Quick Summary
TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE
July 17 & 18, 2003

<u>Topic 1:</u> Safety of bovine bone gelatin in oral and topic drugs, food and cosmetics

The TSEAC has discussed the safety of gelatin twice before at previous meetings. During those meetings, representatives of the Gelatine Manufacturers of Europe (GME) presented reports of validation studies on the capability of gelatin manufacturing processes to remove and/or inactivate TSE agents. The Committee concluded those studies were not complete and requested that additional studies be performed. Results of the new studies were presented and discussed. The Committee was then asked the following questions:

1. Do the results of these new studies demonstrate a reduction in infectivity that is sufficient to protect human health?

The Committee voted: 7 yes, 1 no, and 1 abstained.

2a. Do the scientific data and information available support the following current FDA recommendation on bone gelatin?

> "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."

The Committee asked that FDA better clarify parts of the above recommendation. FDA should define the meaning of "BSE-free herd" and removal of spine and spinal cords "directly after slaughter." FDA should also clarify if it recommends removal of spinal cord and spine together or separately. Removal of the spinal column from bones for gelatin processing was considered necessary, however, the location where the column was removed from the carcass during the slaughtering process and the timing of its removal was not deemed to be a major issue. The Committee

requested that the processor give assurance that their sources have been protected from exposure to the BSE agent. Vertebral bones were of greatest concern because of adjacent spinal cord and because dorsal root ganglia cannot be separated from vertebrae. The Committee stated that PrPres (PrP^{Sc}) testing of slaughter cattle from which bones came was not a critical determinant in risk reduction. The USDA representative noted that cattle in a BSE-free herd should never have been fed meat-and-bone meal and that such a herd should have in place a BSE surveillance program equal to or exceeding that recommended by the OIE. Individual Committee members wondered why, considering that so much bovine bone gelatin is used to manufacture photographic film, U.S. bovine bones could not be used preferentially to fill the U.S. need for oral and cosmetic gelatin.

The Committee then voted: 6 yes , 2 no and 1 abstained.

2b. If the answer is NO, what specific changes does the Committee recommend?
In view of the vote for question 2a. this question was not applicable.

<u>Topic 2:</u> Potential Exposure of Blood Donors in North America to BSE agent

* FDA is undertaking an assessment of the BSE exposure risk to blood donors in the US and Canada in light of the single BSE case that has been reported in Canada.
* Although it is premature for the FDA to present any results of this ongoing assessment, we believe that the likelihood of exposure to the BSE agent for both Canada and the US is and has been very small.
* The exact magnitude of BSE risk for Canada and the U.S. will be difficult to quantify because of methodological limitations. However, preliminary considerations suggest that
    1. The risk of exposure of blood donors in North America to the BSE agent has been extremely low and is even lower now than it was several years ago.
    2. In particular, implementation of the feed ban of 1997 has significantly reduced the likelihood of human exposures to the BSE agent for both Canada and the U.S.A.
* FDA does not believe that there are sufficient data at this time to warrant changing our blood donor deferral guidance.
* We will continue to study this issue and take further action as appropriate.

<u>Topic 3:</u> Reprocessing of Medical Devices, Contaminated or Potentially Contaminated with TSE Agents

The Committee listened to presentations from several national and international experts as well as CBER, CDRH, NIH, and Veterans Administration staff. The Committee then discussed what published data could be used to establish methods for decontaminating medical devices after potential exposure to TSE agents, the limitations that exist in applying these data to procedures that decontaminate medical devices, methods for validating the sterility of medical devices, and approaches for designing and interpreting

inactivation studies for TSE agents. The Committee then discussed the following questions. The questions were not addressed independently or in order.

1. What information in the published literature should be viewed as supportive data to establish methods and procedures for reprocessing medical devices potentially contaminated with TSE? **The Committee consensus was that, due to the wide spectrum of medical devices and equipment of different design and composition, the questions should be discussed on a product-by-product basis. Available published data may not be generalizable and, thus, not transferable. Each situation must be evaluated individually.**

2. Data in the published scientific literature or developed from in-house studies with a specific medical device may not be applicable to other medical devices. For example, differences in device fabrication material, device design, methods for cleaning, or changes in device intended use may alter the effectiveness of a TSE inactivation procedure. **While a myriad of data shows that the infective TSE agent can be inactivated by different procedures, very little of that information is directly applicable to hospital settings. Additional studies are needed to determine the inactivation of infectivity contaminating those materials under conditions resembling real clinical settings. Studies to determine the scope of current hospital practices would also be helpful.**

3. Please discuss which aspects of a medical device and its use should be considered when determining whether a new TSE inactivation study might be needed for a specific device? **The surface of a device, the presence of "nooks and crannies" or areas of the device which are difficult to clean, and the device's ability to withstand harsh decontamination procedures, and the tissue with which it comes in contact are all factors to analyze on a product-by-product basis**.

    a. Please provide guidance on how these aspects of a medical device should be included in the TSE inactivation study design.

