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Medical devices utilizing animal tissues and their derivatives —

Part 2: Controls on sourcing, collection and handling

Dispositifs médicaux utilisant des tissus animaux et leurs dérivés —

Partie 2: Contrôles de l'origine, de la collecte et du traitement

Reference number
ISO 22442-2:2007(E)

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 22442-2 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*.

ISO 22442 consists of the following parts, under the general title *Medical devices utilizing animal tissues and their derivatives*:

— *Part 1: Application of risk management*

— *Part 2: Controls on sourcing, collection and handling*

— *Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

Introduction

Certain medical devices utilize materials of animal origin.

Animal tissues and their derivatives are used in the design and manufacture of medical devices to provide performance characteristics that have been chosen for advantages over non-animal based materials. The range and quantities of materials of animal origin in medical devices vary. These materials can comprise a major part of the device (e.g. bovine/porcine heart valves, bone substitutes for use in dental or orthopaedic applications, haemostatic devices), can be a product coating or impregnation (e.g. collagen, gelatine, heparin), or can be used in the device manufacturing process (e.g. tallow derivatives such as oleates and stearates, foetal calf serum, enzymes, culture media).

Tissues and derivatives for use in medical devices are typically obtained by the manufacturer from a range of sources such as animal herds or flocks and commercial harvesting (including fishing). Some specialized industries also process materials of animal origin to manufacture a finished product (e.g. gelatine) which is incorporated as a raw material into the finished medical device by the manufacturer.

NOTE To show compliance with this part of ISO 22442, its specified requirements should be fulfilled. The guidance given in the Notes and informative annexes is not normative and is not provided as a checklist for auditors.

Medical devices utilizing animal tissues and their derivatives —

Part 2:
Controls on sourcing, collection and handling

1 Scope

This part of ISO 22442 specifies requirements for controls on the sourcing, collection and handling (which includes storage and transport) of animals and tissues for the manufacture of medical devices utilizing materials of animal origin, other than *in vitro* diagnostic medical devices. It applies where required by the risk management process as described in ISO 22442-1.

NOTE 1 Selective sourcing is considered to be especially important for transmissible spongiform encephalopathy (TSE) risk management.

NOTE 2 Manufacturers should refer to ISO 22442-3 for information on the validation of the elimination and/or inactivation of viruses and TSE agents.

This part of ISO 22442 does not cover the utilization of human tissues in medical devices.

This part of ISO 22442 does not specify a quality management system for the control of all stages of production of medical devices.

NOTE 3 It is not a requirement of this part of ISO 22442 to have a full quality management system during manufacture, but it does specify requirements for some of the elements of a quality management system. Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. The quality management system elements that are required by this part of ISO 22442 can form a part of a quality management system conforming to ISO 13485.

NOTE 4 A general principle for the application of ISO 22442 is that it is advisable to give due consideration to the requirements and recommendations contained in all three parts of the standard.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 22442-1:2007, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 22442-1 and the following apply.

3.1
collection
removal of tissues from animals

3.2
low risk herd
closed herd
herd of bovine animals in which for at least the previous eight years:

a) there has been documented veterinary monitoring;

b) there has been no case of BSE;

c) there has been no feeding of mammalian-derived protein;

d) there is a fully documented breeding history;

e) there is a fully documented use of veterinary medicines and vaccines;

f) each animal is traceable;

g) genetic material has been introduced only from herds with the same BSE-free status

NOTE By analogy, low risk herd is applicable to other species naturally affected by TSE. Additional precautionary measures may be required.

3.3
veterinarian
person designated by the relevant competent authority as suitably qualified for the responsibility delegated to him or her relating to ante- and post-mortem inspection of animals and/or relevant certification

NOTE 1 Under certain jurisdictions it is a requirement that the veterinarian be a professionally qualified person in veterinary medicine.

NOTE 2 Under certain jurisdictions the function of inspection and of certification can be carried out by different individuals. In such cases, the certificate can be signed by a person who is not designated by the competent authority. This function is covered in the quality management system of the medical device manufacturer.

4 General requirements

4.1 General

Apply the requirements of this part of ISO 22442 as determined by the risk assessment (see ISO 22442-1).

Annex A shall be applied as appropriate.

