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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

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 22442-2:2015).

The main changes compared to the previous version are as follows:

— update of the weblink on stunning technique in A.3.2.5 Note 1;

— clarification on scope inclusion of cervid-sourced materials, and other TSE susceptible species;

— clarification on atypical BSE types, especially in combination with intracranial applications;

— enhanced expectation of using validated biochemical testing to establish TSE presence.

A list of all parts in the ISO 22442 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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.

This document is intended to be used in conjunction with the other two parts of the ISO 22442 series. Local safety regulations can apply. The manufacturers should refer to ISO 22442-3 for information on the validation of the elimination and/or inactivation of viruses and TSE agents.

It is not a requirement of this document 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 document can form a part of a quality management system conforming to ISO 13485.

Medical devices utilizing animal tissues and their derivatives —

Part 2: Controls on sourcing, collection and handling

1 Scope

This document 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 Selective sourcing is especially important for transmissible spongiform encephalopathy (TSE) risk management, i.e. when utilising animal tissue and/or their derivative originating from bovine, ovine and caprine species, deer, elk, mink or cats.

This document does not cover the utilization of human tissues in medical devices.

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

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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, *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.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
collection
removal of tissues from animals

3.2
closed herd
herd governed by standard operating procedures (SOPs) that specify criteria restricting admission of new animals to ensure that all introduced animals are at the same or higher health standard, compared to the residents of the herd

Note 1 to entry: Such SOPs typically include:

Note 2 to entry: a) a documented veterinary monitoring process;

Note 3 to entry: b) a fully documented disease history, including a fully documented negligible TSE risk status of the herd including logged TSE history;

Note 4 to entry: c) a process to prevent feeding of mammalian-derived protein, including a fully documented feed history, source and traceability;

Note 5 to entry: d) a fully documented breeding history;

Note 6 to entry: e) a fully documented use of veterinary medicines and vaccines;

Note 7 to entry: f) a process of traceability towards each individual animal;

Note 8 to entry: g) a process to control introduction of genetic material from animals outside the closed herd, including from herds with the deviating TSE status;

Note 9 to entry: h) a fully documented record of animals kept with or in close proximity to the closed herd and procedures to control vermin or pest.

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 to entry: Under certain jurisdictions, it is a requirement that the veterinarian be a professionally qualified person in veterinary medicine.

Note 2 to entry: 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 document as determined by the benefit-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.

Compliance is checked by inspection of the appropriate documents, including:

a) specification of the age and 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, including full traceability to the slaughterhouse.

   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.

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 The use of risk analysis/risk management tools (such as HACCP, FMEA[3],[5]) are useful in determining residual risk.

4.3 Procedures

The documented procedures and instructions required by this document 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 document. 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], [13].

5 Sourcing

5.1 General

Subclauses 5.2 to 5.6 and Clauses 6 to 8 shall be applied by the 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).

For the animal material sourced from species that are not intended for human consumption the justification for the missing inspection and certification is to be documented. Relevant quality criteria for this type of material are to be defined by the manufacturer.

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

In case animal by-products not intended for human consumption are sourced, these have to be 'Category 3 (i.e. safe) materials or equivalent'[16].

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.

NOTE Specific guidance as regards requirements for bovine blood can be found in the "Guideline on the use of bovine serum in the manufacture of human biological medicinal products" [14].

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, cervids,

mink, cat). If individual animals cannot be inspected, the justification for this shall be documented and a relevant sampling plan provided.

Bovine, caprine, 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; Tallow derivatives, animal charcoal, and amino acids `Category 3 (i.e. safe) materials or equivalent' [13], [16].

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 the following:

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 validated biochemical test for the presence of TSE in the source animal. Such validated in vitro tests are indicative for TSE positive status but can only be relied on for confirming the negative stats of an animal once such test is universally accepted as being state of the art on this aspect.

Animal tissues derived from certain species (e.g. fish, crustaceans, cervids, mink, cat) 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 document 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. Traceability to the slaughterhouse should be assured, as well as traceability by suppliers of processed animal materials. The exact extent of traceability shall be defined by the outcome of the risk-benefit assessment taking into account those official information systems that exist.

NOTE Traceability cannot 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 following:

— the limits of responsibilities;

— specifications of the material;

— documentation provided by the supplier allowing the manufacturer to meet the requirements of this document;

— 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.

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 the documented procedures.

8 Storage, transport and labelling

8.1 Collected material shall be stored and transported in closed or other appropriate 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, transport and labelling of the material is conducted in accordance with the documented procedures.

8.4 Primary container of the collected material shall be labelled appropriately to avoid cross contamination and mix up during the transport and storage. The label shall at least contain details of the material, collection date and the location for traceability.

Annex A
(normative)

Additional requirements relating to the application of this document to bovine-sourced materials and other TSE relevant animal species

A.1 General

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 ISO 22442-1:2020, Annex D). These needs 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.

