PRELIMINARY SUMMARY
TSEAC MEETING
October 25 & 26, 2001
(revised 11/2/01)

TOPIC 1. FDA's Draft Guidance on Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products (published in the Federal Register on August 29, 2001

Dr. Dorothy Scott, Medical Reviewer, OBRR, FDA, presented a summary of the previous committee discussion on donor deferral issues from the June 28 & 29 TSEAC meeting. She then gave an overview of FDA's draft guidance, focusing upon the new donor deferrals for risk of vCJD, as recommended by the TSEAC on June 28, 2001. Dr. Scott briefly reviewed the rationale for not deferring donors who lived in the U.K. since 1996, which is based upon effective measures to prevent entry of BSE into the human food chain. She mentioned the recent finding of BSE in Japan, which is under discussion at FDA. In addition, she reviewed the rationale for deferring blood, but not Source plasma donors who have lived in Europe, for vCJD exposure risk. This draft recommendation is based upon scientific studies, which suggest that plasma derivative manufacturing removes TSE agents, and upon concerns about the impact of such a deferral upon availability of products such as IGIV and Factor VIII. Finally, she reviewed efforts which are being made, within the guidance, and without, to attenuate the impact of new deferrals on the blood supply. A more comprehensive review of this issue by the TSEAC is anticipated in the near future. The draft guidance will be open for public comment until October 28, 2001.

Next the Committee received a report from Dr. Stephen Nightingale, (Executive Secretary DHHS Advisory Committee on Blood Safety and Availability) on DHHS 's recent monitoring program for blood supply and current plans to extend this monitoring program to the supply of plasma derivatives and their recombinant analogs. He then gave a summary of the DHHS meeting held on September 24, 2001 to discuss the Department's BSE/TSE Action plan (draft summary on web site). The committee then heard presentations from America's Blood Centers, American Red Cross, New York Blood Center and the Department of Defense. As a result of the open public hearing and these presentations the committee received suggestions for improving the DHHS monitoring program, and suggestions for FDA's consideration on their Draft Guidance. The committee chair stated that it would be nice to have a uniform set of blood donor deferral criteria, but that two sets of criteria can exist and that the two sets of criteria may eventually evolve and the differences may be reduced.

TOPIC 2. Discussion of Amino Acid Sourcing and Production, and the Theoretical Risk of Transmission of the BSE Agent Through Their Use in Biopharmaceutical Products

The committee heard presentations from major amino acid manufacturers on their current and previous sourcing of amino acids and their production processes.
The committee's discussion focused on reducing risk of TSE transmission as a result of the use of amino acids as reagents or excipients in other CBER regulated compounds. They discussed the possibility of requiring manufacturers to validate their process if they choose to use bovine derived material (with the exception of milk and hair). They suggested that although the risk of TSE transmission was low, that manufactures should avoid using bovine material and if used, it should be sourced from a BSE-free country. However, they acknowledged that the designation of BSE free countries was difficult and constantly changing and in most cases the manufacturers had already switched from bovine to vegetable sources. They emphasized that due to the amino acid production processes which included hydrolysis, purification, chromatography and filtration that the risk of TSE transmission was very small.

It should be noted that the committee stated that the potential risk posed by amino acids for production of products already on the market is so minimal that no effort need be made in constraining use or availability of these products.

The committee then voted on the following three questions.

Questions

1. Does the committee think that the current manufacturing process and control methods utilized by the manufacturers of amino acids can minimize the risk to allow bovine-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products?

   The committee voted: 1 yes vote, 18 no votes, and 0 abstentions.

   The committee then voted on a recommendation formulated by the chair: That the committee should recommend to FDA not to allow ruminant source material (with the exception of material such as milk and hair) to be used from BSE countries.

   The committee voted: 18 yes votes, 1 no vote (one member changed his vote to this "no" vote after the initial count, but before the meeting adjourned) and 0 abstentions.

2. The committee modified this question to - Does the committee think that in all circumstances the risk:benefit ratio would still be in favor of a subject receiving any product where suspect amino acids had been used during manufacture of that product?

   The committee voted: 19 yes votes, 0 no votes, and 1 abstention.

