Legal aspects — This note for guidance has been given the force of law by virtue of Annex I to European Parliament and Council Directives 2001/82/EC and 2001/83/EC (as amended by Commission Directive 2003/63/EC [1]) governing the veterinary and human medicinal products, respectively. These directives require that applicants for marketing authorisation for human and veterinary medicinal products must demonstrate that medicinal products are manufactured in accordance with the latest version of this note for guidance published in the *Official Journal of the European Union*. This is a continuing obligation after the marketing authorisation has been granted.

By definition, the principle of specified risk materials as defined in Regulation (EC) No 999/2001 of the European Parliament and of the Council [2] does not apply to medicinal products. The use of substances derived from high infectivity tissues must be fully justified following an appropriate benefit/risk evaluation (see further below).

This note for guidance should be read in conjunction with the various European Community legal instruments including Commission decisions progressively implemented since 1991. Where appropriate, references to these decisions are given in the text. Position statements and explanatory notes made by the Committee for Proprietary Medicinal Products (CPMP) and Committee for Veterinary Medicinal Products (CVMP) are still applicable for the purpose of regulatory compliance unless otherwise superseded by this note for guidance.

A general monograph entitled: 'Products with risk of transmitting agents of animal spongiform encephalopathies' is included in the European Pharmacopoeia. This monograph refers to a general chapter of the European Pharmacopoeia, which is identical to this note for guidance. The monograph forms the basis for issuing certificates of suitability as a procedure for demonstrating TSE compliance for substances and materials used in the manufacture of human and veterinary medicinal products.

Clarification of note for guidance — As the scientific understanding of TSEs, especially the pathogenesis of the diseases, is evolving, from time to time CPMP and its Biotechnology Working Party in collaboration with CVMP and its Immunologicals Working Party may be required in the future to develop supplementary guidance in the form of position statements or explanatory notes for the purpose of clarifying this note for guidance. The supplementary guidance shall be published by the Commission and on the website of the European Agency for the Evaluation of Medicinal Products (EMEA) and taken into consideration accordingly in the scope of the certification of the European Directorate for the Quality of Medicines (EDQM).

Implementation of this revised note for guidance — All authorised medicinal products in the EU have demonstrated compliance with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 — Rev. 1) in line with the legal requirement as inscribed in Annex I to Directives 2001/82/EC (veterinary medicines) or Directive 2001/83/EC as amended by Directive 2003/63/EC (medicines for human use). This revised note for guidance is to be applied prospectively, i.e. for all medicinal products that will be authorised or whose marketing authorisation will be renewed after the time of coming into operation of this revised note for guidance.

2. SCOPE OF THE NOTE FOR GUIDANCE

TSE-relevant animal species — Cattle, sheep, goats and animals that are naturally susceptible to infection with transmissible spongiform encephalopathy agents or susceptible to infection through the oral route other than humans [3] and non-human primates are defined as 'TSE-relevant animal species' [4].

Materials — This note for guidance is concerned with materials derived from 'TSE-relevant animal species' that are used for the preparation of:

— active substances,

— excipients and adjuvants,

— raw and starting materials and reagents used in production (e.g. bovine serum albumin; enzymes; culture media including those used to prepare working cell banks, or new master cell banks for medicinal products which are subject to a new Marketing Authorisation).

This note for guidance is also applicable to materials that come into direct contact with the equipment used in manufacture of the medicinal product or that come in contact with the medicinal product and therefore have the potential for contamination.

Materials used in the qualification of plant and equipment, such as culture media used in media fill experiments to validate the aseptic filling process, shall be considered in compliance with this note for guidance provided that the constituent or constituents are derived from tissues with no detectable infectivity (category C tissues), where the risk of cross-contamination with potentially infective tissues has been considered (see section 3.3) and where the materials are sourced from a GBR I/II country (see section 3.2). Such information shall be provided in the dossier for a marketing authorisation and verified during routine inspection for compliance with good manufacturing practice (GMP).

[1] OJ L 159, 27.6.2003, p. 46.

[2] OJ L 147, 31.5.2001, p. 1.

[3] Regulatory guidance and position papers have been issued by the Committee for Proprietary Medicinal Products and its Biotechnology Working Party on human tissue derived medicinal products in relation with CJD and vCJD. Such guidance can be found on http://www.emea.eu.int

[4] Pigs and birds, which are animal species of particular interest for the production of medicinal products, are not naturally susceptible to infection via the oral route. Therefore they are not TSE-relevant animal species within the meaning of this note for guidance. Also dogs, rabbits and fish are non TSE-relevant animal species within the meaning of this note for guidance.

Other materials such as cleaning agents, softeners and lubricants that come into contact with the medicinal product during its routine manufacture or in the finishing stage or in the primary packaging are considered in compliance with this note for guidance if they are derived from tallow under the conditions described in section 6.

Seed lots, cell banks and routine fermentation/production [5] — For the purpose of regulatory compliance, master seeds or master cell banks in marketing authorisation applications lodged after 1 July 2000 (for human medicinal products) or 1 October 2000 (for veterinary medicinal products) are covered by this note for guidance.

