.

## DURA MATER

There were two speakers at the Open Public Hearing for this topic. The first speaker was Jeanne C. Mowe who read a statement prepared by the President of the American Association of Tissue Banks, Michael J. Joyce, M.D... The second speaker read a statement drafted by Hogan & Hartson, a law firm representing Biodynamics International.

**Kiki Hellman, Ph.D., Center for Devices and Radiological Health, FDA** presented an "Update and FDA Proposed Course of Action on Human Dura Mater Issue" She then presented FDA's proposed course of action that includes considerations for a revised letter to manufacturers and publication in the Federal Register as General Guidance, Level 1. The committee discussed the proposals and made some minor

changes. There were no votes, only discussion, comments and clarifications. **Please review the transcripts for all detailed comments.**

## **FDA'S CONSIDERATIONS FOR A REVISED LETTER TO MANUFACTURERS**

**1) Brain Biopsy and Histological Examination:** A full brain biopsy including gross and histological examination should be conducted by a competent neuropathologist. At a minimum, an adequate biopsy sample of frontotemporal cortex of donor's brain should be obtained after dura mater collection. The histological examination, which is intended to identify evidence of TSE changes in the donor's brain, should be performed by a qualified neuropathologist.

The committee recommended revision as follows: a full brain autopsy including gross and full histopathological examination should be conducted by a competent neuropathologist. Brain biopsies should be obtained after dura mater collection. The histological examination, which is intended to identify evidence of TSE changes in the donor's brain, should be performed by a qualified neuropathologist.

**2) PrP-RES Testing of Brain Tissue:** While reagents for PrP-RES testing are available from certain research laboratories, testing remains a research/investigational-use only tool. There is no licensed or validated PrP-RES test for the screening of CJD in brain tissue. Nevertheless, a negative PrP-RES test is considered by experts in the field as significant in increasing the level of confidence that the brain and the dura are free of the CJD agent. The FDA encourages the validation of PrP-RES testing as an aid in the determination that brain and dura tissues are not contaminated with the CJD agent.

Manufacturers should continue to monitor scientific developments associated with PrP-RES testing and should incorporate testing as a screening tool for dura mater donors when its usefulness for this intended use becomes apparent, and the test itself becomes more readily available.

The committee recommended revision to encourage the approval of the PrP-RES testing. They also recommended that a 5 to 10 g biopsy sample of frontotemporal-cortex of donor brain, obtained after dura mater collection, should be used for PrP-RES testing.

**3) Acceptable Donor Dura:** Only dura mater procured from donors who have negative histories for TSE risk factors (such as receipt of growth hormone, dura mater recipient, family history of neurological degenerative diseases), have normal gross brain examination, and are negative for histological evidence of TSE changes should be considered suitable for transplantation; a negative PrP-RES test should be considered an additional safeguard.

The committee recommended revision to "Only dura mater procured from donors who have negative histories for TSE risk factors (such as receipt of growth hormone, or

dura mater recipient) have a negative family history for neurological /neuro-degenerative disease, have normal gross brain examination, and are negative for histological evidence of TSE changes should be considered suitable for transplantation; a negative PrP-RES test should be considered an additional safeguard.

**4) Archiving of Donor Brain Biopsy Tissue:** While archiving of donor brain biopsy tissue does not add to the safety assurance of the product immediately, collection of such tissue permits testing for TSE-induced changes by new testing methods as they become available and may later permit confirmation of potential transmission of CJD from a dura graft. Providers of dura mater allografts should archive donor brain biopsy tissue at -70 degrees centigrade for the shelf-life of dura product.

The committee suggested archiving BOTH brain (a 5 gram sample of the frontotemporal cortex) and dura mater.

The FDA suggests that a nationally-supported archive for dura donor brain tissue be considered, since that would help to further the science of CJD transmission through dura mater grafts.

**5) Donor Suitability and Dura Mater Retrieval Protocols:** The FDA encourages dura mater providers and their professional organizations to reassess the appropriateness of existing donor suitability and dura retrieval protocols. Further, the FDA recommends that industry and government agencies reach consensus on appropriate industry standards and guidance in this area.

The committee suggested that such guidance may also be applicable for other allograft tissues.

**6) Dura Mater Processing:** The FDA recognizes that sourcing considerations, i.e., donor suitability and dura retrieval, together with appropriate testing, constitute the primary safety controls for dura allograft.

However, additional processing safeguards, while maintaining the clinical utility of the product, may help minimize the potential infectivity of dura mater allografts. The FDA recognizes that there is limited evidence that treating dura mater with NaOH will reduce CJD infectivity while preserving the tissue's clinical utility. In order to minimize even further the risk of CJD transmission, the FDA encourages the use of either a NaOH protocol or other procedure during dura mater processing that has been validated to reduce CJD infectivity.

Additionally, dura mater allografts must not be co-mingled at any step in the processing procedures. Every effort should be made to eliminate even the theoretical possibility for co-mingling of donor dura grafts.

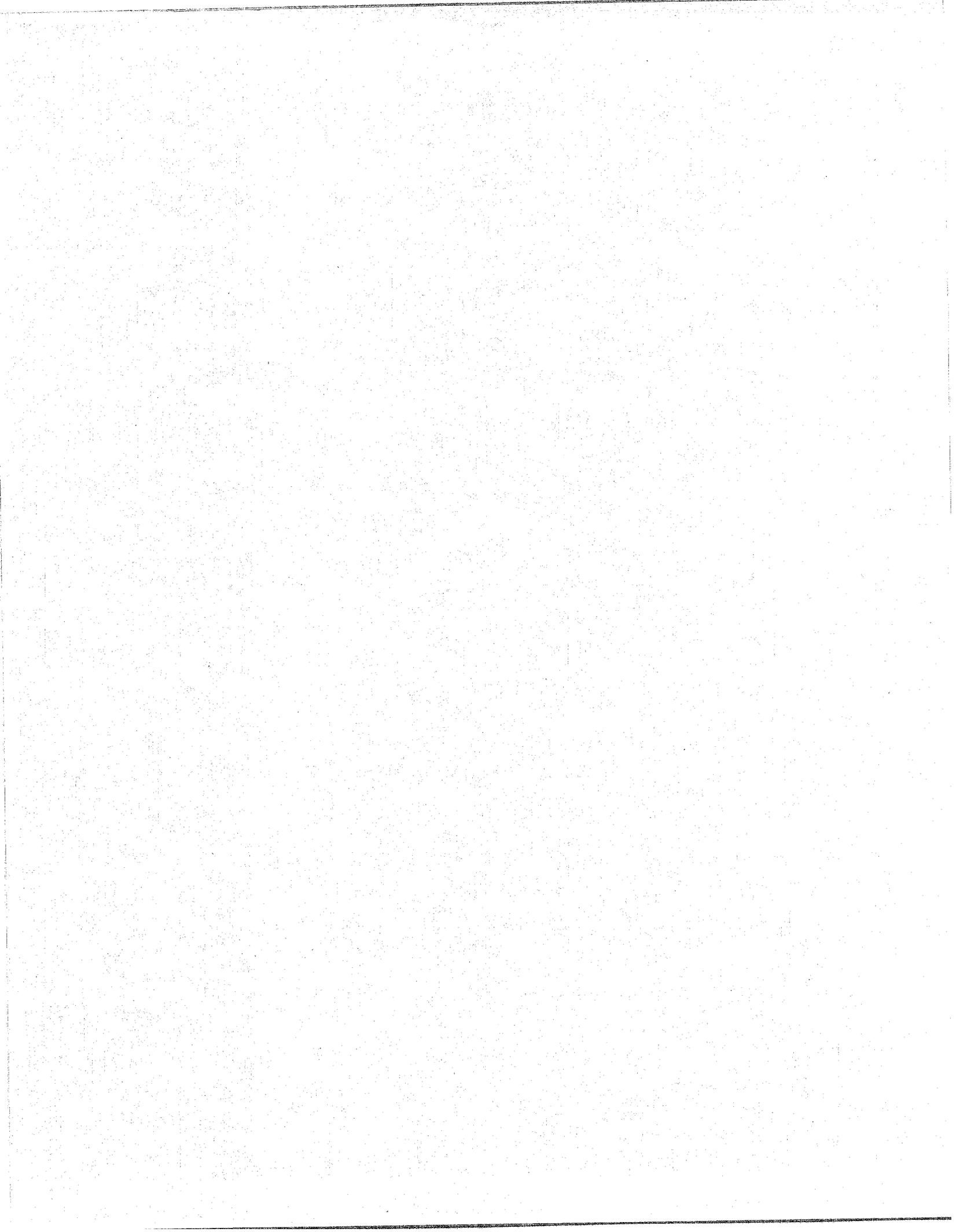
The committee wanted to emphasize that extreme caution should be used to prevent any possible cross contamination during any processing step by any means.

