INTERNATIONAL STANDARD

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Medical devices utilizing animal tissues and their derivatives —

Part 1: Application of risk management

Dispositifs médicaux utilisant des tissus animaux et leurs dérivés —

Partie 1: Application de la gestion des risques

Reference number
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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 on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT), see the following URL: Foreword — Supplementary information.

The committee responsible for this document is ISO/TC 194, *Biological and clinical evaluation of medical devices*, SC 1, *Tissue product safety*.

This second edition cancels and replaces the first edition (ISO 22442-1:2007), of which it constitutes a minor revision.

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*

— *Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes* [Technical Report]

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).

ISO 14971 is a general standard which specifies a process for a manufacturer by identifying hazards and hazardous situations associated with medical devices, including *in vitro* medical devices, to estimate and evaluate the risks associated with those hazards, to control these risks and to monitor the effectiveness of the control throughout the life cycle. This part of ISO 22442 provides additional requirements and guidance for the evaluation of medical devices manufactured utilizing animal tissues or derivatives which are non-viable or rendered non-viable.

This part of ISO 22442 is intended to cover medical devices including active implantable medical devices such as implantable infusion pumps.

This part of ISO 22442 does not apply to *in vitro* diagnostic devices.

This part of ISO 22442 can only be used in combination with ISO 14971 and is not a “standalone” standard.

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 1: Application of risk management

1 Scope

This part of ISO 22442 applies to medical devices other than *in vitro* diagnostic medical devices manufactured utilizing materials of animal origin, which are non-viable or have been rendered non-viable. It specifies, in conjunction with ISO 14971, a procedure to identify the hazards and hazardous situations associated with such devices, to estimate and evaluate the resulting risks, to control these risks, and to monitor the effectiveness of that control. Furthermore, it outlines the decision process for the residual risk acceptability, taking into account the balance of residual risk, as defined in ISO 14971, and expected medical benefit as compared to available alternatives. This part of ISO 22442 is intended to provide requirements and guidance on risk management related to the hazards typical of medical devices manufactured utilizing animal tissues or derivatives, such as

a) contamination by bacteria, moulds or yeasts;

b) contamination by viruses;

c) contamination by agents causing Transmissible Spongiform Encephalopathies (TSE);

d) material responsible for undesired pyrogenic, immunological or toxicological reactions.

For parasites and other unclassified pathogenic entities, similar principles can apply.

This part of ISO 22442 does not stipulate levels of acceptability which, because they are determined by a multiplicity of factors, cannot be set down in such an International Standard except for some particular derivatives mentioned in Annex C. Annex C stipulates levels of TSE risk acceptability for tallow derivatives, animal charcoal, milk and milk derivatives, wool derivatives and amino acids.

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

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

NOTE 1 It is not a requirement of this part of ISO 22442 to have a full quality management system during manufacture. However, attention is drawn to International Standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices.

NOTE 2 For guidance on the application of this part of ISO 22442, see Annex A.

2 Normative references

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

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Control on sourcing, collection and handling*

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*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 14971 and the following apply.

3.1
animal
any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans (*Homo sapiens*)

3.2
cell
smallest organized unit of any living form which is capable of independent existence and of replacement of its own substance in a suitable environment

3.3
derivative
substance obtained from an animal material by a manufacturing process

EXAMPLE Hyaluronic acid, collagen, gelatine, monoclonal antibodies, chitosan, albumin.

3.4
elimination
removal process by which the number of transmissible agents is reduced

Note 1 to entry: The effectiveness of the process for the elimination of viruses and TSE agents should be expressed mathematically in terms of a reduction factor (see C.2 and ISO 22442-3:2007, Annex F).

Note 2 to entry: Elimination aims to prevent infection or pathogenic reaction caused by transmissible agents.

3.5
inactivation
process by which the ability to cause infection or pathogenic reaction by a transmissible agent is reduced

Note 1 to entry: The effectiveness of the process for inactivation of viruses and TSE agents should be expressed mathematically in terms of a reduction factor (see ISO 22442-3:2007, Annex F).

Note 2 to entry: Inactivation aims to prevent infection by, and replication of, transmissible agents.

3.6
medical device
any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s):

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body;

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

Note 1 to entry: This definition has been developed by the Global Harmonization Task Force (GHTF)[40]

Note 2 to entry: This part of ISO 22442 does not apply to *in vitro* diagnostic devices.

3.7
non-viable
having no potential for metabolism or multiplication

3.8
technical agreement
binding contract between two or more parties that assigns responsibilities for technical requirements

3.9
tissue
organization of cells and/or extra-cellular constituents

3.10
transmissible agents
bacteria, mould, yeast, parasites, viruses, TSE agents and unclassified pathogenic entities

4 Risk management process

4.1 General

The manufacturer shall justify the use of animal material (including the choice of animal species and tissues) based on the residual risk acceptability, taking into account the balance of residual risk and expected medical benefit, as compared to available alternatives.

The requirements of ISO 14971 and 4.2 to 4.5 apply. Compliance with these requirements shall be verified by inspection of the risk management file.

