MINIMISING THE RISK OF TRANSMITTING AGENTS CAUSING SPONGIFORM ENCEPHALOPATHY VIA MEDICINAL PRODUCTS

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MINIMISING THE RISK OF TRANSMITTING AGENTS CAUSING SPONGIFORM ENCEPHALOPATHY VIA 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 the disease for medicinal products and methods for minimising the risk of transmission by their use.

The naturally occurring spongiform encephalopathies include scrapie (in sheep and goats), chronic wasting disease (in mule deer and elk), bovine spongiform encephalopathy (BSE; in cattle) as well as Creutzfeldt-Jakob Disease (CJD) and Kuru (in humans). Agents causing these diseases replicate in infected individuals without being detectable by diagnostic tests applicable to the living organism. After incubation periods of up to several years the agents cause disease and, finally, lead to a fatal outcome. No means of therapy are known.

Diagnosis is based on clinical signs with post mortem confirmation of characteristic brain lesions by histopathology or immunological 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 with an incubation period of months or years. Iatrogenic transmission of spongiform encephalopathies has been reported. In sheep scrapie has been accidentally transmitted via the application of Louping III vaccine prepared from pooled, formaldehyde treated ovine brain and spleen in which material from scrapie infected sheep had been inadvertently incorporated. In humans 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.

There is no evidence that spongiform encephalopathies have been transmitted from animals to humans. However, the possibility of such transmissions, although remote, cannot be dismissed. Therefore due prudence is warranted if biological materials are used for the manufacture of medicinal products from species affected via non-experimental routes by those diseases, primarily ruminants and among these especially cattle, sheep and goats.

Information on the characteristics of the agents is limited. They are extremely resistant to 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 usually involving efficient routes of administration and high doses of agent. Studies on laboratory animals have shown that intracerebral inoculation is much more efficient than any other route and is followed in decreasing order of efficiency, by intravenous, intraperitoneal and subcutaneous administration. The oral route is less efficient than the parenteral routes. In some cases species barriers can be crossed only after passage of the agent through intermediary species.
Human beings must have been naturally exposed to the scrapie agent for at least 200 years, but despite extensive epidemiological studies no sign of transmission of scrapie to humans has been detected. Insofar as BSE is different from scrapie, it is conceivable that also the species barriers may be different. Therefore the recommendations below should be followed.

The acceptability of a particular medicinal product containing or derived from bovine materials will be influenced by a number of factors including the selection and processing of source materials, the age and geographical origin of the individual source animal, the intended use of the product, its stipulated dose and route of administration, production process and quality control. The state of science and technology must be taken into consideration. All products will be considered on a case by case basis.

2. SCOPE OF THE NOTE FOR GUIDANCE

This note for guidance covers all medicinal products which contain active substances and/or excipients derived from bovines, as well as medicinal products for which the production process involves bovine materials.

The note also covers the use of such materials in procedures which are indirectly associated with the manufacturing process, for example, in test media used in the validation of plant and equipment to avoid cross-contamination.

3. MANUFACTURE (INCLUDING COLLECTION OF SOURCE MATERIALS)

The safety of medicinal products can be further secured, and the risk of transmission of infectious agents greatly reduced by combinations of the measures specified in this note for guidance or other appropriate measures. The pharmaceutical manufacturers and the producers of medicinal products of animal origin are responsible for the selection of adequate measures.

3.1 Animals as source of materials

Careful selection of source materials is the most important criterion for the safety of medicinal products. The use of source materials from countries where there is a high incidence of BSE is to be avoided.

The following criteria should be taken into account when sourcing materials.

3.1.1 Materials may be sourced from countries which have not reported cases of BSE, if they have an effective veterinary service capable of detecting a low incidence of disease and if BSE is reportable. Official certification should be presented.

In addition, it should be ensured that there is no risk of BSE infection from the following factors:

a) the feeding to ruminants of ruminant protein derived from the specified offal (brain, spinal cord, spleen, thymus, tonsil and intestine from duodenum to rectum, placenta), either produced in the country or imported from other countries;

b) the processes used in the rendering industry;
c) scrapie-associated factors:
   - the incidence and prevalence of scrapie;
   - the ratio of sheep and goats to cattle;
   - the relative geographical distribution of sheep and goats to cattle, where this
     might have led to the use of sheep material in cattle feed in the past;

d) importation of cattle above the age of 6 months from countries where a high incidence
   of BSE has occurred and/or importation of progeny of affected females.

3.1.2 Materials may also be sourced from countries where a low number of cases have
occurred, if in addition to the factors in paragraph 3.1.1:
   - BSE has been made legally notifiable;
   - the carcasses of all affected animals are destroyed;
   - the progeny of affected females are not used.