**7) Record Keeping/Tissue Tracking:** Each recipient of dura graft should be notified accordingly, and a card containing all information on tissue sourcing, including the lot number of the product, should be included in the recipient's hospital record.

Dura mater allograft providers are expected to maintain documentation of tissue distribution and identification of recipients. However, currently, they are not expected to have the ability to track the recipient over time.

Manufacturers should continue to follow their standard operating procedures regarding donor suitability, processing, shipping/distribution, and tissue utilization record keeping that do not contradict the above recommendations.

**Detailed comments and discussion are available in the transcript which will be posted on the CBER home page shortly after it is received.**



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

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).<sup>1</sup> 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)<sup>2</sup> (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



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 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.

<sup>1</sup>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.

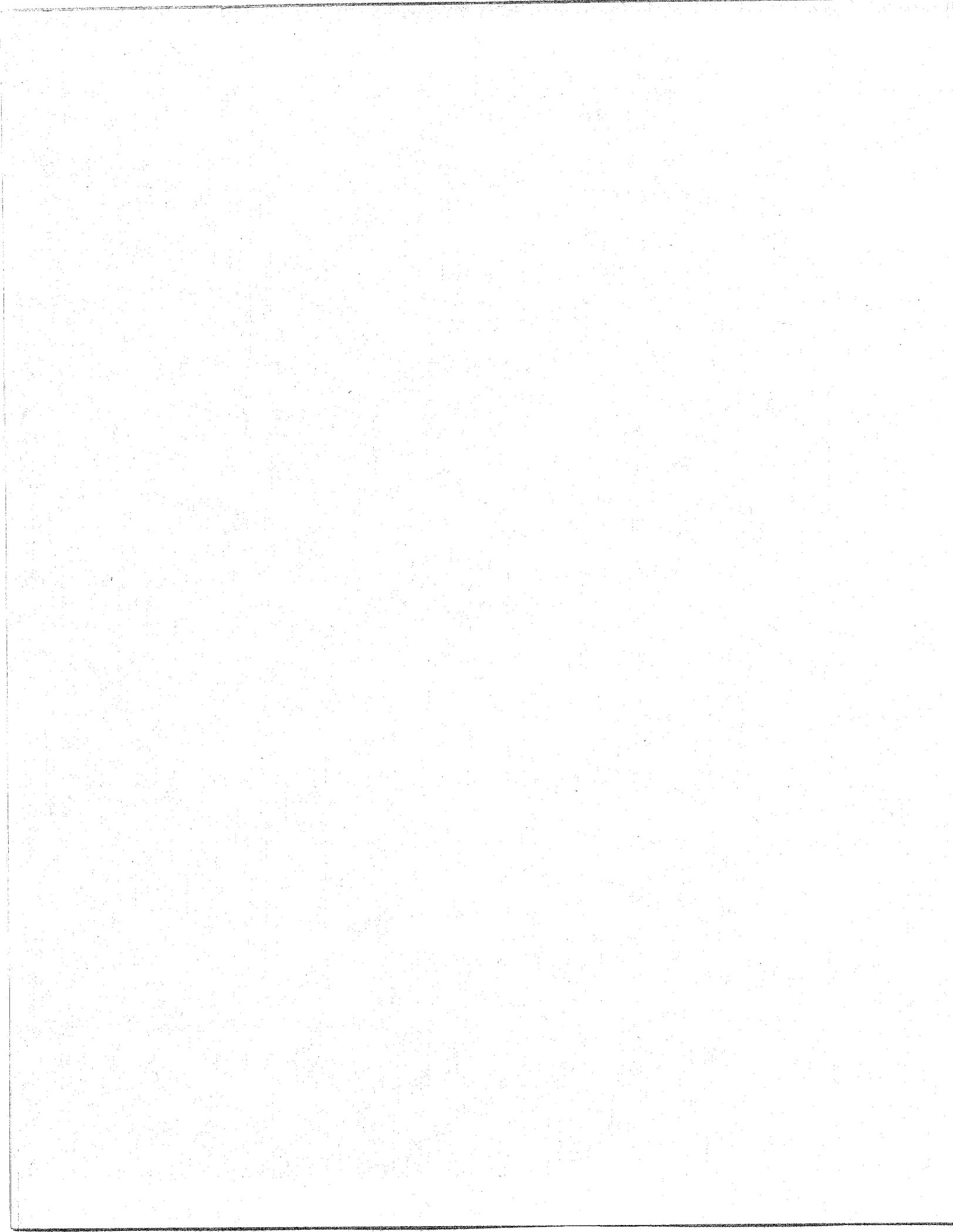
<sup>2</sup>Office International des Epizooties. 1997. *International Animal Health Code*, Special Edition, Chapter 3.2.13. pp. 267-274, Paris.

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**FDA HOME PAGE**  
September 1997



# OPINION ON THE SAFETY OF GELATINE

Adopted at the Scientific Steering Committee at its

plenary meeting of 26-27 March 1998

Following a public consultation on the preliminary

opinion adopted on 19-20 February 1998

(Version updated on 3.04.98:

see double underlined sections in Chapters 5.4.3 and 8)

## I. REPORT ON THE SAFETY OF GELATINE

### 1. Definition

For the purpose of the present report, gelatine is defined as a mixture of polypeptides obtained by partial hydrolysis of the collagen contained in bones and hides mainly from bovines and/or skins from pigs after successive treatments: degreasing, acid treatment and/or alkaline treatment (liming), washing, filtration, ion exchange and sterilisation.

### 2. Introductory note (Stryer, 1981)

Collagen is a family of fibrous proteins having a very high tensile strength found in connective tissues such as the organic matrices of bones, hides and skins, tendons, cartilage, the cornea of the eye, blood vessels and teeth.

The structural unit of collagen is tropocollagen. This protein is formed of three helical units wrapped around one another with a right handed twist. Each of these helices contains about 1000 aminoacids. The amino-acid sequence of collagen is highly distinctive; nearly every third residue is glycine (35%). Other important aminoacids are alanine (11%), proline (12%), aside the unusual hydroxyproline (9%) and a few % of hydroxylysine.

The triple stranded helical rod is about 3000 Å long and 15 Å in diameter. The structure is stabilised by hydrogen and other bonds, changing with the age of the animal.

When a solution of collagen is heated in water, the viscosity is abruptly decreased, the helical structure denatured and disorganised with the production of gelatine.

### 3. Background

The mandate of the Scientific Steering Committee was to advise the Commission on the risk exposure of humans and animals to BSE from gelatine and its co-product dicalcium-phosphate. For humans special attention should be focused on the use of gelatine in the food chain, pharmaceuticals and cosmetics including parenteral use.

As stated in the opinion of 9 April 1996 of the Scientific Veterinary Committee, there are three major factors that influence the risk of exposure from animal by-products in relation to BSE:

- (1) The titre of infectivity likely to be found in the tissue used in its manufacture.
- (2) The effectiveness of the process used for the inactivation (or the elimination) of the agent.
- (3) The kind of application (e.g. food, cosmetics and medicinal products).

The Scientific Veterinary Committee stressed also "that the full data on all gelatine manufacturing processes have not been published, hence a full risk analysis cannot be carried out for gelatine." By-products, such as gelatine, aminoacids and dicalciumphosphate were recognised as giving the best possible guarantees of safety if produced in a process which ensures that all material is subjected to degreasing, followed by acid and/or alkaline treatment followed by heating to 120° and these up to 138-140°C for 4 seconds. The product should be labelled to show the process to which it has been subjected. The Scientific Veterinary Committee emphasised also that: *"the specified bovine offals from UK cattle (brain, spinal cord, thymus, spleen, intestine and tonsils) as well as vertebral column and any tissues resulting from trimming carried out in accordance with EC and UK legislation on BSE, should not be used for any purpose (food, feed, medical, pharmaceutical or cosmetic use), whatever the process to which they are subjected."*

A similar procedure should also be carried out for material originating from other countries with native cases of BSE.

The preceding opinion differs largely from the 1992 and 1994 opinions expressed by the Scientific Veterinary Committee, stating that *"whatever the tissue source, there is a negligible risk from trading in gelatine for technical use, for consumption or in cosmetics additional guarantees are therefore not necessary"*.

