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Biological evaluation of medical devices —

Part 2: Animal welfare requirements

Évaluation biologique des dispositifs médicaux —
Partie 2: Exigences relatives à la protection des animaux

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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 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,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and 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 10993-2:2006), which has been technically revised.

The main changes are as follows:

— laboratory animal veterinarian and their responsibilities and authority have been clarified;

— requirements for trained veterinary care staff have been added;

— ILAR Guide, IACLAM and AAALAC International have been added;

— aseptic methods, monitoring, pharmaceutical grade of chemical usage for surgery have been added.

A list of all parts in the ISO 10993 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

The goal of the ISO 10993 series is the protection of humans in the context of the use of medical devices.

This document supports the goal of the ISO 10993 series by promoting good science through paying proper regard to maximizing the use of scientifically sound non-animal tests and by ensuring that those animal tests performed to evaluate the biological properties of materials used in medical devices are conducted humanely according to recognized ethical and scientific principles.

The application of such humane experimental techniques, including high standards of animal care and accommodation, both help to ensure the scientific validity of safety testing and enhance the welfare of the animals used.

Biological evaluation of medical devices —

Part 2:
Animal welfare requirements

1 Scope

This document specifies the minimum requirements to be satisfied to ensure and demonstrate that proper provision has been made for the welfare of animals used in animal tests to assess the biocompatibility of materials used in medical devices. It is aimed at those who commission, design and perform tests or evaluate data from animal tests undertaken to assess the biocompatibility of materials intended for use in medical devices, or that of the medical devices themselves.

This document makes recommendations and offers guidance intended to facilitate future further reductions in the overall number of animals used, refinement of test methods to reduce or eliminate pain or distress in animals, and the replacement of animal tests by other scientifically valid means not requiring animal tests.

This document applies to tests performed on living vertebrate animals, other than man, to establish the biocompatibility of materials or medical devices.

This document does not apply to tests performed on invertebrate animals and other lower forms; nor (other than with respect to provisions relating to species, source, health status, and care and accommodation) does it apply to testing performed on isolated tissues and organs taken from vertebrate animals that have been euthanized.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1 and the following apply.

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

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

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

3.1
alternative method
test method that replaces an *animal test* (3.3), reduces the numbers of *animals* (3.2) used or refines the procedures applied

3.2
animal
live non-human vertebrate, excluding immature forms during the first half of gestation or incubation

3.3
animal test
use of an *animal* (3.2) for scientific purposes

Note 1 to entry: The definition of an animal test excludes acts of recognized veterinary practice applied for the benefit of an animal or the group of animals of which it is part; recognized husbandry practices to manage or conserve the animal or the group of which it is part; marking by methods which cause no more than momentary pain or distress; and *euthanasia* (3.5).

Note 2 to entry: The prevention of pain, suffering, distress or lasting harm by the effective use of anaesthesia or analgesia or other methods of rendering the animal insentient to pain (e.g. decerebration) does not place animal tests outside the scope of this definition. The administration of anaesthetics, analgesics or other methods of rendering the animal insentient to pain are considered to constitute an integral part of the animal test.

3.4
competent authority
body designated or recognized by a national government to take responsibility for overseeing, supervising or regulating *animal tests* (3.3), or the breeding and supply of *purpose-bred animals* (3.10) for use on such tests, within the scope of this document

3.5
euthanasia
humane killing of an *animal* (3.2) by a method causing minimal physical and mental suffering

3.6
humane endpoint
pre-determined, specific criteria and measures to be implemented to minimize or terminate pain, suffering or distress caused by *animal tests* (3.3) as soon as

— the scientific objectives have been met, or

— when it is realized they cannot be met, or

— when the *animal* (3.2) welfare problems being encountered are greater than can be justified by the importance, potential benefits, objectives and nature of the study

3.7
laboratory animal veterinarian
qualified laboratory animal veterinarian
person responsible for the health and well-being of all laboratory *animals* (3.2) used at the institution

Note 1 to entry: Often called “attending veterinarian” who is certified or has training or experience in laboratory animal science and medicine or is otherwise qualified in the care of the species being used.

