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Information and Notices

(1) Text with EEA relevance

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III *Notices*

Commission

EN

[1] Text with EEA relevance

I

(Information)

COMMISSION

Euro exchange rates [1]

27 January 2004

(2004/C 24/01)

1 euro =

	Currency	Exchange rate		Currency	Exchange rate
USD	US dollar	1,2517	LVL	Latvian lats	0,6675
JPY	Japanese yen	132,51	MTL	Maltese lira	0,4297
DKK	Danish krone	7,4485	PLN	Polish zloty	4,7234
GBP	Pound sterling	0,69085	ROL	Romanian leu	40 804
SEK	Swedish krona	9,1591	SIT	Slovenian tolar	237,34
CHF	Swiss franc	1,5681	SKK	Slovak koruna	40,585
ISK	Iceland króna	86,72	TRL	Turkish lira	1 655 012
NOK	Norwegian krone	8,601	AUD	Australian dollar	1,6197
BGN	Bulgarian lev	1,9559	CAD	Canadian dollar	1,6416
CYP	Cyprus pound	0,58606	HKD	Hong Kong dollar	9,7185
CZK	Czech koruna	32,918	NZD	New Zealand dollar	1,8596
EEK	Estonian kroon	15,6466	SGD	Singapore dollar	2,1271
HUF	Hungarian forint	262,65	KRW	South Korean won	1 473,25
LTL	Lithuanian litas	3,4529	ZAR	South African rand	8,9168

[1] *Source:* reference exchange rate published by the ECB.

Information procedure — Technical rules

(2004/C 24/02)

(Text with EEA relevance)

Directive 98/34/EC of the European Parliament and of the Council of 22 June 1998 laying down a procedure for the provision of information in the field of technical standards and regulations and of rules on Information Society services (OJ L 204, 21.7.1998, p. 37; OJ L 217, 5.8.1998, p. 18).

Notifications of draft national technical rules received by the Commission

Reference [1]	Title	End of three-month standstill period [2]
2003/474/S	Administrative provisions of the Swedish National Road Administration (VVFS 2003;24) on mopeds and trailers drawn by mopeds	22.3.2004
2003/475/A	Proposal for an act on precautionary measures for genetic engineering (Genetic Engineering Precautionary Measures Act)	23.3.2004
2003/476/NL	Regulation amending various regulations in connection with the lapsing of the requirement to have skills in the field of Morse telegraphy	23.3.2004
2003/477/I	Draft standard for the commissioning and use of pressure equipment and assemblies pursuant to Legislative Decree No 93 of 25 February 2000	23.3.2004
2003/478/NL	Draft Decree changing the Decree on alcohol tests	24.3.2004
2003/479/DK	Sixth edition of DS 413:2003 code of practice for the structural use of timber	24.3.2004
2003/480/A	Air interface descriptions 'Private mobile radio' interface numbers: FSB-LS031, FSB-LS036	24.3.2004
2003/481/A	Air interface description 'Radio systems' interface number: FSB-LM001, FSB-LM020	24.3.2004
2003/482/A	Air interface description 'Transmission of sound and images' interface number: FSB-LT003, FSB-LT005, FSB-LT009, FSB-LT012, FSB-LT013, FSB-LT014	24.3.2004
2003/483/A	Air interface description 'Radio relay' interface number: FSB-RR001, FSB-RR004, FSB-RR014, FSB-RR015, FSB-RR016, FSB-RR020, FSB-RR025, FSB-RR040, FSB-RR041, FSB-RR042	24.3.2004
2003/484/A	Air interface description 'Satellite communications' interface number: FSB-RU015	24.3.2004
2003/485/A	Act of . . . amending the Structural Engineering Act	24.3.2004
2003/486/F	Draft Decree on blood-derived medicinal products and medical devices incorporating a substance that, if used separately, may be considered to be a blood-derived medicinal product and amending Books V and Va of the Public Health Code (second part: Council of State Decrees)	30.3.2004

[1] Year — registration number — Member State of origin.

[2] Period during which the draft may not be adopted.

[3] No standstill period since the Commission accepts the grounds of urgent adoption invoked by the notifying Member State.

[4] No standstill period since the measure concerns technical specifications or other requirements or rules on services linked to fiscal or financial measures, pursuant to the third indent of the second paragraph of Article 1(11) of Directive 98/34/EC.

[5] Information procedure closed.

The Commission draws attention to the judgment delivered on 30 April 1996 in the 'CIA Security' case (C-194/94 – ECR I, p. 2201), in which the Court of Justice ruled that Articles 8 and 9 of Directive 98/34/EC (formerly 83/189/EEC) are to be interpreted as meaning that individuals may rely on them before national courts which must decline to apply a national technical regulation which has not been notified in accordance with the Directive.

This judgment confirms the Commission's communication of 1 October 1986 (OJ C 245, 1.10.1986, p. 4).

Accordingly, breach of the obligation to notify renders the technical regulations concerned inapplicable and consequently unenforceable against individuals.

For more information on the notification procedure, please write to:

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Also consult the website: http://europa.eu.int/comm/enterprise/tris/

If you require any further information on these notifications, please contact the national departments listed below:

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Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 — October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP)

(2004/C 24/03)

This revision of the TSE (Transmissible Spongiform Encephalopathy) note for guidance has been undertaken to introduce, *inter alia*, risk assessment into the regulatory compliance process, to provide clarification on a variety of terms and classifications, and to take into account advances in scientific knowledge, Community legislation and rules affecting the authorisation of medicinal products for human or veterinary use. It replaces the previous revision of the note for guidance (EMEA/410/01 Rev. 1 published in the *Official Journal of the European Communities* C 286, 12.10.2001, p. 4). The date of application of this note for guidance is 1 July 2004.

1. **INTRODUCTION**

1.1. *SCIENTIFIC BACKGROUND*

Transmissible Spongiform Encephalopathies (TSEs) are chronic degenerative nervous diseases characterised by the accumulation of an abnormal isoform of a cellular glycoprotein known as PrP or prion protein). The abnormal isoform of PrP (PrP^{Sc}) differs from normal PrP (PrP^{c}) in being highly resistant to protease and heat denaturation treatments. PrP^{Sc} is considered to be the infective agent responsible for transmitting TSE disease.

