The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POSITION PAPER ON THE ASSESSMENT OF THE RISK OF TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS BY MASTER SEED MATERIALS USED IN THE PRODUCTION OF VETERINARY VACCINES

BACKGROUND

Since 1993, manufacturers of immunological veterinary medicinal products (IVMPs) have been required to comply with the 'Note For Guidance For Minimising the Risk of transmitting Animal Spongiform Encephalopathy Agents Via Veterinary Medicinal Products', as adopted and periodically updated by the Committee for Veterinary Medicinal Products (CVMP). Commission Directive 1999/104/EC gave this Note for Guidance the force of Community law. To ensure consistency in terms of the requirements imposed on manufacturers, Member States need to have a harmonised position on TSE risk assessment for starting materials used in the manufacture of IVMPs.

In January 2001, the CPMP and CVMP agreed to harmonise the separate Notes for Guidance into one Note for Guidance for medicinal products for human and veterinary use. The CVMP, having considered that the exclusion of milk and milk derivatives would be inappropriate for veterinary medicinal products administered to ruminants, have added the proviso that, when assessing and minimising the risks associated with veterinary medicinal products intended for use in ruminant species, additional factors of specific relevance only to these species must be considered by the Applicant and relevant Competent Authorities.

This Position Paper therefore makes reference to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products ("the Joint CPMP/CVMP Note for Guidance").

Seed materials used to produce vaccines lodged for registration after the 1st of October 2000 should fully comply with the requirements of the Joint CPMP/CVMP Note for Guidance, in accordance with Directive 1999/104/EC (new seeds). This position paper is therefore restricted to consideration of seed materials used to produce vaccines with marketing authorisations lodged before this date (established seeds).

This paper assumes that compliance with the Joint CPMP/CVMP Note for Guidance eliminates, as far as possible, the risk of introducing TSE infectivity into an IVMP during the process of manufacture through the use of materials of biological origin which are used in routine production (e.g. serum and blood products, tissue or tissue extracts). If this assumption is correct, then the only risk that remains to be addressed is that posed by the seed materials i.e. master and working seeds.

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SCOPE OF THE DOCUMENT

This paper considers the factors that should be addressed when assessing the risk posed by established seed materials so that a systematic and consistent risk assessment can be made. Seed materials (SM) are defined as Master Seeds and Working Seeds for viruses, micro-organisms, parasites and cells. The individual risk factors are identified and the likelihood of their occurrence is discussed in relation to different types of vaccines. Where relevant, the potential consequences of the risk are assessed.

1 - RISK THAT SEED MATERIALS ARE CONTAMINATED WITH TSE INFECTIVITY

LIKELIHOOD OF OCCURRENCE

Contamination of seed material could arise from either the original source of the agent/cell line or from materials used in the production and/or storage of the seed.

The risk of contamination either at source or during production of a seed with TSE infectivity can be assessed by reference to the Joint CPMP/CVMP Note for Guidance in relation to the source of the animal of origin, the nature of the material and the process used to derive or treat the seed or any material used in its production. Particular attention should be paid to the species of origin in relation to both TSE risk at source and in relation to the intended species of use. As much information as possible should be gathered about the nature and source of substances of animal origin used in the isolation, passage and storage of the seed material.

In relation to seed materials, the following factors should be considered in particular:

- The time that the seed was isolated/laid down in relation to the history of BSE in the country of origin of the material concerned. This is particularly relevant for seed materials laid down before the emergence of BSE. The FDA considers 1980 to be the cut-off date after which a risk assessment should be carried out on materials of animal origin sourced from European countries.

- In the case of other TSE's, such as scrapie, the history of the material should be reviewed in relation to the history of the TSE concerned, the origin of the material and the susceptibility of the target species.

- The passage history of the material and whether or not infectivity could have been introduced subsequent to the original isolation/laying down of the seed. This is particularly relevant to Working Seeds which may have been laid down later than Master Seeds at a time when the risk of infectivity in the starting materials used in media production etc. was higher.

- Cell cultures may be used either as the substrate for Master or Working Seed Viruses or as Master or Working Cell Seeds themselves. In either case the risk of contamination will usually be increased if primary cell cultures are used and reference should be made to the Joint CPMP/CVMP Note for Guidance in relation to the source of origin of the cell culture.

- It is likely that for old master seed material some of the required information will not be available either because it was never recorded or because it has been lost. In such cases an assessment shall be made of the potential significance of this missing data in terms of overall risk of TSE infectivity. Factors such as the country in which the material was

handled at the time and the actual or likely sources of any substances of animal origin used should be taken into account, together with any relevant history of TSEs in the countries or species concerned.

CONSEQUENCES

In many cases, the risk of contamination will be judged to be low or extremely low, due to either the time that the seed materials were laid down or due to the species of origin of the materials used to produce them. However, unless full compliance with the Joint CPMP/CVMP Note for Guidance can be certified and justified, then the overall risk of transmission that the seed represents should be assessed taking into account the following factors.

