The European Agency for the Evaluation of Medicinal Products
Pre-authorisation evaluation of medicines for human use

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JOINT CPMP/CVMP NOTE FOR GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICINAL PRODUCTS

EXPLANATORY NOTE FOR MEDICINAL PRODUCTS FOR HUMAN USE ON THE SCOPE OF THE GUIDELINE

Background

Commission Directive 1999/82/EC gives force of law to the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (CPMP TSE Guideline).

The European legislation requires that for:

- new applications from 1 July 2000 demonstrate compliance with the CPMP TSE Guideline; and
- marketing authorisation holders (MAHs) of already authorised human medicinal products to have demonstrated compliance by 1 March 2001.

Currently, MAHs may choose to use the certificate of suitability as a means of demonstrating compliance for those starting materials that are covered by the European Pharmacopoeia Monograph *Products with risk of transmitting agents of animal spongiform encpehalopathies*, or apply to the relevant competent regulatory authorities for a variation supported by relevant scientific data.

The purpose of this explanatory note is to define more precisely the scope of the guideline and to address areas that may have presented difficulties in terms of their interpretation and application from a scientific viewpoint.

During the January 2001 CPMP meeting and the February 2001 CVMP meeting, the *Joint CPMP/CVMP Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human or veterinary medicinal products* was adopted. This joint TSE guideline has already come into operation. However, for the time being, this explanatory note only applies to human medicinal products.

a. Scope of the TSE Guideline

The Note for Guidance was first adopted in 1991 by the CPMP to cover materials derived from ruminants such as cattle, sheep and goats for the reasons that such materials are known to naturally contract transmissible spongiform encephalopathy and may potentially infect human beings. The identification of variant form of Creutzfeldt-Jakob Disease (vCJD) in 1995 and the possible association of consumption of infected bovine products and the appearance of vCJD underlines the relevance of control measures laid down in the guideline to the use of ruminant materials especially those derived from bovine sources. The scope of the TSE Guideline should be limited to ruminant derived materials and materials derived from animals which are susceptible to infection with transmissible spongiform encephalopathy through the oral route. For this reason, materials derived from pigs or birds are currently excluded from the scope of this guideline. Materials derived from

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humans and non-human primates are outside the scope of this guideline. The CPMP/BWP will review the scientific data on an on-going basis as to whether or not the scope should be extended to other animal species that may be capable of transmitting TSEs into humans.

b. Does the Note for Guidance cover either ruminant derived materials used in the preparation of established master seed lots or master cell banks?

Master seeds (MSs) or cell banks (MCBs) for application for marketing authorisation lodged after the 1 July 2000, are covered by the guideline. However, MSs and MCBs for already authorised medicinal products such as vaccines, for which the clinical safety and efficacy has been established, are not covered by the guideline. In particular, MSs and MCBs of vaccine antigens, which have already been approved as a constituent of an authorised mono-component or multi-component vaccine, are outside of the scope of the guideline, even if they are incorporated in marketing authorisation applications lodged after 1 July 2000.

However, the origin and nature of the material used to establish the existing MSs and MCBs should be documented and a risk assessment performed. It is recognised that these MSs and MCBs may have been prepared more than 30 or 40 years ago, using ruminant materials either from low or no detectable infectivity as defined in this guideline or from countries where there were no reported cases of BSE. In some cases, the information on the origin of the materials used may not be available given the passage of time. Furthermore, the ruminant material used in establishing MSs and MCBs is present at low level and is subject to a high dilution factor down-stream (e.g. MSs→WSs→processing→finished product). Since this guideline is intended to minimise TSE risk, taking all these factors into consideration, from a public health protection viewpoint, there is no scientific justification to re-establish such master seeds or master cell-banks. It is potentially more risky re-establishing the master seeds or master cell banks because in so doing, it leads to a new product with unknown clinical safety and efficacy against the background of theoretical risk of using such material.

However, ruminant derived materials used in fermentation/routine production and in the establishment of working seeds and working cell banks should be in full compliance with the TSE guideline. In situations where full compliance of working seeds can not be certified, a commitment should be received from the MAH that they will submit a variation to the authorisation to replace such materials with working seeds produced using starting materials fully compliant with the joint CPMP/CVMP Note for guidance as soon as possible and within a specific timescale agreed with the Competent Authority.