

**Outline and Pre-Read for the Open Session of the Joint meeting of the
TRANSMISSIBLE SPONGIFORM ENCEPHALOPHATHIES ADVISORY
COMMITTEE and the VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE**

Holiday Inn
Versailles Ballrooms I, II, and III
Bethesda, Maryland 20814
July 27, 2000

Thursday, July 27, 2000
Open Session (9:00am to 5:00pm)

Aventis Pasteur Open Session Presentation (15 minutes)

Presented by Dr. Jeffrey Almond

- I. Introductory slide
 - Strategy is to reduce the potential risks of transmission of disease by materials of animal origin
 - Ultimately, the goal is to remove materials of ruminant origin from all manufacturing steps
 - First priority is to not source materials of ruminant origin from Europe

- II. Review the known range of materials that may pose a risk for licensed and development products manufacturing and identify "safe sources" as well as time of use

- III. Generic risk analysis

- IV. Actions and Conclusion
 - For AvP products there is no apparent Public Health risk. However, as a precaution, materials will no longer be sourced from Europe.

PRE-READ: TSE ADVISORY COMMITTEE MEETING ON 27 JULY 2000**OPEN SESSION (9:00am to 5:00pm)**

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Introduction

A number of materials used in the pharmaceutical and biological industries have been traditionally derived from animals. For example, bacterial growth media have used components such as beef broths, blood (hemin) and/or serum agars, lactoalbumin and casein acid hydrolysates. Such materials may be used in various processes as a nutrient for bacterial growth both at the stage of preparation of seeds and in fermentation and various production steps. Calf serum has been, and for most processes remains an essential component of tissue culture to enhance virus propagation.

There are also less obvious materials of animal origin in use, some of which may be used only at the research level. For example, some enzymes, (alkaline phosphatase is traditionally derived from calf intestine); gelatine, derived from skin and bone; sugars such as lactose derived from milk, and even certain chemicals such as tween, cholesterol and fatty acids may be derived from cattle tallow. Clearly it is essential to know the origin of all the materials that go into our research, development, and industrial processes.

Aventis Pasteur has long been aware of the potential risks involved in the use of materials from animal origin and has taken the necessary measures to minimize any risk.

Range of the materials which may pose a risk

Based on the results of the UK investigations the European Commission has defined 4 levels of risk materials, as follows:

- **Category I / High infectivity**
Brain, spinal cord, (eye)
- **Category II / Medium infectivity**
Ileum, lymph nodes, proximal colon, spleen, tonsil, (dura mater, pineal gland, placenta), cerebrospinal fluid, pituitary, adrenal
- **Category III / Low infectivity**
Distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus
- **Category IV / No detectable activity***
Blood clot, faeces, heart, kidney, mammary gland, milk, ovary, saliva, saliva gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, foetal tissue, (bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine).

(* No infectivity was transmitted in bioassays involving inoculation of up to 5 mg of tissue into rodent brains)

The potential risk of materials used will vary according to the source tissue defined above. In addition, the country from which the materials are sourced and their date of purchase are essential to determine whether there are any potential risks. For the products of ruminant origin Aventis Pasteur has collected the available data on source and date of purchase.

The risks of materials used will also depend on the manufacturing process used in deriving the product. Some materials may be chemically derived from animal extracts using harsh procedures that would destroy any potential BSE infectivity. For example, although cholesterol, traditionally derived from animal sources, could be considered to pose a risk, sodium cholesterol sulphate (SCS), a derivative of cholesterol used in certain pharmaceutical preparations, is much less risky. This is because preparing SCS from cholesterol involves treatment with 10% sodium hydroxide at 180°C, and with chlorosulphonic acid (a powerful and very reactive chlorosulphonating and condensing agent). These treatments would destroy effectively BSE infectivity. Such processes need to be recognised when carrying out risk assessments..

Risk assessment

Risk assessment methods used by the UK Spongiform Encephalopathy Advisory Committee (SEAC) have been published. These assessment methods have been used to determine the possible (theoretical) risks associated with the use of animal materials.. The assessments are made using published figures of levels of infectivity in different tissues, disease incidence and conditions of TSE inactivation.

Aventis Pasteur has made risk assessments for our vaccine products when materials of ruminant origin have been sourced from European countries. In the meeting, an example of this risk assessment method will be presented.

The Aventis Pasteur Approach

Since the recognition of BSE as a new disease, action on minimising any theoretical risk has been underway. The goal of Aventis Pasteur is to remove materials of ruminant origin from the manufacturing steps for our products.

In some cases, animal origin materials can be removed from the manufacturing process without significant changes. For example, Tween from plant origin has and will replace Tween derived from bovine origin.

In other cases, where substantial work is required to demonstrate that the animal origin material can be removed from the process without altering the characteristics of the vaccine, as a precaution, the company has mainly used and will use only materials sourced from non-European countries.

The plans for the different vaccines will be developed in close collaboration with regulatory agencies.