NOTE Further discussion of medical benefits and the risk/benefit analysis can be found in ISO 14971:2007, D.6.

4.2 Risk analysis

4.2.1 Identification of qualitative and quantitative characteristics related to the safety of medical devices

4.2.1.1 Does the device come into contact with the patient or other persons?

The quantity of material, the contact surface area and the type(s) of the material coming into contact with body tissues or fluids as well as the type of body tissue or fluid it comes into contact with, shall be addressed in the risk analysis. For TSE, guidance can be found in D.3.7.

NOTE 1 Medical devices such as orthopaedic shoes or components such as leather straps that come into contact only with intact skin represent a low infective risk.

NOTE 2 The quantity of material coming into contact is one of the factors in producing biological effects. See ISO 10993 (all parts) for the evaluation of such effects.

NOTE 3 The structure of animal tissues being processed can affect the inactivation and/or elimination of transmissible agents, and the potential for retaining viable cells can be affected by the structure of the animal tissues and derivatives being processed.

4.2.1.2 What materials and/or components are incorporated in the medical device or are used with, or are in contact with, the medical device?

The following factors shall be addressed, if applicable:

a) if viable animal materials are utilized in the manufacture of the medical device, verification that the final medical device contains no viable animal material;

b) the intended use of any animal tissue or derivative;

c) geographical source, species, age and feeding (including use of animal-derived protein) of animals;

d) veterinary control, conditions under which the animal materials are recovered, potential for cross-contamination;

e) the type and anatomical source of tissue;

f) the production process, particularly if it uses materials pooled from more than one animal;

g) the nature of material utilized in the medical device, (e.g. intact tissue, highly purified derivative);

h) the method of utilization or incorporation into the medical device.

In the case of medical devices utilizing several relevant constituents (e.g. from various species, origin or tissues) or several similar types of constituents produced using different methods, each individual constituent should be analysed separately.

4.2.1.3 Is the device supplied sterile or intended to be sterilized by the user or are other microbiological controls applicable?

Given the biological nature of animal tissues or derivatives, variations in the bioburden of bacteria, mould and yeast of the animal material shall be estimated.

NOTE See also ISO 11737-1 and ISO 14160.

4.2.1.4 Are there unwanted outputs of substances?

The possible presence of toxic residue related to the manufacturing process utilized or degradation by-products shall be addressed taking into account the physical characteristics (e.g. porosity, heterogeneity) and chemical composition of animal tissues or derivatives.

NOTE See also ISO 10993-1, ISO 10993–9, ISO 10993–17, ISO 10993–18 and ISO 10993–19.

4.2.2 Identification of hazards and hazardous situations

The possible hazards associated with animal tissues or derivatives shall be identified and documented. Particular attention shall be applied to possible hazards posed by animal tissues or derivatives with regard to

— potential contamination by transmissible agents and their susceptibility to elimination and/or inactivation during processing;

— potential for contaminants on the finished material which can cause an undesired pyrogenic, immunological or toxicological reaction;

— potential for the finished material itself to cause an undesired pyrogenic, immunological or toxicological reaction.

4.3 Risk evaluation

In accordance with ISO 14971, all identified risks shall be evaluated. Biological safety shall be evaluated in accordance with ISO 10993-1. Risk evaluation for transmissible agents shall be implemented by separately addressing the risks related to different categories of transmissible agents. Annex B identifies the main categories of risk that should be considered. Regarding the TSE risk, compliance with requirements specified in Annex C for certain animal materials can indicate risk acceptability.

NOTE Annex C combines elements of risk evaluation and risk control.

4.4 Risk control

4.4.1 General

The risk control options shall be documented and justified.

The flowchart in Annex B gives an overview of the risk management process. If additional risks are identified when using this part of ISO 22442, the medical device manufacturer may choose to follow any other relevant standard or any other route. The decision should be justified and documented.

4.4.2 Risk control for viruses and TSE agents

Risk control shall be implemented by separately addressing the risks related to different categories of viruses and TSE agents. After defining the characteristics of the product, the medical device manufacturer shall comply with the relevant requirements of both ISO 22442-2 and ISO 22442-3, except where either the animal species is such that manufacturers cannot fully meet the requirements of ISO 22442-2 or an inactivation process in accordance with ISO 22442-3 would cause unacceptable degradation.

Tallow derivatives, animal charcoal, and amino acids that are acceptable for TSE risk as discussed in Annex C, due to their processing and not their sourcing, shall also be considered to have acceptable risk regarding viruses.

Regarding TSE risk, risk control measures specified in Annex C for certain animal materials shall be applied where relevant. If the manufacturer considers any requirement not to be relevant, the rationale and justification shall be documented.

For medical devices where an inactivation process causes unacceptable degradation, manufacturers may rely on ISO 22442-2 in order to meet the requirements of this part of ISO 22442.

If the animal species is such that manufacturers cannot fully meet the requirements of ISO 22442-2, they shall demonstrate that the level of inactivation of transmissible agents in a validated manufacturing process, as required in ISO 22442-3, is sufficient to achieve an acceptable level of risk.