TSE diseases in animals include:

— bovine spongiform encephalopathy (BSE) in cattle,

— scrapie in sheep and goats,

— chronic wasting disease (CWD) in cervids (deer and elk),

— transmissible mink encephalopathy (TME) in farmed mink,

— feline spongiform encephalopathy (FSE) in felidae (specifically domestic cats and captive large cats), and

— spongiform encephalopathy of exotic ungulates in zoos.

In humans, spongiform encephalopathies include different forms of Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI).

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 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 dura mater and cornea.

Interspecies TSE transmission is restricted by a number of natural barriers, transmissibility being affected by the species of origin, the prion strain, dose, route of exposure and, in some species, the host allele of the PrP gene. Species barriers can be crossed under appropriate conditions.

Bovine spongiform encephalopathy (BSE) was first recognised in the United Kingdom in 1986 and a large number of cattle and individual herds have been affected. It is clear that BSE is a food borne disease associated with feeding meat and bone meal derived from TSE affected animals. Other countries have experienced cases of BSE, either in animals imported from the United Kingdom or in indigenous animals. There is convincing evidence to show that the variant form of CJD (vCJD) is caused by the agent which is responsible for BSE in cattle. Therefore, a cautious approach continues to be warranted if biological materials from species naturally affected by TSE diseases, especially bovine species, are used for the manufacture of medicinal products.

Scrapie occurs worldwide and has been reported in most European countries. It has the highest incidence in the United Kingdom. While humans have been exposed to naturally occurring scrapie for over 200 years, there is no epidemiological evidence directly linking scrapie to spongiform encephalopathies in humans. However, there remains a theoretical and currently unquantifiable risk that some BSE-contaminated protein supplement may have been fed to sheep. If such feed causes a recurrent BSE infection in sheep, it may be diagnosed as scrapie and might as such pose a risk of human TSEs. Further, it should also be assumed that any BSE agent introduced into the small ruminant population via contaminated feed is likely to be recycled and amplified.

1.2. *REGULATORY COMPLIANCE*

Risk assessment — Since the use of animal-derived materials is unavoidable for the production of some medicinal products and that complete elimination of risk at source is rarely possible, the measures taken to manage the risk of transmitting animal TSEs via medicinal products represent risk minimisation rather than risk elimination. Consequently, the basis for regulatory compliance should be based on a risk assessment, taking into consideration all pertinent factors as identified in this note for guidance (see below).

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).

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(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.

([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. 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.

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.

([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).

Notice of initiation of an anti-dumping proceeding concerning imports of polyester high tenacity filament yarn originating in Belarus, the Republic of Korea and Taiwan

(2004/C 24/05)

The Commission has received a complaint pursuant to Article 5 of Council Regulation (EC) No 384/96 [1], as last amended by Council Regulation (EC) No 1972/2002 [2] ('the basic Regulation'), alleging that imports of polyester high tenacity filament yarn, originating in Belarus, the Republic of Korea and Taiwan ('the countries concerned'), are being dumped and are thereby causing material injury to the Community industry.

1. COMPLAINT

The complaint was lodged on 15 December 2003 by the Comité International de la Rayonne et des Fibres Synthétiques ('the complainant') on behalf of producers representing a major proportion, in this case more than 70 %, of the total Community production of polyester high tenacity filament yarn.

2. PRODUCT

The product allegedly being dumped is high-tenacity yarn of polyesters (other than sewing thread), not put up for retail sale, including monofilament of polyesters of less than 67 decitex originating in Belarus, the Republic of Korea and Taiwan ('the product concerned'), normally declared within CN code 5402 20 00. This CN code is only given for information.

3. ALLEGATION OF DUMPING

The allegation of dumping for the Republic of Korea and Taiwan is based, in the absence of reliable data on domestic prices, on a comparison of a constructed normal value with the export prices of the product concerned to the Community.

In view of provisions of Article 2(7) of the basic Regulation, the complainant established normal value for Belarus on the basis of a constructed normal value in a market economy country, which is mentioned in paragraph 5.1(d) of this notice. The allegation of dumping is based on a comparison of normal value, thus calculated, with the export prices of the product concerned when sold for export to the Community.

On this basis, the dumping margins calculated are significant for all exporting countries concerned.

4. ALLEGATION OF INJURY

The complainant has provided evidence that imports of the product concerned from Belarus, the Republic of Korea and Taiwan have increased overall in absolute terms and in terms of market share.

It is alleged that the volumes and the prices of the imported product concerned have, among other consequences, had a negative impact on the market share held, the quantities sold and the level of prices charged by the Community industry, resulting in substantial adverse effects on the overall performance and the financial situation of the Community industry.

5. PROCEDURE

Having determined, after consulting the Advisory Committee, that the complaint has been lodged by or on behalf of the Community industry and that there is sufficient evidence to justify the initiation of a proceeding, the Commission hereby initiates an investigation pursuant to Article 5 of the basic Regulation.

5.1. Procedure for the determination of dumping and injury

The investigation will determine whether the product concerned originating in Belarus, the Republic of Korea and Taiwan is being dumped and whether this dumping has caused injury.

(a) *Sampling*

In view of the apparent large number of parties involved in this proceeding, the Commission may decide to apply sampling in accordance with Article 17 of the basic Regulation.

(i) Sampling for exporters/producers in the Republic of Korea

In order to enable the Commission to decide whether sampling is necessary and, if so, to select a sample, all exporters/producers, or representatives acting on their behalf, are hereby requested to make themselves known by contacting the Commission and providing the following information on their company or companies within the time limit set in paragraph 6(b)(i) and in the format indicated in paragraph 7 of this notice:

— name, address, e-mail address, telephone, and fax, and/or telex numbers and contact person,

— the turnover in local currency and the volume in tonnes of the product concerned sold for export to the Community during the period 1 January 2003 to 31 December 2003,

— the turnover in local currency and the sales volume in tonnes for the product concerned on the domestic market during the period 1 January 2003 to 31 December 2003,

[1] OJ L 56, 6.3.1996, p. 1.