Particular focus should be given to atypical BSE types such as H type and L type. Especially the L type of prion may show more infectivity to testing animals. Although the risk of bovine meat was reported to be very low or negligible due to the infectivity of oral dosing of BSE prions to muscles of testing animals, intra-cranial dosing was reported to show higher infectivity than oral dosing. When addressing the medical devices safety, in particular for intra-cranial devices, sporadic atypical BSE should be addressed in the risk assessment.

This annex only addresses factor a) which, for many devices sourced from bovine material, is the principal method of TSE risk control.

NOTE 1 ISO 22442-1:2020, Annex C contains specific requirements for certain animal materials or derivatives.

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 2 Equivalent measures can be applicable to caprine-, ovine-, and cervid-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;

NOTE 1 The infectivity of the source tissue depends on geographical origin, age of the animal, nature of the material, and the measures in place to avoid cross-contamination.

NOTE 2 See Reference [13] for additional information.

c) measures to prevent cross-contamination from other animals or tissues, especially for materials and/or animals with higher risk.

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. To address the risk for transmission of the extremely rare atypical BSE the age of the source cattle should considered as the important parameter.

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 or materials of higher BSE risk.

NOTE Clauses 6, 7, 8, and A.5 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 according to OIE /equivalent show that neither BSE, scrapie, nor chronic wasting disease (CWD) 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). As regards classification of countries or regions according to their BSE risk verification should be based primarily on the classification by the World Organisation for Animal Health (OIE).

Manufacturers should take into account published assessments relating to BSE risks associated with specific countries.

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 Factors involved in the BSE status of a country include the following:

a) the incidence of the disease in the country;

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

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

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

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

f) whether or not specified risk materials are removed and destroyed after slaughter;

g) whether or not "fallen stock"/animals with "downer syndrome" are subject to specific control including testing for BSE.

Very few cases of atypical BSE have been reported even for category A countries. To address the resulting risk for medical devices coming into contact with the central nervous system age related sourcing shall be considered.

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 Negligible BSE risk

If BSE has not been previously recognized in the country or region of origin or when every indigenous case was born more than 11 years ago, 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.

NOTE Manufacturers can find the "Guidelines for the Evaluation of Veterinary Services" included in the Terrestrial Animal Health Code (Chapters 1.3.3 and 1.3.4) from OIE/World Organization for Animal Health (available at http://www.oie.int/international-standard-setting/terrestrial-code/) of assistance in their discussions with veterinary competent authorities. Although intended to assist in the evaluation of veterinary services in general terms, the article can help to interpret statements made by authorities in the specific context of BSE.

Verification should be provided by reference to OIE classification systems and information provided by national or regional authorities.

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 22442-1:2020, 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 ensured, and risk of BSE cross-contamination shall be avoided.

A.3.2.3 Controlled 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;

— that their progeny are not used as source animals;

— that the surveillance system is effective.

Verification should be provided by reference to classification systems and information provided by national or regional authorities.

Depending on the evaluation of overall residual risk acceptability (see ISO 22442-1:2020, 4.5), additional risk control measures shall be considered for materials sourced from such countries or regions.

Sourcing from controlled BSE risk countries (OIE Category B) is allowed for certain materials provided that there are adequate controls and defined requirements are fulfilled.

NOTE More information on such materials and specific requirements can be found in Reference [13].

A.3.2.4 Undetermined 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, or where for another reason it cannot be demonstrated that it meets the requirement of another category, shall not be used in the manufacture of medical devices except as noted in A.3.2.5.

Sourcing from "countries with undetermined BSE risk" (OIE Category C) is only allowed for few materials provided that there are adequate controls and defined requirements are fulfilled. If animals from countries with undetermined BSE risk (Category C) are used a justification shall be provided.

A.3.2.5 Particular circumstances

In particular circumstances, the evaluation of overall residual risk acceptability (see ISO SO 22442-1:2020, 4.5) can result in the conclusion 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 (available at https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_ssc_out245_en.pdf) and opinion of the EFSA working group on BSE risk from dissemination of brain particles in blood and carcass. EFSA-Q-2003–122 adopted on 21 October 2004 (available at https://www.efsa.europa.eu/en/efsajournal/pub/123).

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 negligible geographical BSE risk or from closed 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 can 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.

A.3.3 Sourcing from closed herds starting material

Starting material can be sourced from herds that have been managed carefully to prevent the introduction of the BSE agent and certified as "closed herd" (see 3.2). The sourcing of materials of animal origin from closed 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 six months can be considered to present a lower BSE risk (see ISO 22442-1:2020, Annex D). Very few cases of atypical BSE have been reported even for category A countries. However, the extremely rare disease is restricted to animals typically older than 8 years. This shall be considered during risk analysis.

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, scrapie, or CWD;

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, shall be estimated by reference to a published assessment (see ISO 22442-1:2020, 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.