
**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) and IEC (the International Electrotechnical Commission) form the specialized system for worldwide standardization. National bodies that are members of ISO or IEC participate in the development of International Standards through technical committees established by the respective organization to deal with particular fields of technical activity. ISO and IEC technical committees collaborate in fields of mutual interest. Other international organizations, governmental and non-governmental, in liaison with ISO and IEC, also take part in the work.

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 document 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 and IEC 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) or the IEC list of patent declarations received (see <http://patents.iec.ch>).

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 22442-1:2015), which has been technically revised.

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

- [4.4.2](#) has been updated;
- weblinks in [C.2](#), bullet point 1, [C.3.3](#) and [C.4.4](#) have been updated;
- the weblink in [D.3.3](#) has been updated;
- [C.10](#) has been added;
- the bibliography has been updated.

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).

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 document 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 document is intended to cover medical devices including active implantable medical devices such as implantable infusion pumps.

This document does not apply to *in vitro* diagnostic devices.

This document can only be used in combination with ISO 14971 and is not a “stand-alone” standard.

NOTE Compliance to this document is shown by fulfilling its specified requirements. The guidance given in the notes and the 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 document 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 document 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 document 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 document does not specify a quality management system for the control of all stages of production of medical devices.

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

NOTE 1 It is not a requirement of this document 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 document, 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: Controls 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.

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

- IEC Electropedia: available at <http://www.electropedia.org/>
- ISO Online browsing platform: available at <http://www.iso.org/obp>

3.1 animal
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* (3.1) material which is involved directly in the manufacturing process of the medical device or is part of the final medical device

EXAMPLE Hyaluronic acid, collagen, gelatine, monoclonal antibodies, chitosan and 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
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, 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 medical purpose(s) of

- 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 by means of *in vitro* examination of specimens derived from the human body,
- and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means

Note 1 to entry: Products which could be considered to be medical devices in some jurisdictions but not in others include:

- disinfection substances;
- aids for persons with disabilities;
- devices incorporating *animal* (3.1) and/or human tissues;
- devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: ISO 13485:2003, 3.7]

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* (3.2) 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 requirements of ISO 14971 apply. Compliance with these requirements shall be verified by inspection of the appropriate documents, e.g. the risk management file.

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.

NOTE Further discussion of medical benefits and the benefit-risk analysis can be found in ISO 14971.

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 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/TS 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 document, 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. If exceptions to ISO 22442-2 and ISO 22442-3 are made, these exceptions shall be documented and justified.

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.

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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 document.

If the animal species is such that manufacturers cannot provide information on the animal sourcing, to 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 can be relevant:

- a) ISO 11135, ISO 11137 (all parts), ISO 11737-1, the ISO 13408 (all parts), ISO 14160, ISO 14937, ISO 17664 and ISO 17665-1, which can be relevant for bacteria, moulds and yeasts;
- b) ISO 10993-2, ISO 10993-3, ISO 10993-4, ISO 10993-5, ISO 10993-6, ISO 10993-7, ISO 10993-9, ISO 10993-10, ISO 10993-11, ISO 10993-12, ISO 10993-13, ISO 10993-14, ISO 10993-15, ISO 10993-16, ISO 10993-17, ISO 10993-18, ISO/TS 10993-19 and ISO/TS 10993-20, which can be used to manage risks related to undesired pyrogenic, immunological or toxicological reactions.

The use of these documents 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 22442-2:2020, 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.