[2] OJ L 305, 7.11.2002, p. 1.

— whether the company intends to claim an individual margin [1] (individual margins can only be claimed by exporting producers),

— the precise activities of the company with regard to the production of the product concerned,

— the names and the precise activities of all related companies [2] involved in the production and/or selling (export and/or domestic) of the product concerned,

— any other relevant information that would assist the Commission in the selection of the sample,

— an indication of whether the company or companies agree to their inclusion in the sample, which implies replying to a questionnaire and accepting an on-the-spot investigation of their response.

In order to obtain the information it deems necessary for the selection of the sample of exporters/producers, the Commission will, in addition, contact the authorities of the exporting country, and any known associations of exporters/producers.

(ii) Sampling for importers

In order to enable the Commission to decide whether sampling is necessary and, if so, to select a sample, all importers, or representatives acting on their behalf, are hereby requested to make themselves known by contacting the Commission and providing the following information on their company or companies within the time limit set in paragraph 6(b)(i) and in the formats indicated in paragraph 7 of this notice:

— name, address, e-mail address, telephone, and fax, and/or telex numbers and contact person,

— the total turnover in euro of the company during the period 1 January 2003 to 31 December 2003,

— the total number of employees,

— the precise activities of the company with regard to the product concerned,

— the volume in tonnes and value in euro of imports into and resales made in the Community market during the period 1 January 2003 to 31 December 2003 of the imported product concerned originating in Belarus, the Republic of Korea and Taiwan,

— the names and the precise activities of all related companies [2] involved in the production and/or selling of the product concerned,

— any other relevant information that would assist the Commission in the selection of the sample,

— an indication of whether the company or companies agree to their inclusion in the sample, which implies replying to a questionnaire and accepting an on-the-spot investigation of their response.

In order to obtain the information it deems necessary for the selection of the sample of importers, the Commission will, in addition, contact any known associations of importers.

(iii) Final selection of the sample

All interested parties wishing to submit any relevant information regarding the selection of the sample must do so within the time limit set in paragraph 6(b)(ii) of this notice.

The Commission intends to make the final selection of the sample after having consulted the parties concerned that have expressed their willingness to be included in the sample.

Companies included in the sample must reply to a questionnaire within the time limit set in paragraph 6(b)(iii) of this notice and must co-operate within the framework of the investigation.

If sufficient co-operation is not forthcoming, the Commission may base its findings, in accordance with Articles 17(4) and 18 of the basic Regulation, on the facts available.

(b) *Questionnaires*

In order to obtain the information it deems necessary for its investigation, the Commission will send questionnaires to the Community industry and to any association of producers in the Community, to the sampled exporters/producers in the Republic of Korea, to the exporters/producers in Belarus and Taiwan, to any association of exporters/producers, to the sampled importers, to any association of importers named in the complaint, and to the authorities of the exporting countries concerned.

[1] Individual margins may be claimed pursuant to Article 17(3) of the basic Regulation by companies not included in the sample.

[2] For guidance on the meaning of related companies, please refer to Article 143 of Commission Regulation (EEC) No 2454/93 concerning the implementation of the Community Customs Code (OJ L 253, 11.10.1993, p. 1).

(i) Exporters/producers in Belarus and Taiwan and importers

All such interested parties should contact the Commission forthwith by fax, but not later than the time limit set out in paragraph 6(a)(i) of this notice, in order to find out whether they are listed in the complaint and, if necessary, request a questionnaire, given that the time limit set in paragraph 6(a)(ii) of this notice applies to all such interested parties.

(ii) Exporters/producers claiming an individual margin in country(ies) concerned

Exporters/producers in the Republic of Korea claiming an individual margin, with a view to the application of Articles 17(3) and 9(6) of the basic Regulation, must submit a completed questionnaire within the time limit set in paragraph 6(a)(ii) of this notice. They therefore have to request a questionnaire within the time limit set in paragraph 6(a)(i) of this notice. However, such parties should be aware that if sampling is applied to exporters/producers, the Commission may nonetheless decide not to calculate an individual margin for them, if the number of exporters/producers is so large that individual examination would be unduly burdensome and would prevent the timely completion of the investigation.

(c) *Collection of information and holding of hearings*

All interested parties are hereby invited to make their views known, submit information other than questionnaire replies and to provide supporting evidence. This information and supporting evidence has to reach the Commission within the time limit set in paragraph 6(a)(ii) of this notice.

Furthermore, the Commission may hear interested parties, provided that they make a request showing that there are particular reasons why they should be heard. This request must be made within the time limit set in paragraph 6(a)(iii) of this notice.

(d) *Selection of the market economy country*

In accordance with Article 2(7)(a) of the basic Regulation, it is envisaged to choose the United States of America as an appropriate market economy country for the purpose of establishing normal value in respect of Belarus. Interested parties are hereby invited to comment on the appropriateness of this choice within the specific time limit set in paragraph 6(c) of this notice.

(e) *Exporters/producers claiming individual treatment in Belarus*

Exporters/producers in Belarus may claim individual treatment pursuant to Article 9(5) of the basic Regulation. Exporters/producers intending to submit duly substantiated claims, requesting individual treatment, must do so within the general time limit set in paragraph 6(a)(ii) of this notice. The Commission will send claim forms to all exporters/producers in Belarus named in the complaint and to any association of exporters/producers named in the complaint, as well as to the authorities of Belarus.

5.2. **Procedure for assessment of Community interest**

In accordance with Article 21 of the basic Regulation and in the event that the allegations of dumping and injury caused thereby are substantiated, a decision will be reached as to whether the adoption of anti-dumping measures would not be against the Community interest. For this reason the Community industry, importers, their representative associations, representative users and representative consumer organisations, provided that they prove that there is an objective link between their activity and the product concerned, may, within the general time limits set in paragraph 6(a)(ii) of this notice, make themselves known and provide the Commission with information. The parties which have acted in conformity with the precedent sentence may request a hearing setting the particular reasons why they should be heard within the time limit set in paragraph 6(a)(iii) of this notice. It should be noted that any information submitted pursuant to Article 21 will only be taken into account if supported by factual evidence at the time of submission.

