

## SUMMARY

### TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE JULY 27, 2000

#### ISSUE

The potential for contamination of biological products with the agent of 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 [1]. The FDA has recommended that 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. The agency has learned that this recommendation for U.S.-licensed biological products has not been followed universally by vaccine manufacturers. The appearance of the human transmissible spongiform encephalopathy (TSE) known as new-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 manufacturing of vaccines. No evidence exists that any case of vCJD has resulted from the administration of a vaccine product. However, the theoretical risk of disease that might result from a contaminated vaccine must be considered by national control authorities including the FDA.

Relevant public health considerations include the importance of universal childhood vaccination and protection against vaccine-preventable diseases [2,3]. The remote theoretical risk associated with the possible exposure to the BSE agent in vaccines must be considered in the context of the real risk of disease, disability, and mortality that would result from a significant decrease in vaccination coverage. The extent to which such a decrease in vaccination coverage could result from product withdrawal or loss of confidence in vaccine safety is difficult to quantify, and therefore the potential impact of

this issue on US public health is unknown. In 1999, the Council on Scientific Affairs (CSA) of the American Medical Association considered the risk of BSE to public health and determined that the current risk of transmission of BSE in the US is minimal [4]. The CSA report concluded that adequate guidelines exist to prevent high-risk bovine materials from contaminating products intended for human use. The CSA report did not address the possibility that regulated industry might not follow recommendations made by the FDA and the impact that this might have on the evaluation of risk.

### **BACKGROUND**

At issue is the potential contamination with the BSE agent of bovine-derived source material used in the manufacture of US-licensed vaccine products and possible exposure of vaccine recipients that might result through the use of serum, gelatin derivatives, tissue and organ extracts, or other substances of bovine origin if these were obtained from animals possibly infected with the BSE agent. Consideration of potential risk must include the vaccine active ingredients, excipients, and in-process reagents, the possibilities for cross-contamination during manufacture of the bovine-derived substance or the vaccine, and the potential impact that the manufacturing processes and production steps – from the generation of master and working seeds and cell banks through expansion and culture, harvest, purification, and formulation of the final vaccine product – might have on any BSE infectivity [5-9]. Information and recommendations on these concerns have been issued previously by the agency in letters and guidance documents, intended to advise manufacturers to take steps toward reducing the risk of exposure to the infectious agent of BSE that could theoretically occur through the administration of vaccines [10-16].

Most recently, in April, 2000, CBER sent a letter to manufacturers [14], reiterating points CBER made in similar letters issued in 1993 and 1996 [12,13] including the recommendation that 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. The April 2000 letter clarified that manufacturing includes production of the original, master, and working seeds and cell banks, and also directed

attention to the conclusion of the United States Department of Agriculture (USDA) articulated in an Interim Rule published in the January 6, 1998 Federal Register, that all European countries must be considered to have BSE or to be suspected of having BSE in their native cattle [17]. Letters to manufacturers and other guidance documents provided to industry are part of the mechanism by which regulated industry and the public have been informed about safety issues and expectations of the FDA regarding the development, testing, and licensure of vaccines. Although a guidance document is non-binding on the agency or regulated industry, it represents the current thinking of the agency on matters relating to the licensure and control of FDA-regulated products.

In a May 1991 letter to manufacturers of biological products, CBER requested information on sourcing and control of animal substances, asking for a list of materials of bovine origin used in the product or during manufacture, as well as supplier information, and a description of controls to assure and document the health and origin of the animals used [10].

In a letter to manufacturers in July 1993, CBER asked manufacturers to review the May 1993 revision of the 1987 document "Points to Consider in the Characterization of Cell Lines Used for the Production of Biologics" [11]. In the revised version of this Points To Consider (PTC) document, CBER indicated that manufacturers should be able to provide detailed information on cell culture history, isolation, media, identity, and adventitious agent testing of cell lines used in the production of biological products [15]. Cell substrate quality control was to include description and characterization of culture media, with accurate records of composition and source for serum or other additives derived from animal sources. CBER stated explicitly that serum should be free from adventitious agents, including the BSE agent, and stressed the importance of control of the sourcing of bovine materials.

In a letter to manufacturers in December of 1993, FDA recommended that bovine materials from BSE-countries should not be used in biological products [12] and specifically cited the Federal Register Notice from USDA referring to Chapter 9 CFR

94.18, for the listing of countries known to have cattle infected with the BSE agent (BSE countries) [18]. The BSE countries listed at that time were France, Great Britain, Northern Ireland, Republic of Ireland, Oman, and Switzerland.

Following the UK announcement, in March 1996, on the probable relationship between BSE and new variant CJD, FDA issued another letter to manufacturers in May 1996, indicating that manufacturers should take whatever steps are necessary to reduce potential risk of transmission of BSE agent, again referring to the listing of BSE countries maintained by USDA under 9 CFR 94.18 [13].

In the FDA Guidance on Sourcing and Processing of Gelatin, September 1997, FDA stated that gelatin from BSE-countries, or those lacking the standards concerning BSE set by Office International des Epizooties (OIE), was not to be used in injectable, ophthalmic, or implanted products, or in their manufacture [16].

In estimating the risk of infecting a recipient with the BSE agent due to contamination of a biological product, one must consider the nature of the potentially contaminated substance, tissue source, age and geographical origin of the animals, rendering practices and other steps in manufacturing the substance, opportunities for cross-contamination, sourcing and process controls, route and dose of exposure, species barrier, and other factors [5-9]. Substances of bovine origin used in vaccine manufacturing include materials such as: milk, lactalbumin hydrolysate, and casein peptone; serum and fetal serum; trypsin and other proteases; meat or organ extracts from skeletal muscle, pancreas, brain, or heart; broths, infusions, and bouillon; gelatin and gelatin derivatives such as polygeline; the tallow derivatives glycerol and Tween 80; and amino acids and casamino acids. Currently, the concerns regarding the theoretical risk of human infection due to possible contamination of US-licensed vaccines with the BSE agent relate to the following bovine substances or their derivatives: serum, gelatin, meat extracts, and pancreatic enzymes. If obtained from animals infected with the BSE agent, these substances would differ in infectivity depending on the age and disease status of the animals and the methods used in slaughtering, rendering, and processing.