In its opinion of 15 April 1996 on products derived from bovine tissues, especially gelatine, tallow and di-calcium-phosphate in relation with Bovine Spongiform Encephalopathy, the Scientific Committee Food concluded: *"Based upon current incomplete knowledge regarding BSE and its possible transmission to humans and the uncertainty about the inactivation of the infective agent, the Committee at present is only able to advise that bovine source materials for these products are to be taken only from geographical areas where BSE does not occur in epidemic conditions. The Committee urges that data required for a scientifically based risk assessment be generated by relevant bodies. Further research is needed especially to develop specific, sensitive and rapid methods for detection of the causative agent in biological materials."*

At its meeting of 16 April, 1996, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) endorsed the following conclusion on the potential risk of gelatine in relation to Bovine Spongiform Encephalopathy (BSE): "Three cumulative factors contribute to the safety of gelatine used in pharmaceuticals:

- Manufacturers of gelatine used for pharmaceutical use should not use tissues derived from bovine animals, slaughtered in the UK .

- The additive effects of washing, acid decalcification followed by acid and/or prolonged alkaline treatment, filtration and sterilisation are sufficient to eliminate any possible risk.
- Source tissues used in the manufacture of gelatine are classified as having no detectable infectivity.

On the 3rd of April, 1997, the Multidisciplinary Scientific Committee (MDSC) expressed a similar opinion to that of the Scientific Veterinary Committee on 9 April, 1996, stressing especially: *"That at the moment no production method can be considered as safe for gelatine and related products if the base material used is potentially infectious."* The opinion further states: "The control of the nature, the geographical origin and the quality of the starting material is currently the only means to assure the protection of public health. The control applied to the starting materials must be subjected to intensive monitoring." The MDSC also confirms its view that *"the following tissues should not be used as starting materials: skull, vertebral column, brain, spinal cord, eye, tonsil, thymus, intestine and spleen. (SEE Commission decision of 11th June, 1996, 96/362/EC). The Committee urgently recommends to establish an effective system for the monitoring and the surveillance of TSEs (especially BSE and scrapie)."*

In its "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (Revised draft 14 - rev.1 of 2nd September 1997), the CPMP concludes that the risk of transmission of infectious agents can be greatly reduced by controlling a number of parameters which include:

- the source of the animals (including on the basis of their age);
- the nature of animal tissue used;
- the production and transformation processes,

The European Commission Decision N° 97/534/EC of 30 July 1997 confirms the conditions for the manufacture of gelatine from bone raw material. In the 15 E.U. member states as well as for third countries exporting to the E.U. (the general rule applies to all: both for human consumption and for pharmaceutical and cosmetic use), the following risk materials should be excluded: skull, brain, eye, spinal cord, tonsils. The decision also excludes the use of the vertebral column of cattle, sheep and goats of over 12 months of age for mechanically recovered meat for human consumption.

So far, bones, a raw material for the production of gelatine, have been considered as a material with no detectable infectivity. Bovine bone marrow, by analogy with bone marrow from sheep with scrapie, was classified as belonging to the category of low potential infectivity materials. In its opinion adopted on 8-9 December 1997, the Scientific Steering Committee states:

*(on) dorsal root ganglia. New (unpublished) evidence shows that the dorsal root ganglia - located within the general structure of the vertebral column - should be considered as having an infectivity for BSE equivalent to that of the spinal cord. The dorsal root ganglia proved infective at the same time after infection as the spinal cord, i.e. 32 months. The trigeminal ganglia were also infective, but so far no autonomic nervous system tissue has been found to be infective. The dorsal root ganglia cannot be removed without extreme difficulty. This therefore means that as a precautionary proposal the removal of the whole vertebral column*

*(other than the coccyx) is now appropriate. Care needs to be taken to ensure that the removal of the vertebral column incorporates the lateral aspect of the vertebral bodies. This dissection may sometimes be difficult in practice unless the musculature is selectively removed from the vertebral bones for selling as bone-free meat.*

**(on) Bone marrow :**

1. *Early studies with mice intracerebrally injected with bone marrow from cattle with spontaneous clinical BSE has not demonstrated infectivity (SEAC, 1994). However, studies on calves, experimentally infected by feeding 100g of BSE infected brain tissue, have now shown bone marrow infectivity in cattle studied at 38 months after feeding the BSE infected brain. These animals were clinically affected by BSE. (MAFF, unpublished evidence 3.12.1997). This has wide-ranging implications because it implies that long bones as well as vertebral columns must be considered potentially infective. The concerns on contamination and the dorsal ganglia mean that on these grounds alone the vertebral columns of older animals should be included in the category of specified risk material.*
2. *Several issues now emerge from the new report on bone marrow infectivity. First the apparent infectivity of bone marrow might need to be redefined. Bone marrow (on the basis of scrapie studies) was placed in Category III, i.e. as showing low infectivity. In previous bone marrow studies on clinical cases of BSE infected cattle, no infectivity was detected which might have suggested that the WHO classification was inappropriate in persisting with a Category III, rather than a Category IV, rating, i.e. no demonstrable infectivity. However, new evidence shows 2 of 18 mice developing late clinical disease after having been injected with marrow from cattle of 38 months post infection. Another 3 mice also show immunocytological evidence of the presence of PrP<sup>Sc</sup>, having been injected with the same bone marrow extract. Given the late development of this demonstrable infectivity in cattle bone marrow despite the substantial infective dose (100 g untreated BSE infective brain) it now seems appropriate to maintain the WHO classification for BSE as well as for scrapie. This signifies that BSE is increasingly being revealed as having a tissue based infectivity which seems similar to that of scrapie.*
3. *This conclusion reinforces the concepts [...] that the different levels of infectivity do reflect a graded phenomenon and that it is unwise to consider the BSE agent as either present or absent in particular tissues.*
4. *The bone marrow findings also raise the issue of whether bones from older animals, e.g. >30 months, should be removed from the human food chain."*

As far as infectivity of bone marrow is concerned, the working group on gelatine of the Scientific Steering Committee noted that the above statements referred to infectivity resulting from a single group of experimentally challenged cattle. However, infectivity of the bone marrow of naturally infected bovines has, to present knowledge, not been detected. According to Hadlow et al. (1982), infectivity has been reported in bone marrow of Suffolk sheep with natural, clinical scrapie but (Hadlow et al., 1980) not in goats with natural scrapie.

**4. On the production of gelatine**

In order to express an opinion on the safety of gelatine it is important to take into account a number of aspects of the gelatine production methodologies and conditions.

#### 4.1 The production of gelatine (see G.M.E., 1997a,b,c; 1998)

Gelatine production includes 3 main processes and 3 types of raw material: an acid process for bovine bones, hides and pig skins, an alkaline process for bovine bones and hides and a heat/pressure process for bones. Pig skins are normally submitted to an acid treatment. Starting from bovine raw materials there are at least five alternatives:

- a) bovine hides and skin lime alkaline treatment
- b) bovine hides and skin soda alkaline treatment
- c) bovine bone lime alkaline treatment
- d) bovine bone acid treatment
- e) bovine hides and skin enzymatic treatment.

##### 4.1.1 The alkaline process

A typical gelatine manufacturing process includes first a degreasing step of fine crushed bones in hot water (80° to 85°C). Regularly shaking removes a high percentage of proteins. The dried bone chips are then submitted, over a total period of 4-5 days, to a sequence of solutions with an increasing hydrochloric acid concentration. The highest concentration being 4% of HCl during 2 days. This demineralisation of the fine bone chips produces a phosphoric liquor that after treatment with lime, will give a precipitate of bicalcium phosphate. (see further). The osseine obtained is washed a further two times with water.

The next step is the liming step. During 45 days the washed osseine is treated with a solution of saturated lime. ( $\text{Ca}(\text{OH})_2$ , pH = 12.5).

During the extraction step that follows, the limed osseine is treated, under stirring, with sulphuric acid until the pH remains below 6. After frequent water washing, the limed osseine is then 4 times extracted with warm water (>50°C). Each extraction is continued until the obtained gelatine concentration is between 3% and 8%.

The filtration may be done in 2 steps. The first with diatomaceous earth, and the second with a cellulose filter. After the filtration step the extract is ion exchanged in sequence over a cation resin and an anion resin. To avoid gel forming a precise temperature is maintained during the filtration and ion exchanged steps.

The gelatine solution is further concentrated by vacuum evaporation to approximately 20%. With appropriate techniques, the concentrated solutions are sterilised during 4 seconds at 138 - 140°C and subsequently cooled.

Finally the concentrated solution is cooled to jellify and after being cut into small pieces, dried for 3 hours in stream of warm air. Careful quality controls are performed on each step in the production chain.

Bovine hides are also treated by alkaline process. According to US-FDA (1997) safe gelatine can be produced from bovine hides from any country, provided that the processors ensure that the bovine hides have not been contaminated with brain, spinal cord or ocular tissues of cattle residing in - or originating from countries with higher than negligible BSE risk and if they exclude hides from cattle that have signs of neurological disease

#### 4.1.2 The acid process

Bovine bones may also be treated by an acid process. Pig skins are normally submitted to an acid treatment. The liming step is then replaced by an acid pre-treatment where the osseine is soaked overnight at pH below 4.