3. If not, does the committee think that the current manufacturing process and control methods utilized by the manufacturers of amino acids can minimize the risk to allow other ruminant-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products?

   Based on the other answers this question is now a "moot point".

4. Question 4 in the briefing packet was not discussed.

TOPIC 3: Bovine Brain, Spinal Cord, and Other Neurological Tissue in Foods, Drugs, and Cosmetics for Human Use

The Committee received an over view and background information from Dr. Robert Brackett of CFSAN, followed by a presentation on "Opportunities to Prevent Contamination of Edible Products in a Slaughter Plant with the BSE Agent" from Dr. William James of the Food Safety Inspection Service, USDA. Dr. James particularly described procedures in slaughtering (e.g., stunning, splitting heads and carcasses) and in mechanical recovery of meat from bones that may, if not performed properly, result in contamination of muscle meat with CNS tissue. There was discussion also of the wide variety of products that bovine CNS and recovered meat may be used in, often without labeling to inform the consumer.

Questions

The committee modified the FDA presented questions to read:
1A. Is there a public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain for human use?

The committee stated that the presence of undiagnosed or pre-clinical BSE should be considered a health risk. Risks can also be due to products coming from countries that were considered to be BSE free which later detected the existence of BSE. And the risk to the consumer of un-knowingly purchasing products that contain brain and CNS tissue should also be considered
The committee voted: 17 yes votes, 1 no votes, and 0 abstentions.

1B. Is there a public health risk to consumers that would warrant consideration of prohibiting the sale of products containing brain for human use?

The committee voted: 18 yes votes, 0 no votes, and 0 abstentions

2. Is there a consistent and appreciable difference in infectivity of various sections/areas of bovine brain? If so, what are the differences in relative degrees of infectivity of these areas?

There are differences in infectivity in different areas of the brain, but those differences are not reproducible and therefore should not be used to rank the relative risk of using various sections of a BSE-infected brain. The committee requested information on the current state of surveillance and Dr. Lisa Ferguson gave a short presentation on USDA surveillance program. The committee stated that the surveillance data are imperfect and that surveillance should be increased.
The committee voted: **0 yes votes, 17 no votes, and 0 abstentions.**

3. Are there other bovine neurological tissues that, if used in consumer products (such as foods, dietary supplements, cosmetics, and certain non-application drugs), could also pose a significant health hazard? If so, what are the differences in relative degrees of infectivity of these tissues?

The committee voted: 17 yes votes, 0 no votes, and 0 abstentions. The committee passed on the second part of the question and referenced their answer to #2.

4. What physical, chemical, or biological factors of tissues and/or processes should FDA consider in reviewing procedures that may have the ability to reduce infectivity of bovine neurological tissues and products containing bovine neurological tissues?

Everything should be considered on a product by product case. One committee member stated that most processing steps would not affect the infectivity of prion protein. It was stated that this question is too complicated and needs a separate meeting, ideally with presentations on different processes which may be used to process these tissues and manufacture products from them.

5. What tests are available to ascertain changes in infectivity in products containing bovine neurological tissues as a result of processing?

There are two to three types of assays, bioassays including those in transgenic mice, cell culture models and *in vitro* conversion assays also test for the abnormal PRP protein. Confirmation dependent immunoassay was mentioned. A member said that the best way to confirm infectivity is through Western Blot, although it was stated earlier that getting a representative sample is a problem with Western blotting procedures.

There are really no ‘practical’ tests available to measure infectivity. It was stated that, like question 4, this is a very complex question which may warrant a separate meeting (perhaps in conjunction with question 4), ideally with presentations on how these tissues are processed.

6. What level of reduction in infectivity is necessary to consider products containing bovine neurological tissues non-infective or "safe" for human use?

There are multiple levels of reduction depending on the origin and the sourcing of the material. Since we do not know the infective dose for humans and the infective dose may vary based on individual genetic composition, we should have a zero tolerance for the infectious unit because any level of infectivity may be unacceptable.

One committee member stated that bovine brain, spinal cord, distal ileum, and eye should not be allowed for use in products in the U.S.