6. **TIME LIMITS**

(a) *General time limits*

(i) For parties to request a questionnaire or other claim forms

All interested parties should request a questionnaire as soon as possible, but not later than 15 days after the publication of this notice in the *Official Journal of the European Union*.

(ii) For parties to make themselves known, to submit questionnaire replies and any other information

All interested parties, if their representations are to be taken into account during the investigation, must make themselves known by contacting the Commission, present their views and submit questionnaire replies or any other information (including the substantiated claims for individual treatment pursuant to Article 9(5) of the basic Regulation) within 40 days of the date of publication of this notice in the *Official Journal of the European Union*, unless otherwise specified. Attention is drawn to the fact that the exercise of most procedural rights set out in the basic Regulation depends on the party's making itself known within the aforementioned period.

Companies selected in a sample must submit questionnaire replies within the time limits specified in paragraph 6(b)(iii) of this notice.

(iii) H e a r i n g s

All interested parties may also apply to be heard by the Commission within the same 40 day time limit.

(b) *Specific time limit in respect of sampling*

(i) The information specified in paragraph 5.1(a)(i) and 5.1(a)(ii) should reach the Commission within 15 days of the date of publication of this notice in the *Official Journal of the European Union*, given that the Commission intends to consult parties concerned that have expressed their willingness to be included in the sample on its final selection within a period of 21 days of the publication of this notice in the *Official Journal of the European Union*.

(ii) All other information relevant for the selection of the sample as referred to in 5.1(a)(iii) must reach the Commission within a period of 21 days of the publication of this notice in the *Official Journal of the European Union*.

(iii) The questionnaire replies from sampled parties must reach the Commission within 37 days from the date of the notification of their inclusion in the sample.

(c) *Specific time limit for the selection of the market economy country*

Parties to the investigation may wish to comment on the appropriateness of the United States of America which, as mentioned in paragraph 5.1(d) of this notice, is envisaged as a market-economy country for the purpose of establishing normal value in respect of Belarus. These comments must reach the Commission within 10 days of the date of publication of this notice in the *Official Journal of the European Union*.

7. **WRITTEN SUBMISSIONS, QUESTIONNAIRE REPLIES AND CORRESPONDENCE**

All submissions and requests made by interested parties must be made in writing (not in electronic format, unless otherwise specified and must indicate the name, address, e-mail address, telephone and fax, and/or telex numbers of the interested party). All written submissions, including the information requested in this notice, questionnaire replies and correspondence provided by interested parties on a confidential basis shall be labelled as 'Limited' [1] and, in accordance with Article 19(2) of the basic Regulation, shall be accompanied by a non-confidential version, which will be labelled 'For inspection by interested parties'.

Commission address for correspondence:

European Commission
Directorate General for Trade
Directorate B
Office: J-79 5/16
Fax (32 2) 295 65 05
Telex COMEU B 21877.

8. **NON-CO-OPERATION**

In cases in which any interested party refuses access to or does not provide the necessary information within the time limits, or significantly impedes the investigation, provisional or final findings, affirmative or negative, may be made in accordance with Article 18 of the basic Regulation, on the basis of the facts available.

Where it is found that any interested party has supplied false or misleading information, the information shall be disregarded and use may be made, in accordance with Article 18 of the basic Regulation, of the facts available. If an interested party does not co-operate, or co-operates only partially, and use of the best facts available is made, the result may be less favourable than if it had co-operated.

9. **SCHEDULE OF THE INVESTIGATION**

The investigation will be concluded, according to Article 6(9) of the basic Regulation within 15 months of the date of the publication of this notice in the *Official Journal of the European Union*. According to Article 7(1) of the basic Regulation, provisional measures may be imposed no later than 9 months from the publication of this notice in the *Official Journal of the European Union*.

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[1] This means that the document is for internal use only. It is protected pursuant to Article 4 of Regulation (EC) No 1049/2001 of the European Parliament and of the Council (OJ L 145, 31.5.2001, p. 43). It is a confidential document pursuant to Article 19 of Council Regulation (EC) No 384/96 (OJ L 56, 6.3.1996, p. 1) and Article 6 of the WTO Agreement on Implementation of Article VI of the GATT 1994 (Anti-dumping Agreement).

Authorisation for State aid pursuant to Articles 87 and 88 of the EC Treaty

Cases where the Commission raises no objections

(2004/C 24/06)

Date of adoption of the decision:	3.12.2003
Member State:	Austria (Steiermark)
Aid No:	N 204/03
Title:	Directive on measures to combat fire blight (Erwinia amylovora) and to compensate related losses in commercial fruit growing
Objective:	Prevention of fire blight. Where the authorities have imposed clearing of the orchard affected by fire blight the fruit growing enterprise can apply for compensation for losses if it proves that the clearing has taken place as ordered. Furthermore, the enterprise has to enter into an obligation to restore the fruit growing area to production by 30th April of the second year following the clearing. The losses of the fruit growing enterprise will be individually calculated by the Styrian plant protection authority (Amtlicher Pflanzenschutzdienst Steiermark). The following losses are eligible: (1) the loss of income in the year the clearing takes place; (2) the replanting costs; (3) the loss of income in the years following replanting; (4) the clearing costs. The aid is 30 % of the above losses and clearing costs. The aid may not be combined with any other aid
Legal basis:	Richtlinie über Bekämpfungsmaßnahmen und die Schadensabgeltung bei Feuerbrand im Erwerbsobstbau
Budget:	Not yet known, because no cases of fire blight have been reported so far in Steiermark
Aid intensity or amount:	30 % of the eligible costs
Duration:	Unlimited

The authentic text(s) of the decision, from which all confidential information has been removed, can be found at

http://europa.eu.int/comm/secretariat_general/sgb/state_aids

Prior notification of a concentration

(Case COMP/M.3249 — Candover/JPMP/3i/ABB)

Candidate case for simplified procedure

(2004/C 24/07)

(Text with EEA relevance)

1. On 20 January 2004 the Commission received a notification of a proposed concentration pursuant to Article 4 of Council Regulation (EEC) No 4064/89 [1], as last amended by Regulation (EC) No 1310/97 [2], by which the undertakings Candover Partners Limited ('Candover', United Kingdom), belonging to the Candover Investments plc group, JPMP Capital Corp. ('JPMP', USA), belonging to the J. P. Morgan Chase & Co. Group, and 3i Group plc ('3i', United Kingdom) belonging to the 3i Group plc, acquire within the meaning of Article 3(1)(b) of the Regulation, joint control of parts of a business division of ABB Group Ltd ('ABB', Switzerland) by way of purchase of shares and assets.

