The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE FOR MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA VETERINARY MEDICINAL PRODUCTS

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Note:

This Note for Guidance has been revised to reflect the current scientific knowledge regarding TSE and is offered without prejudice to future measures, which Community Institutions might take in this area.

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Interim Report on the
"Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products"

The purpose behind this Note for Guidance is to set out the scientific principles which minimise the risk of transmission of spongiform encephalopathy agents via medicinal products. These principles include a number of control measures such as sourcing and the quality control of starting materials, and the design and control of the manufacturing procedure. All of these measures in combination give assurance on product safety. Particular attention has been placed on the sourcing of material and the categorisation of tissues.

The Guideline has been updated to take account of comments of member states and other interested parties.

The Commission has issued a decision (97/534/EC) on 30 July 1997 which prohibits the use of certain "specified risk materials". The Guideline has also been updated in line with this decision.

NOTE FOR GUIDANCE FOR MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA VETERINARY MEDICINAL PRODUCTS

1. GENERAL REMARKS

Bovine spongiform encephalopathy (BSE) was first recognised in the United Kingdom in 1986. Since then a large number of cattle and individual herds have been affected. This Note for Guidance considers the implication of this and other related diseases for veterinary medicinal products and methods of minimising the risk of transmission when material of bovine origin are used in the manufacture of such products.

The transmissible spongiform encephalopathies (TSE) include scrapie in sheep and goats, chronic wasting disease in mule deer and elk, bovine spongiform encephalopathy (BSE) in cattle, as well as Kuru and Creutzfeldt-Jakob Disease (CJD) in humans. Agents causing these diseases replicate in infected individuals generally without evidence of infection detectable by available diagnostic tests applicable *in vivo*. After incubation periods of up to several years the agents cause disease and, finally, lead to death. No means of therapy are known.

Diagnosis is based on clinical signs with *post mortem* confirmation of characteristic brain lesions by histopathology or detection of the fibrillary proteins specific for the spongiform encephalopathies. The demonstration of infectivity by the inoculation of suspect tissue into target species or laboratory animals may also be used for confirmation but may have an incubation period of months or years.

Iatrogenic transmission of spongiform encephalopathies has been reported. In sheep, scrapie has been accidentally transmitted by the use of Louping Ill vaccine prepared from pooled, formaldehyde treated ovine brain and spleen in which material from scrapie infected sheep had been inadvertently incorporated. In man, cases of transmission of CJD have been reported which have been attributed to the repeated parenteral administration of growth hormone and gonadotropin derived from human cadaveric pituitary glands. Cases of CJD have also been attributed to the use of contaminated instruments in brain surgery and with the transplantation of human meninges and cornea.

Information on the characteristics of these agents is limited. They are extremely resistant to most of the chemical and physical procedures that inactivate conventional viruses. They do not induce a detectable immune response. There are natural barriers which limit the interspecies spread of infection, but they can be crossed under appropriate circumstances. This is usually dependent upon strain, dose, route of exposure and the size of the species barrier. Studies on laboratory animals have shown that intracerebral inoculation is the most efficient route.

Humans have been naturally exposed to the scrapie agent of sheep for at least 200 years, but despite extensive epidemiological studies no sign of transmission of scrapie to humans has been detected. Although BSE was first recognised in the United Kingdom in 1986, other countries have had some cases of BSE reported, either in animals imported from UK or in indigenous animals. It is clear that BSE is a food-borne infection. Insofar as the biological properties of the BSE agent differ from those of scrapie, it is conceivable that also the species barriers may be different and transmission to man may be possible. There is convincing evidence to show that the new varient of CJD is caused by the agent that is responsible for BSE in cattle.

The appearance of a new variant form of human CJD has raised further concerns that the BSE agent can be transmitted to man. Therefore, due prudence continues to be warranted if biological materials from species affected by those diseases other than by experimental challenge, especially bovine species, are used for the manufacture of human and veterinary medicinal products.

Therefore the recommendations below should be followed to minimise the risk of contamination.

Notwithstanding this guidance note it should be highlighted that the potential risks associated with a given medicinal product will have to be considered individually in the light of specific circumstances and current knowledge.