Note 2 to entry: It is recommended that a laboratory animal veterinarian appropriately qualified by the relevant competent authority should be used as an attending veterinarian.

Note 3 to entry: There is an International Association of Colleges of Laboratory Animal Medicine (IACLAM) that is an association of associations, specifically the member Colleges of laboratory animal medicine. Each college has members that, in addition to their demonstrated proficiency in laboratory animal medicine, also possess subspecialization in a variety of areas that have direct bearing on the care, use and welfare of laboratory animals.

3.8
procedural training
prior training and acclimatizing of *animals* (3.2) to the interventions to be performed during an animal test, with a view to minimizing stress to the animal when animal tests are conducted

3.9
protocol
documentation prepared in advance of *animal tests* (3.3) being undertaken setting out the justification, rationale and test method [including scientific and *humane endpoints* (3.6)] for the animal tests

3.10
purpose-bred animal
animal (3.2) bred with the intention that it be used in *animal tests* (3.3) or for other experimental or scientific purposes

3.11
reduction
decrease to the essential minimum the number of *animals* (3.2) used in an *animal test* (3.3) to meet a defined scientific objective

3.12
refinement
total of the measures taken to safeguard the welfare of the *test animals* (3.14) by minimizing any resulting pain, suffering, distress or lasting harm to the *animals* (3.2) that are used

3.13
replacement
scientifically valid and reasonably and practically available test method that either completely or partially replaces the use of living vertebrate *animals* (3.2) with test methods that have not the potential to cause pain or distress to animals

3.14
test animal
animal (3.2) used in in vivo *animal tests* (3.3), or used to provide tissue for ex vivo or in vitro tests

3.15
validation
formal process by which the reliability and relevance of a test method is established for a particular purpose

3.16
veterinary care
responsibility for promoting an *animal*'s (3.2) health and welfare before, during and after animal procedures and providing advice and guidance based on best practice

Note 1 to entry: Veterinary care includes attention to the physical and behavioural status of the animal.

Note 2 to entry: The *laboratory animal veterinarian* (3.7) shall have authority and responsibility for making judgements concerning animal welfare.

Note 3 to entry: Veterinary advice and care shall be available at all times.

4 Requirements

4.1 General

This document sets forth essential requirements when animal tests are being considered, planned or performed for the biological evaluation of materials used in medical devices.

It has been developed to protect the welfare of animals used in the biological evaluation of materials used in medical devices without compromising, indeed to help to ensure, the scientific validity of the test results and the risk assessments that shall subsequently be performed.

This document focuses on the need to demonstrate that animal welfare is properly considered when expert judgement has to be exercised in relation to the biological evaluation of medical device materials, and that the principles of humane experimental technique are demonstrably applied to the design and conduct of animal tests.

This document requires that the need to perform animal tests is justified, and any pain, suffering, distress or lasting harm that is caused during essential animal tests is minimized.

This document sets out essential requirements that safeguard animal welfare by minimizing the pain and distress caused when animal tests are considered or undertaken by:

— establishing a framework that reflects the relevant ethical and, in many jurisdictions, the legal considerations relating to the use of animals for experimental or other scientific purposes;

— minimizing the number of animal tests by the appropriate use of literature searches, data-sharing, validated replacement alternatives, and appropriate testing strategies and study designs;

— minimizing any pain, suffering, distress and lasting harm caused to animals used in tests to evaluate the biocompatibility of materials used in medical devices by requiring appropriate use of relevant reduction and refinement alternatives;

— promoting consistent, high standards of accommodation and care to safeguard both the welfare of the animals used and the scientific validity and the reproducibility of the data generated;

— appropriate veterinary care program overseen by a qualified laboratory animal veterinarian is implemented.