NOTE Criteria and principles relevant to the management of TSE risks are described in Annex D. Annex D contains information on relevant risk control measures

4.4.3 Risk control of other hazards

Risk control related to bacteria, moulds and yeasts, as well as undesired pyrogenic, immunological and toxicological reactions shall be implemented according to available standards.

Tallow derivatives, animal charcoal, and amino acids that are acceptable for TSE risk as discussed in Annex C, due to their processing and not their sourcing, shall also be considered to have acceptable risk regarding bacteria, moulds and yeasts, subject to maintenance of proper storage conditions.

The manufacturer shall conduct periodic microbiological studies to identify and quantify the initial bioburden of the incoming animal material for the production of the medical device.

NOTE The following International Standards may be relevant:

a) ISO 11135, ISO 11137, ISO 11737-1, ISO 13408, ISO 14160, ISO 14937, ISO 17664 and ISO 17665-1, which can be relevant for bacteria, moulds and yeasts (see References [19] to [33]);

b) all relevant parts of ISO 10993, which can be used to manage risks related to undesired pyrogenic, immunological or toxicological reactions (see References [1] to [18]).

The use of these International Standards is illustrated in Annex B.

4.4.4 Residual risk evaluation

4.4.4.1 General

Residual risk evaluation shall be performed for each risk.

4.4.4.2 TSE risk

The TSE risk may be judged acceptable if the following criteria are both met, taking into account the availability of alternative materials:

a) the residual risk estimate indicates that the TSE risk has been controlled at an acceptable level;

b) the medical benefit arising from the intended use of the device is judged to outweigh the residual risk estimate.

NOTE Guidance on risk management applicable to TSE agents is given in Annex D. Acceptability can be based on conformity with requirements specific to some animal materials given in Annex C or requirements relevant to sourcing, collection and handling of bovine materials given in ISO 22442-2:2015, Annex A.

Regarding the TSE residual risk, specific considerations are provided in Annex C. Some derivatives such as tallow derivatives, animal charcoal, milk derivatives, wool derivatives and amino acids manufactured according to conditions mentioned in Annex C are considered as presenting an acceptable TSE risk.

Where the TSE risk has not been controlled at a level that presents an acceptable level of risk to users or recipients, the overall risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations.

4.5 Evaluation of overall residual risk acceptability

4.5.1 General

The evaluation of the overall residual risk acceptability shall take into account the balance between the residual risk after implementation of all risk control measures and the expected medical benefit, as compared to available alternatives. Where residual risks exist with regard to the contamination with transmissible agents, the evaluation should specifically discuss the risks and benefits of

— using alternative materials that do not present the risk of contamination with these transmissible agents, such as synthetic materials, materials from other animal species, or materials from human origin, and

— applying whole product alternatives for the same intended purposes.

Where the risk has not been controlled at a level that presents an acceptable level of risk to users or recipients, the overall risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations.

4.5.2 Documentation

The rationale that the risk is acceptable shall be documented in the risk management file.

4.6 Production and post-production information system

Manufacturers shall ensure that the system will identify changes in the zoonosis status of the chosen source of animal materials.

Annex A
(informative)

Guidance on the application of this part of ISO 22442

A.1 General

Wherever in this part of ISO 22442 it is stated that something "be addressed", the reader should either take action to control the risk or justify in the risk management report why they have not done so.

A.2 Application to materials from animal sources

This International Standard is applicable to materials such as

— porcine heart valves, bovine bones, cattle ligaments and bovine pericardium;

— derivatives of animal tissues, such as chondroitin sulfate obtained from shark and collagen derived from hides, and of animal blood or serum;

— materials produced *in vivo* by relevant animals, e.g. antibodies utilized in the manufacturing process;

— starting materials such as bovine serum albumin, enzymes, culture media including those used to prepare working cell banks, master cell banks or master seeds for products such as hyaluronic acid.

A.3 Application to materials supplied by third parties

This part of ISO 22442 can be applied when the materials used by medical device manufacturers have been prepared from animal sources by third parties or subcontractors. An example is gelatine derived from animal hides or bones. In considering the risks associated with the use of these products, the medical device manufacturers should seek evidence from their suppliers as to whether relevant requirements of this International Standard have been applied in assessing the suitability of the animal material or whether alternative approaches were applied. The information obtained should be incorporated in the risk management report relating to the medical device, as appropriate, but may need to be supplemented by information supplied by the third party or subcontractor.

Annex B
(informative)

Graphical representation of part of the risk management process for medical devices utilizing animal material

See Figure B.1 overleaf.