2. SCOPE OF THE NOTE FOR GUIDANCE

This Note for Guidance considers the implications of TSE for all veterinary medicinal products and includes measures for minimising the risk of transmission by the use of materials of animal origin and particularly those of ruminant origin, when used for the preparation of:

- active substances
- excipients
- raw materials and reagents used in production (e.g. bovine serum albumin and enzymes culture media including those to prepare cell banks)

The Note also covers the use of such materials in procedures which are indirectly associated with the manufacturing process and which could potentially contaminate the product, for example, in test media used in the validation of plant and equipment.

Although this note for guidance relates particularly to BSE and bovine material, similar considerations are also applicable to material from sheep, goats and other species known to be susceptible to TSEs, other than by experimental challenge. Great care must therefore be taken when choosing the source of such substances for use in manufacture of veterinary medicinal products. As with all considerations of the risk of extraneous agents, this is particularly the case when the source species and target species for the product are the same.

This note for guidance should be read in conjunction with the various Commission Decisions progressively implemented since 1991. Where appropriate, references to these decisions are given in the text.

3. MANUFACTURE (INCLUDING COLLECTION OF SOURCE MATERIALS)

In addition to complying with the provisions of the Commission Decision (97/534/EC)[1],. marketing authorisation holders should avoid the use of ruminant material wherever possible. Where this is not possible, their use should be justified. Where manufacturers have a choice to use ruminant or non-ruminant material, the use of non-ruminant material is preferred. Substitution of ruminant source materials by material from other species which are recognised to suffer from TSEs, or which can be infected experimentally by the oral route, would not normally be acceptable.

Available epidemiological and laboratory data on natural spongiform encephalopathies and the absence of species barriers indicate that, in the case of veterinary medicinal products, the risk may be greatest when bovine or ovine materials are used in products intended for either bovine or ovine animals.

In the Marketing Authorisation application the applicant should give details of the source of the material and the other measures taken to minimise the transmission of TSE agents (including the geographical origin of the animal).

In conformity with GMP guidelines the pharmaceutical manufacturer should audit the supplier of these materials to ensure that they are sourced and handled in conformity with this **N**ote for Guidance and appropriate quality control systems.

[1] Commission Decision 97/534/EC, OJ L No 216, page 95, 8 August 1997

The risk of transmission of infectious agents can be greatly reduced, by controlling a number of parameters. These parameters include,

- source of animals
- nature of animal tissue used in manufacture
- production process(es)

No single approach will necessarily establish the safety of a product and therefore the three approaches cited above should be used complementary to each other for minimizing the risk of contamination.

3.1 Animals as source of material

Careful selection of source materials is the most important criterion for the safety of medicinal products.

3.1.1 The most satisfactory source of materials is from countries which have not reported cases of BSE following the criteria taken from the current OIE document[2] and have:

- a compulsory notification, and
- compulsory clinical and laboratory verification of suspected cases.

Official certification should be presented. In addition, it should be ensured that a risk of BSE infection is not introduced from the following factors:

- importation of cattle from countries where a high incidence of BSE or scrapie in sheep has occurred.
- importation of progeny of affected females.
- the use in ruminant feed of Meat and Bone Meal containing any ruminant protein which originates from countries with a high or low incidence of BSE and/or scrapie, or of unknown status [(3)]

3.1.2 Materials may also be sourced from countries where a low number of indigenous cases have occurred, if in addition to the factors in paragraph 3.1.1:

- carcasses of all infected animals are destroyed
- the progeny of affected females are not used
- the feeding to ruminants of mammalian derived protein (Commission Decision 94/381/EC as amended) is banned
- Source animals should be born after the feeding ban was imposed. If the date of birth of the animals is not known, safety of the sourcing should consider both the implementation date of the ban and the incubation period of TSE.
- herds with reported cases of BSE are not used for sourcing

3.1.3 Source materials should not be used from countries where there is a high incidence of BSE[4] or scrapie.

Along with these measures the marketing authorisation applicants should justify their strategy for sourcing, in relation to the category of materials, the quantity of raw material and the intended use of the finished medicinal product in animals. In supplying countries, source of bovine materials from well monitored herds may provide an extra safety margin (see Annex).