Master seeds and master cell banks,

(a) for vaccine antigens;

(b) for a biotechnology-derived medicinal product within the meaning of Part A of the Annex to Council Regulation (EC) No 2309/93; and

(c) for other medicinal products using seed lots or cell banking systems in their manufacture,

that have already been approved for the manufacture of a constituent of an authorised medicinal product shall be considered in compliance with this note for guidance even if they are incorporated in marketing authorisation applications lodged after 1 July 2000 (for human medicinal products) or 1 October 2000 (for veterinary medicinal products).

Master cell banks and master seeds established before 1 July 2000 (for human medicinal products) or 1 October 2000 (for veterinary medicinal products), but not yet approved as a constituent of an authorised medicinal product shall demonstrate that they fulfil the requirements of this note for guidance. If, for some raw or starting materials or reagents used for the establishment of these cell banks or seeds, full documentary evidence is not/no longer available, the applicant should present a risk assessment as described in Section 4 of this note for guidance.

Established working seeds or cell banks used in the manufacture of medicinal products authorised before 1 July 2000 (human medicines) or 1 October 2000 (veterinary medicines), which have been subjected to a properly conducted risk assessment by a competent authority of the Member States or the EMEA and declared to be acceptable, shall also be considered compliant.

However, where materials derived from the 'TSE-relevant animal species' are used in fermentation/routine production processes or in the establishment of working seeds and working cell banks, the applicant must demonstrate that they fulfil the requirements of this note for guidance.

3. GENERAL CONSIDERATIONS

3.1. *SCIENTIFIC PRINCIPLES FOR MINIMISING RISK*

When manufacturers have a choice the use of materials from 'non TSE-relevant animal species' or non-animal origin is preferred. The rationale for using materials derived from 'TSE-relevant animal species' instead of materials from 'non-TSE-relevant species' or of non-animal origin should be given. If materials from 'TSE-relevant animal species' have to be used, consideration should be given to all the necessary measures to minimise the risk of transmission of TSE.

Readily applicable diagnostic tests for TSE infectivity *in vivo* are not yet available. Diagnosis is based on *post mortem* confirmation of characteristic brain lesions by histopathology and/or detection of PrP^{Sc} by Western Blot or immunoassay. The demonstration of infectivity by the inoculation of suspect tissue into target species or laboratory animals is also used for confirmation. However, due to the long incubation periods of all TSEs, results of *in vivo* tests are available only after months or years.

Several *in vitro* diagnostic tests capable of detecting PrP^{sc} in brain samples from infected animals have been approved for use but in the main they are less sensitive than *in vivo* infectivity assays. Nonetheless, screening of source animals by *in vitro* tests may prevent the use of animals at late stages of incubation of the disease and may provide information about the epidemiological status of a given country or region.

Minimising the risks of transmission of TSE is based upon three complementary parameters:

— the source animals and their geographical origin,

— nature of animal material used in manufacture and any procedures in place to avoid cross-contamination with higher risk materials,

— production process(es) including the quality assurance system in place to ensure product consistency and traceability.

3.2. *SOURCE ANIMALS*

The source materials used for the production of materials for the manufacture of medicinal products shall be derived from animals fit for human consumption following *ante-* and *post mortem* inspection in accordance with Community or equivalent (third country) conditions, except for materials derived from live animals, which should be found healthy after clinical examination.

[5] See also: 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 (EMEA/CVMP/019/01 — February 2001) adopted by the Committee for Veterinary Medicinal products (CVMP) in July 2001, *Official Journal of the European Communities* C 286 of 12 October 2001, p. 12.

3.2.1. GEOGRAPHICAL SOURCING

3.2.1.1. ***Bovine materials***

There are currently two organisations involved in the assessment of the BSE status of a specified country or zone. Firstly, the Organisation Internationale des Epizooties (OIE) [6] lays down the criteria for the assessment of the status of countries in the chapter of the International Animal Health Code on bovine spongiform encephalopathy. OIE also provides a list of notified BSE cases worldwide. Secondly, the European Commission Scientific Steering Committee (SSC) [7] has established a system for classifying the countries according to their geographical BSE risk (GBR).

Regulation (EC) No 999/2001 of the European Parliament and of the Council laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies (TSE Regulation) [2] entered into force on 1 July 2001. While medicinal products, medical devices and cosmetics are excluded from the scope of this regulation, the principles for the determination of BSE status should be taken into account in the categorisation of the BSE status of a given country or region.

For the purposes of this note for guidance the SSC GBR classification should be used as the indicator of the status of a given country. However, when countries are categorised according to Regulation (EC) No 999/2001, this categorisation should be used.

European Commission Scientific Steering Committee Classification

The European Scientific Steering Committee classification for geographical BSE risk (GBR) gives an indication of the level of likelihood of the presence of one or more cattle clinically or pre-clinically infected with BSE in a given country or region. A definition of the four categories is provided in the table:

GBR level	Presence of one or more cattle clinically or pre-clinically infected with BSE in a geographical region/country
I	Highly unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed at a lower level
IV	Confirmed at a higher level [1]

[1] ≥ 100 cases/1 million adult cattle per year.

Reports of the GBR assessment of the countries are available on the SSC website [8]. If the BSE status of a country has not been classified by the SSC, a risk assessment shall be submitted taking into account the SSC criteria for the GBR classification.

Where there is a choice, animals should be sourced from countries with the lowest possible GBR level unless the use of material from higher GBR countries is justified. Some of the materials identified in Section 6, 'Specific conditions' can be sourced from GBR Category III and, in some cases, Category IV countries, provided that the controls and requirements as specified in the relevant sections below are applied. Apart from these exceptions, animals must not be sourced from Category IV countries, and justifications for the use of animals from Category III countries must always be provided.