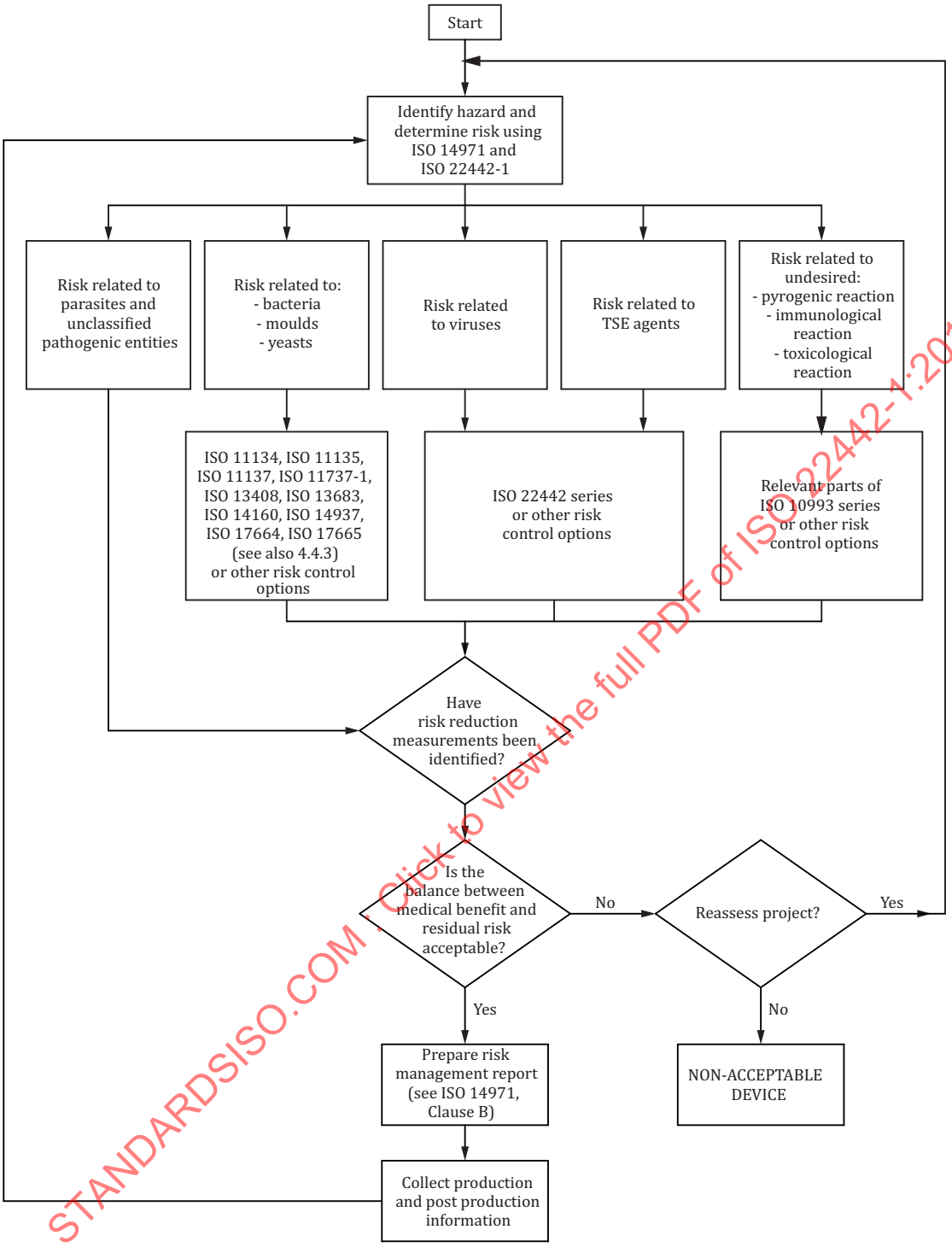

Figure B.1 — Graphical representation of part of the risk management process

This chart illustrates part of the risk management process in accordance with ISO 14971 and this part of ISO 22442. The risk management process should address all relevant risks shown in this chart.

Annex C
(normative)

Special requirements for some animal materials considering the risk management for TSE agents

C.1 General

The requirements of this Annex do not obviate the need to undertake a risk assessment for TSE risks, including the requirements in Clause 4, as part of the risk assessment and management process described in ISO 14971.

Risk management can be addressed by processing, sourcing, or a combination of both. Tallow derivatives, animal charcoal and amino acids are acceptable for TSE risk due to their processing and not their sourcing.

ISO 22442-2:2015, Annex A, contains additional requirements relating to the application of this part of ISO 22442 to bovine-sourced materials.

To demonstrate compliance with the requirements of this part of ISO 22442 it is necessary to implement a technical agreement between the medical device manufacturer and the animal material/derivative supplier (see ISO 22442-2:2015, Clause 6).

C.2 Collagen

Collagen is a fibrous protein component of mammalian connective tissue.

For collagen, documentation to demonstrate compliance with this part of ISO 22442 shall be provided, taking into account the relevant requirements of this Annex.

When completing the risk management required by this part of ISO 22442, consider the following.

— For collagen produced from bone, the bone shall be sourced from countries with minimal exposure to BSE. Sourcing bone from countries with limited exposure to BSE shall be justified by reference to other applicable risk control measures (see ISO 22442-2:2015, Annex A). Bone shall not be sourced from countries where infection with the BSE agent is confirmed at a higher level, unless from a low risk herd as defined in ISO 22442-2.

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

— Collagen produced from hides and skins does not usually present a significant TSE risk provided that cross-contamination with potentially infected materials, for example central nervous tissues, is avoided during their procurement. To demonstrate compliance with the requirements of this part of ISO 22442, it is necessary to incorporate measures to prevent cross-contamination (see ISO 22442-2) and to document the measures that are adopted in the technical agreement between the collagen supplier and the medical device manufacturer to prevent such cross-contamination.