4.2 Quality system elements

A documented system shall be established and maintained to control the quality of materials of animal origin and shall be verified by the medical device manufacturer. Specific requirements relating to collection are included in Clause 6.

This system shall address the animal source and the following factors:

a) specification of the geographical origin (such as country or region) of the animal material, state of health of the animals, and acceptance criteria for animals taking into account the source-species, perceived risk from pathogens and ability to obtain appropriate assurances;

NOTE 1 The geographical origin can include the animal's place of birth and the countries or regions in which it has lived during its lifetime, as well as its place of slaughter. It is advisable that the manufacturer document the extent to which the geographical origin of the animal can be traced taking into account the application of risk management (see ISO 22442-1).

b) hygiene and quality assurance requirements to be met by the slaughterer, including the provisions in the slaughterhouse to prevent cross-contamination within and between animals;

c) procedures for the collection, preservation, handling, storage and transport of materials of animal origin;

d) documented evidence of the effectiveness of controls defined in a), b) and c);

e) records to be maintained (including as a minimum items a), b), c) and d); see also 5.5).

For the control of processed animal material suppliers, the medical device manufacturer shall document, to the extent feasible, the practices of the specialized industries to which clauses of the various parts of ISO 22442 have been applied.

NOTE 2 Manufacturers should apply relevant provisions of ISO 22442 to natural substances such as milk, hair and wool, although these are not covered by the definition of derivatives.

NOTE 3 The use of risk analysis/risk management tools (such as HACCP, FMEA, see Annex G of ISO 14971:2007) are useful in determining residual risk.

4.3 Procedures

The documented procedures and instructions required by this part of ISO 22422 shall be established, implemented and maintained. These procedures and instructions shall be approved on issue and shall be controlled as follows.

The manufacturer shall establish and maintain procedures to control all documents and data that relate to the requirements of this part of ISO 22442. These documents shall be reviewed and approved for adequacy by authorized personnel prior to issue.

This control shall ensure that

a) the pertinent issues of appropriate documents are available at all locations where operations essential to the effective functioning of the quality system are performed and

b) obsolete documents are promptly removed from all points of issue or use.

Changes to documents shall be reviewed and approved by the same functions/organizations that performed the original review and approval unless specifically designated otherwise. The designated organizations shall have access to pertinent background information upon which to base their review and approval.

Where practicable, the nature of each change shall be identified in the document or the appropriate attachments.

A master list or equivalent document control procedure shall be established to identify the current revision of documents in order to preclude the use of non-applicable documents.

4.4 Personnel

Responsibility for the collection, handling and storage of materials shall be assigned to qualified personnel as follows.

The manufacturer shall establish and maintain procedures for identifying the training needs and provide for the training of all personnel performing activities affecting quality.

The manufacturer shall ensure that personnel performing specific assigned tasks are qualified on the basis of appropriate education, training and/or experience as required. Appropriate records of training shall be maintained.

Personnel directly involved in the collection and handling of material of animal origin shall be personnel employed by the device manufacturer or designated and adequately trained abattoir employees or the equivalent. The same requirements apply to personnel of all subcontractors.

The manufacturer shall identify the in-house verification requirements, and shall provide adequate resources and assign trained personnel for verification activities.

Audits shall be carried out by personnel independent of those having direct responsibility for the work being performed.

4.5 Current regulatory requirements and guidance

Due account shall be taken of relevant current regional regulatory requirements or guidance, including the OIE International Animal Health Code [4].

5 Sourcing

5.1 General

Subclauses 5.2, 5.3, 5.4, 5.5, 5.6, and Clauses 6, 7 and 8, shall be applied by suppliers of animal materials, intermediaries and medical device manufacturers as relevant under the risk management plan in compliance with ISO 22442-1.

The animal material shall not be compromised by cross-contamination before, during or after slaughter. Animals shall be confirmed as having been declared fit for human consumption (see 5.5).

It is the responsibility of the manufacturer to ensure that the material is fit for its intended use.

5.2 Species and strain

For each material or derivative, the risk of certain diseases is dependent on the animal species and possibly strain, and this shall be taken into account for the establishment of control measures.

5.3 Geography

The risk of certain diseases is dependent on the geographical origin and this shall be taken into account for the establishment of control measures.

