Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

(EMEA/410/01 Rev. 1 — May 2001)

adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal Products (CVMP)

July 2001

(2001/C 286/04)

NB: 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.

This joint CPMP-CVMP note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products replaces the following guidelines:

— CPMP note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products, revision September 2000 (CPMP/BWP/1230/98/Rev. 1),

— CVMP note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products, revision June 1999 (EMEA/CVMP/143/97 Revision).

Background note

The purpose behind this joint CPMP/CVMP note for guidance is to set out the scientific principles which minimise the possible risk of transmission of spongiform encephalopathy via human and veterinary 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 note for guidance has been updated to take account of comments of Member States and other interested parties.

The note for guidance should be understood and applied together with the EU legislation regarding TSE (1).

(1) Commission Decision 2000/418/EC defines specified risk materials; but medicinal products, their starting materials and intermediate products are excluded from this legislation.

However, subject to legal constraints, specified risk materials, as defined in Decision 2000/418/EC or in any future updates, should not normally be used in the manufacture of medicinal products, their starting materials and intermediate products (including active substances, excipients and reagents), unless justified.

In exceptional and justified circumstances, the use of specified risk materials could be envisaged for the manufacture of active substances, when, after performing the risk assessment (as described in the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products) and taking into account the intended clinical use, a positive benefit/risk can be presented by the marketing authorisation applicant.

1. GENERAL REMARKS

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 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 fibrillar 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 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. Bovine spongiform encephalopathy (BSE) was first recognised in the United Kingdom in 1986. A large number of cattle and individual herds have been affected. It is clear that BSE is a food-borne infection. Other countries have had some cases of BSE, either in animals imported from UK or in indigenous animals. In so far as the biological properties of the BSE agent differ from those of scrapie, it is conceivable that also the species barriers may be different. There is convincing evidence to show that the new variant 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 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 human and veterinary medicinal products and measures for minimising the risk of transmission by their use. Therefore, it applies to materials of animal origin and particularly if they are of ruminant origin, which are used for the preparation of:

— active substances,
— excipients,
— raw or source materials and reagents used in production (e.g. bovine serum albumin, enzymes, culture media including those to prepare working cell banks or new master cell banks).

This note for guidance is also applicable to materials which come into direct contact with the equipment used in manufacture (and therefore have the potential to allow contamination), for example, in test media used in the validation of plant and equipment.

This note for guidance relates to material of all ruminants. The proposed measures are especially applicable for bovine material and may need to be adapted for measures regarding material from sheep, goats and other species known to be susceptible to TSEs, other than by experimental challenge.

In the light of the current scientific knowledge and irrespective of the geographical origin, milk is unlikely to present any risk of TSE contamination (1). Therefore, milk and materials derived only from milk are excluded from the scope of the guideline provided milk is sourced from healthy animals in the same conditions as milk collected for human consumption. Derivatives of milk from ruminants prepared with the use of other ruminant materials (e.g. pancreatic enzyme digests of casein), are not excluded from the scope of the guideline because of the use of these other ruminant materials.

Derivatives of wool and hair of ruminants, such as lanolin, wool alcohols and amino acids are also excluded from the scope of the guideline, provided the wool and hair are sourced from live animals. Derivatives of wool and hair from ruminants prepared with the use of other ruminant materials (such as pancreatic enzymes) are not excluded from the scope of the guideline because of the use of these other ruminant materials.

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)

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.

In the marketing authorisation application the applicant should give details of the source of the material (including the geographical origin of the animal) and the other measures taken to minimise the risk of transmission of TSE agents. The pharmaceutical manufacturer should audit the supplier of these materials to ensure that they are sourced and handled in conformity with this note for guidance and appropriate quality control systems.

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,

(1) 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. These factors are detailed in related position paper (EMEA/ CVMP/121/01).
No single approach will necessarily establish the safety of a product and therefore the three approaches cited above may need to be complementary to each other for minimising 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 (1) and have:

— a compulsory notification, and

— compulsory clinical and laboratory verification of suspected cases.