Collagen shall be obtained from animals declared as fit for human consumption (see ISO 22442-2).

Source countries with “Minimal exposure to BSE” should be interpreted as countries with negligible BSE risk[1) 2) 3)], or countries on the APHIS List[4)] or from low risk herds as defined in ISO 22442-2.

Source countries with “Limited exposure to BSE” should be interpreted in the same way as countries with controlled BSE risk.

C.3 Gelatine derived from hides and bones

C.3.1 General

Gelatine 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 gelatine, documentation to demonstrate compliance with this part of ISO 22442 shall be provided, taking into account the relevant requirements listed in this Annex.

Gelatine shall be obtained from animals declared as fit for human consumption.

When completing the risk evaluation and control required by this part of ISO 22442, consider C.3.2 to C.3.4.

C.3.2 Hides as the starting material

On the basis of current knowledge, hides used for gelatine production represent a safer source material when compared to bones.

Gelatine produced from hides does not usually present a significant TSE risk provided that cross-contamination with potentially infected materials, for example central nervous tissues, is avoided during their procurement. To demonstrate compliance with the requirements of this part of ISO 22442, it is necessary to incorporate measures to prevent cross-contamination (see ISO 22442-2) and to document the measures that are adopted to prevent such cross-contamination in the technical agreement between the gelatine supplier and the medical device manufacturer.

C.3.3 Bones as the starting material

Where bones are used to manufacture gelatine, the quality of the starting materials is the primary parameter that will ensure the safety of the final product. Therefore, the following shall be applied.

— Subject to national legislation, bone shall be sourced from countries with minimal or limited exposure to BSE. Bone shall not be sourced from countries where infection with the BSE agent is confirmed at a higher level, unless from a low risk herd as defined in ISO 22442-2.

— Skulls and spinal cords shall be removed from the collected bones (raw/starting material) from cattle of a specific age as defined in national legislation.

— Additionally, vertebrae shall be removed from the raw/starting materials from cattle of all ages from countries with limited exposure to BSE.

1) The World Organisation of Animal Health (OIE) maintains a list of OIE Member Countries officially recognised as having a negligible or controlled BSE risk status, available on the OIE Web site at http://www.oie.int/en/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/

2) The European Union has published documents on Geographical BSE Risks for a number of countries, available on the Web site of the Scientific Steering Committee of the Commission of the European Union: http://ec.europa.eu/food/fs/sc/ssc/outcome_en.html

3) The EFSA permitted list can be found at http://www.efsa.europa.eu/en/topics.htm

4) The permitted list published by the Animal and Plant Health Inspection Service can be found at http://www.aphis.usda.gov/wps/portal/aphis/home/

C.3.4 Manufacturing methods

No specific measures with regard to the processing conditions are required for gelatine produced from hides provided that control measures be put in place to avoid cross-contamination both during the sourcing of the hides and during the manufacturing process (see C.3.2).

Where bones are used as the starting material, use one of the manufacturing methods described below.

— Although the alkaline extraction process (prior to the finishing steps) has shown a slightly higher inactivation/elimination capacity compared to the acid process, both the acid and the alkaline manufacturing methods to produce the final gelatine have shown similar overall inactivation/elimination of TSE infectivity in the gelatine validation experiments. Studies have shown that an additional alkaline treatment (pH 13, 1 h) of the bones/ossein further increases the TSE inactivation/elimination capacity of the acid manufacturing process.

— For a typical alkaline manufacturing process, bones are finely crushed, degreased with hot water and demineralized with diluted 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 (at least pH 12,5) for a period of at least 20 d. The gelatine is extracted, washed, filtered and concentrated. A flash heat treatment step using 138 °C to 140 °C for 4 s is applied. 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. In the heat/pressure process, the dried, degreased, crushed bones are autoclaved with saturated steam at a pressure greater than 3 bar and a minimum temperature of 133 °C for at least 20 min, followed by extraction of the protein with hot water. The finishing steps for both the acid and heat/pressure process are similar to the alkaline process.

C.4 Bovine blood derivatives

C.4.1 General

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. The foetal blood shall be harvested in a dedicated space or area by cardiac puncture into a closed collection system using an aseptic technique.

New born calf serum is obtained from calves aged less than 20 d; calf serum from animals aged less than 12 months. In the case of donor bovine serum, given that it can be derived from animals less than 36 months old, the BSE 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 and the precautions necessary to avoid cross-contamination with higher risk tissues.

For bovine blood derivatives, documentation to demonstrate compliance with this part of ISO 22442 shall be provided, taking into account the relevant requirements listed in this Annex. When completing the risk management required by this part of ISO 22442, consider C.4.2 to C.4.4.

C.4.2 Traceability

Traceability to the slaughterhouse shall be ensured for each batch of serum or plasma. Slaughterhouses shall have available lists of farms from which the animals are sourced. If serum is produced from living animals, records shall be available for each serum batch to ensure traceability to the farms and to the individual animal. When traceability to the individual animal is not possible, this shall be justified in the risk management file.