Geographical origin can include conception, birth, rearing and slaughtering (for bovine species, see Annex A).

If required by the risk management process, in the case of domesticated/farmed species the geographical region/country of birth and the summary of main locations of residence up to time of slaughter shall be recorded.

In the case of wild species, the region/location of capture and the country/region of birth shall be recorded if known. The use of wild mammalian species shall be addressed in the risk assessment (see ISO 22442-1).

5.4 Inspection

Sourcing of animal material shall be subject to control and individual inspection by a veterinarian. There will however be some source-species where this is not possible (e.g. fish, crustaceans). If individual animals cannot be inspected, the justification for this shall be documented and a relevant sampling plan provided.

Bovine, caprine, cervid, equine, ovine, and porcine species shall be subject to ante-mortem veterinary inspection. Animals showing locomotive system abnormalities or neurological disorders shall not be used for the production of medical devices except for tallow derivatives, animal charcoal, and amino acids that are acceptable as discussed in 4.4.2 and 4.4.3 of ISO 22442-1:2007 due to their processing and not their sourcing.

Prior to certification, a post-mortem inspection of bovine, caprine, cervid, equine, ovine, and porcine species shall be performed by a veterinarian immediately after slaughter according to local custom and practice. The inspection shall include at least:

a) visual inspection;

b) palpation of specified organs;

c) incision of organs and lymph nodes;

d) investigation of anomalies, e.g. inconsistency, colour and smell;

e) if necessary, laboratory tests.

Where indicated by risk assessment, for materials (including pooled blood supplies) for direct use in medical devices and that are not subject to a validated process to reduce TSE risk in line with ISO 22442-3, consideration shall be given to the application of a test for the presence of TSE in the source animal.

NOTE Animal tissues derived from certain species (e.g. fish, crustaceans) require a modified approach since veterinary surveillance is not practicable in the same way as for other animal tissues. Manufacturers should apply relevant sections of this International Standard to such materials but may need to rely on other procedures which have been shown to be effective for risk reduction (see ISO 22442-1).

5.5 Certification

Material of animal origin intended for utilization in medical devices shall originate from animals confirmed by a veterinarian as being fit for human consumption. Records to demonstrate conformance with veterinary inspection criteria at the abattoir, certificate details and source shall be available (see for example Annex B). For species where such certification by a veterinarian cannot be obtained, a status equivalent to “fit for human consumption” is required, such as a confirmation of apparent good health.

5.6 Traceability

Where the risk management undertaken according to ISO 22442-1 indicates that it is both necessary and feasible, a traceability system shall be established. The extent of traceability shall be defined by the outcome of the risk assessment taking into account those official information systems that exist.

NOTE Traceability may not be practicable if materials of animal origin are collected, pooled and manufactured by processed animal material suppliers.

6 Collection

6.1 Between the manufacturer of the medical device and the supplier of material of animal origin there shall be a technical agreement defining:

— the limits of responsibilities;

— specifications of the material;

— documentation;

— inspection criteria;

— procedures (including specific measures to prevent cross-contamination);

— audits;

— procedures for ensuring that all deliveries have traceability of relevant certificates.

Materials derived from TSE susceptible species (including pooled blood supplies), intended for direct use in medical devices and that are not subject to a validated process in line with ISO 22442-3 to reduce TSE risks to an acceptable level determined by the risk management process, shall be harvested from slaughterhouses designated by the medical device manufacturer.

6.2 The manufacturer shall be responsible for ensuring that the collection of the material is conducted in accordance with the documented procedures.

6.3 The manufacturer shall review and specify the systems for certification and traceability when tissues of animal origin are pooled at the place of slaughter or subsequently. The limits of pooling permitted shall be justified and documented.

7 Handling

7.1 If any material of animal origin requires further dissection or trimming, it shall be removed as soon as possible to an area separate from that used for slaughtering and collection. This area shall be suitably equipped and maintained at an appropriate level of cleanliness and environmental protection. Implements for dissection and trimming shall be kept clean to minimize risk of cross-contamination.

NOTE Ideally, a dedicated set of tools should be used for trimming and kept separate from the ones used for harvesting.

7.2 Source materials to be utilized in medical devices shall be segregated for delivery according to a documented procedure.