2. The business activities of the undertakings concerned are:

— Candover: private equity company,

— JPMP: international private equity company,

— 3i: international venture capital company,

— ABB (the acquired activities): products and services to the oil, gas and petroleum industry.

3. On preliminary examination, the Commission finds that the notified concentration could fall within the scope of Regulation (EEC) No 4064/89. However, the final decision on this point is reserved. Pursuant to the Commission Notice on a simplified procedure for treatment of certain concentrations under Regulation (EEC) No 4064/89 [3], it should be noted that this case is a candidate for treatment under the procedure set out in the notice.

4. The Commission invites interested third parties to submit their possible observations on the proposed operation.

Observations must reach the Commission not later than 10 days following the date of this publication. Observations can be sent by fax (No (32-2) 296 43 01 or 296 72 44) or by post, under reference COMP/M.3249 — Candover/JPMP/3i/ABB, to:

European Commission,
Directorate-General for Competition,
Merger Registry,
J-70,
B-1049 Brussels.

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[1] OJ L 395, 30.12.1989, p. 1; corrigendum: OJ L 257, 21.9.1990, p. 13.

[2] OJ L 180, 9.7.1997, p. 1; corrigendum: OJ L 40, 13.2.1998, p. 17.

[3] OJ C 217, 29.7.2000, p. 32.

III

(Notices)

COMMISSION

Operation of scheduled air services

Invitation to tender issued by France pursuant to Article 4(1)(d) of Council Regulation (EEC) No 2408/92 for the operation of scheduled air services between Tarbes (Lourdes-Pyrénées) and Paris (Orly)

(2004/C 24/08)

(Text with EEA relevance)

1. **Introduction:** Pursuant to Article 4(1)(a) of Regulation (EEC) No 2408/92 of 23 July 1992 on access for Community air carriers to intra-Community air routes, France has decided to impose public service obligations on scheduled air services between the airports of Tarbes (Lourdes-Pyrénées) and Paris (Orly). The standards required by these public service obligations were published in the *Official Journal of the European Union* No C 22 of 27 January 2004.

   If on 1 April 2004 no air carrier has commenced or is about to commence operating scheduled air services between Tarbes (Lourdes-Pyrénées) and Paris (Orly) in accordance with the public service obligations imposed and without requesting financial compensation, France has decided, in accordance with the procedure laid down in Article 4(1)(d) of the abovementioned regulation, to limit access to a single air carrier and to offer the right to operate such services from 1 May 2004 by public tender.

2. **Subject of the invitation to tender:** Operation from 1 May 2004 of scheduled air services between Tarbes (Lourdes-Pyrénées) and Paris (Orly) in accordance with the public service obligations imposed on this route, as published in the *Official Journal of the European Union* No C 22 of 27 January 2004.

3. **Participation in the invitation to tender:** All Community air carriers who hold a valid operating licence issued in accordance with Council Regulation (EEC) No 2407/92 of 23 July 1992 on licensing of air carriers may take part.

4. **Tender procedure:** This invitation to tender is subject to the provisions of Article 4(1)(d), (e), (f), (g), (h) and (i) of Regulation (EEC) No 2408/92.

5. **Tender dossier:** The full tender dossier, including the specific rules for this invitation to tender and the public service delegation agreement and its technical annex (text of the public service obligation published in the *Official Journal of the European Union*) is obtainable free of charge from:

   Chambre de commerce et d'industrie de Tarbes et des Hautes-Pyrénées, Centre Kennedy, BP 350, F-65003 Tarbes Cedex. Tel.: 33 (0)5 62 51 88 88. Fax: 33 (0)5 62 44 14 38.

6. **Financial compensation:** Tenders must explicitly state the amount of compensation required for the operation of the route for three years from the planned date of commencement of operation (with an annual breakdown). The exact amount of compensation finally granted will be determined annually ex post on the basis of the costs and revenue actually generated by the service, within the limits of the amount stated in the tender. This maximum limit may be revised only in the event of unforeseen changes in operating conditions.

   The annual payments will be made in the form of instalments and a balance. The balance will be paid only after approval of the carrier's accounts for the route in question and verification that the service has been operated in accordance with the conditions laid down in point 8 below.

   In the event of termination of the contract before its normal expiry date, point 8 will be applied as soon as possible to allow payment to the carrier of the balance due, the maximum amount referred to in the first subparagraph being reduced, where appropriate, in proportion to the actual duration of the service.

7. **Duration of the contract:** The duration of the contract (public service delegation agreement) is three years from the date scheduled for the beginning of the services mentioned in point 2 of this invitation to tender.

8. **Verification of the operation of the service and of the carrier's accounts:** The operation of the service and the carrier's cost accounting for the route in question will be examined at least once a year in cooperation with the carrier.

9. **Cancelletion and notice:** The contract may be cancelled by either contracting party before the end of the normal period of validity by giving six months' advance notice. Should the carrier fail to comply with a public service obligation, he shall be deemed to have terminated the contract without notice if he fails to resume the service in accordance with the public service obligation within one month of the serving of formal notice.

10. **Penalties:** Failure by the carrier to observe the period of notice referred to in point 9 will be subject either to a fine of up to 7 622,45 EUR in application of Article R.330-20 of the Civil Aviation Code, or to a penalty calculated according to the number of months of default and the real deficit of the service for the year concerned, with a ceiling of the maximum financial compensation provided for in point 6.