C.4.3 Geographical origin

Bovine blood shall be sourced from countries with minimal exposure to BSE unless otherwise justified and authorized.

C.4.4 Stunning methods

If blood is obtained from slaughtered animals, the method of slaughter is of importance to ensure the safety of the material. 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 stunning methods shall be described for the bovine blood collection process unless the material is sourced from a country of negligible geographical BSE risk (see ISO 22442-2:2015, A.3.1).

Where sourcing of blood is from countries with limited exposure to BSE, a non-penetrative stunner or electro-narcosis shall be used for slaughter of animals over 12 months of age. The use of non-penetrative stunning shall be justified on the basis of an estimate of the risk of dissemination of brain particles into the blood.

NOTE Additional information on stunning techniques can be found in 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://ec.europa.eu/food/fs/sc/ssc/out245_en.pdf) and Report of the EFSA Working Group on BSE risk from dissemination of brain particles in blood and carcass. Question N° EFSA-Q-2003–122 adopted on 21 October 2004 (http://www.efsa.europa.eu/en/scdocs/doc/123.pdf).

C.5 Tallow derivatives

Tallow is fat obtained from tissues including subcutaneous, abdominal and inter-muscular areas and bones.

Tallow derivatives, such as glycerol and fatty acids, manufactured from tallow by rigorous processes, are thought unlikely to be infectious. For this reason, such materials manufactured under the conditions at least as rigorous as those given below shall be considered as presenting an acceptable TSE risk, irrespective of the geographical origin and the nature of the tissues from which tallow derivatives are derived. The following are examples of rigorous processes:

a) trans-esterification or hydrolysis at not less than 200 °C for not less than 20 min under pressure (glycerol, fatty acids and fatty acid esters production);

b) saponification with sodium hydroxide solution, at a concentration of 12 mol/l (glycerol and soap production):

   1) batch process: at not less than 95 °C for not less than 3 h;

   2) continuous process: at not less than 140 °C, under pressure for not less than 8 min, or equivalent;

c) distillation at 200 °C.

C.6 Animal charcoal

Animal charcoal is prepared by carbonization of animal tissues, such as bones, using a temperature >800 °C.

Irrespective of the geographical origin and the nature of the tissue, animal charcoal prepared under these conditions shall be considered as presenting an acceptable TSE risk.

C.7 Milk and milk derivatives

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 abomasums, or rennet derived from other ruminants. A risk assessment for lactose and other whey derivatives

produced using calf rennet was performed[5)] and concluded that the TSE risk is negligible if the calf rennet is produced in accordance with the process described in the CPMP risk assessment report[44].

Subject to national legislation, milk derivatives manufactured according to the conditions below are considered as presenting an acceptable TSE risk:

— the milk is sourced from healthy animals under the same conditions as milk collected for human consumption;

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

C.8 Wool and its derivatives

Wool and its derivatives, such as lanolin and wool alcohols, shall be considered in compliance with this part of ISO 22442, provided the wool is sourced from live healthy animals.

Wool derivatives produced from wool that is sourced from slaughtered animals declared "fit for human consumption" are considered as presenting an acceptable TSE risk if the manufacturing process in relation to pH, temperature and duration of treatment meets at least one of the stipulated processing conditions listed below:

— treatment at pH ≥13 (initial; corresponding to concentrations of sodium hydroxide ≥0,1 mol/l) at ≥60 °C for at least 1 h; this normally occurs during the reflux stage of the organic-alkaline treatment;

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

C.9 Amino acids

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

Amino acids prepared using the following processing conditions are considered as presenting an acceptable TSE risk:

— 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 >11, followed by heat treatment at 140 °C for 30 min at 3 bar;

— the resulting amino acids or peptides shall be filtered after production;

— analysis shall be performed using a validated and sensitive method to control any residual intact macromolecules with a justified limit set.

5) The 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 animal from which abomasums are obtained is particularly important.

Annex D
(informative)

Information relevant to the management of TSE risk

D.1 General

The naturally occurring transmissible spongiform encephalopathies (TSE) include scrapie (in sheep and goats), chronic wasting disease (in mule-deer and elk), bovine spongiform encephalopathy (BSE) in cattle as well as kuru and Creutzfeldt-Jakob disease (CJD) in humans. It is difficult to detect agents causing these diseases *in vivo.* After latency periods of up to many years the agents cause disease and, finally, lead to death. No means of therapy is known.

Current information on the characteristics of the causative agents is limited. These agents are extremely resistant to most of the chemical and physical procedures that inactivate conventional viruses. They do not induce a detectable immune response. There are natural barriers which limit their interspecies spread of transmissible agent, but they can be crossed under appropriate circumstances. This is usually dependent upon strain, dose, route of exposure and the species barrier. Studies in laboratory animals have shown that intracerebral inoculation is the most efficient route of transmission.