3.1.3 Satisfactory source materials may be obtained from established and monitored herds,
where their feeding and breeding history is documented. This is possible even in countries
with a high incidence of BSE.

3.2 Age of animals

Natural scrapie or BSE has not been detected in animals under the age of 6 months.
Therefore, cattle yielding source materials should not be older than 6 months unless
otherwise justified.

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

In the infected animal different organs and secretions contain different maximum
concentrations of infectivity. On the basis of experimental data on transmissible spongiform
encephalopathies, organs, tissues and fluids can be classified into four main groups bearing
different potential risks, as shown in the table below. These potential risks, amongst other
criteria, should be considered for the selection of source materials.

Although being based on studies of natural scrapie, the classification can be applied to the
related diseases in mule deer (CWD) and cattle (BSE), which have similar incubation
periods. However, 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 (1-3). In experimental models using agent strains
     adapted to laboratory animals, higher titres and a slightly different classification of
     tissues may occur (4-5). For experimental intraspecies transmission, titres of up to 10^{10}
     have been reported (4-5). Therefore, the risks could be higher when medicinal products
     are manufactured from, and used in, the same species;
   - the potential risks 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;

- dura mater, hypophysis and pineal gland from animals older than six months should be regarded as belonging to group 2 only if contamination with brain tissue can be avoided;

- body fluids should be collected with minimal damage to tissue, and cellular components should be removed; e.g. foetal blood should be collected without contamination from placenta and amniotic fluids.

The information currently available suggests that, given assurances of adequate collection and processing, certain materials and their derivatives are unlikely to present any risk of contamination. These include: milk and its derivatives, for example, lactose and casein; skin and its derivatives, for example, gelatine; hair and wool and their derivatives, for example, wool alcohols and lanolin.

In addition, materials derived from rendered carcasses and subjected to rigorous processes of extraction and purification (for example, triglycerides, glycerol, sorbitan esters, etc. manufactured from tallow) may be considered unlikely to be contaminated.
RELATIVE SCRAPIE INFECTIVITY TITRES IN TISSUES AND BODY FLUIDS FROM NATURALLY INFECTED SHEEP AND GOATS WITH CLINICAL SCRAPIE

CATEGORY I
High infectivity  
brain, spinal cord, (eye)

CATEGORY II
Medium infectivity  
ilium, lymph nodes, proximal colon, spleen, tonsil, (dura mater, pineal gland, placenta), cerebrospinal fluid, pituitary, adrenal

CATEGORY III
Low infectivity  
distal colon, nasal mucosa, sciatic nerve, bone marrow, liver, lung, pancreas, thymus

CATEGORY IV
No detectable infectivity **  
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)

3.4 Cellular substrates
Cell lines known to be capable of concentrating or amplifying agents causing spongiform encephalopathies must not be used in the manufacture of medicinal products, except for reasoned exceptional cases.

4. PROCEDURES WHICH REMOVE OR INACTIVATE AGENTS CAUSING SPONGIFORM ENCEPHALOPATHIES
Removal and inactivation procedures contribute to the reduction of the risk of infection. Their effectiveness in removing infectivity during a given production process must be tested and validated using appropriate model systems (presently: animal infection experiments).

* Tissues in brackets were not titrated in the original studies1-3, 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.

** No infectivity was transmitted in bioassays involving inoculation of up to 5 mg tissue into rodent trains.
Whereas none of the following procedures may guarantee complete inactivation of the infectious agents, the efficiency of the first three methods on this list is considered greatly superior to that of the remaining ones:

- autoclaving at appropriate conditions (recommended parameters are 134-138°C for 18 minutes for porous-load autoclaving, and 132°C for one hour for gravity-displacement autoclaving;
- treatment with sodium hydroxide (preferably: 1 N solution, for 1 h at 20°C);
- treatment with sodium hypochlorite (preferably: solution containing at least 2% available chlorine, for 1 h at 20°C);
- autoclaving at shorter times and/or lower temperatures than those given above;
- extraction by organic solvents (use the organic phase);
- removal of protein by precipitation, ultracentrifugation or absorption;
- preparation of filtrates by passage through 10-nm-filters;
- passage through appropriate chromatographic columns (before reusing treat columns for 4 h with at least 0.1 N sodium hydroxide);
- treatment with 6M urea (6).

5. CONCLUDING REMARK

Although this note for guidance relates particularly to BSE and materials of bovine origin, similar considerations are also applicable to material from sheep, goats and other species affected via non-experimental routes by agents causing spongiform encephalopathies. Finally, while this note for guidance has general applicability, it may not be necessary to fulfil all of the listed measures for all products. The potential risks associated with a given medicinal product will have to be considered individually in the light of specific circumstances and current knowledge.