4. What criteria should be considered when analyzing the results of TSE inactivation studies? For example, is log reduction of TSE infectivity, (expressed as), an appropriate endpoint for such studies?

    a. If so, what magnitude of reduction in log LD50 would be considered safe?

    b. Are there other endpoints, such as the presence of PrPres that would be acceptable surrogate markers for infectivity?

The appropriate decontamination methods depend on the type of surgery and the equipment involved. This situation must be approached with caution. The overall risk of transmitting CJD by contaminated surgical instruments is low (due to the low incidence of CJD), and some decontamination processes might themselves introduce a significant new risk of adverse event.

Wet sterilization is clearly more effective than dry heat in inactivating TSE agents. Studies should evaluate inactivation with bases or other agents less toxic than NaOH. Enzymatic decontamination procedures have never been adequately investigated and might offer a benefit in some situations.

Most of the WHO-recommended decontamination procedures for TSE agents are very stringent. FDA should explore the possible use of less severe methods, if and when reliable information shows that such methods are equally effective and have been validated.

The Committee proposed that FDA convene an open international meeting of experts from academia, industry and government to seek a consensus on decontamination procedures appropriate to a variety of devices and their use in specific situations. Such a conference might evaluate such issues as the necessity of using animal models to validate claims of decontamination, novel cell culture methods, and other approaches. Procedures to be discussed should include cleaning of devices, autoclaving, and other methods of decontamination and terminal sterilization. The appropriate use of identified and validated surrogate markers would be another useful topic for discussion. This proposed forum might discuss development of validation assays, based on estimates of risk and effects of procedures suitable for use in actual clinical and other settings, i.e., industry settings of device reprocessing. Although the Committee discussed the amounts of residual infectivity that might be considered tolerable and recognized that risk cannot be zero, one member strongly asserted—without challenge—that there is no threshold value below which exposure to a TSE agent should be considered safe.

Acceptable decontamination procedures should inactivate or remove infectious TSE agents while maintaining integrity of the device. Validation studies can provide scientific data about decontamination procedures under specified conditions. Results can provide assurance that risk of contamination has been minimized to achieve some margin of safety. However, in many cases, decontamination procedures cannot guarantee absolutely "safe" products. Use of existing methods cannot assure complete removal of TSE agent from all materials under all circumstances.

5. The extent of TSE inactivation required for any reprocessing procedure depends on the amount of infectious agent present in/on the device.

    a. Considering the scientific literature describing the level of infectious material present in different human tissues, please discuss what amounts of infectious material may be present on contaminated medical devices.

    b. Please provide guidance on how the level of infectious material on a medical device should be considered when designing and interpreting a TSE inactivation study.

The extent of inactivation required to decontaminate a device depends on the amount of TSE infectivity present, which in turn depends on the type of tissue in contact with the device. At two extremes are high-risk tissues, such as dura mater, and low-risk tissues, such as blood. Procedures to remove contamination must be evaluated on a risk/ benefit basis. Obviously, the risk of contamination is far greater when instruments have been used for CJD patients or suspect CJD patients. Since the complexity of medical devices is quite diverse, specific decontamination procedures must be tailored to each device. The greatest concern is for decontamination of neurosurgical instruments used on CJD or CJD high-risk patients.

The highest tissue risk for CJD infectivity is inside the cranium, followed by the spinal cord and the dorsal root ganglia. For vCJD the lymphoreticular system and gastrointestinal tract are also at risk, but at a lower level. The log reduction criteria are appropriate, but will depend on the tissue. Additional data may result in the need to modify procedures as they become available. The validation procedures should also check the rinse solutions from the procedure to minimize risk of spreading the contaminant.

See the previous discussion.

<u>Topic 4 Part 1</u>: Methods to Decontaminate Facilities and Equipment Used to Prepare Human Cells, Tissue and Cellular and Tissue-Based Products (HCT/Ps), and Human Blood Products, Including Plasma Derivatives, to Reduce the Theoretical Risk of Transmitting TSE Agents

FDA asked the TSEAC to consider whether specific methods for decontamination of facility work surfaces and surgical instruments should be introduced at this time, to prevent contamination and cross-contamination by TSE agents during recovery and processing of ocular tissue, in cases where post-donation information reveals that a donor had or may have had a TSE. FDA asked for advice on whether these methods should be used routinely by eye banks, or only as additional procedures in cases where post-donation information reveals definite or suspected TSE in a donor, and whether the methods should be used in recovery and processing of other tissues with low risk of containing TSE infectivity, either for cases of known or suspected TSE or routinely.

<u>QUESTIONS</u>

Considering (a) current practices using conventional methods of decontaminating facility work surfaces and equipment/instruments used in the recovery and processing of human tissues for transplantation, (b) other precautions currently in place (e.g., aseptic techniques, donor screening for TSE), and (c) concerns about availability of tissues,

1. With regard to the recovery and processing of ocular tissue from donors later discovered to have TSE or possible TSE:

    A. Does the committee believe that surgical instruments used in recovery and processing should be destroyed by incineration, if practical?

