

**Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC)
October 25, 2001**

**TOPIC 2
Overview**

**Amino acid production and the associated theoretical risk of BSE
transmission from their use in the production of biologics, drugs and
medical devices**

Issue:

The potential for contamination of biological products with the agent that causes bovine spongiform encephalopathy (BSE) has been a concern of the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration (FDA) for many years [CBER letters to manufacturers of biological products, May 3, 1991]. Since 1993, the FDA has recommended that most bovine-derived materials from countries in which BSE is known to exist, or from countries whose BSE status is unknown, not be used in the manufacture of biological products [Notices on bovine-derived materials: Agency letters (1993) to manufacturers of FDA-regulated products intended for humans or animals FR 1994;59:44591-4]. The appearance of the human transmissible spongiform encephalopathy (TSE) known as new-variant or variant Creutzfeldt-Jakob Disease (vCJD) in the UK and its attribution to oral exposure to the infectious agent of BSE have raised additional concerns regarding the potential for human exposure to the BSE agent that might result from the use of bovine-derived materials in the manufacture of a biologic product. No evidence exists that any case of vCJD has resulted from the administration of a bio-pharmaceutical product. However, national control authorities including the FDA must consider the theoretical risk of disease that might result from a contaminated product.

Amino acids are ubiquitous components of the production process for bio-pharmaceuticals. As such, they should be pure and safe. However, although anecdotal accounts suggest that some amino acids may be derived from bovine carcasses, there is little published or public information regarding the materials from which amino acids are derived commercially or the processes used to manufacture and purify them. At issue is the potential contamination with the BSE agent of bovine-derived source material used in the manufacture of US-licensed bio-pharmaceutical products and possible exposure of product recipients that might result through the use of amino acids of bovine origin if these were obtained from animals infected with the BSE agent. Consideration of potential risk must include the use of amino acids as in-process reagents, and the potential impact that the manufacturing process and production steps – from the generation of the master and working bacterial or viral seeds and cell banks through expansion and culture, harvest, purification, and formulation of the final product – might have on BSE infectivity. Similar issues concern the use of amino acids as active ingredients, excipients or in-process reagents in the manufacture

of drugs and as in-process reagents in the manufacture of FDA-regulated medical devices, particularly implanted devices.

Charge

The TSEAC is requested to consider the safety of amino acids produced from ruminant derived materials from BSE and BSE risk countries with regard to the likelihood of transmission of the BSE agent. If such a risk exists, the TSEAC is requested to consider the appropriate precautions that should be taken regarding the use of ruminant-derived amino acids in the manufacture of bio-pharmaceutical products, drugs or medical devices when those materials are obtained from countries in which BSE is known to exist or from countries where the USDA has been unable to assure the FDA that BSE does not exist. The committee is also asked to consider the potential risks and possible actions to be taken with regard to licensed, approved or investigational products that may be affected.

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?
2. If not, does the committee feel that there any circumstances where the risk:benefit ratio would still be in favor of a subject receiving a product where suspect amino acids had been used during manufacture of that product?
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?
4. If the committee recommends removal of all ruminant-derived amino acids sourced from BSE countries for use as reagents and excipients in pharmaceutical production, is there a specific timeframe for this removal?