
**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

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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.

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.

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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

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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:

ISO 22442-1:2015(E)

- 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.