#### 4.1.3 The heat/pressure process

In stead of applying an acid or alkaline treatment after degreasing, the bones are submitted to a heat/pressure process of 133°C during 20 minutes at 3 bars, followed by filtering. The gelatine obtained is of limited quality and use.

### 5. Some considerations regarding the safety of gelatine

Regarding the safety of gelatine, the Scientific Steering Committee noted the following:

#### 5.1 The opinion of the association Gelatine Manufacturers of Europe (GME) on the quality and the sourcing of raw material

The total amount of raw material transformed yearly into gelatine in Europe is estimated to be near 500.000 tons with 100.000 tons gelatine produced: 52% from pig skins, 21% from bovine bones and 27% from bovine hides. The world-wide production of gelatine is 220.000 tons from which 44% is produced in Europe.

Raw material for one given plant may originate from several sources and may be a mixture of materials from different slaughterhouses and suppliers. Various parts of the production process itself may be spread over several locations. The number of critical points<sup>1</sup> in the whole production chain from source to final product which need to be controlled to minimise or neutralise the risk of possible residual infectivity of the final product, is large and their monitoring may not always be easy and evident.

According to the association of Gelatine Manufactures of Europe (GME), which represents most of the EU's gelatine producers, all of their associated gelatine-manufacturing sites in the European Union are certified according to ISO 9000 international standards. The GME's gelatine manufacturers claim to respect the following sanitary guarantees, which are also recommended in OIE documents: no sourcing from countries with high BSE infectivity (UK); sourcing only from countries with low infectivity or BSE free. Bones and skins are collected from the meat industry controlled by the official veterinary services; they come from animals recognised as suitable for human consumption. For each gelatine lot (even from outside E.U. countries) full documentation allows manufacturers to trace the raw materials "origin" from their reception in gelatine plants. Upstream, bovine bones are subject to a similar traceability in the degreasing plants.

*However, given the complexity and multitude of critical points in the overall production process, and given the fact that they are not limited to the conditions within the factory, the SSC is of the opinion that respecting ISO 9000 standards is probably not a sufficient guarantee of the safety of the end product, but that the*

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<sup>1</sup> In terms of possible hazards in terms of risk for remaining BSE infectivity in the final product

*respect of HACCP<sup>2</sup> procedures should be guaranteed and documented. Some of these points are (non exhaustive list): traceability, the source of the raw materials which may be multi-country and multi-supplier, whether or not specified risk materials have been removed, the physical conditions of the various production processes which may be carried out at several places, separate labelling and/or storage of the material according to the intended final use of the gelatine, etc.*

### **5.2 Scientific opinions from the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) and from the FAO-WHO.**

Since 1991 the CPMP (part of the EMEA since 1995) emphasises three principles to minimise the risk of transmission of BSE which are scientifically sound: selective sourcing, tissue of origin and safety of the extraction process. For what concerns medicinal products, the CPMP indicated the following conditions for the safety of gelatine (EMEA, 1996):

- raw material from the UK to be excluded
- the source tissues are to be classified as having no detectable infectivity
- the additive effects of washing, acid decalcification, followed by acid and prolonged alkaline treatment, filtration and sterilisation are considered to be sufficient to eliminate risk.

The EMEA opinion concludes that, provided that it is well established that the starting material for pharmaceutical use (active ingredients or excipients) is safe regarding the BSE risk, on the basis of the various measures proposed in the EU guidelines and documented in the application dossier, the finished product is also safe.

In its revised draft of 2 September 1997 of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (EMEA, 1997), the CPMP states that "*For gelatine manufacture, risk from central nervous tissue attached to skulls or vertebrae can be reduced by excluding these bones from the source material.*"

The FAO-WHO granted gelatine the status of foodstuff if it has been processed according to good manufacturing practices. (NMRS report 48 TRS 462-XIV/12). The last opinion of the WHO (27/03/97) was in the same line as their previous opinion: "*The new information does not change previous recommendations regarding milk and gelatine safety in relation of the BSE transmission.*"

### **5.3 The US FDA's opinion and proposal**

The opinion of the FDA is based on the preliminary data presented in 1994 by the gelatine industry in relation to the BSE transmission routes and excludes from its recommendations concerning other bovine ingredients in U.S. FDA regulated products (Federal register of Aug. 29, '94; 55FR.44584) from countries that have reported BSE.

As new information became available suggesting that BSE may be transmissible to humans and because of updated data from the study on the effect of gelatine processing on infectivity, the U.S. FDA decided in 1996 to review its previous guidance on the use of gelatine.

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<sup>2</sup> HACCP: Hazard Analysis Critical Control Points

On April 23-24th, 1997 the FDA stressed that the current scientific evidence did not justify the continued exemption of gelatine from restrictions recommended by FDA for other bovine derived material from BSE countries. Based on this review, the FDA decided in September 1997 upon the following recommendations concerning the acceptability of gelatine 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 gelatine for human use.
2. Gelatine produced from bones and hides obtained from cattle residing or originating from countries reporting BSE or from countries that do not meet the latest BSE standards of the O.I.E., should not be used either in injectable, ophthalmic or implanted FDA regulated products or in their manufacture.
3. Gelatine can be used for oral consumption and cosmetics when the gelatine is produced from bones coming from BSE free herds in BSE countries and if SRM's (WHO list) are removed. (heads, spines and spinal cords) or if the bones come from countries BSE free, but fail to meet O.I.E. standards and with removal of heads, spine, spinal cord.
4. Gelatine can be produced from bovine hides from any country, provided that the 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.
5. At this time bovine bones and hides from the US and/or from BSE free countries may be used for gelatine production, provided that they meet the O.I.E. standards.
6. At this time porcine skin from any source country, may be used for gelatine production for human use. Cross-contamination with bovine materials originating from BSE countries or from countries that do not meet the O.I.E. standards are to be avoided and certified.

Thus it seems clear for the U.S. FDA that the potential risk of BSE transmission from bovine bone derived gelatine, varies depending on the country of origin, the raw material, the type of tissue used, the gelatine process used and the route of administration or exposure. Finally it is noteworthy that gelatine-a poor source of protein- and other bovine-derived products intended for animal use are banned by the USDA/APHIS (United States Department of Agriculture / Animal and Plant Health Inspection Service) in the US if they come from BSE countries.

#### **5.4 Other sources of information on the safety of gelatine**

##### **5.4.1 Opinion of the pharmaceutical industry.**

The pharmaceutical industry believes that, provided certain conditions are complied with, removal of SRM's from the production chains is not necessary to ensure the safety of gelatine vis a vis risks of BSE transmission. This is based on the following arguments:

- Advice from scientific expert bodies. (see 6.2)
- Present traceability and sourcing practices for gelatine production.
- The nature of the current standard processing conditions (see 5)

Traceability and sourcing of the raw material seems more important than the nature of the processing conditions.

The European Federation of Pharmaceutical Industries Associations (EFPIA, 1997, 1998) claim to use gelatine only from countries with no or very low BSE disease incidence, or where SRMs are already eliminated from the production process. In addition, it is claimed that each batch of gelatine supplied to the pharmaceutical industry is accompanied by a veterinary certificate which certifies that only healthy animals (fit for human consumption) have been used in the source material, indicates the countries of origin and ensures rigorous traceability.

According to the European Federation of Pharmaceutical Industries Associations the relevant CPMP guidelines have been followed at least since 1991. These guidelines (see above) advocate a combination of careful control of source material and processing conditions. *[EFPIA recommends that the safety of products should be analysed on a case-by-case basis and that the pharmaceutical industry should assess risk and validate the end product]*

*The Scientific Steering Committee considers that many pharmaceutical products (including drugs, vaccines, ophthalmic and biotechnology based products as well as injectables are produced using bovine components in their manufacturing process as starting materials, processing ingredients and excipients in final formulations. Pharmaceuticals however are administered with the purpose of conveying benefit and the risk assessment should more appropriately be a risk benefit assessment for individual products, balancing the benefit conferred against the risks identified. The SSC notes that several research institutes are developing and validating methods for assessing risk of BSE in pharmaceutical products, but that a standardised and generally accepted method is still not available. Many of these rely upon the control of source selection of tissues and processing, which remain the best means of minimising risk to patients.*

#### 5.4.2. Results from Manzke et al. (1996)

In the production process it is interesting to note that German researchers (Manzke et al., 1996) have shown that during the degreasing step 98-99% of the protein of nervous origin (e.g. S100<sup>3</sup>, GFAP<sup>4</sup> and others) are removed. The method used (Elisa test) was very sensitive with a detection threshold from 30 picogr. for S100 and 7 picogr. for GFAP.