7.3 The manufacturer shall be responsible for ensuring that the handling of the material is conducted in accordance with documented procedures.

8 Storage and transport

8.1 Collected material shall be stored and transported in closed containers.

8.2 The conditions for storage and transport shall not compromise compliance with the relevant qualities of the animal material, in particular by environmental or enzymatic degradation or microbial proliferation.

8.3 The manufacturer shall be responsible for ensuring that the storage and transport of the material is conducted in accordance with documented procedures.

Annex A
(normative)

Additional requirements relating to the application of this part of ISO 22442 to bovine-sourced materials

A.1 Introduction

This annex contains requirements applicable to non-viable material derived from cattle and intended for use in medical devices. ISO 22442-1 requires that, for materials sourced from species that are susceptible to transmissible spongiform encephalopathies (TSEs), risk control measures are implemented and the overall TSE risk is estimated and assessed in relation to the medical benefits of the intended use, taking into account the availability of alternatives. These requirements apply to cattle that are susceptible to bovine spongiform encephalopathy (BSE) and that are used as a source of material for use in medical devices.

A variety of risk control measures can be applicable to a particular medical device (see Annex D of ISO 22442-1:2007). These need to be considered on a case-by-case basis to estimate the overall BSE risk and provide assurance that the residual risk of infectivity with the BSE agent is acceptably low. The overall BSE risk can be estimated by taking account of the following contributory factors:

a) the likelihood that the source material is infected with or contaminated by the BSE agent;

b) measures to remove or inactivate the BSE agent;

c) the extent and nature of human exposure to potentially infective material.

This annex addresses only the first of these factors, which, for many devices sourced from bovine material, is the principal method of TSE risk control.

NOTE 1 Annex C of ISO 22442-1:2007 contains specific requirements for certain animal materials or derivatives.

NOTE 2 Taking into account the current state of science and technology, similar principles to those discussed in this annex should also be applicable to other transmissible spongiform encephalopathies in animals.

NOTE 3 Equivalent measures may be applicable to caprine- and ovine-sourced materials.

A.2 General aspects

The BSE risk associated with the source material shall be estimated, taking into account the following factors:

a) the likelihood of infectivity in the source animals;

b) the infectivity of the source tissue;

c) measures to prevent cross-contamination from other animals or tissues.

When animal material sourced from more than one animal is pooled, and one is identified as high risk, this risk shall apply to the whole pool.

A.3 The likelihood of infectivity in the source animals

A.3.1 General

The likelihood of the BSE agent being present in the source cattle shall be estimated by reference to published assessments (see A.3.2.1, Note 1) and other relevant data, where applicable.

Where a low probability of infectivity in the source animals is a significant factor in the BSE risk estimate, the procurement and manufacturing processes shall incorporate measures to prevent cross-contamination from animals of higher BSE risk.

NOTE Clauses 6, 7, 8 and A.5 of this part of ISO 22442 can be applied in such situations.

The estimate of the likelihood that the BSE agent is present in the source cattle shall take into account the following factors.

A.3.2 The BSE status of the countries or regions of origin

A.3.2.1 General

In assessing the BSE status, consideration shall be given to each of the countries in which an animal has lived from birth, through rearing to slaughter. This information shall be taken into account in the risk assessment.

The incidence of BSE in cattle depends on the measures taken by national authorities to prevent, control or eradicate the disease. The accuracy of determinations of the incidence of disease depends on the extent and quality of surveillance measures. The best assurances can be given when the results of effective surveillance show that neither BSE nor scrapie exist in a country, region, herd or flock.

The BSE risk estimate relating to geographical sourcing shall take into account the prevalence of BSE infection in domestic cattle in the countries or regions, historical data on the importation of the BSE agent and an assessment of the effectiveness of the surveillance programme.

Assurance on the BSE risk for the relevant countries or regions shall be verified using the latest information on BSE status from national or regional authorities or OIE or FAO (http://www.fao.org). The manufacturer shall assess the incidence of BSE (including the trend, using at least the last eight years' data).