    Should the carrier fail to comply with the public service obligations, he may be deemed to have terminated the contract without notice.

    Should the carrier fail in a limited way to comply with the public service obligations, the maximum financial compensation provided for in point 6 shall be reduced, without prejudice to the application of the provisions of Article R.330.20 of the Civil Aviation Code. Such reductions shall take account, as appropriate, of the number of flights cancelled for reasons directly attributable to the carrier, the number of flights made with less than required capacity, the number of flights not complying with the public service obligations regarding stopovers, the number of flights not complying with the public service obligations regarding time at destination, fares charged or the use of computerised reservation services.

11. **Submission of tenders:** Tenders must be sent by registered letter with acknowledgement of receipt, date as postmarked, or delivered by hand with receipt, at the earliest on month and at the latest five weeks after the date of publication of this invitation to tender in the *Official Journal of the European Union* before 17.00 (local time) to the following address:

    Chambre de commerce et d'industrie de Tarbes et des Hautes-Pyrénées, Centre Kennedy, BP 350, F-65003 Tarbes Cedex. Tel.: 33 (0)5 62 51 88 88. Fax: 33 (0)5 62 44 14 38.

12. **Validity of the invitation to tender:** In accordance with Article 4(1)(d) of Regulation (EEC) No 2408/92 of 23 July 1992, the validity of this invitation to tender is subject to the condition that no Community carrier presents by 1 April 2004 a programme for operating the route in question from 1 May 2004 in accordance with the public service obligations imposed, without receiving any financial compensation.

Operation of scheduled air services

Invitation to tender issued by France under Article 4(1)(d) Council Regulation (EEC) No 2408/92 for the operation of scheduled air services between Toulon-Hyères and Lyon-Saint-Exupéry

(2004/C 24/09)

(Text with EEA relevance)

1. **Introduction:** Pursuance of Article 4(1)(a) of Regulation (EEC) No 2408/92 of 23 July 1992 on access for Community air carriers to intra-Community air routes, France has decided to impose public service obligations in respect of scheduled air services operated between Toulon-Hyères and Lyon-Saint-Exupéry. The terms of these public service obligations were published in the *Official Journal of the European Union* No C 22 of 27.1.2004.

   Insofar as by 1 April 2004, no air carrier has commenced or is about to commence scheduled air services between Toulon-Hyères and Lyon-Saint-Exupéry in accordance with the public service obligations imposed and without requesting financial compensation, France has decided, in the accordance with the procedure laid down in Article 4(1)(d) of that Regulation, to limit access to only one air carrier and to offer by public tender the right to operate such services from 1 May 2004.

2. **Object of hte invitation to tender:** Operation from 1 May 2004 of scheduled air services between Toulon-Hyères and Lyon-Saint-Exupéry in accordance with the public service obligations imposed on that route and published in the *Official Journal of the European Union* No C 22 of 27.1.2004.

3. **Participation:** Participation is open to all carriers holding a valid operating licence issued by a Member State under Council Regulation (EEC) No 2407/92 of 23.7.1992 on licensing of air carriers.

4. **Tender procedure:** This invitation to tender is subject to points (d), (e), (f), (g), (h) and (i) of Article 4(1) of Regulation (EEC) No 2408/92.

5. **Tender dossier:** The complete tender dossier, comprising the specific rules for this invitation to tender and the public service delegation agreement together with its technical annex (text of the public service obligation published in the *Official Journal of the European Communities*) may be obtained free of charge from:

   l'Aéroport Toulon-Hyères, Direction, boulevard de la Marine, F-83418 Hyères Cedex. Tel.: (33) 4 94 00 84 03. Fax: (33) 4 94 00 84 13

6. **Financial compensation:** The tenders submitted will indicate the amount required by way of compensation for operating the service for three years from the scheduled starting date (with an annual breakdown). The exact amount of compensation finally granted will be determined each year ex-post on the basis of the costs and revenue actually generated by the service, within the limits of the amount stated in the tender. This maximum limit may be revised only in the event of unforeseen changes in operating conditions.

   The annual payments will be made in the form of instalments and a balance. The balance will be paid only after approval of the carrier's accounts for the route in question and verification that the service has been operated in accordance with the conditions laid down in point 8 below.

   In the event of termination of the contract before its normal expiry date, point 8 will be applied as soon as possible to allow payment to the carrier of the balance due, the maximum amount referred to in the first subparagraph being reduced, where appropriate, in proportion to the actual duration of the service.

7. **Duration of the contract:** The duration of the contract (public service delegation agreement) is three years from the date scheduled for the beginning of the services mentioned in point 2 of this invitation to tender.

8. **Verification of the operation of the service and of the carrier's accounts:** The operation of the service and the carrier's cost accounting for the route in question will be the subject of at least one annual examination in cooperation with the carrier.

9. **termination of contract and notice:** The contract may be terminated by either party before its normal expiry date only six months' notice is given. If the carrier fails to respect a public service obligation, it shall be deemed to have terminated the contract without notice if it does not resume the service in accordance with the public service obligation within one month of the serving of formal notice.

10. **Penalties:** Failure by the carrier to observe the period of notice referred to in point 9 will be subject either to an administrative fine of up to 7 622,45 EUR pursuant to Article R.330-20 of the Civil Aviation Code or to a penalty calculated on the basis of the number of months of default and the real operating loss of the service during the year in question, not exceeding the maximum financial compensation provided for in point 6.

    In the event of serious breaches of the public service obligation, the contract may be cancelled and the carrier deemed to have terminated the contract without notice.

    In the event of minor breaches of the public service obligation, the maximum financial compensation provided for in point 6, shall be reduced, without prejudice to the application of the provisions of Article R330-20 of the Civil Aviation Code. Such reductions shall take account, where appropriate, of the number of flights cancelled for reasons attributable to the carrier, the number of flights made with a capacity lower than that required, the number of flights which failed to comply with the public service obligation as regards stopovers, and the number of days on which the public service obligation was not complied with as reagards time at destination, fares charged, and the use of computerised reservation services.