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[2] Organisation Internationale Epizooties (OIE) International Annual Health Code Chapter on BSE adopted on 26-30 May 1997 at the 65th general session OIE Paris. Revised versions of this document are published regularly and can be obtained from OIE, 12 Rue de Prony, 75017 Paris, France, fax no +33 .1.42.67.09.87

[3] Quoted as risk factor in the abovementioned OIE document (Point 4 a) and Article 3.3.13.11)

[4] Commission Decision 96/239/EC of 27th March 1996 on emergency measures to protect against BSE

3.2 Parts of animal bodies, body fluids and secretions as starting materials

Commission Decision 97/534/EC prohibits the use of "specified risk material" for any purpose. "Specified Risk Material" is defined in the Decision as:

(a) the skull, including the brain and eyes, tonsils and spinal cord of:

- bovine animals aged over 12 months
- ovine and caprine animals which are aged over 12 months or have a permanent incisor tooth erupted through the gum;

(b) The spleens of ovine and caprine animals

In a TSE infected animal, different organs and secretions have different levels of infectivity. On the basis of data on natural scrapie, organs, tissues and fluids have been classified into four main groups bearing different potential risks, as shown in the table 1. Although it is now known that the distribution of infectivity in BSE affected cattle appears to be much more restricted, the classification of tissues and body fluids in table 1 should continue to be considered for the selection of source materials.

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 infectivity [5]	blood clot, faeces, heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, foetal tissue, (bile, bone[6], cartilaginous tissue, connective tissue, hair, skin, urine)

Table 1: Relative scrapie infectivity titres in tissues and body fluids from naturally infected sheep and goats with clinical scrapie[7]

The categories listed in table 1 are only indicative and it is important to note the following points.

- the classification of tissues shown in the table is based on titration of infectivity in mice by the intracerebral route. In experimental models using strains adapted to laboratory animals, higher titers and a slightly different classification of tissues may occur.

[5] No infectivity was transmitted in bioassays involving inoculation of up to 5 mg of tissue into rodent brains.
[6] Especially for skull and vertebrae see point 3.2, page 7, second bullet relating to cross contamination.
[7] Tissues in brackets were not titrated in the original studies, but their relative infectivity is indicated by other data on spongiform encephalopathies. Materials not listed may be classified by analogy to those mentioned on the basis of their composition.

- In certain situations there could be cross-contamination of tissues of different categories of infectivity. The potential risk will be influenced by the circumstances in which tissues were removed, especially by contact of material of a low-risk group with that of a high-risk group. Thus, the contamination of some tissues may be increased if infected animals are slaughtered by penetrative brain stunning or if the brain and/or spinal cord is sawed; The risk of cross contamination will be decreased if body fluids are collected with minimal damage to tissue and cellular components when removed and if fetal blood is collected without contamination from other maternal or fetal tissues including placenta, amniotic and allantoic fluids.

- The risk of cross-contamination will be dependent on several complementary factors including:

  - precautions adopted to avoid contamination during collection of tissues,
  - the level of contamination (amount of the contaminating tissue),
  - amount of material to be used,
  - process to which the material will be subject during the manufacturing process,

  Manufacturers should present an assessment of the risk.

3.3 Process validation

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Controlled sourcing is the most important criterion in achieving acceptable safety of the product due to the documented resistance of TSE agents to most inactivation procedures.

Validation studies of removal/inactivation procedures are difficult to interpret as it needs to take into consideration the nature of the spiked material and its relevance to the natural situation, the design of the study (including scaling-down of processes) and the method of detection of the agent (*in vitro* or *in vivo* assay), after spiking and after the treatment. Further research is needed to develop an understanding of the most appropriate methodology for validation studies. Therefore, validation studies are currently not generally required. However, if claims are made for the ability of manufacturing processes to remove or inactivate TSE agents, these will have to be substantiated by appropriate validation studies. Validation studies are process specific.

Beyond the particular limitations which apply to TSE validation studies and their interpretation, the major hurdle is identifying steps which will effectively remove or inactivate TSE agents during the manufacture of biological medicinal products. Manufacturers are encouraged to continue their investigations into removal and inactivation methods to identify steps/processes which would have benefit in assuring the removal or inactivation of TSE agents.