D.2 Risks for humans

There is considerable circumstantial evidence that the variant form of human CJD (vCJD) arose from BSE and it is prudent to accept that the BSE agent can be transmitted to man. This part of ISO 22442 therefore contains a number of requirements to ensure that risks are controlled if biological materials from species susceptible to TSE are used for the manufacture of medical devices. This Annex provides guidance that should be followed to minimize the risks of contamination. It identifies where requirements elsewhere in this part of ISO 22442 are applicable and where information from other sources is relevant. All devices should be considered on a case-by-case basis.

D.3 Risk management for TSE agents

D.3.1 Principle

The safety of a medical device, in terms of its potential for passing on a TSE agent, is dependent on a number of factors. The eight most important factors below should be analysed, evaluated and managed:

— animal species used (see D.3.2);

— geographical sourcing (see D.3.3);

— nature of starting tissue (see D.3.4);

— slaughtering and processing controls to prevent cross-contamination (see D.3.5);

— methods used to inactivate or remove TSE agents (see D.3.6);

— quantities of animal starting material required to produce one unit of the medical device (see D.3.7.1);

— quantities of material of animal origin coming into contact with the patients and users (see D.3.7.2);

— route of administration (see D.3.7.3).

When manufacturers have the choice, the use of materials from non-TSE relevant animal species or non-animal origin is preferred.

D.3.2 Animal species used (see ISO 22442-2)

The TSE risk is related to the source species, strains and nature of the starting tissue.

As the accumulation of TSE infectivity occurs over an incubation period of several years, sourcing from young, healthy animals is considered to be a factor reducing the risk. The use of older animals can increase the risk. Sourcing from animals under the age of 6 months can provide a reduced level of risk. The use of fallen stock, emergency-slaughtered and TSE-suspected animals might substantially increase the risk and should be excluded. Risks of this nature are addressed by demonstrating conformity with requirements in ISO 22442-2:2015, Annex A.

D.3.3 Geographical sourcing (see ISO 22442-2)

Certain factors influence the geographical risk of BSE infection associated with the use of raw tissues or derivatives from individual countries. They will apply particularly to BSE but can also be used to determine risk from TSEs in other species.

Manufacturers should take into account published assessments relating to BSE risks associated with specific countries. For example, the OIE has published documents on the BSE status for a number of countries (the OIE Terrestrial Code relating to BSE is available at http://www.oie.int/international-standard-setting/terrestrial-code/). The United States Department of Agriculture has published a list of permitted and unauthorized source countries (see Annex C, Footnote 5). Japan's Ministry of Health, Labour and Welfare has also published a similar list of permitted and unauthorized source countries (see Reference [47]).

D.3.4 Nature of starting tissue

The manufacturer should take into account the classification of the hazards relating to different types of starting tissue. Sourcing of animal tissue should be subject to control and individual inspection by a veterinarian and the animal carcass should be certified as fit for human consumption, whenever possible, according to local custom and practice. The manufacturer should not source animal tissue classified as having potentially high TSE infectivity. The only exception is if there is an absence of an alternative starting tissue and there are significant medical benefits for the patient.

A classification of the hazards relating to different types of animal starting material has been established and approved by the World Health Organization[42]. Tables D.1 to D.3 are based on the WHO classification of tissues in 2006, and WHO Tables on Tissue Infectivity Distribution in TSE updated 2010[43]. Risk assessments should be revised in the light of more recent information, as it becomes available, and should take into account the level of uncertainty inherent in the data available.

In Tables D.1, D.2 and D.3, the following data entry symbols are used:

+ presence of infectivity or PrP^{TSE} [a];

– absence of detectable infectivity of PrP^{TSE};

NT not tested;

NA not applicable;

? uncertain interpretation;

( ) limited or preliminary data;

[ ] infectivity or PrP^{TSE} data based exclusively on bioassays in transgenic (Tg) mice over-expressing the PrP-encoding gene or PrP^{TSE} amplification methods.

[a] PrP^{TSE} = prion protein — TSE infectious isoform

The placement of a given tissue in one or another category can be disease-specific and subject to revision as new data accumulate from increasingly sensitive tests. In fact, it is conceivable that the detection of infectivity using transgenic mice that over-express genes encoding various prion proteins, or the detection of PrP^{TSE} using some newly developed amplification methods, might prove to be more sensitive than transmission studies in wild-type bioassay animals, and thus may not correlate with disease transmission in nature.

It is critically important to understand that categories of infectivity are not the same as categories of risk, which require consideration not only of the level of infectivity in tissue, but also of the amount of tissue to which a person or animal is exposed, and the route by which infection is transmitted. For example, although the level of tissue infectivity is the most important factor in estimating the risk of transmission by instrument cross-contamination during surgical procedures (e.g. neurosurgery versus general surgery), it will be only one determinant of the risk of transmission by blood transfusions, in which a large amount of low-infectivity blood is administered intravenously, or the risk of transmission by foodstuffs that, irrespective of high or low infectivity, involves a comparatively inefficient oral route of infection.