3.2.1.2. ***Sheep and goats (small ruminants)***

Naturally occurring clinical scrapie cases have been reported in a number of countries worldwide. As BSE in sheep could possibly be mistaken for scrapie, as a precautionary measure, sourcing of materials derived from small ruminants shall take into account the prevalence of both BSE and scrapie in the country and the tissues from which the materials are derived.

The principles related to 'BSE negligible risk (closed) bovine herds' (see section 3.2.2) could equally be applied in the context of small ruminants in order to develop a framework to define the TSE status of a flock of small ruminants. For sheep, because of the concern over the possibility of BSE in sheep, the use of a genotype(s) shown to be resistant to BSE/scrapie infection shall be considered in establishing TSE free flocks. However, goats have not been studied sufficiently with regard to a genotype specific sensitivity.

Material of small ruminant origin should preferably be sourced from countries with a long history of absence of scrapie, such as New Zealand or Australia or from proven TSE-free flocks. Justification shall be required if the material is sourced from some other origin.

3.2.2. BSE NEGLIGIBLE RISK (CLOSED) BOVINE HERDS

The safest sourcing is from countries where the presence of BSE is highly unlikely, i.e. GBR I. Other countries may have or have had cases of BSE at some point in time and the practical concept of 'Negligible risk (closed) bovine herds' has been developed by the SSC and endorsed by the CPMP and CVMP. Criteria for establishing and maintaining a 'BSE negligible risk (closed) bovine herd' can be found in the SSC opinion of 22-23 July 1999 [9].

For the time being it is not possible to quantify the reduction of the geographical BSE risk for cattle from BSE negligible risk (closed) bovine herds. However, it is expected that this risk reduction is substantial. Therefore, sourcing from such closed bovine herds shall be considered in the risk assessment in conjunction with the GBR classification of the country.

[6] http://www.oie.int

[7] The Scientific Steering Committee established by Commission Decision 97/404/EC shall assist the Commission to obtain the best scientific advice available on matters relating to consumer health. Since May 2003, its tasks have been taken over by the European Food Safety Agency (EFSA): http://www.efsa.eu.int

[8] http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html

[9] SSC scientific opinion on the conditions related to 'BSE negligible risk (closed) bovine herds' adopted at the meeting of 22-23 July 1999, http://europa.eu.int/comm/food/fs/sc/ssc/out56_en.html

3.3. *ANIMAL PARTS, BODY FLUIDS AND SECRETIONS AS STARTING MATERIALS*

In a TSE infected animal, different organs and secretions have different levels of infectivity ([10]). The tables in the Annex of this note for guidance ([11]) summarise current data about the distribution of infectivity and PrP^{Sc} in cattle with BSE, and in sheep and goats with scrapie.

The information in the tables is based exclusively upon observations of naturally occurring disease or primary experimental infection by the oral route (in cattle) but does not include data on models using strains of TSE that have been adapted to experimental animals, because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease. Because immunohistochemical and/or western blot detection of misfolded host protein (PrP^{Sc}) have proven to be a surrogate marker of infectivity, PrP^{Sc} testing results have been presented in parallel with bioassay data. Tissues are grouped into three major infectivity categories, irrespective of the stage of disease:

Category A: High-infectivity tissues: central nervous system (CNS) tissues that attain a high titre of infectivity in the later stages of all TSEs, and certain tissues that are anatomically associated with the CNS.

Category B: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or PrP^{Sc} in at least one form of TSE.

Category C: Tissues with no detectable infectivity: tissues that have been examined for infectivity, without any infectivity detected, and/or PrP^{Sc}, with negative results.

Category A tissues and substances derived from them shall not be used in the manufacture of medicinal products, unless justified (see section 5).

Although the category of lower risk tissues (category B tissues) almost certainly includes some (e.g. blood) with a lower risk than others (e.g. lymphoreticular tissues), the data about infectivity levels in these tissues are too limited to subdivide the category into different levels of risk. It is also evident that the placement of a given tissue in one or another category can be disease and species specific, and subject to revision as new data emerges.

For the risk assessment (see section 4), manufacturers and/or marketing authorisation holders/applicants shall take into account the tissue classification tables in the Annex to this note for guidance ([12]).

The categories in the tables are only indicative and it is important to note the following points:

— 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 tissues with lower-infectivity tissues or no detectable infectivity (Categories B and C tissues) with high-infectivity tissues (Category A tissues). Thus, 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. For certain tissues, it is very difficult or impossible to prevent cross-contamination with Category A tissues (e.g. skull). This has to be considered in the risk assessment.

— For certain classes of substances the stunning/slaughtering techniques used may be important in minimising the potential risk ([13]) because of the likelihood of disseminating the brain particles into the peripheral organs, particularly to the lungs. Stunning/slaughtering techniques should be described as well as the procedures to remove high infectivity tissues. The procedures to collect the animal tissues/organs to be used and the measures in place to avoid cross-contamination with a higher risk material must also be described in detail.

— The risk of contamination of tissues and organs with BSE-infectivity potentially harboured in central nervous material as a consequence of the stunning method used for cattle slaughtering depends on the following factors:

  — the amount of BSE-infectivity in the brain of the slaughtered animal,

  — the extent of brain damage,

  — the dissemination of brain particles in the animal body.