2- RISK THAT TSE INFECTIVITY COULD BE PROPAGATED DURING THE MANUFACTURING PROCESS

Scientific evidence to date indicates that it is difficult to establish, and to maintain, TSE infectivity *in vitro*. In general, high titres of infectious material have been required to initiate the *in-vitro* changes that are correlated with infectivity and specialised cell lines and *in vitro* conditions are required to maintain these presumed correlates of infectivity. There are currently no published reports which demonstrate transmission of disease through the use of "infectious" material generated *in vitro*.

Taking into account the above factors, the risk of *in vitro* propagation of TSE infectivity during vaccine manufacture is likely to be low in the majority of cases. However, TSE infectivity can be passaged by experimental inoculation between species, whether or not the recipient species is susceptible to the particular TSE concerned. A risk assessment taking into account this uncertainty shall therefore be carried out where the production process itself involves inoculation of animals and harvest of material from those animals. In addition, an assessment of risk shall be carried out in those exceptional cases where a particular cell type capable of *in vitro* propagation of TSE infectivity (e.g. a neuronal cell line) is used either as a seed material or to propagate other seed materials. In these cases reference should be made to the Joint CPMP/CVMP Note for Guidance and, in very exceptional cases, it may be necessary to require additional data to assess directly whether or not there is a risk of propagation of TSE infectivity.

3- RISK THAT INFECTIVITY PRESENT IN THE MASTER SEED MATERIAL COULD STILL BE PRESENT IN THE FINAL PRODUCT AND TRANSMIT INFECTION

This risk is relatively straightforward to estimate and will vary according to the method of manufacture. For bacterial vaccines, a dilution estimate can usually be made of how much seed material might be present in the final harvest. For viral vaccines, the amount of original material remaining will depend on the method used for passage (e.g. dilution vs. adsorption followed by washing off of the original material). It should be possible to estimate approximately how much of the original volume of inoculum could remain in the final harvest. This estimation should take into account the effect that any subsequent purification steps might have on the amount of infectivity remaining e.g. washing of bacterial harvests, centrifugation, purification, concentration steps, and dilution of the antigen concentrate for final formulation. For vaccines blended from different bulks, the amount of potential residual infectivity could vary on a batch-by-batch basis.

For the majority of vaccines the dilution factors are likely to be high and the amount of possible infectivity present in the seed material low. This will often result in incalculably small amounts of possible infectivity potentially remaining in the final product. However, until such time as the infectious doses for the various TSEs are established, the risk posed by residual infectivity cannot be completely overlooked. In addition, for vaccines, there is at least a theoretical risk of accumulated infectivity as they are often administered on more than one occasion to the same animal.

The risk of transmission of a TSE due to any residual, contaminated seed material present in the final vaccine will depend principally on the species to which the product is administered and the route of administration. The species of origin of any potential infectivity should be assessed in relation to the recipient species of the vaccine and the consequent presence or absence of 'species barriers' to infectivity. Susceptibility to experimental TSEs varies according to the route of administration of the infectious material. The relative efficiencies of transmission, ranked in decreasing order are; intra-cerebral, intra-venous, intra-peritoneal, subcutaneous/intra-dermal and oral/intragastric. Efficiency by the intramuscular route is thought to be similar to that of the intra-peritoneal route. The risk of transmission is also related to the dose administered but, relative to the other factors involved, this is unlikely to be a major factor in the overall risk assessment.

OVERALL RISK ASSESSMENT

By combining the assessments of the individual factors it should be possible to arrive at an overall risk assessment for the seed materials contained in a vaccine.

PRACTICAL OUTCOMES

This position paper does not address the requirements for seed materials used for the production of vaccines for which authorisations are lodged after 1st October 2000. All materials used in the storage and passage of such seed materials shall fully comply with the requirements of the Joint CPMP/CVMP Note for Guidance. In the case of establishing a new master seed, the Joint CPMP/CVMP Note for Guidance should be followed to minimise the risk of contamination at source. Full attention should be given to factors such as the TSE history of the animal, herd and country of origin, the type of material from which the strain is isolated and any possible measures that can be taken to minimise the risk following

subsequent processing.

For established master seed materials, Marketing Authorisation Holders (MAHs) should demonstrate that they have assessed the risk posed by these materials by reference to this position paper. Conversely, Competent Authorities should refer to this position paper in their assessment as to whether or not these risks are considered acceptable in the overall risk/benefit analysis of the product.

In view of (i) the factors decribed in this Position Paper, (ii) the control measures indicated below that can be put in place to minimise the risks associated with working seeds and (iii) the likely history of the safe use of the product over several years, it is likely that only in exceptional circumstances might the Competent Authority consider the risk represented by the use of a master seed material to be unacceptable. In these exceptional cases, the MAH should discuss with the Competent Authority how this risk might be reduced to an acceptable level, possibly through a combination of manipulation through replacement by an equivalent but compliant master seed or, if no other alternative ultimately exists, by removal of the product from the market.

Use of working seeds should only be accepted by Competent Authorities if full compliance with the Joint CPMP/CVMP Note for Guidance can be certified and justified. In situations where full compliance of working seeds cannot be certified, a commitment should be received from the MAH that they will submit a variation to their 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. Unless new information or events result in a substantially revised risk assessment for the established working seeds, Competent Authorities should generally allow sale of vaccines produced using these seeds up to the end of their shelf life.