The likelihood that animal bones in continental Europe are contaminated with nervous tissue from animals suffering from BSE was previously estimated to be at most 0.0005 (weight) % (Schrieber and Seybold, 1993). It was also noted that total protein from bones before degreasing was 12.9 g/kg and was reduced to 2.4 g/kg after degreasing.

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<sup>3</sup> S100 is a nervous protein, soluble in 100% saturated ammonium sulphate.

<sup>4</sup> GFAP stands for glial fibrillary acid protein.

(=82% reduction). After the succeeding step in gelatine manufacture, the acid treatment of degreased bones (HCl 4%) during 4-5 days, specific nerve proteins were no longer detectable.

In an other experiment, finely crushed bovine heads were used which implies extremely high contamination with brain tissue. Since 1 September 1997, heads as such are no longer used in routine gelatine manufacture. The results obtained confirm those obtained with crushed bone chips: a reduction of specific nerve tissue proteins by 98-99% after degreasing, additionally, total protein content is reduced from 31.8 g/kg to 3.7 g/kg (88%) and no specific nerve proteins were detectable after the acid treatment step using degreased heads.

The authors conclude that "*there is hardly any reason to assume that prions would not be removed similarly as nervous proteins.*"

*The Scientific Steering Committee comments that TSE infectivity is not limited to nervous (brain) proteins but is also present in the lympho-reticular system of sheep but not so far in BSE infected bovines, even after spleen and lymph nodes were injected intercerebrally into cattle. The SSC also notes that the above conclusion may be valid for the reduction in protein levels, but not necessarily for infectivity.*

#### 5.4.3. Gelatine manufacturers validation studies.

With respect to the possible BSE transmission through gelatine, the *Gelatine Manufacturers of Europe* (GME) took the initiative for a validation study on the removal/inactivation capacity of a typical gelatine manufacturing process, assumed to be the most stringent one in terms of possible reduction of TSE infectivity. For establishing this opinion, the draft final report presenting the results after 18 months had been made available by GME (Inveresk Research International, 1998b).

Two key chemical treatments in the manufacturing process of gelatine were validated for BSE inactivation: the acid treatment and the liming treatment.

The material used consisted of scrapie infected mouse brain ( $\log_0 ID_{50}=7.44$ ) for the acid treatment and  $\log_{10} ID_{50}= 7.90$  for the liming treatment. This material was inoculated intracerebrally to susceptible mice to calculate the reduction factors of infectivity in the two respective steps of the gelatine manufacturing process.

*The acid treatment shows only limited efficiency in the inactivation of potential prion contamination: after 18 months inoculation, the reduction factor was 1.17  $\log_{10}$  (approx. 10 fold).*

*The liming treatments after 20 days, 45 days and 60 days, gave also partial reduction of potential infectivity of respectively 2.33  $\log_0$ , 2.23  $\log_{10}$  and 2.10  $\log_{10}$ . The level of reduction of infectivity by liming seems not to be associated linearly with the length of incubation.*

In an the additional stage of the above Validation study of the clearance of scrapie from the manufacturing process of gelatine (Inveresk Research International, 1998c), a combined chemical treatment (acid treatment and lime treatment) was selected and artificially challenged with high titre scrapie agent ME7 (titre:  $\log_0 ID_{50}= 7.90$ ). The results show that, 18 months after inoculation, the reduction factor was 2.84  $\log_{10}$ . If both processe were fully additive, then the reduction factor should have been 3.40  $\log_{10}$ .

Another study is planned by G.M.E. (GME, 1997b) to evaluate the impact of the extraction, filtration, ion exchange and sterilisation steps on the inactivation of the BSE agent.

The Pharmaceutical Research and Manufacturers of the America (PhRMA) accepts that acid treatment and the liming step should substantially reduce any BSE infectivity by at least  $10^5$ . (Based upon the risk assessment carried out by PhRMA (Bader et al, 1997), one might expect to see one case of n.v.-C.J.D. per one thousand billion patients treated for one year as a result of pharmaceutical use of gelatine, under the conditions of sourcing and processing indicated in the report as an example)

*The SSC is concerned of the fact that, according to GME (GME, 1998c; INVERESK, 1998b), the material used for the validation study on the removal or inactivation capacity of the TSE agent did not consist of spiked bones but of scrapie infected brains, which are two different environments. It recommends that research on the elimination and inactivation of TSE, including BSE, agents during the gelatine manufacturing process should also be carried out on raw material really used for gelatine production and for the production process as a whole, starting with the degreasing step of infected material, and not as individual research studies covering each of the production steps separately and that the results should be compared with the above results. This will make it possible to confirm or infirm the cumulative effect of different sequential treatments.*

## II. THE OPINION

### 6. The question

On the basis of what precedes, the working group addressed the following question:

*"Can gelatine be considered to be free of BSE infectivity?"*

*If not, under which conditions of sourcing of the material (geographical and animal) and/or of type of material used (e.g. specified risk materials and/or age of the animal and/or production process can it be considered as safe?"*

### 7. Scientific opinion

Introductory note:

In its opinion of 22-23 January 1998 defining the BSE risk for specific geographical areas, the Scientific Steering Committee has listed the factors contributing to the incident and propagation risks in a geographical area. On 20 February 1998 the SSC adopted that list, slightly amended, as final opinion. More work needs to be done on the definition of risk regions or countries. The Committee is preparing a further opinion on the geographical aspects of BSE risks.

The four classes of the geographical aspect of BSE risks used in the opinion hereafter, are therefore indicative and, for the time being, are: "high risk countries", "lower risk countries", "countries considered free of BSE or classified as at negligible risk" and "Countries with an unknown TSE status". The

corresponding wording of the opinion hereafter may thus possibly have to be revised / updated in accordance with the forthcoming Scientific Steering Committee opinion on the geographical aspects of TSE/BSE risks.

The Scientific Steering Committee is presently developing a methodology for the geographical risk assessment.

On the basis of the report of the working group, approved by the TSE/BSE ad hoc group, the Scientific Steering Committee adopted on 26-27 March 1998 the following final opinion on the safety of gelatine:

**"7.1. Definitions:**

- *For the purpose of the present opinion, gelatine is defined as a mixture of polypeptides obtained by partial hydrolysis of the collagen contained in bones and skins mainly from bovines and/or pigs after successive treatments: degreasing, acid treatment, and/or alkaline treatment (liming), washing, filtration, ion exchange and sterilisation.*
- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem inspection and that are certified by a competent veterinary authority and identifiable as fit for human consumption on the basis of the existing national and EU legislation. The Scientific Steering Committee stresses that positive identification of material not fit for human consumption should be possible, to avoid possible entering of such material in the food or feed chains.*
- *Unless otherwise specified, the wording "Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.*
- *"Industrial use" means that the end product is not for direct nor indirect human or animal consumption or use, including not as a cosmetic nor as a pharmaceutical product.*
- *Appropriate production processes in the opinion hereafter refer to processing bone materials and are those processes which have an appropriate efficacy in terms of eliminating TSE agents. For the transformation of bones sourced from countries or regions where the BSE risk is not negligible or zero or where the BSE status is unknown, only those processes are "appropriate" with the highest possible efficacy to eliminating TSE agents. An example of an appropriate production process is: bones finely crushed and degreased with hot water and treated with dilute hydrochloric acid (at a maximum concentration of 4% and pH <1.5) over a period of at least two days, followed by an alkaline treatment of saturated lime solution (pH >12.5) for a period of 20 to 50 days with a sterilisation step of 138-140°C during 4 seconds. Regarding the sterilisation step, the SSC notes that the appropriate technique should be used, as its efficacy in contributing to the elimination / inactivation of a*

*TSE agent will also depend upon the time needed to reach the temperature, the duration of the cooling and the atmospheric pressure during the process.*

*Alternative methods with demonstrated equivalent efficacy in terms of eliminating TSE agents may be acceptable. However, such methods must be evaluated and acknowledged on a case by case basis, also against the BSE status of the source region or country and the type of material used. For bones coming from high or low risk countries, the alkaline step should always be included.*

*The Scientific Steering Committee calls for the results of the research on the TSE agent inactivation during the manufacturing of gelatine to be made urgently available, in order to possibly revise or broaden the above definition of appropriate production processes.*

- *For "special grade gelatine", the ruminant raw materials should be sourced from either:*
  - a) *geographic areas where there is reliable evidence of zero to negligible risk, or:*
  - b) *animals from a no-risk offspring population within a given country or region with a negligible BSE risk, if a number of criteria are being met which exclude the possible risk of infectivity: age, traceability of the descendance of the individual animal and of the herd of origin, no history of feeding feedstuffs of animal origin, etc.*