  These factors must be considered in conjunction with the GBR classification of the source animals, the age of the animals in the case of cattle and the *post mortem* testing of the cattle using a validated method.

([10]) If materials from 'TSE-relevant animal species' have to be used, consideration should be given to use of materials of the lowest category of risk.

([11]) The tissue classification tables are based upon the most recent 'WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products' (February 2003) WHO/BCT/QSD/03.01.

([12]) The introduction of the three-category tissue classification system does not invalidate the risk-assessments based on the previously used four-category tissue classification, performed for authorized medicinal products.

([13]) SSC opinion on stunning methods and BSE risk (The risk of dissemination of brain particles into the blood and carcass when applying certain stunning methods), adopted at the meeting of 10-11 January 2002, http://europa.eu.int/comm/food/fs/sc/ssc/out245_en.pdf

The underlying principles indicated above would be equally applicable to sheep and goats.

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

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

— level of contamination (amount of the contaminating tissue),

— amount and type of materials collected at the same time.

Manufacturers or the marketing authorisation holders/applicants should take into account the risk with respect to cross-contamination.

3.4. *AGE OF ANIMALS*

As the TSE infectivity accumulates in bovine animals over an incubation period of several years, it is prudent to source from young animals.

3.5. *MANUFACTURING PROCESS*

The assessment of the overall TSE risk reduction of a medicinal product shall take into account the control measures instituted with respect to:

— sourcing of the raw/starting materials, and

— the manufacturing process.

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

A quality assurance system, such as ISO 9000 certification, HACCP ([14]) or GMP, must be put in place for monitoring the production process and for batch delineation (i.e. definition of batch, separation of batches, cleaning between batches). Procedures shall be put in place to ensure traceability as well as self-auditing and auditing suppliers of raw/starting materials.

Certain production procedures may contribute considerably to the reduction of the risk of TSE contamination, e.g. procedures used in the manufacture of tallow derivatives (see section 6). As such rigorous processing cannot be applied to many products, processes involving physical removal, such as precipitation and filtration to remove prion-rich material, are likely to be more appropriate than chemical treatments. A description of the manufacturing process, including in-process controls applied, shall be presented and the steps that might contribute to reduction or elimination of TSE contamination should be discussed. Whenever different manufacturing sites are involved, the steps performed at each site shall be clearly identified. The measures in place in order to ensure traceability of every production batch to the source material should be described.

Cleaning process — Cleaning of process equipment may be difficult to validate for the elimination of TSE agents. It is reported that after exposure to high titre preparations of TSE agent, detectable infectivity can remain bound to the surface of stainless steel. The removal of all adsorbed protein by the use of sodium hydroxide or chlorine releasing disinfectants (e.g. 20 000 ppm. chlorine for 1 hour) have been considered acceptable approaches where equipment that cannot be replaced has been exposed to potentially contaminated material. In the case of using Category A materials in the manufacture of a product, dedicated equipment shall be used, unless otherwise justified.

If risk materials are used in the manufacture of a product, cleaning procedures, including control measures, shall be put in place in order to minimise the risk of cross-contamination between production batches. This is especially important if materials from different risk categories are handled in the same plant with the same equipment.

Removal/Inactivation validation — Validation studies of removal/inactivation procedures for TSEs are difficult to interpret. It is necessary 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). Further research is needed to develop an understanding of the most appropriate 'spike preparation' for validation studies. Therefore, validation studies are currently not generally required. However, if claims are made for the safety of the product with respect to TSEs based on the ability of manufacturing processes to remove or inactivate TSE agents, they must be substantiated by appropriate validation studies.

In addition to appropriate sourcing, manufacturers are encouraged to continue their investigations into removal and inactivation methods to identify steps/processes that would have benefit in assuring the removal or inactivation of TSE agents. In any event, a production process wherever possible shall be designed taking account of available information on methods which are thought to inactivate or remove TSE agents.

4. RISK ASSESSMENT OF MATERIALS OR SUBSTANCES USED IN THE MANUFACTURE AND PREPRATATION OF A MEDICINAL PRODUCT IN THE CONTEXT OF REGULATORY COMPLIANCE

The assessment of the risk associated with TSE needs careful consideration of all of the parameters as outlined in section 3.1 (Scientific Principles for Minimising Risk).

([14]) Hazard Analysis Critical Control Point.

As indicated in the introduction to this note for guidance, regulatory compliance is based on a favourable outcome from a risk assessment. The risk assessments, conducted by the manufacturers and/or the marketing authorisation holders or applicants for the different materials or substances from 'TSE-relevant animal species' used in the manufacture of a medicinal product shall show that all TSE risk factors have been taken into account and, where possible, risk has been minimised by application of the principles described in this note for guidance. TSE Certificates of suitability issued by the EDQM may be used by the marketing authorisation holders or applicants as the basis of the risk assessments.

An overall risk assessment for the medicinal product, conducted by the marketing authorisation holders or applicants, shall take into account the risk assessments for all the different materials from 'TSE-relevant animal species' and, where appropriate, TSE reduction or inactivation by the manufacturing steps of the active substance and/or finished product.

The final determination of regulatory compliance rests with the competent authority.