11. **Submission of tenders:** Tenders must be sent by registered letter with acknowledgement of receipt, the postmark serving as proof, or delivered by hand with receipt, at the latest six weeks from the date of publication of this invitation to tender in the *Official Journal of the European Union*, before 17.00 hours (local time) to the following address:

    Chambre de Commerce et d'Industrie du Var, Service juridique, 236, boulevard Maréchal Leclerc, BP 5501, F-83 097 Toulon Cedex. Tel.: 33.(0)4.94.22.80.00. Fax: 33.(0)4.94.22.80.01.

12. **Validity of the invitation to tender:** In accordance with Article 4(1)(d) of Regulation (EEC) No 2408/92 of 23 July 1992, the validity of this invitation to tender is subject to the condition that no Community carrier presents by 1 April 2004 a programme for operating the route in question as from 1 May 2004, in accordance with the public service obligations imposed, without receiving any financial compensation.

Operation of scheduled air services

Invitation to tender issued by France under Article 4(1)(d) of Council Regulation (EEC) No 2408/92 in respect of the operation of scheduled air services between Épinal and Paris (Orly)

(2004/C 24/10)

(Text with EEA relevance)

1. **Introduction:** Pursuant to Article 4(1)(a) of Regulation (EEC) No 2408/92 of 23 July 1992 on access for Community air carriers to intra-Community air routes, France has decided to impose public service obligations in respect on scheduled air services operated between Épinal and Paris (Orly). The terms of these public service obligations were published in the *Official Journal of the European Union* No C 22 of 27 January 2004.

    Infsofar as by 1 April 2004 no air carrier has commenced or is about to commence scheduled air services between Épinal and Paris (Orly) in accordance with the public service obligations imposed and without requesting financial compensation, France has decided in accordance with the procedure laid down by Article 4(1)(d) of that regulation, to limit access to only one air carrier and to offer by public tender the right to operate such services from 1 May 2004.

2. **Object of invitation to tender:** Operation from 1 May 2004 of scheduled air services between Épinal and Paris (Orly) in accordance with the public service obligations imposed on that route and published in the *Official Journal of the European Union* No C 22 of 27 January 2004.

3. **Participation:** Participation is open to all air carriers holding a valid operating licence issued by a Member State under Council Regulation (EEC) No 2407/92 of 23 July 1992 on licensing of air carriers.

4. **Tender procedure:** This invitation to tender is subject to points d, e, f, g, h and i of Article 4(1) of Regulation (EEC) No 2408/92.

5. **Tender dossier:** The complete tender dossier, comprising the specific rules governing the invitation to tender and the public service delegation agreement together with its technical annex (text of the public service obligations published in the *Official Journal of the European Union*) may be obtained free of charge from:

   Chambre de commerce et d'industrie d'Épinal, 10, rue Claude Gelée, F-88026 Épinal Cedex. Tel.: 33 (0)3 29 35 18 14. Fax: 33 (0)3 29 64 01 88. E-mail: cci@epinal.cci.fr. URL: www.epinal.cci.fr.

   A brochure on Épinal-Mirecourt airport and a brochure on the demographic and socio-economic situation of the airport's catchment area can be obtained free of charge from the same address.

6. **Financial compensation:** The tenders submitted will indicate the amount required by way of compensation for operating the service for three years from the scheduled stating date (with an annual breakdown) The exact amount of compensation finally granted will be determined each year ex post on the basis of the costs and revenue actually generated by the service, within the limits of the amount stated in the tender. This maximum limit may be revised only in the event of an unforeseen change in the operating conditions.

   The annual payments will be made in the form of instalments and a balance. The balance will be paid only after approval of the carrier's accounts for the route in question and verification that the service has been operated in accordance with the conditions laid down in point 8 below.

   In the event of termination of the contract before its normal expiry date, point 8 will be applied as soon as possible to allow payment to the carrier of the balance due, the maximum amount referred to in the first subparagraph being reduced, where appropriate, in proportion to the actual duration of the service.

7. **Duration of the contract:** The duration of the contract (public service delegation agreement) is three years from the date scheduled for the beginning of the services mentioned in point 2 of this invitation to tender.

8. **Verification of the operation of the service and of the carrier's accounts:** The operation of the service and the carrier's cost accounting for the route in question will be the subject of at least one annual examination.

9. **Termination of contract and notice:** The contract may be terminated by either party before its normal expiry date only if six months' notice is given. If the carrier fails to respect a public service obligation, it shall be deemed to have terminated the contract without notice if it does not resume the service in accordance with the public service obligation within one month of the serving of formal notice.

10. **Penalties:** Failure by the carrier to observe the period of notice referred to in point 9 will be subject either to an administrative fine of up to 7 622,45 EUR pursuant to Article R.330-20 of the Civil Aviation Code, or to a penalty calculated on the basis of the number of months of default and the real operating loss of the service during the year in question, not exceeding the maximum financial compensation provided for in point 6.

    In the event of serious breaches of the public service obligation, the contract may be cancelled and the carrier deemed to have terminated the contract without notice.

    In the event of minor breaches of the public service obligation, the maximum financial compensation provided for in point 6 shall be reduced, without prejudice to the application of the provisions of Article R.330-20 of the Civil Aviation Code. Such reductions shall take account, where appropriate, of the number of flights cancelled for reasons attributable to the carrier, the number of flights made with a capacity lower than that required, the number of flights which failed to comply with the public service obligation as regards stopovers, and the number of days on which the public service obligation was not complied with as regards time at destination, fares charged, and the use of computerised reservation services.

11. **Submission of tenders:** Tenders must be sent by registered letter with acknowledgement of receipt, the postmark serving as proof, or delivered by hand with receipt, at the latest six weeks from the date of publication of this invitation to tender in the *Official Journal of the European Union*, before 17.00 (local time) to the following address:

    Chambre de commerce et d'industrie d'Épinal, 10, rue Claude Gelée, F-88026 Épinal Cedex. Tel.: 33 (0)3 29 35 18 14. Fax: 33 (0)3 29 64 01 88. E-mail: cci@epinal.cci.fr. URL: www.epinal.cci.fr.