*In either case, materials should be processed in dedicated production lines, but these could be lines used previously for more general purposes provided that there is a sufficient "clean-out" before the start of a dedicated production run.*

7.2. *Because of existing evidence of the possible presence of remaining impurities, and given the fact that the number of critical points<sup>5</sup> in the whole production chain is quite large and that their monitoring may not always be easy and evident,*

*the Scientific Steering Committee is of the opinion that the optimum level of safety can be obtained from a combination of safe source of raw material used and a well documented process with defined minimum levels of treatment.*

7.3. *The Scientific Steering Committee strongly recommends that gelatine manufacturers implement and respect HACCP<sup>6</sup> procedures. It is essential to identify and describe hazards and critical points for the different processes utilised in gelatine production. Two of these points are the traceability and treatment at origin (e.g. removal of specified risk materials) of the raw material.*

7.4. *The sections of the opinion hereafter cover the approach to be followed if the risk of infectivity in the remaining impurities is to be reduced to the lowest*

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<sup>5</sup> In terms of possible risk for remaining BSE infectivity in the final product

<sup>6</sup> Hazard Analysis and Critical Control Points

possible level. As an alternative, a more detailed quantitative risk analysis should be carried out to assess the remaining risk for a population or individual. Such assessment would take account of:

- the type of final product and infectivity reduction capacity of the production procedure;
- the geographical origin of the raw material;
- the type of raw material, including the age of the animals;
- the removal or not of specified risk materials;
- the incidence and propagation components of the BSE borne risk, as specified in the opinion of 22-23 January 1998 of the Scientific Steering Committee defining the BSE risk for specified geographical areas.

This assessment requires results of experiments on and justified estimates of, reduction factors during the various steps of the production process, from sourcing to marketing. Such data are not always available, as some experiments are still ongoing or only in a planning phase. In order to provide the Commission with two alternative choices, the Scientific Steering Committee will eventually complete the in this opinion followed approach to reduce the risk of infectivity in the final product to the lowest possible level with a quantitative risk analysis. The results of the latter analysis may eventually change or ask for an update of the recommendations hereafter.

7.5. The SSC acknowledges the US-FDA (1997) opinion that gelatine can safely be produced from bovine hides from any country, provided that the bovine hides have not been contaminated with specified risk materials and that hides from cattle showing signs of neurological disease have been excluded.

7.6. The raw material should - depending upon the intended end-use as listed hereafter- be obtained from appropriate sources (geographical, herd, animal and its age), animal species and tissues.

7.7. In any case, the raw materials should be submitted to an appropriate production process, as indicated in the above definition.

7.8. The end use of gelatine is human consumption as well as cosmetic product.

7.8.1. For countries considered to be 'BSE free or classified as at negligible risk':

Raw material (bovine bones and skins) can be used free without removal of specified risk materials when coming from animals certified as fit for human consumption.

7.8.2. For lower risk countries:

Specified risk materials should first be removed to minimise the risks of possible contamination. The origin of the bovine raw materials should be certified to be exclusively from animals that are fit for human consumption.

7.8.2. For high risk countries:

Given the existing production procedures which do not always permit the tracing back of specified risk materials and their geographical origin, the SSC recommends that no sourcing of bovine raw materials (except hides) from high

risk countries is allowed. If hides are used, they should be obtained from animals fit for human consumption. However, in certain circumstances, the risk profile can be changed, e.g. on the basis of age of the animals, the origin (source herd) of the animal, etc. This could result in bovine material from high risk areas to be possibly acceptable for gelatine production, provided those circumstances carry no risk and provided the conditions applicable for lower risk countries are respected.

Material from pigs can be used, provided that the animals are certified as fit for human consumption and processed on separate lines in slaughterhouses.

- 7.8.4. Countries with an unknown BSE status should be evaluated individually on the basis of a detailed evaluation using appropriate criteria. If no judgement on the basis of available evidence or because of a lack of information is possible, they should be considered as high risk countries.

Remark: The previous statement does not prejudge the opinion of the SSC on the TSE/BSE status of any country. Work on geographical risk assessment is ongoing.

- 7.9. **The end use of gelatine in registered pharmaceutical products and for parenteral use.**

Gelatine in pharmaceuticals may be administered by the oral, topical or parenteral route. In the case of implantable medical devices they may persist at the site of administration for longer periods of time. The standards required for manufacture of gelatine for use in pharmaceuticals may therefore vary according to the route or site of application.

- 7.9.1 Gelatine for oral or topical use (excluding ophthalmic use).

The same conditions as for food and cosmetic use set out in paragraph 8 should apply, recognising that pharmaceutical products should confer benefits which outweigh risks. Consideration should be given to the use of a special grade gelatine in topical products where these are likely to be applied to large areas of damaged skin or to open wounds.

- 7.9.2. Gelatine for parenteral or ophthalmic administration or for use in implantable devices (including use as excipients in this group of products).

The SSC recommends that a special grade of gelatine should be considered for these products containing gelatine. The conditions set out in the above paragraph 8 should apply and appropriate purification procedures should be used.

Parenterally administered pharmaceuticals and implantable medical devices are available only through a regulatory licensing process, and the benefit/risk determination with respect to the source and process for the manufacture of gelatine should be considered on a case by case basis as a part of that licensing process.

- 7.10. **The end use of the gelatine is as a reagent in the manufacture of pharmaceuticals.**

*Where the end products, for which gelatine is needed during the manufacturing process, are for parenteral or ophthalmic use or vaccines, the Scientific Steering Committee considers that it would be safer to apply the same stringent controls as set out in above paragraph 9.2. (The state of knowledge on BSE is indeed still developing and the causative agent, its infectivity and distribution in tissues require much further research. Vaccines are a special case as they are administered to large numbers of healthy subjects for preventive purposes and therefore should carry a minimal risk.)*

**7.11. The end use is exclusively industrial (for example photographic products and miscellaneous technical applications and products).**

*The raw material should be submitted to an appropriate production process, as indicated in the definition above. Protection measures at workplace to avoid direct contact should be in place. If ingestion or exposure of the gelatine with the human body may be expected under normal conditions of use, the gelatine should comply with the conditions described in the above paragraph 8.*

**Summary table: the safety of gelatine derived from ruminant bones and from hides possibly contaminated with specified risk materials<sup>7</sup>**

END USE:	Human consumption and cosmetic products	Registered pharmaceutical products and parenteral use			Industrial use
		Oral or topological	Parenteral, ophthalmic; implantable product	Gelatine as component in manufacture	
<b>Source: BSE FREE or NEGLIGIBLE RISK</b>	- Fit for human consumption - Appropriate production process <sup>8</sup>	- As for Human consumption and cosmetic products; - Special grade gelatine if applied to large areas of damaged skin or to open wounds; - Regulatory licensing <sup>10</sup>	- As for Human consumption and cosmetic products;  - Special grade gelatine if applied to large areas of damaged skin or to open wounds;	- Manufacture of products for parenteral or ophthalmic use or for vaccines: as for implantable products	- Appropriate production process <sup>8</sup> .
<b>Source: LOW R RISK</b>	- Fit for human consumption SRMs <sup>9</sup> excluded - Appr. product process <sup>8</sup>				- Appropriate production process <sup>8</sup> ;
<b>Source: HIGH RISK</b>	- Exclude: all ruminant materials, except hides <sup>11</sup> ; - hides only from animals fit for human consumption; - Pig materials to be processed on separate lines. - Appr. product process <sup>8</sup>		- if bovine material used it should be of negligible risk; - Appropriate and validated purification process; - Regulatory licensing <sup>10</sup> - Dedicated production lines;		- Appropriate production process <sup>8</sup> ; - Appropriate protection of workers. - If ingestion or exposure risk: as for human use;
<b>Status unknown</b>	To be evaluated; if no judgement on the basis of available evidence or because of a lack of information is possible: consider as high risk <sup>12</sup>				

<sup>7</sup> Non contaminated hides are in principle safe. Hides of cattle that have signs of a neurological disease should always be excluded.

<sup>8</sup> Appropriate production processes may vary according to the BSE status of the source region or country and the type of material used (bones and/or hides).

<sup>9</sup> Specified risk materials refer to the tissues listed in the opinion adopted on 8-9.12.97 and amended on 19-20.02.98. However, the SSC considers the possibility of making a selection of SRMs on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.

<sup>10</sup> For placing pharmaceutical products on the market.

<sup>11</sup> In certain circumstances, the risk profile can be changed, e.g., on the basis of age of the animal, the origin (source) of the animal, etc. This could result in bovine material from high risk areas to be possibly acceptable for gelatine production provided those circumstances carry no risk and provided the conditions applicable for lower risk countries are respected

<sup>12</sup> This statement does not prejudice the opinion of the SSC on the TSE/BSE status of any country.