It is incumbent upon the manufacturers and/or the marketing authorisation holders or applicants for both human and veterinary medicinal products to select and justify the control measures for a given 'TSE-relevant animal species' derivative, taking into account the state of the art of science and technology.

5. BENEFIT/RISK EVALUATION

In addition to the parameters as mentioned in sections 3 and 4, the acceptability of a particular medicinal product containing materials derived from a 'TSE-relevant animal species', or which as a result of manufacture could contain these materials, shall take into account the following factors:

— route of administration of the medicinal product,

— quantity of animal material used in the medicinal product,

— maximum therapeutic dosage (daily dose and duration of treatment),

— intended use of the medicinal product and its clinical benefit.

High-infectivity tissues (Category A tissues) and substances derived thereof shall not be used in manufacture of medicinal products, their starting materials and intermediate products (including active substances, excipients and reagents), unless justified. A justification why no other materials can be used shall be provided. In these exceptional and justified circumstances, the use of high-infectivity tissues could be envisaged for the manufacture of active substances, when, after performing the risk assessment as described in section 4 of this note for guidance, and taking into account the intended clinical use, a positive benefit/risk assessment can be presented by the marketing authorisation applicant. Substances from Category A materials, if their use is justified, must be produced from animals of GBR I countries.

6. SPECIFIC CONSIDERATIONS

The following materials prepared from 'TSE-relevant animal species' are considered in compliance with this note for guidance provided that they meet at least the conditions specified below. The relevant information or a certificate of suitability granted by the EDQM shall be provided by the Marketing Authorisation applicant/holder.

6.1. *COLLAGEN*

Collagen is a fibrous protein component of mammalian connective tissue.

For collagen, documentation to demonstrate compliance with this note for guidance needs to be provided taking into account the provisions listed in sections 3 to 5. In addition, consideration should be given to the following:

— For collagen produced from bones, the conditions specified for gelatin are applicable (see below).

— Collagen produced from tissues such as hides and skins do not usually present a measurable TSE risk provided that contamination with potentially infected materials, for example spillage of blood and/or central nervous tissues, is avoided during their procurement.

6.2. *GELATIN*

Gelatin is a natural, soluble protein, gelling or non-gelling, obtained by the partial hydrolysis of collagen produced from bones, hides and skins, tendons and sinews of animals.

For gelatin, documentation to demonstrate compliance with this note for guidance needs to be provided taking into account the provisions listed in sections 3 to 5. In addition, consideration should be given to the following:

(i) **The source material used**

Gelatin used in medicinal products can be manufactured from bones or hides.

— Hides as the starting material — On the basis of current knowledge, hides used for gelatin production represent a much safer source material as compared to bones. However, it is highly recommended that measures should be put in place to avoid cross-contamination with potentially infected materials during procurement.

— Bones as the starting material — Where bones are used to manufacture gelatin, more stringent production conditions shall be applied (see below). In any case, the removal of skulls and spinal cords from the starting material is considered as a first precautionary measure, which largely affects the safety of the product. As far as practicable, bones should be sourced from countries classified as GBR I and II. Bones from Category GBR III countries can be used if the gelatin is manufactured under defined conditions as indicated below and if vertebrae from cattle over 12 months of age are removed from the raw/starting materials ([15]).

(ii) **Manufacturing methods**

No specific measures with regard to the processing conditions are required for gelatin produced from hides provided that control measures are put in place to avoid cross-contamination both during the procurement of the hides and during the manufacturing process.

However, the mode of manufacture must be taken into account where bones are used as the starting material.

— Bones (including vertebrae) for the production of gelatin using acid treatment shall be sourced only from GBR Category I or II countries. An additional alkaline treatment (pH 13, 1 hour) of the bones/ossein may further increase the TSE safety of acid-derived bone gelatin.

For bones sourced from a GBR Category III country, the alkaline process shall be applied. However, this manufacturing method is optional for bones coming from GBR Category I and II countries.

— For a typical alkaline manufacturing process, bones are finely crushed, degreased with hot water and demineralised with dilute hydrochloric acid (at a minimum of 4 % and pH < 1,5) over a period of at least two days to produce the ossein. This is followed by an alkaline treatment with saturated lime solution (pH at least 12,5) for a period of at least 20 days. The gelatin is extracted, washed, filtered and concentrated. A 'flash' heat treatment (sterilisation) step using 138-140 °C for 4 seconds is applied. Bovine hide gelatin can also be produced by the alkaline process. Bovine bones may also be treated by an acid process. The liming step is then replaced by an acid pre-treatment where the ossein is soaked overnight at pH < 4.

([15]) Regulation (EC) No 1774/2002 of the European Parliament and of the Council laying down health rules concerning animal by-products not intended for human consumption shall apply unless justified. Regarding the manufacturing of gelatin and collagen or import of raw material for such manufacturing for use in pharmaceutical products, only material from animals fit for human consumption shall be used. The use of vertebrae from such animals from Category II countries, which according to the risk assessment is safe, shall continue to be allowed.

6.3. *BOVINE BLOOD DERIVATIVES*

Foetal bovine serum is commonly used in cell cultures. Foetal bovine serum should be obtained from foetuses harvested in abattoirs from healthy dams fit for human consumption and the womb should be completely removed and the foetal blood harvested in dedicated space or area by cardiac puncture into a closed collection system using aseptic technique.