To these ends the design and conduct of animal tests to evaluate the biocompatibility of materials used in medical devices shall be formed by, and incorporate, relevant strategies for the replacement, reduction and refinement of animal tests.

Commissioning animal tests without seeking and obtaining this information, exercising these judgements and implementing these measures does not comply with the essential requirements of this document.

NOTE These principles, and the essential requirements of this document, can also be relevant to animal use for medical device training and development.

4.2 Justification for animal tests

When required to make proper provision to ensure human safety, animal testing to enable the proper biological characterization of materials used in medical devices is acceptable.

For the purposes of the ISO 10993 series, animal tests shall only be deemed to be justified when:

— the resulting data are not otherwise available, but are essential to properly characterize the test material in the context in which it is to be used;

— when no suitable scientifically validated test method not involving the use of living animals is reasonably and practically available;

— when relevant reduction and refinement strategies have been identified and implemented including, if appropriate, obtaining test data from manufacturers and suppliers, and literature searches for toxicity and biocompatibility data.

To avoid unnecessary duplication, before animal tests to evaluate the biocompatibility of materials used in medical devices are undertaken, a review of available, relevant information on the properties of the test material shall be undertaken and documented. This shall include taking reasonable steps to enable data sharing.

Animal tests are deemed to be justified only when:

— they have been shown to be relevant and reliable for the purposes for which they are undertaken;

— the resulting data are essential to properly characterize and evaluate the test material in the context in which it is to be used in medical devices;

— no scientifically valid test method not requiring the use of living animals is reasonably and practically available;

— other relevant and appropriate strategies to minimize the pain, suffering, distress and lasting harm caused to the animals that are used have been identified and implemented.

4.3 Competence of personnel

Animal tests shall be designed, conducted and interpreted by persons competent to discharge the responsibilities assigned to them.

Animal tests shall be designed and conducted with the involvement of personnel with expertise in veterinary science, laboratory animal science and medicine, and animal husbandry and care.

Details of how staff are equipped by experience, qualification and training (including continued professional development) to satisfy these requirements shall be documented.

NOTE 1 Although this document does not provide an objective specification, it is considered important that those involved in the conduct of animal tests demonstrate a caring and respectful attitude to the animals used, i.e. that they have an appropriate "culture of care".

NOTE 2 For further information on assurance of training and competency, see 7.8.5 of Reference [1].

4.4 Planning and performance of animal tests

4.4.1 General

The selection and design of animal tests shall be appropriate to meet the specific scientific objectives of the study while minimizing the pain, suffering, distress or lasting harm that can be produced to the test animals.

As specified in 4.2, animal testing shall only be undertaken when the information required is essential to characterize the test material, is not otherwise available and when no suitable scientifically validated test method not involving the use of living animals is reasonably and practically available.

Following consideration of relevant and reasonably available potential replacement, reduction and refinement strategies, and before animal tests are undertaken, principal investigators and/or sponsors shall attest and document that no other replacement, reduction or refinement strategies are required to minimize the animal welfare costs of the studies.

NOTE In some instances pilot studies can be required to optimize study design before definitive studies can be designed and performed.

Where the provisions of the ISO 10993 series require or permit that an informed choice be made from a range of species, stages of development or animal numbers for an animal test, the decisions taken shall both safeguard the scientific validity of the test and minimize any pain, suffering, distress or lasting harm to the animals used. The rationale for the decisions taken shall be documented.

4.4.2 Re-use

The need to avoid undue cumulative welfare costs to the individual animals used shall be balanced against the need to minimize the number of animals used.

In general, an animal should not be used for more than one test.

Animals that have experienced pain and distress in the course of an animal test, or whose previous use can influence the outcome of further tests, shall not be re-used.

Re-use shall be consistent with the scientific objective and shall not impose unreasonable cumulative welfare costs on the individual animal.

Any re-use shall be documented, giving summary details of the earlier use and confirming that the requirements set out in this subclause are considered and met.