**8. Non exhausting list of relevant scientific and technical material.**

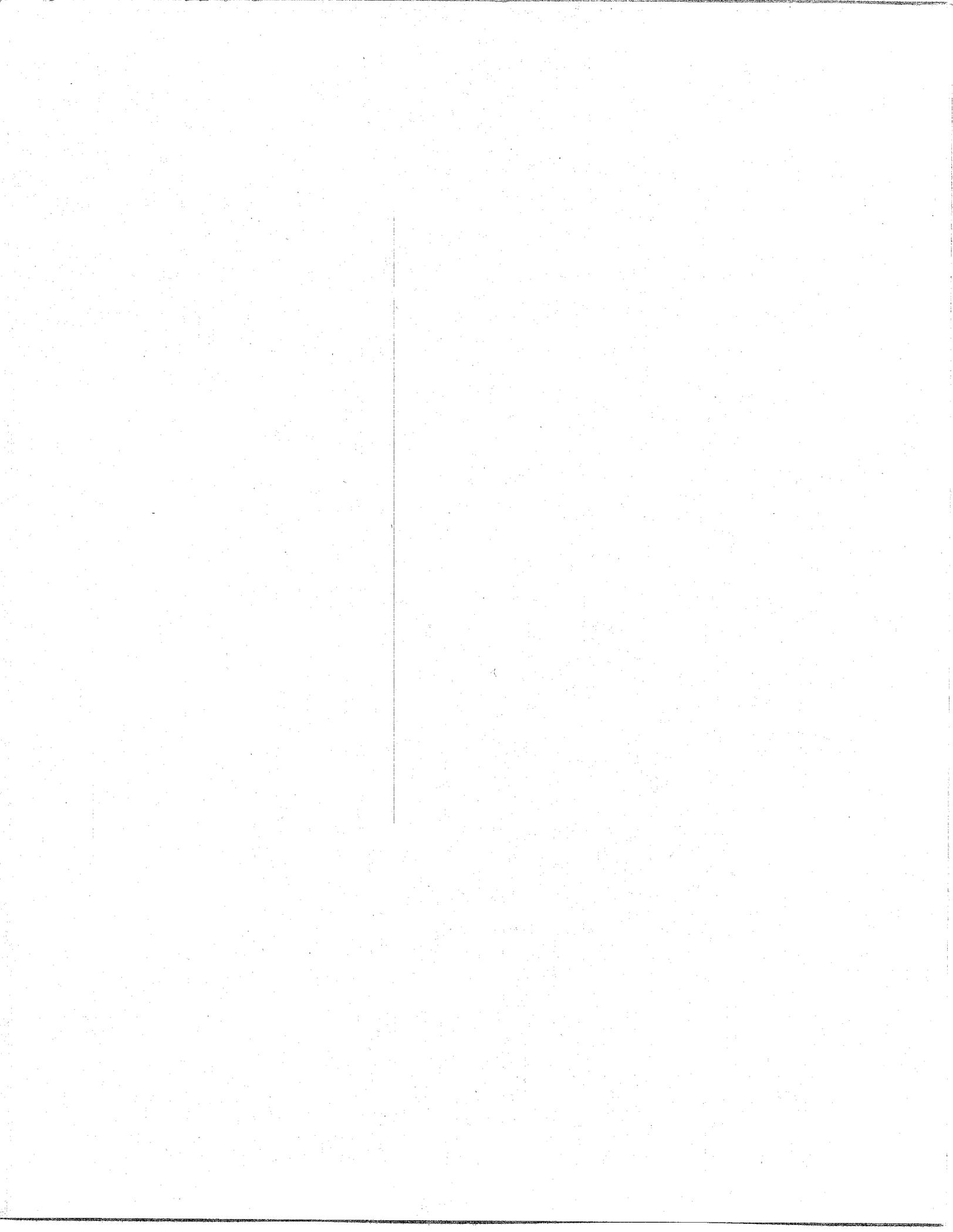
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## GELATIN MANUFACTURERS OF EUROPE

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### Briefing paper for the TSE Advisory Committee

*The following considerations reflect only the standpoint of the European gelatin industry and concentrate on the use of bovine bone material as raw material for the production of gelatin. The Gelatin Manufacturers of Europe (GME) do not have the authority to represent other non-European gelatin producers or associations.*

Gelatin is a protein obtained from partial hydrolysis of the collagen contained in animal bones or skins. In practice, most gelatin is produced from bovine or porcine bones, cattle hide, or pigskins. Smaller volumes from other raw materials such as fish skin or fish bone are also available.

### *Market Dynamics*

The total worldwide market is about 255,000 metric tons (1999). Forty percent thereof is pigskin gelatin, 30% bone gelatin and the remaining 30% is made from cattle hides. The choice of raw material depends on the technical application requirements and on the customer's preference (very often for religious reasons). Most bovine bone gelatin is used in the photographic industry or for capsule making. A limited volume is also used for edible applications.

The US production of gelatin is estimated at 57,000 metric tons (1999) of which 17,000 are bovine bone gelatin. The major part of the bone gelatin production is used in the local photographic industry, while some minor volumes are sold for edible applications or are exported outside the US. About 5,000 metric tons remain available for the US capsule industry. Since the total need for capsule production in the US amounts to approximately 10,000 metric tons, at least another 5,000 metric tons have to be imported from outside the US to fulfill the basic gelatin requirement of the US capsule industry.

### *Raw Material Availability*

Bone gelatin is produced from degreased bone chips. Since these are a dry material they can be stored for a long time without quality loss and can be transported worldwide. The total production of bone chips in the US amounts to 133,000 metric tons. Traditionally, and for economic and quality reasons, the major part is used as raw material for photographic gelatin, not only in the US but also in Europe and Japan. The rest is used for the production of capsule gelatin – of which, however, a substantial part is used by capsule makers outside the US. In terms of bone availability this leaves about 28,000 metric tons to produce gelatin for the US capsule makers. In order to fulfill the 10,000 metric ton gelatin requirement of the US capsule

industry, an additional 32,000 metric tons of degreased bones have to be sourced outside the US.

### ***Safety of Raw Materials and Gelatin***

The BSE-related safety of gelatin is fundamentally based on the choice of raw materials. The potential capacity of the gelatin production process to remove or destroy TSE infectivity is considered only as an additional guarantee for the safety of the final product.

Whether it concerns bones, pigskins or cattle hides, the raw materials used by the European gelatin producers all fulfill the same requirements as far as health conditions and BSE-related safety are considered, no matter where they are sourced:

- Only raw materials coming from *healthy animals* are used. These animals have been declared *fit for human consumption* after ante- and post-mortem inspection. In practice this means that the raw materials come from the same animals that are the sources of meat is offered for human consumption.
- The slaughtering and deboning is done only in *officially registered facilities* where the *official veterinary authorities* do the inspection and certification.
- Aside from the inspection by the local authorities, the gelatin producers themselves regularly audit all suppliers of raw materials to the gelatin industry. The audits concern mainly traceability, compliance with legal requirements, documentation and certification, hygiene, and sanitary conditions.
- In procuring the raw materials, the gelatin suppliers follow the restrictions set in the GBR (geographical BSE risk) classification of the *Office Internationale des Epizooties (OIE)* and the *EC Scientific Steering Committee (SSC)*. Bovine raw materials from category IV countries are not used for gelatin production.
- The whole supply chain and production process, up to the final product, is fully documented for traceability. In the unlikely event that unsuitable raw material would enter the gelatin production process, it is possible to retrace all gelatin produced with this raw material and to withdraw the gelatin from the market. Due to the length of the production process (depending on the type of gelatin up to 3 months) such event would most likely be detected before the final gelatin would have left the plant.
- All European gelatin producers comply with the current EU legislation for food and pharmaceutical products. Those supplying gelatin to the US also comply with the FDA Guidance for Industry. Since usually several types of gelatin (technical, pharmaceutical and edible) are produced in the same plant, the most stringent of the EU legal requirements for these types are applied to the total production of that plant.

- In line with the European legislation, all tissues posing a risk as far as BSE infection is concerned (*Specified Risk Materials (SRM)*) are removed from the raw materials by the slaughterhouse or deboning facility. Raw materials are again visually checked on a sorting belt before entering the gelatin production process.
- All European gelatin producers are under supervision of the national and EU authorities. They are all ISO 9000 certified and HACCP compliant. Furthermore, major customers, both from the food- and pharmaceutical industry, regularly perform audits of the gelatin production facilities.