New born calf serum is obtained from calves under 20 days old and calf serum from animals under the age of 12 months. In the case of donor bovine serum, given that it may be derived from animals less than 36 months old, the TSE status of the donor herd shall be well defined and documented. In all cases, serum shall be collected according to specified protocols by personnel trained in these procedures to avoid cross-contamination with higher risk tissues.

For bovine blood derivatives, documentation to demonstrate compliance with this note for guidance needs to be provided taking into account the provisions listed in sections 3 to 5. In addition, consideration should be given to the following:

(i) **Traceability**

Traceability to the slaughterhouse must be assured for each batch of serum or plasma. Slaughterhouses must have available lists of farms from which the animals are originated. If serum is produced from living animals, records must be available for each serum batch which assures the traceability to the farms.

(ii) **Geographical origin**

Whilst tissue infectivity of BSE in cattle is more restricted than scrapie, as a precautionary measure bovine blood must be sourced from countries classified GBR I and II, unless otherwise justified.

(iii) **Stunning methods**

If it is sampled from slaughtered animals, the method of slaughter is of importance to assure the safety of the material. It has been demonstrated that stunning by captive bolt stunner with or without pithing as well as by pneumatic stunner, especially if it injects air, can destroy the brain and disseminate brain material into the blood stream. Negligible risk can be expected from a non-penetrative stunner and from electro-narcosis ([16]). The stunning methods must therefore be described for the bovine blood collection process.

([16]) SSC opinion on stunning methods and BSE risk (The risk of dissemination of brain particles into the blood and carcass when applying certain stunning methods) adopted at the meeting on 10-11 January 2002, http://europa.eu.int/comm/food/fs/sc/ssc/out245_en.pdf

If sourcing is allowed from countries where cases of BSE have been detected (GBR III) a non-penetrative stunner shall be used for slaughter.

6.4. *TALLOW DERIVATIVES*

Tallow is fat obtained from tissues including subcutaneous, abdominal and inter-muscular areas and bones. Tallow used as the starting material for the manufacture of tallow derivatives shall be Category 3 material or equivalent, as defined in Regulation (EC) No 1774/2002 ([17]) of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption.

Tallow derivatives, such as glycerol and fatty acids, manufactured from tallow by rigorous processes are thought unlikely to be infectious and they have been the subject of specific consideration by CPMP and CVMP. For this reason, such materials manufactured under the conditions at least as rigorous as those given below shall be considered in compliance for this note for guidance, irrespective of the geographical origin and the nature of the tissues from which tallow derivatives are derived. Examples of rigorous processes are:

— trans-esterification 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 3 hours

  — continuous process: at not less than 140 °C, under pressure for not less than 8 minutes, or equivalent,

— distillation at 200 °C.

Tallow derivatives manufactured according to these conditions are unlikely to present any TSE risk and shall therefore be considered compliant with this note for guidance.

Tallow derivatives produced using other conditions must demonstrate compliance with this note for guidance.

6.5. *ANIMAL CHARCOAL*

Animal charcoal is prepared by carbonisation of animal tissues, such as bones, using high temperature at > 800 °C. Unless otherwise justified, the starting material for the manufacture of animal charcoal shall be Category 3 material or equivalent, as defined in Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption. Irrespective of the geographical origin and the nature of the tissue, for the purpose of regulatory compliance, animal charcoal shall be considered in compliance with this note for guidance.

Charcoal manufactured according to these conditions are unlikely to present any TSE risk and shall therefore be considered compliant with this note for guidance. Charcoal produced using other conditions must demonstrate compliance with this note for guidance.

6.6. *MILK AND MILK DERIVATIVES*

In the light of the current scientific knowledge and irrespective of the geographical origin, milk is unlikely to present any risk of TSE contamination.

Certain materials, including lactose, are extracted from whey, the spent liquid from cheese production following coagulation. Coagulation can involve the use of calf rennet, an extract from abomasum, or rennet derived from other ruminants. The CPMP/CVMP have performed a risk assessment for lactose and other whey derivatives produced using calf rennet and concluded that the TSE risk is negligible if the calf rennet is produced in accordance with the process described in the risk assessment report ([18]). The conclusion was endorsed by the SSC ([19]), which has also performed an assessment of the TSE risk of rennet in general ([20]).

Milk derivatives manufactured according to the conditions below are unlikely to present any TSE risk and shall therefore be considered compliant with this note for guidance.

— The milk is sourced from healthy animals in the same conditions as milk collected for human consumption, and

— no other ruminant materials, with the exception of calf rennet, are used in the preparation of such derivatives (e.g. pancreatic enzyme digests of casein).

([17]) OJ L 273, 10.10.2002, p. 1.

([18]) Committee for Proprietary Medicinal Products and its Biotechnology Working Party conducted a risk and regulatory assessment of lactose prepared using calf rennet. The risk assessment included the source of the animals, the excision of the abomasums and the availability of well-defined quality assurance procedures. The quality of any milk replacers used as feed for the animals from which abomasums are obtained is particularly important. The report can be found on http://www.emea.eu.int

([19]) Provisional statement on the safety of calf-derived rennet for the manufacture of lactose. Adopted by the SSC at its meeting of 4-5 April 2002 (http://europa.eu.int/comm/food/fs/sc/ssc/out255_en.pdf).