The Committee voted: 12 yes, 0 no, and 0 abstained.

    B. If destruction of instruments is not practical, does the committee believe that, at this time, there exist established, effective methods that are adequate for decontaminating instruments and surfaces?

The Committee recommended accepting the WHO Guidelines, when possible in the order of priority listed by WHO consultants. The most effective feasible method of decontamination is to be preferred.

    C. If so, please comment on the specific methods listed in the WHO Guidelines (see Appendix). In particular, does the committee consider that only those WHO methods using sodium hydroxide or sodium hypochlorite are adequate?

    D. If so, should such methods be employed by eye banks in the circumstance noted above?

    E. Does the committee believe that the number of decontamination cycles performed with the instruments after the index donor tissue was recovered and processed should determine whether or not these additional specified decontamination procedures are needed? A decontamination cycle involves two stages: physical cleaning, typically using a mechanical washer/drier, followed by inactivation of any remaining infectious material, e.g., by autoclaving (2).

2. With regard to the recovery and processing of ocular tissue, should additional decontamination procedures discussed in question #1 be used routinely, i.e. even when TSE has not been suspected?

The Committee voted: 0 yes , 12 no, and 0 abstained.

3. Should similar decontamination procedures be used for instruments and surfaces used to recover and process other tissues with a low risk of TSE infectivity from cases of known or suspected TSE?

The Committee revised this question to read as follows:

3. a) Should instruments used to recover and process other tissues with a low risk of TSE infectivity from cases of known or suspected TSE be destroyed by incineration, if practical?

It was noted that vertebrae are high-risk tissues and would not be included in considering this question.

The Committee voted: 9 yes, 2 no, and 1 abstained.

3. b) No question was asked and no vote taken on the following question: If destruction of instruments is not practical, should TSE decontamination procedures, such as those recommended by WHO, be used? The Chair concluded that, based upon the votes on question 3a, this question need not be addressed.

4. With regard to the recovery and processing of other tissues with a low risk of TSE infectivity, should additional decontamination procedures be used routinely, i.e. even when TSE has not been suspected?

The Committee voted: 0 yes, 12 no, and 0 abstained.

Topic 4, Part 2: Methods used in Plasma Derivative Manufacturing

The Committee was presented with updates of methods and models to address the scientific question of how best to prevent TSE cross-contamination of batches during manufacturing of products derived from human plasma, a low-risk tissue. The Plasma Protein Therapeutics Organization (PPTA) presented a summary of common and routinely used cleaning methods for equipment between batches (campaigns) of plasma derivatives, which included use of NaOH and NaOCl solutions.
The Committee discussed the following points regarding facilities and equipment used in plasma fractionation:

- The risk that the starting material (plasma) might be contaminated with the agent of vCJD
- The likelihood that existing, conventional cleaning methods, especially those that include exposure to solutions of sodium hydroxide and/or sodium hypochlorite as cleaning agents for stainless steel equipment—methods that are validated by assessment of remaining total protein and/or total organic carbon—may clear contaminating TSE agents
- The removal of TSE infectivity by precipitations, filtrations, chromatography and discarding of resins during plasma processing
- Experimental observations that TSE infectivity may be retained by chromatographic columns
- The current state of knowledge about effective cleaning methods for TSE agents

They then answered the following **Questions**:

Considering current facility cleaning practices, the low risk of vCJD infectivity in human plasma, and the ability of plasma fractionation methods to clear TSE agents,

1. Does the committee feel that current facility cleaning methods, e.g., the use of solutions of sodium hydroxide or sodium hypochlorite followed by extensive

rinsing cycles, are adequate to minimize the possibility that an infectious dose of the vCJD agent may be carried over from one manufactured lot into the next?

The Committee voted: 12 yes, 0 no, 0 abstained.

2. Are the available scientific data sufficient for FDA to recommend specific methods for cleaning of equipment used in the manufacture of plasma derivatives with respect to TSE agent clearance or inactivation?

    a. If so, please identify which methods can be recommended.
    b. If not, please describe what additional studies would assist in development of such recommendations.

The Committee did not vote on this question but discussed the issue. They acknowledged that blood was a low-risk tissue and that the current processing of plasma was likely to greatly reduce the risk of infectivity in most derivative products. There was consensus that the processes for cleaning of equipment that many manufactures are currently performing is adequate, but cleaning procedures should be standardized and effective methods adopted by all manufacturers. When new scientific information relevant to plasma processing equipment becomes available it should be reviewed, and current cleaning techniques should be reevaluated.

THIS QUICK SUMMARY WAS WRITTEN PRIOR TO RECEIPT OF THE TRANSCRIPTS. PLEASE REFER TO THE MEETING TRANSCRIPTS FOR A DETAILED ACCOUNT OF THE COMMITTEE DISCUSSIONS.