Official certification should be available. 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 high incidence of BSE has occurred,

— importation of progeny of affected females,

— the use in ruminant feed of meat and bonemeal containing any ruminant protein which originates from countries with a high or low incidence of BSE, or of unknown status (2).

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 protein (4) is banned.

3.1.3. Source materials should not be used from countries where there is a high incidence of BSE (5).

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

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

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 below. Although it is now known that the distribution of infectivity in BSE affected cattle appears to be more restricted, the classification of tissues and body fluids in the table should continue to be considered for the selection of source materials. The categories in the table 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 titres and a slightly different classification of tissues may occur.

— 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 cross-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 are removed, and if foetal blood is collected without contamination from other maternal or foetal tissues including placenta, amniotic and allantoic fluids.

(1) Both the Office international des Epizooties (OIE) and the Scientific Steering Committee (SSC) of the European Commission are in the process of developing criteria for classification of countries or zones according to their BSE status. The most recent version of the OIE 'International annual health code chapter on BSE' can be found on the OIE website: http://www.oie.int. Opinions of the SSC are available on the Commission website: http://europa.eu.int/comm/food/fs/bse/index_en.html. If necessary, this guideline will be updated when the OIE/SSC classification has been finalised.

(2) Protein as referred to in Commission Decision 94/381/EC as amended.

(3) Council Decision 98/256/EC of 16 March 1998 concerning emergency measures to protect against BSE.
— The risk posed by cross-contamination will be dependent on several complementary factors including:

— precautions adopted to avoid contamination during collection of tissues (see above),

— 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.

Relative scrapie infectivity titres in tissues and body fluids from naturally infected sheep and goats with clinical scrapie

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>High infectivity</th>
<th>Medium infectivity</th>
<th>Low infectivity</th>
<th>No detectable infectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>brain, spinal cord, (eye)</td>
<td>ileum, lymph nodes, proximal colon, spleen, tonsil, (dura mater, pineal gland, placenta), cerebrospinal fluid, pituitary, adrenal</td>
<td>distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus</td>
<td>blood clot, faeces. heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, foetal tissue, (bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine)</td>
</tr>
</tbody>
</table>

(1) 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.

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

(3) For skull and vertebrae see, also, point 3(2), second indent, relating to cross contamination.

3.3. Process validation

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

**Tallow** used as the starting material for the manufacture of tallow derivatives should be produced by a method at least as robust and rigorous as those referred to in Commission Decision 92/562/EC. 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:

— transesterification or hydrolysis at not less than 200 °C 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 95 °C for not less than three hours,

  — continuous process: at not less than 140 °C, under pressure for not less than eight minutes, or equivalent.
Gelatin

— For gelatin produced from bovine bones (\(^6\)), 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 (\(^7\)),

— it is also recommended that vertebrae be excluded, especially depending on the geographical origin,

— the current preferred manufacturing method is the ‘alkaline process’,

— 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 etc.),

— 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.

Manufacturers should present an assessment of the risk.

4. CONCLUDING REMARKS

The assessment of the risk associated with TSE 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 the products produced by 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.

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 judgment.

\(^6\) Starting material is considered as bones before degreasing.

\(^7\) The future geographical distribution of BSE/TSEs can not be predicted. Any change in the geographical distribution of BSE/TSEs could result, in the worst case scenario, in a recall of pharmaceuticals containing gelatin. Due to the large number of medicinal products containing gelatin as an excipient and the ‘long life’ of gelatin from its production up to the end of the shelf life of the pharmaceuticals, any recall could have dramatic consequences in terms of supply for essential medicinal products. Therefore, skull and spinal cord should be removed from the starting materials of bovine bone-derived gelatin whatever the geographical origin of the source animals.
ANNEX

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

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

The criteria for well-monitored herds include:

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

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.

The above criteria are cumulative.