

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE MEETING

February 12 and 13, 2004

Silver Spring, MD

Issue Summary, Topic 4.C

The Use of Bovine-derived Products in the Manufacture of
Vaccines and Allergenic Products

Current Regulatory Approach to Vaccines and Allergenic Products Manufactured with Bovine-derived Materials

Background

Vaccines and allergenic products may utilize bovine-derived materials during manufacturing or in the final formulation. FDA and CBER have requested, in a series of letters and in a Points to Consider document on cell substrates (1993), that materials from cattle born, raised, or slaughtered in countries where BSE is known to exist not be used in the manufacture of FDA-regulated products intended for administration to humans; FDA has referenced the USDA (APHIS) list of BSE-countries. Since BSE has spread beyond Europe, it has become increasingly difficult to ensure consistent sourcing of all bovine materials from BSE-free areas. Switching sources for bovine-derived materials to countries not on the USDA list requires considerable time and raises a number of issues related to products that are in distribution, products that are in the process of being manufactured, as well as cell and seed banks that have been established prior to the recognition of BSE in a country.

Types of Bovine Materials Used in Vaccines and Allergenic Products

Bovine-derived products are used during the manufacture or formulation of a large number of vaccines and allergenic products (molds). The bovine-derived products that are commonly used include: fetal calf serum, beef muscle/organ extracts, gelatin, and a variety of small molecules (such as, protein digests, lactose, Tween, and glycerol). These materials are used in the derivation of master and working cell banks, master and working bacterial and viral seed banks, cell culture and fermentation, immunogen purification, and product formulation.

FDA Actions to Minimize the Risk of TSE Agents in Vaccines and Allergenic Products

In an effort to minimize risks from TSE agents, FDA has:

- ?? Requested manufacturers to source bovine materials from non-BSE countries
- ?? Reviewed the use of all bovine-derived materials and their sources for licensed and IND products
- ?? Encouraged the use of non-animal sources when feasible

In addition to these measures, product labeling provides risk communication and the Office of Vaccines Research and Review website contains a discussion of BSE-related issues that have arisen (*vide infra*). For products that contain human serum albumin (e.g., the mumps, measles, and rubella vaccine), the warnings section of the package insert contains the statement: *“This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing, it carries an extremely remote risk for transmission of viral diseases. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral disease have ever been associated with the use of albumin.”*

In 2000, CBER learned that its recommendations regarding sourcing of bovine-derived materials were not universally followed for all vaccines and allergenic products. OVRP reviewed the use of bovine-derived products and their sources for all vaccines and allergenic products. Recommendations were made to the affected manufacturers and subsequently discussed in a joint session with the TSE Advisory Committee and the Vaccines and Related Biological Products Advisory Committee [see, <http://www.fda.gov/cber/bse/bse.htm>]. Issues that were discussed included: the use of fetal calf serum from the U.K. in the establishment of several master and working seeds and cell banks, the use of European-sourced beef muscle/organ extract for bacterial fermentation, the use of European-sourced gelatin derivatives, and the use of a number of European-sourced low molecular weight materials in vaccine manufacture. In assessing the potential risk of vaccines, CBER and the joint Committees considered: (1) the likelihood that any cattle that were used might be infected (i.e., the time period and country of origin) and animal husbandry procedures; (2) the amount of bovine material that might be present in the final vaccine; and (3) the inherent infectivity of the various types of bovine materials that were used. The joint Committees concluded that the risk of vCJD posed by vaccines in the scenarios presented was theoretical and remote. They also noted that the benefits of vaccination far outweigh any remote risks of vCJD. However, the joint Committees recommended that: (1) bovine-derived materials used in the routine production of vaccines and sourced from countries on the USDA list should be replaced with bovine-derived materials from countries not on the USDA list; (2) working bacterial and viral seed banks and working cell banks that were established using bovine-derived material from countries on the USDA list be re-derived using bovine-derived materials from countries not on the USDA list; (3) master cell and seed banks established using

bovine-derived materials from countries on the USDA list need not be re-derived with bovine-derived materials from countries not on the USDA list, the risk to altering the vaccine through re-derivation being significantly greater than the theoretical risk from the BSE agent; (4) these issues are of public concern and the public should be informed about the safety of vaccines that used bovine-derived materials from countries on the USDA list and the assessment of the nature of any risk for vCJD from such vaccines. These recommendations from CBER and the Advisory Committees have been implemented for vaccines. Several similar issues were identified with allergenic mold extracts; the mold master stocks were re-derived.

A number of bovine-derived materials that are used in U.S.-licensed vaccines, and in vaccines under development, are sourced from, inter alia, North America (the U.S. or Canada) or Canada. These bovine-derived materials are used either in manufacture or in the derivation or cell and seed banks. Based on an continuing assessment of risks and benefits, the Office of Vaccines Research and Review has not requested manufacturers to seek alternate sources of bovine-derived materials for products where Canadian sourced materials are, or have been, used.