NOTE 1 Manufacturers should take into account published assessments relating to BSE risks associated with specific countries. For example, the European Union has published documents on Geographical BSE Risks (GBR) for a number of countries (available on the Web site of the Scientific Steering Committee of the Commission of the European Union: *http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html*). Additional GBR documents are available at the European Food Safety Authority Web site (*http://www.efsa.eu.int/science/tse_assessments/gbr_assessments/catindex_en.html*). The United States Department of Agriculture has published permitted and unauthorized source countries (published by the Animal And Plant Health Inspection Service, *http://www.aphis.usda.gov/vs/ncie/country.html#BSE*). Japan's Ministry of Health, Labor and Welfare also has published the list of permitted and unauthorized source countries (see Reference [7]). The OIE Terrestrial Code relating to BSE is available at http://www.oie.int/eng/normes/mcode/en_chapitre_2.3.13.htm.

NOTE 2 In particular, it is advisable to make reference to the chapters relating to BSE and, if relevant, scrapie, of the OIE Terrestrial Animal Health Code [4] and to any relevant guidance or legislation.

NOTE 3 Factors involved in the BSE status of a country include:

1) the incidence of the disease in the country;

2) whether or not there is compulsory notification of the disease (official veterinary surveillance);

3) whether or not there is compulsory clinical and laboratory verification of suspected cases;

4) whether or not there is an effective ban on feeding ruminant materials to animals;

5) whether or not BSE tests for cattle older than a specified age are mandatory;

6) whether or not Specified Risk Materials are removed and destroyed after slaughter;

7) whether or not “fallen stock”/animals with “downer syndrome” are subject to specific control, including testing for BSE.

The requirements and criteria given in A.3.2.2 to A.3.2.4 apply, depending on the geographical estimate of BSE risk.

A.3.2.2 Low geographical BSE risk

If BSE has not been previously recognised in the country or region of origin, the manufacturer shall obtain documentary evidence to confirm whether and when the disease became officially notifiable and whether and since when the source country has a veterinary service capable of detecting a low incidence of the disease (see Annex C).

NOTE Verification should be provided by reference to classification systems and information provided by national or regional authorities. These circumstances correspond to the EU classification, GBR I.

Material obtained from countries or regions where the presence of BSE in domestic cattle is considered highly unlikely may be considered to present no appreciable BSE risk, providing high infectivity tissues are excluded (see ISO 22442-1:2007, Table D.1).

Materials (including pooled blood supplies) for direct use in medical devices and that are not subject to a validated process to reduce TSE risk in line with ISO 22442-3 shall, where feasible, be sourced from countries or regions where the presence of BSE in domestic cattle is considered highly unlikely.

If animals from countries or regions with minimal exposure to BSE incidence are imported into a high incidence country for the purpose of medical device manufacturing, information on individual traceability of the animals within the importing country shall be assured, and risk of BSE cross-contamination shall be avoided.

A.3.2.3 Intermediate geographical BSE risk

If the country or region of origin has been confirmed as having limited exposure to BSE, the manufacturer shall obtain documentary evidence to confirm when the disease became officially notifiable, that individual BSE-affected animals are killed separately from those for human consumption and their carcasses completely destroyed, and that their progeny are not used as source animals, and on the effectiveness of the surveillance system in place.

NOTE Verification should be provided by reference to classification systems and information provided by national or regional authorities. These circumstances correspond to the EU classifications, GBR II and III.

Depending on the evaluation of overall residual risk acceptability (see 4.5 of ISO 22442-1:2007), additional risk control measures shall be considered for materials sourced from such countries or regions.

A.3.2.4 High geographical BSE risk

Materials derived from cattle which were born, reared and/or slaughtered in countries or regions where BSE has been confirmed at high incidence, shall not be used in the manufacture of medical devices, except as noted in A.3.2.5.

A.3.2.5 Particular circumstances

In particular circumstances, the evaluation of overall residual risk acceptability (see 4.5 of ISO 22442-1:2007) can conclude that the measures prevent cross-contamination.

Precautions shall be taken to avoid cross-contamination during slaughter, collection, handling, storage and transport of animal material.

The manufacturer of the medical device shall document and justify the method of stunning used and whether the tissues are to be derived from single animals or are to be pooled.

It has been demonstrated that stunning by a 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. There is evidence that non-penetrative stunning can cause some Central Nervous System (CNS) embolism. The methods of stunning shall be described.