Table D.1 — Category A: High-infectivity tissues

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								
	Humans				**Cattle**		**Sheep and goats**	
Tissues	**vCJD**		**Other TSEs**		**BSE**		**Scrapie**	
	Infectivity[a]	PrP^{TSE}	Infectivity[a]	PrP^{TSE}	Infectivity[a]	PrP^{TSE}	Infectivity[a]	PrP^{TSE}
Brain	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+
Retina	NT	+	+	+	+	NT	NT	+
Optic nerve[b]	NT	+	NT	+	+	NT	NT	+
Spinal ganglia	+	+	NT	+	+	NT	+	+
Trigeminal ganglia	+	+	NT	+	+	+	NT	+
Pituitary gland[c]	NT	+	+	+	–	+	+	+
Dura mater[c]	NT	(+)	+	–	NT	NT	NT	NT

[a] Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); 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; for example, two goats (but no sheep) have contracted BSE naturally.

[b] In experimental models of TSE, the optic nerve has been shown to be a route of neuroinvasion and contains high titres of infectivity.

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

Table D.2 — Category B: Lower-infectivity tissues

Peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE								
	Humans				Cattle		Sheep and goats	
Tissues	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Peripheral nervous system								
Peripheral nerves	+	+	(–)	+	[+]	+	+	+
Autonomic ganglia[a]	NT	+	NT	(–)	NT	+	NT	+
Lymphoreticular tissues								
Spleen	+	+	+	+	–	–	+	+
Lymph nodes	+	+	+	–	–	–	+	+
Tonsil	+	+	NT	–	+	–	+	+
Nictitating membrane	NA	NA	NA	NA	+	–	[+]	+
Thymus	NT	+	NT	–	–	NT	+	+
Alimentary tract[b]								
Oesophagus	NT	–	NT	–	–	NT	[+]	+
Fore-stomach[c] (ruminants only)	NA	NA	NA	NA	–	NT	[+]	+
Stomach/abomasum	NT	–	NT	–	–	NT	[+]	+
Duodenum	NT	–	NT	–	–	–	[+]	+
Jejunum[d]	NT	+	NT	–	–	+	[+]	+
Ileum[d]	NT	+	NT	–	+	+	+	+
Appendix	(–)	+	NT	–	NA	NA	NA	NA
Colon/caecum[d]	NT	+	NT	–	–	–	+	+
Rectum	[+]	+	NT	NT	NT	NT	NT	+
Reproductive tissues								
Placenta[e]	NT	–	(+)	–	–	NT	+	+
Ovary[f]	NT	– (+)	NT	–	–	NT	–	–
Uterus[f]	NT	– (+)	NT	–	–	NT	–	–

Table D.2 — *(continued)*

Peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE								
	Humans				Cattle		Sheep and goats	
Tissues	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}	Infectivity	PrP^{TSE}
Other tissues								
Mammary gland/udder[f,g]	NT	–	NT	–	–	NT	–	+
Skin[f,h]	NT	– (+)	NT	–	–	NT	–	+
Adipose tissue	NT	–	(–)	–	–	NT	NT	NT
Heart/pericardium	NT	–	–	–	–	NT	–	NT
Lung	NT	–	+	–	–	NT	–	–
Liver[f]	NT	– (+)	+	–	–	NT	+	–
Kidney[f,i]	NT	– (+)	+	–	–	-	[+]	+
Adrenal	NT	+	–	–	[+]	+	+	–
Pancreas[f]	NT	– (+)	NT	–	–	NT	+	NT
Bone marrow[j]	–	–	(–)	–	(+)	NT	+	NT
Skeletal muscle[k]	NT	+	(–)	+	(+)	NT	+	+
Tongue[l]	NT	–	NT	–	–	NT	[+]	+
Blood vessels	NT	+	NT	+	–	NT	NT	+
Nasal mucosa[m,l]	NT	NT	NT	+	–	NT	+	+
Salivary gland	NT	–	NT	–	–	NT	+	NT
Cornea[n]	NT	–	+	–	NT	NT	NT	NT
Body fluids								
CSF	–	–	+	–	–	NT	+	–
Blood[o]	+	?	–	?	–	?	+	?
Saliva	NT	–	–	NT	NT	NT	–	NT
Milk[p]	NT	NT	(–)	NT	–	–	+	[+]
Urine[q]	NT	–	–	–	–	NT	–	–
Faeces[q]	NT	NT	–	NT	–	NT	–	NT

[a] In cattle, PrP^{TSE} is reported to be inconsistently present in the enteric plexus in the distal ileum, but immunohistochemical examination of tissues from a single "fallen stock" case of BSE in Japan suggested (albeit equivocally) involvement of myenteric plexuses throughout the small and large intestine.

[b] In vCJD, PrP^{TSE} is limited to gut-associated lymphoid and nervous tissue (mucosa, muscle, and serosa are negative).

[c] 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.

[d] When a large BSE oral dose was used to infect cattle experimentally, infectivity was detected in the jejunum and the ileo-caecum junction in Tg mice overexpressing PrP. PrP^{TSE} was detected at low incidence in lymphoid tissue of ileum and has been detected at an even lower frequency in jejuna lymphoid tissue of cattle similarly infected by the oral route.

[e] A single report of transmission of sporadic CJD infectivity from human placenta has never been confirmed and is considered improvable.