12. **Validity of invitation to tender:** In accordance with Article 4(1)(d) of Regulation (EEC) No 2408/92 of 23 July 1992, the validity of this invitation to tender is subject to the condition that no Community carrier presents by 1 April 2004 a programme for operating the route in question as from 1 May 2004, in accordance with the public service obligations imposed, without receiving any financial compensation.

Operation of scheduled air services

Invitation to tender issued by France pursuant to Article 4(1)(d) of Council Regulation (EEC) No 2408/92 for the operation of scheduled air services between Saint-Étienne (Bouthéon) and Paris (Orly)

(2004/C 24/11)

(Text with EEA relevance)

1. **Introduction:** Pursuant to Article 4(1)(a) of Regulation (EEC) No 2408/92 of 23 July 1992 on access for Community air carriers to intra-Community air routes, France has decided to impose public service obligations on scheduled air services between the airports of Saint-Étienne (Bouthéon) and Paris (Orly). The standards required by these public service obligations were published in the *Official Journal of the European Communities* No C 194 of 14 August 2002.

   If on 1 March 2004 no air carrier has commenced or is about to commence operating scheduled air services between Saint-Étienne (Bouthéon) and Paris (Orly) in accordance with the public service obligations imposed and without requesting financial compensation, France has decided, in accordance with the procedure laid down in Article 4(1)(d) of the abovementioned regulation, to limit access to a single air carrier and to offer the right to operate such services from 1 May 2004 by public tender.

2. **Subject of the invitation to tender:** Operation from 1 May 2004 of scheduled air services between Saint-Étienne (Bouthéon) and Paris (Orly) in accordance with the public service obligations imposed on this route, as published in the *Official Journal of the European Communities* No C 194 of 14 August 2002.

3. **Participation in the invitation to tender:** All Community air carriers who hold a valid operating licence issued in accordance with Council Regulation (EEC) No 2407/92 of 23 July 1992 on licensing of air carriers may take part.

4. **Tender procedure:** This invitation to tender is subject to the provisions of Article 4(1)(d), (e), (f), (g), (h) and (i) of Regulation (EEC) No 2408/92.

5. **Tender dossier:** The full tender dossier, including the specific rules for this invitation to tender and the public service delegation agreement and its technical annex (text of the public service obligation published in the *Official Journal of the European Communities*) is obtainable free of charge from:

   Chambre de commerce et d'industrie de Saint-Étienne Bouthéon / Montbrison, direction administrative et financière, 57, Cours Fauriel, F-42024 Saint-Étienne Cedex 2. Tel.: 04.77.43.04.42. Fax: 04.77.43.04.14.

6. **Financial compensation:** Tenders must explicitly state the amount of compensation required for the operation of the route for three years from the planned date of commencement of operation (with an annual breakdown). The exact amount of compensation finally granted will be determined annually ex post on the basis of the costs and revenue actually generated by the service, within the limits of the amount stated in the tender. This maximum limit may be revised only in the event of unforeseen changes in operating conditions.

   The annual payments will be made in the form of instalments and a balance. The balance will be paid only after approval of the carrier's accounts for the route in question and verification that the service has been operated in accordance with the conditions laid down in point 8 below.

   In the event of termination of the contract before its normal expiry date, point 8 will be applied as soon as possible to allow payment to the carrier of the balance due, the maximum amount referred to in the first subparagraph being reduced, where appropriate, in proportion to the actual duration of the service.

7. **Duration of the contract:** The duration of the contract (public service delegation agreement) is three years from the date scheduled for the beginning of the services mentioned in point 2 of this invitation to tender.

8. **Verification of the operation of the service and of the carrier's accounts:** The operation of the service and the carrier's cost accounting for the route in question will be examined at least once a year in cooperation with the carrier.

9. **Cancellation and notice:** The contract may be cancelled by either contracting party before the end of the normal period of validity by giving six months' advance notice. Should the carrier fail to comply with a public service obligation, he shall be deemed to have terminated the contract without notice if he fails to resume the service in accordance with the public service obligation within one month of the serving of formal notice.

10. **Penalties:** Failure by the carrier to observe the period of notice referred to in point 9 will be subject either to a fine of up to 7 622,45 EUR, in application of Article R.330-20 of the Civil Aviation Code or to a penalty calculated according to the number of months of default and the real deficit of the service for the year concerned, with a ceiling of the maximum financial compensation provided for in point 6.

    Should the carrier fail to comply with the public service obligations, he may be deemed to have terminated the contract without notice.

    Should the carrier fail in a limited way to comply with the public service obligations, the maximum financial compensation provided for in point 6 shall be reduced, without prejudice to the application of the provisions of Article R.330.20 of the Civil Aviation Code. Such reductions shall take account, as appropriate, of the number of flights cancelled for reasons directly attributable to the carrier, the number of flights made with less than the required capacity, the number of flights not complying with the public service obligations regarding stopovers, the number of flights not complying with the public service obligations regarding time at destination, fares charged or the use of computerised reservation services.

11. **Submission of tenders:** Tenders must be sent by registered letter with acknowledgement of receipt, date as postmarked, or delivered by hand with receipt, at the earliest one month and at the latest five weeks after the date of publication of this invitation to tender in the Official Journal of the European Union before 17.00 (local time) to the following address:

    Chambre de commerce et d'industrie de Saint-Étienne Bouthéon / Montbrison, 57, Cours Fauriel, F-42024 Saint-Étienne Cedex 2. Tel.: 04.77.43.04.42. Fax: 04.77.43.04.14.

12. **Validity of the invitation to tender:** In accordance with Article 4(1)(d) of Regulation (EEC) No 2408/92 of 23 July 1992, the validity of this invitation to tender is subject to the condition that no Community carrier presents by 1 April 2004 a programme for operating the route in question as from 1 May 2004 in accordance with the public service obligations imposed, without receiving any financial compensation.