In any event, a production process wherever possible should be designed taking note of available information on methods which are thought to inactivate or remove TSE agents.

Certain production procedures may contribute considerably to the reduction of the risk of TSE contamination, e.g. procedures used in the manufacture of tallow and its derivatives (see below).

3.4 Age of animals

As the accumulation of TSE infectivity occurs over an incubation period of several years, sourcing from young animals may be prudent.

3.5 Specific Products

- Milk and its derivatives are unlikely to present any risk of contamination.

- Certain materials and their derivatives such as hair and wool used to make wool alcohols and lanolin are unlikely to present any risk of contamination given assurances of adequate collection and processing.

- Tallow derivatives, such as glycerol and fatty acids which are manufactured from tallow by rigorous processes have been the subject of specific consideration and are thought unlikely to be infectious. Examples of rigorous processes are:

  - Transesterisation of hydrolysis at not less than 200ºC for not less than 20 minutes under pressure (glycerol, fatty acids and fatty acid esters production)
  - Saponification with NaOH 12 M (glycerol and soap production)
  - Batch process: at not less than 95ºC for not less than 3 hours;
  - Continuous process: at not less than 140ºC, 2 bars for not less than 8 minutes, or equivalent.

- For gelatin manufacture, risk from central nervous tissue attached to skulls or vertebrae can be reduced by excluding these bones from the source material. Furthermore, the following parameters will contribute to the safety of this product:
  - For gelatin produced from bovine bones[8], all of the following parameters will contribute to the safety of this product:
    - The geographical origin of the source animals.
    - Skulls and spinal cords should be removed from the starting material[9].
    - It is also recommended that vertebrae be excluded, especially depending on the geographical origin.
    - The current preferred manufacturing method is the 'alkaline process'.

Manufacturers should present an assessment of the risk.

- Systems such as ISO 9000 certification and HACCP should be in place for monitoring of the production process and for batch delineation (i.e. definition of batch, separation of batches, cleaning between batches...).
- Procedures should be in place to ensure traceability and to audit suppliers of starting materials.
- For bovine hide gelatin:
  - Cross contamination with possible infectious material should be avoided.

4. CONCLUDING REMARKS

The assessment of the risk associated with BSE needs careful consideration of all of the parameters cited and the preferred option should be to avoid the use of material derived from animals known to be susceptible other than by experimental challenge to TSEs in products produced by the pharmaceutical industry.

The acceptability of a particular medicinal product containing these materials or which as a result of manufacture could contain these materials will be influenced by a number of factors, including:

- documented and recorded source of animals;
- nature of animal tissue used in manufacture;
- production process(es);
- route of administration;
- quantity of tissue used in the medicinal products;
- maximum therapeutic dosage (daily dosage and duration of treatment);
- intended use of the product.

[8] The future geographical distribution of BSE/TSEs cannot be predicted. Therefore, certain types of bovine bones should be removed from the starting materials of bovine bone derived gelatin whatever the geographical origin of the bones.

[9] Starting material is considered as bones before degreasing.

Pharmaceutical manufacturers and producers of medicinal products of animal origin are responsible for the selection and justification of adequate measures. The state of science and technology must be taken into consideration.

Notwithstanding this guidance note it should be highlighted that the potential risks associated with a given medicinal product will have to be considered individually in the light of specific circumstances and current knowledge.

These guidelines should also be used in the evaluation of individual products based on a Risk/Benefit judgement.

ANNEX

" Draft-requirements for sourcing from well monitored herds of materials intended to be used for the manufacture of veterinary medicinal products"

The scientific principle behind the concept of well-monitored herds is an interesting one, the implementation and policing requires further consideration.

Well-monitored herds are defined as**:**

- having had no cases of BSE.
- having never been fed mammalian derived protein (Commission Decision 94/381/EC as amended).
- having a fully documented breeding history.
- having had introduced new genetic material only from herds with the same BSE-free status.

The additional safeguards provided by well-monitored herds would depend on:

- establishment and supervision system put in place by both the applicant and the Control Authorities of the concerned Country(ies**)** of well-monitored herds.
- feasibility and performance of proper inspections and controls which are dependent upon the size of the herd and amount of material to be collected.
- accuracy of the relevant certificates.