NOTE 1 Additional information on stunning technique can be found in SSC Opinion on methods of stunning and BSE risk (The risk of dissemination of brain particles into the blood and carcass when applying certain methods of stunning) adopted at the meeting on 10-11 January 2002 (http://europa.eu.int/comm/food/fs/sc/ssc/out245_en.pdf) and Opinion of the EFSA Working Group on BSE risk from dissemination of brain particles in blood and carcass. Question No. EFSA-Q-2003-122 adopted on 21 October 2004 (http://www.efsa.europa.eu/en/science/biohaz/biohaz_opinions/731.html).

The following practices shall be adopted, unless a validated manufacturing process is to be used which has been shown to inactivate or remove TSE agents:

a) for all materials, the potential for extraneous contamination shall be minimized, especially in countries with known cases of BSE; for materials which are not pooled at collection, single-use or suitably decontaminated containers (suitably closed to prevent cross-contamination, and labelled) may be placed in one large container for transit;

b) whenever possible, materials from animals from different geographical sources shall not be pooled, unless they are obtained from countries of low geographical BSE risk or from low risk herds;

c) documented procedures shall be established, justified and maintained to prevent cross-contamination from other animals or from higher risk tissues.

NOTE 2 Regional regulatory requirements might apply.

Precautions shall be taken to avoid contamination during subsequent manufacturing operations.

Use of certain materials sourced from such a country or region is permissible. For example, the use of a suitably processed, low infectivity tissue in circumstances of limited human tissue exposure may be justifiable, such as the use of leather in an orthopaedic shoe.

NOTE 3 These circumstances correspond to the EU classification GBR IV.

A.3.3 Sourcing from closed/low risk herds

Starting material can be sourced from herds that have been managed carefully to prevent the introduction of the BSE agent and certified as “low risk” or “closed” (see 3.2). The sourcing of materials of animal origin from low risk herds shall be regarded as providing a level of safety equivalent to sourcing from a country or region where the presence of BSE in domestic cattle is considered highly unlikely.

A.3.4 The age of the donor animals

Use of younger animals poses a lower risk compared with older animals. Materials sourced from animals below 6 months may be considered to present a lower BSE risk (see Annex D of ISO 22442-1:2007).

A.3.5 The feeding history of the donor animals

Materials (including pooled blood supplies) for direct use in medical devices, that are not subject to a validated process to reduce TSE risk in line with ISO 22442-3, shall not be sourced from countries where ruminant material is fed to ruminants or where the feeding history is not known.

NOTE 1 The use of material from countries that do not allow feeding of mammalian-derived proteins to animals can provide a greater degree of safety.

For all other bovine-sourced materials, the manufacturer shall obtain published evidence of the procedures that have been implemented in the country of origin of the source cattle to ensure that the potential for transmission of a causative agent of BSE is minimized. The following evidence shall be addressed in the risk assessment:

a) whether or not protein derived from ruminants, produced locally or imported, has been fed to ruminants, and the date of effective implementation of any statutory ban on such feeding;

b) where materials are derived from cattle fed with ruminant-derived protein during the preceding eight years, verification that protein has not been obtained from countries where there is a high incidence of BSE or scrapie;

c) whether or not cattle over the age of six months, or cattle under the age of six months which are retained beyond that age, and/or progeny of affected females, are or have been imported from countries with a high incidence of BSE; such cattle may increase the risk of introducing the BSE agent if their tissues are rendered and subsequently fed to ruminants

NOTE 2 Implementation of an effective ban on feeding ruminant materials to animals is one of the factors relevant to the BSE status of a country or region. Assurance on feeding history can therefore be provided by reference to classification systems and information provided by national and regional authorities.

A.4 The infectivity of the source tissue

The likelihood that the BSE agent would be present in the particular tissue used, if obtained from an infected animal, shall be estimated by reference to a published assessment (see ISO 22442-1:2007, D.3.4). Since the data upon which studies of tissue infectivity are based may be incomplete, take into account an estimate of uncertainty based on an evaluation of the quality and quantity of the underlying data. The most up to date information shall be used.

A.5 Measures to prevent cross-contamination

Precautions shall be taken to avoid cross-contamination during slaughter, collection, handling, storage and transport of animal material.