Within the limits of detection of the bioassays used, infectivity has not been detected in some of these materials. However, none of the available tests are able to exclude entirely the possibility that a given tissue or material might be infectious.

Uncertainties about the ability of laboratory tests to determine low levels of infectivity led to the use of safe sourcing practices to control against the possibility of contamination of pharmaceutical products with the BSE agent. Uncertainties about the BSE status of an animal, herd, or geographical region led FDA to recommend that manufacturers of biologicals not use materials derived from ruminants born, raised, or slaughtered in countries where BSE is known to exist. Uncertainties about the ability of some surveillance programs to assure BSE-free status of certain countries led to the inclusion of all of Europe in the list maintained by the USDA. There have been no general guidance issued advising manufacturers on how to proceed in the event that a country used as a source of bovine-derived materials is subsequently added to the USDA list, nor on what must be done with existing stocks of bulk and final vaccine products should such an event occur.

### **CHARGE**

The TSEAC and VRBPAC are requested to consider appropriate precautions to be taken with regard to the use of bovine-derived materials in the manufacture of vaccines 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 committees are also asked to consider the potential risks and possible actions to be taken with regard to licensed or investigational vaccine products that may be affected.

### **QUESTIONS**

1. Please discuss the potential risk presented by the use of bovine-derived materials, sourced from Europe (including the UK), in currently licensed vaccines. In this

discussion, please comment on the various risk estimates that have been presented to the Committee. In this discussion, please include:

- a) Preparation of bacterial and viral master and working seeds; preparation of master and working cell banks (e.g., use of calf serum, fetal calf serum).
- b) Fermentation process (e.g., use of bovine-derived media)
- c) Formulation of the final products (e.g., use of gelatin, etc.)

Additionally, in this discussion, please include risk assessments for bovine materials sourced, at different times, from different European countries (e.g., UK, Germany, France).

2. The following item pertains to currently licensed US vaccines that contain bovine-derived material obtained from Europe (including the UK).

Please discuss those circumstances, if any, under which FDA should take specific regulatory action regarding these vaccines. Some examples of regulatory actions which are available to the FDA include product recall, modification of the package insert, and/or issuance of a "Dear Doctor/Health Care Provider" letter.

3. The following item pertains to investigational (non-US licensed) vaccines that contain bovine-derived material obtained from Europe (including the UK). This includes certain investigational vaccines (used under IND) that contain currently-US licensed vaccines as components (such as components of a new investigational combination vaccine). In addition, this includes the "usual" investigational vaccines without previously US licensed components.

Please discuss those circumstances, if any, under which FDA should take specific regulatory action regarding these investigational vaccines, such as stopping a clinical trial (pending an acceptable remedy of the product) or modification of the informed consent form.

## REFERENCES

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3. CDC. Notice to Readers: Recommended Childhood Immunization Schedule -- United States, 2000. *MMWR* 49(2):35-47.
4. Tan L; Williams MA; Khan MK; Champion HC; Nielsen NH. Risk of transmission of bovine spongiform encephalopathy to humans in the United States: report of the Council on Scientific Affairs. *American Medical Association [see comments]. JAMA* 1999 Jun 23-30;281(24):2330-9.
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6. Listing of Specified Risk Materials: a scheme for assessing relative risks to man - Opinion of the Scientific Steering Committee adopted on 9 December, 1997. (Re-edited version adopted by the Scientific Steering Committee during its Third Plenary Session of 22-23 January 1998.)
7. Preliminary Opinion of the Scientific Steering Committee on the Geographical Risk of Bovine Spongiform Encephalopathy (GBR), 25 May 2000.
8. Opinion on Oral Exposure of Humans to the BSE Agent: Infective dose and species barrier. Adopted by the Scientific Steering Committee at its meeting of 13-14 April 2000.
9. Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products, Revision April 1999. Committee for Proprietary Medicinal Products, the European Agency for the Evaluation of Medicinal Products.
10. CBER. Letter to Manufacturers. May 3, 1991.
11. CBER. Letter to Manufacturers. July 12, 1993.
12. FDA. Letters to Manufacturers. December 17, 1993. (Federal Register 59(166): 44591-4, August 29, 1994. Notices on Bovine-Derived Materials: Agency Letters to Manufacturers of FDA-Regulated Products Intended for Humans or Animals.)

13. FDA. Letter to Manufacturers. May 9, 1996.

14. CBER. Letter to Manufacturers. April 19, 2000.

15. Points to Consider in the Characterization of Cell Lines Used for the Production of Biologics. CBER. May, 1993.

16. FDA. 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. CBER. September, 1997. (Federal Register 62(194): 52345-6, October 7, 1997. Notice of availability of gelatin guidance.)

17. Federal Register 63(3):406-8, Tuesday, January 6, 1998. Restrictions on the Importation of Ruminants, Meat and Meat Products From Ruminants, and Certain Other Ruminant Products. USDA, APHIS, 9 CFR Parts 94 and 96.

18. Federal Register 56(235):63865-63870, Friday, December 6, 1991. Importation of Animal Products and Byproducts from Countries Where BSE Exists. USDA, APHIS, 9 CFR Parts 94 and 95.

Additional reading:

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