([20]) The SSC issued an opinion on the safety of animal rennet in regard to risks from animal TSE and BSE in particular, adopted at its meeting of 16 May 2002 (http://europa.eu.int/comm/food/fs/sc/ssc/out265_en.pdf).

Milk derivatives produced using other processes or rennet derived from other ruminant species must demonstrate compliance with this note for guidance.

6.7. *WOOL DERIVATIVES*

Derivatives of wool and hair of ruminants, such as lanolin and wool alcohols derived from hair shall be considered in compliance with this note for guidance, provided the wool and hair are sourced from live animals.

Wool derivatives produced from wool, which is sourced from slaughtered animals declared 'fit for human consumption' and the manufacturing process in relation to pH, temperature and duration of treatment meets at least one of the stipulated processing conditions listed below are unlikely to present any TSE risk and shall therefore be considered compliant with this note for guidance.

— Treatment at pH ≥ 13 (initial; corresponding to a NaOH concentration of at least 0,1 M NaOH) at ≥ 60 °C for at least 1 hour. This occurs normally during the reflux stage of the organic-alkaline treatment,

— molecular distillation at ≥ 220 °C under reduced pressure.

Wool derivatives produced using other conditions must demonstrate compliance with this note for guidance.

6.8. *AMINO ACIDS*

Amino acids can be obtained by hydrolysis of materials from various sources.

Unless otherwise justified, the starting material for the manufacture of amino acids shall be Category 3 material or equivalent, as defined in Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption.

Amino acids prepared using the following processing conditions, in accordance with Commission Decision 98/256/EC [21] and Commission Decision 2001/376/EC [22], are unlikely to present any TSE risk and shall be considered compliant with this note for guidance.

— Amino acids produced from hides and skins by a process which involves exposure of the material to a pH of 1 to 2, followed by a pH of > 11, followed by heat treatment at 140 °C for 30 minutes at 3 bar,

— the resulting amino acids or peptides must be filtered after production, and

— analysis is performed using a validated and sensitive method to control any residual intact macromolecules, with an appropriate limit set.

Amino acids prepared using other conditions must demonstrate compliance with this note for guidance.

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[21] OJ L 113, 15.4.1998, p. 32.

[22] OJ L 132, 15.5.2001, p. 17.

ANNEX

MAJOR CATEGORIES OF INFECTIVITY

The tables below are adapted from the 'WHO Guideline on Transmissible Spongiform Encephalopathies in Relation to Biological and Pharmaceutical Products' (February 2003).

Data entries are shown as follows:

\+ Presence of infectivity or PrP^{TSE} (1)

– Absence of detectable infectivity or PrP^{TSE}

NT Not tested

? Controversial or uncertain results

Category A: High-infectivity tissues

Tissues	Cattle		Sheep and goats	
	BSE		Scrapie	
	Infectivity (1)	PrP^{TSE}	Infectivity (1)	PrP^{TSE}
Brain	+	+	+	+
Spinal cord	+	+	+	+
Retina, optic nerve	+	NT	NT	+
Spinal ganglia	+	NT	NT	+
Trigeminal ganglia	+	NT	NT	+
Pituitary gland (2)	–	NT	+	NT
Dura mater (2)	NT	NT	NT	NT

(1) Infectivity bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats not all results are consistent for both species.

(2) No experimental data about infectivity in human pituitary gland or dura mater have been reported, but cadaveric dura mater patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to scores of people and therefore must be included in the category of high-risk tissues.

Category B: Lower-infectivity tissues

Tissues	Cattle		Sheep and goats	
	BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Peripheral nervous system				
Peripheral nerves	–	NT	+	NT
Enteric plexuses (1)	NT	+	NT	+
Lymphoreticular tissues				
Spleen	–	–	+	+
Lymph nodes	–	–	+	+
Tonsil	+	NT	+	+

(1) In the main body of this note for guidance the abnormal isoform of the prion protein is referred to as PrP^{Sc}. However, as these tables are transcribed directly from the WHO guideline mentioned above, the WHO nomenclature for the abnormal prion protein (PrP^{TSE}) has been maintained.

Tissues	Cattle		Sheep and goats	
	BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Nictitating membrane	NT	–	NT	+
Thymus	–	NT	+	NT
Alimentary tract				
Esophagus	–	NT	NT	+
Fore-stomach (2) (ruminants only)	–	NT	NT	+
Stomach/abomasum (2)	–	NT	NT	+
Duodenum	–	NT	NT	+
Jejunum	–	NT	NT	+
Ileum (3)	+	+	+	+
Large intestine	–	NT	+	+
Reproductive tissues				
Placenta	–	NT	+	+
Other tissues				
Lung (*)	–	NT	–	NT
Liver	–	NT	+	NT
Kidney (*)	–	–	–	–
Adrenal	NT	NT	+	NT
Pancreas	–	NT	+	NT
Bone marrow	+	NT	+	NT
Blood vessels	–	NT	NT	+
Olfactory mucosa	–	NT	+	NT
Gingival tissue (*)	NT	NT	NT	NT
Salivary gland	–	NT	+	NT
Cornea (4) (*)	NT	NT	NT	NT
Body fluids				
CSF	–	NT	+	NT
Blood (5)	–	NT	+	–

(1) In cattle, limited to the distal ileum.

(2) Ruminant forestomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.

(3) In cattle and sheep, only the distal ileum has been bioassayed for infectivity.