### ***Legal Requirements***

Aside from the general standards for food (e.g., AFNOR, CODEX) and pharmaceutical products (e.g., the European, US, and Japanese Pharmacopoeia), the gelatin industry is regulated mainly by three European directives:

- Decision 99/724/EC (amending Decision 92/118/EC): setting the general minimum conditions for the raw materials and process conditions for gelatin for food applications.
- Decision 2000/418/EC (and amendments): setting the BSE related conditions for raw materials to be used for the production of food products.
- The major requirements are the removal of *Specified Risk Materials (SRM)*, including the vertebrae of animals older than 12 months, and the compulsory BSE testing of all bovine animals older than 30 months.
- Decision 99/82/EC (amending 75/318/EC): compliance with the European Pharmacopoeia, concerning raw materials and process conditions of pharmaceutical gelatin. This decision requires the European gelatin suppliers of pharmaceutical gelatin to apply for an individual certificate of compliance, issued by the *European Directorate for the Quality of Medicines (EDQM)*.

In addition, those gelatin producers supplying gelatin directly to the US market or for final products to be shipped to the US fulfill the requirements of the FDA Guidance for Industry.

### ***Production Process***

The production process of bone gelatin consists of several steps:

- Degreasing of the fresh bones: crushing of the bones and removal in a hot (75°-90°C) water bath of the remaining tissues (e.g., meat, fat, blood) that adhere to the fresh bone.

A typical yield of a degreasing operation is 20%, meaning that 5 tons of fresh bones yields 1 ton of degreased bone chips.

- Acidulation (demineralization): treatment of the degreased bone chips with hydrochloric acid to remove the inorganic component. The acidulated bones are called ossein.
- Liming: treatment of the ossein with a solution of supersaturated lime (pH approximately 12.5) to purify the collagen by breaking down the other components of the ossein, and to condition the collagen. Depending on the required physical properties of the gelatin, liming can take from 20 to more than 80 days. A typical liming period is  $\pm 55$  days.

In case of the production of *acid bone gelatin* this step is omitted.

- Neutralization of the limed ossein with diluted acid.
- Extraction of the gelatin in several steps at different temperatures. The first extraction step is usually done at  $\pm 50^{\circ}\text{C}$ , and the last one at  $100^{\circ}\text{C}$ . The gelatin concentration of the extract is normally between 3 and 8%.
- Filtration to remove insoluble particles. This is usually done on diatomaceous earth and on cellulose filters. Some producers also apply ultra-filtration.
- Ion exchange on both cation and anion exchangers to remove all dissolved salts.
- Concentration in vacuum evaporators.
- Sterilization of the gelatin solution for at least 4 seconds at a temperature of  $138^{\circ}$ - $140^{\circ}\text{C}$  under 3-4 bar pressure by direct steam injection.
- Drying in temperatures ranging from  $25^{\circ}\text{C}$  to  $60^{\circ}\text{C}$ . The drying time can take up to 6 hours.
- Grinding, sieving, blending and packaging.

An alternative extraction process, used by one European producer only, is the *heat and pressure process*. Compared to the above-described traditional process, the alkaline treatment is done for two hours with a 0.3 N NaOH solution and extraction is done in an autoclave with steam at 3 bar and  $133$ - $135^{\circ}\text{C}$ .

## *TSE Prion Inactivation Studies*

### *Background*

The safety of gelatin from the perspective of TSE risk is based on two principles: (1) the use of safe raw materials from healthy animals, and (2) the use of a manufacturing process that inactivates any potential infectivity. The safety of gelatin has been recognized by a number of health authorities throughout the world, such as the Committee on Sanitary and Phytosanitary Measures of the World Trade Organization ( Feb. 28<sup>th</sup>, 2001), the World Health Organization (WHO, 1996) and the Scientific Steering Committee of the European Commission (SSC, 1998 and 2000).

Since 1994 the gelatin industry has investigated to what extent any potential TSE infectivity associated with bovine bone raw materials would be removed or inactivated by different steps of the gelatin manufacturing process. In addition, we have studied published literature on other inactivation procedures to find out what effects other manufacturing processes (not tested by the gelatin industry itself) might have. The summary of this knowledge gained has led to the conclusion that bovine gelatins manufactured according to certain standard procedures are safe and present no concerns for transmission of TSE to humans. Nevertheless, it was desirable for some of the conclusions drawn from earlier experiments to be confirmed in studies using laboratory scale gelatin manufacturing equipment and procedures which closely simulate the actual gelatin production processes. The *GME multicenter TSE inactivation study* has now been done, using both Scrapie and BSE infectivity for artificial spiking of the bones, and some preliminary results are available.

### *Prior studies*

- The University of Göttingen studied the effect of the bone degreasing operation with regard to the removal of central nervous system tissue (CNS) by testing for the presence of specific CNS marker proteins. No such marker proteins were detected in degreased bones produced on commercial production scale, indicating that this production step is removing CNS to below the detection level. An exaggerated experiment was also conducted in order to obtain a quantitative value of CNS removal. These experiments, in which only heads, including the brain, were processed, showed that between 97 % and 99 % of the ingoing CNS was removed by the degreasing process. This means that between 1.5 log<sub>10</sub> and 2 log<sub>10</sub> removal of infectivity is achieved by this process, assuming that there is any infectivity connected with the CNS. The use of bovine heads does of course not reflect the actual gelatin manufacturing practice.
- In another study, Scrapie-infected mouse brain was treated with hydrochloric acid or with a saturated lime solution for different periods of time to simulate the acidulation and liming of the bones during the gelatin manufacturing process. Only qualitative results could however be obtained from this study because of a wrong combination of

starting infectivity and the number of dilutions in the mouse bioassay.

When this study was repeated with the same design but using more dilution steps the following quantitative results were obtained. The acidulation step, which is used to remove the dicalcium-phosphate from the bones, destroyed about 90 % of the ingoing infectivity (1 log<sub>10</sub>) and the treatment with lime destroyed about 99 % of infectivity (2 log<sub>10</sub>). The inactivation by liming was independent of the duration of the treatment between 20 and 60 days. In a subsequent test it was shown that if these two treatments are applied in sequence, as occurs in gelatin production, the inactivation effect is essentially cumulative (2.84 log<sub>10</sub>).

- A study initiated by an Australian gelatin company has tested the effect of a treatment of brain with dilute NaOH (0.25 N and 0.30 N) over five or seven days respectively. In both cases a reduction factor of about 5 log<sub>10</sub> was found.
- Based on our prior investigations and on the scientific literature, we hypothesized that the removal effect of the filtration and ion-exchange production steps would be at least 1 log<sub>10</sub> and the inactivation effect of the UHT-sterilization (min. 4 sec. at 138° – 140° C) would be somewhere between 2 log<sub>10</sub> and 3 log<sub>10</sub>. However, these steps had never been tested with gelatin or under conditions used by the gelatin industry.
- Furthermore, the question was raised whether those results achieved with the ME7 mouse adapted strain of Scrapie could be replicated with 263-K-hamster adapted strain of Scrapie or 301-V-mouse adapted BSE strain, which is known to be very resistant to heat treatment.

### *The GME multicenter TSE inactivation study*

The laboratory scale production of gelatin and the inoculation of mice and hamsters has now been completed. Conclusive results from the different tests are expected in the course of 2001. At the present time two significant intermediate results are available:

1. The effects of degreasing, acidulation and lime treatments are essentially cumulative.

It has been shown that, as expected, these three different consecutive process steps each contribute to the inactivation of BSE infectivity. Another interesting observation is that the cumulative effect of degreasing, acidulation and a two-hour treatment of the ossein (degreased and acidulated bones) with 0.3 N NaOH, instead of lime, results in an extracted gelatin which has no detectable residual infectivity. (That is, none of the mice that were exposed to this undiluted gelatin solution, injected into the brain, have died, which indicates that no infectivity has remained to cause the disease in these very sensitive animals.)

2. Filtration, ion-exchange and UHT-sterilization.

The test results for filtration and ion-exchange have also confirmed that the infective agent (263K scrapie) is removed by at least a factor of 1.5 log<sub>10</sub> by mechanical trapping. These results are somewhat better than expected from the literature. Also the achieved 4 log<sub>10</sub> for the UHT-sterilization is better than expected based on published studies.

### *Conclusion*

Based on the results of the different studies, one can conclude that the complete limed bone gelatin manufacturing process has the potential to remove and/or destroy infectivity to the extent of about 9 log<sub>10</sub>. Assuming that there is any infectivity in the bones used for commercial manufacturing of gelatin, that infectivity could not conceivably be higher than 2 log<sub>10</sub>. Therefore, the results clearly show that the process is able to provide gelatin that is completely safe for human consumption. This assessment does not take into consideration the extensive controls that are in place to help assure that raw materials carry no infectivity. These controls provide already an initial basic assurance of the safety of gelatin.

Gelatin Manufacturers of Europe  
Brussels, May 24<sup>th</sup>, 2001