The manufacturer of the medical device shall document and justify the method of stunning used and whether the tissues are to be derived from single animals or pooled.

It has been demonstrated that stunning by a 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. There is evidence that non-penetrative stunning can cause some CNS embolism.

NOTE 1 Additional information on stunning techniques can be found in SSC Opinion on methods of stunning and BSE risk (The risk of dissemination of brain particles into the blood and carcass when applying certain methods of stunning) adopted at the meeting on 10-11 January 2002 (http://europa.eu.int/comm/food/fs/sc/ssc/out245_en.pdf) and Opinion of the EFSA Working Group on BSE risk from dissemination of brain particles in blood and carcass, Question No. EFSA-Q-2003-122 adopted on 21 October 2004 (http://www.efsa.europa.eu/en/science/biohaz/biohaz_opinions/731.html).

For collection and handling, the following practices shall be adopted, where indicated by the risk assessment:

a) for all materials, the potential for extraneous contamination shall be minimized, especially in countries with known cases of BSE; for materials which are not pooled at collection, single-use or suitably decontaminated containers (suitably closed to prevent cross-contamination, and labelled) may be placed in one large container for transit;

b) whenever possible materials from animals from different geographical sources shall not be pooled, unless they are obtained from countries of low geographical BSE risk, or from low risk herds;

c) documented procedures shall be established and maintained to prevent cross-contamination from other animals or from higher risk tissues.

NOTE 2 Regional regulatory requirements might apply.

Annex B
(informative)

Certification and attestation [1)]

B.1 Example of a certificate to be issued

Certificate Number: .....

Certificate for an animal material to be utilized in medical devices

Country in which animal was slaughtered _____

Geographical source of animal [2)] _____

Approval number of slaughterhouse (if applicable) _____

Establishment name and location _____

Material of (state animal species) _____

Age of animal [3)] _____

Nature of tissue or organ _____

Packaging materials used _____

Number of containers/packages _____

Name of veterinarian _____

Collection date(s) _____

Signed: _____

(Responsible person)

1) The format in the examples in this annex may be copied.

2) Where available and if not already known to the manufacturer, information should be included on the identification and traceability of the source animal during its lifetime.

3) Where practicable and applicable, e.g. for animals susceptible to naturally occurring transmissible spongiform encephalopathies.

B.2 Example of a health attestation to be issued by a veterinarian

Health attestation

I, the undersigned veterinarian, certify that the material described in Certificate Number _____ was obtained from animals considered to be fit for human consumption and subject to ante- and post-mortem inspection:

Carried out at: ....., (date) .....

_____

(Signature of the veterinarian)

_____

Name

Annex C
(informative)

Veterinary services

Annex A introduces the concept of obtaining statements from competent authorities that they have veterinary services capable of detecting low incidence of BSE. Manufacturers may find the document referred to below of assistance in their discussions with veterinary competent authorities. Although intended to assist in the evaluation of veterinary services in general terms, the article may help in interpreting statements made by authorities in the specific context of BSE. The following article is available in English, French and Spanish:

“Guidelines for the Evaluation of Veterinary Services” are included in the Terrestrial Animal Health Code (chapters 1.3.3 and 1.3.4) from OIE/World Organisation for Animal Health (http://www.oie.int/eng/normes/mcode/en_sommaire.htm).

Bibliography

[1] ISO 9001, *Quality management systems — Requirements*

[2] ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

[3] ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

[4] ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

[5] Terrestrial Animal Health Code from OIE — Office International des Epizooties/World Organisation for Animal Health (http://www.oie.int/)

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

[7] Supplement 1, Japanese Pharmacopoeia XIV, 17. Basic Requirements for Viral safety of Biotechnological/Biological Products listed in Japanese Pharmacopoeia, pp.1618-1631, 2003

[8] Notification No. 177 of the Ministry of Health, Labour and Welfare on the standard for biological ingredients, 31 March 2005 on *Standards for Raw Materials Originating from Living Organisms* (http://www.nihs.go.jp/cgtp/cgtp/guidline/03052001.pdf) (in Japanese)

[9] Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin

[10] Code of hygienic practice for meat CAC/RCP 58-2005

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