(4) Because only one or two cases of CJD have been plausibly attributed to corneal transplants among hundreds of thousands of recipients, cornea is categorised as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.

(5) Early reports on the transmission of disease to rodents from the blood of patients with sCJD have not been confirmed, and evaluation of the ensemble of experimental and epidemiological data relevant to TSE transmission through blood, blood components, and therapeutic plasma products fails to suggest transmission from blood of patients with any form of 'classical' TSE. Not enough data has accumulated to be able to make the same statement about blood from patients with vCJD. Foetal calf blood contains no detectable infectivity, but in genotypically susceptible sheep with natural scrapie or experimentally induced BSE, transfusion of large blood volumes has transmitted disease to healthy sheep. Infectivity has also been demonstrated in studies of rodent-adapted strains of TSE.

(*) These tissues have been classified under Category B — Lower-infectivity tissues, because infectivity and/or PrP^{TSE} have been found in human CJD (vCJD or other).

Category C: Tissues with no detected infectivity

Tissues	Cattle		Sheep and goats	
	BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Reproductive tissues				
Testis	–	NT	–	NT
Prostate/Epididymis/ Seminal vesicle	–	NT	–	NT
Semen	–	NT	NT	NT
Ovary	–	NT	–	NT
Uterus (Non-gravid)	–	NT	–	NT
Placenta fluids	–	NT	NT	NT
Foetus (1)	–	NT	–	NT
Embryos (1)	–	NT	?	NT
Musculo-skeletal tissues				
Bone	–	NT	NT	NT
Skeletal muscle (2)	–	NT	–	NT
Tongue	–	NT	NT	NT
Heart/pericardium	–	NT	–	NT
Tendon	–	NT	NT	NT
Other tissues				
Trachea	–	NT	NT	NT
Skin	–	NT	–	NT
Adipose tissue	–	NT	NT	NT
Thyroid gland	NT	NT	–	NT
Mammary gland/udder	–	NT	–	NT
Body fluids, secretions and excretions				
Milk (3)	–	NT	–	NT
Colostrum (4)	NT	NT	–	NT
Cord blood (4)	–	NT	NT	NT
Saliva	NT	NT	–	NT
Sweat	NT	NT	NT	NT

Tissues	Cattle		Sheep and goats	
	BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Tears	NT	NT	NT	NT
Nasal mucus	NT	NT	NT	NT
Urine (4) (5)	–	NT	NT	NT
Faeces	–	NT	–	NT

(1) Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made on foetal calf tissues other than blood (negative mouse bioassay). Calves born of dams that received embryos from BSE-affected cattle have survived for observation periods of up to seven years, and examination of the brains of both the unaffected dams and their calves revealed no spongiform encephalopathy or PrP^{TSE}.

(2) Intracerebral inoculation of muscle homogenates has not transmitted disease to (1) primates from humans with sCJD; (2) mice or cattle from cattle with BSE; and (3) mice from sheep and goats with natural or experimentally-induced scrapie. However, older reports described single instances of transmission from goat and hamster muscle, and a more recent report described transmission from the muscle of wild type and transgenic mice, but as each of these studies were conducted with passaged strains of TSE, their relevance to natural disease remains undetermined. A recent human case report described a patient with CJD and inclusion body myositis with abundant PrP^{TSE} in diseased muscle. After much deliberation, the committee nevertheless elected to retain muscle in the 'no detected infectivity' tissue category until more information about uncomplicated natural infections becomes available.

(3) Evidence that infectivity is not present in milk includes temporo-spatial epidemiologic observations failing to detect maternal transmission; clinical observations of over a hundred calves nursed by infected cows that have not developed BSE; and experimental observations that milk from infected cows has not transmitted disease when administered intracerebrally or orally to mice. Experiments are in progress in which large volumes of milk from experimentally infected cows are concentrated and tested for the presence of PrP^{TSE}.

(4) Single reports of transmission of CJD infectivity from human cord blood, colostrum, and urine have never been confirmed and are considered improbable.

(5) A previously unreported PrP type, termed PrP^{u}, has been identified in the urine of sporadic and familial CJD patients, but its significance for transmission risk remains to be determined.

Notice of the expiry of certain anti-dumping measures

(2004/C 24/04)

Further to the publication of a notice of impending expiry (1), following which no request for a review was received, the Commission gives notice that the anti-dumping measures mentioned below will shortly expire.

This notice is published in accordance with Article 11(2) of Council Regulation (EC) No 384/96 of 22 December 1995 (2) on protection against dumped imports from countries not members of the European Community.

Product	Country(ies) of origin or exportation	Measures	Reference	Date of expiry
Hardboard	Bulgaria Estonia Latvia Lithuania Poland Russia	Duty	Regulation (EC) No 194/1999 (OJ L 22, 29.1.1999, p. 16) as last amended by Regulation (EC) No 1899/2001 (OJ L 261, 29.9.2001, p. 1)	29.1.2004
	Bulgaria Estonia Lithuania Poland	Undertaking	Decision 1999/71/EC (OJ L 22, 29.1.1999, p. 71) as last amended by Decision 2001/707/EC (OJ L 261, 29.9.2001, p. 65)	

(1) OJ C 100, 26.4.2003, p. 11.

(2) OJ L 56, 6.3.1996, p. 1, as last amended by Council Regulation (EC) No 1972/2002 (OJ L 305, 7.11.2002, p. 1).