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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

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).

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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.

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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.

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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

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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

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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.

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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;

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— 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.

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4.5 Test strategy — Sequence of in vitro and in vivo tests

Testing strategies shall, as appropriate, adopt a tiered or hierarchical approach to minimize both the amount of animal testing required and any pain or distress that can be caused when animal tests are justified and undertaken. Specifically, unnecessary animal tests shall not be performed before appropriate, scientifically valid, and reasonably and practically available preliminary in vitro tests have been carried out, and the results evaluated.

Animal tests shall not be performed if the available data (e.g. from literature and/or database searches, results from previous screening tests, validated in vitro tests, previous animal tests or any other available relevant evidence) provide sufficient information on the biocompatibility of the test material for a sound, relevant risk assessment to be undertaken.

The rationale for the testing strategy shall be documented.

4.6 Animal care and accommodation

4.6.1 General

Purpose-bred animals shall be used whenever possible and specific justification is required for the use of non-purpose bred animals.

When purpose-bred animals are not used, the justification and details of the origin or source of the animals that are used shall be documented.

High standards of care and accommodation enhance the welfare of the animals used and promote the scientific validity of animal testing. Animal care and accommodation shall demonstrably, as a minimum, conform to relevant relevant national or regional regulations, published national or international animal care, accommodation and husbandry guidelines.

The relevant guidelines or requirements shall be referenced, and evidence of compliance (or details of non-compliance accompanied by an assessment of its likely impact on the welfare of the animals used and the validity of the data obtained) shall be explained, justified and documented.

Any component of the husbandry system that does not make best provision for the welfare of the test animals, can compromise the scientific validity of the test or inappropriately influence the nature or interpretation of the test result, shall be documented.

Social species shall be housed as stable, compatible pairs or groups unless single-housing is required for veterinary, husbandry, animal welfare or scientific reasons.

When it is not possible to pair- or group-house social species, the veterinary, husbandry, animal welfare or scientific justification for the need for single housing and its duration shall be documented. The impact of the decision made on the scientific outcome should also be evaluated and documented.

Custom and practice shall not, of themselves, be deemed to be acceptable justifications.

NOTE Reference [8] describes animal care and accommodation as a guideline.

4.6.2 Restraint

When animal tests require that animals be restrained, the degree, duration and nature of the restraint shall be the minimum consistent with achieving the scientific objective, and shall be documented.

4.6.3 Surgical procedures

All surgical procedures shall be performed on anaesthetized animals, incorporating surgical principles and practices with aseptic methods to minimize the incidence of intra-operative sepsis. The incidence of surgical sepsis shall be documented.

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Proper provision and monitoring shall be made for the pre-, peri- and post-operative care of the animals, including the responsible and effective use of analgesics in accordance with good contemporary clinical veterinary practice. Non-pharmaceutical grade of chemicals shall not be used. The regimens followed shall be documented.

4.7 Humane end points

4.7.1 General

Humane end points are required to meet several eventualities and shall not be reserved only for animals that are moribund or have other signs indicative of severe welfare problems.

The welfare of all test animals and the conditions in which they are kept, shall be checked at least once a day by a competent person such as laboratory animal veterinarian and veterinary care trained staff. The findings and actions taken shall be documented.

The observation schedule shall be intensified when significant adverse welfare effects are expected.

Appropriate supportive, symptomatic and specific treatments shall be provided to minimize welfare problems arising in the course of an animal test and shall be as agreed with, or directed by, a qualified laboratory animal veterinarian. The provision of such treatments and/or the rationale for withholding such treatments shall be documented.

Animals experiencing severe pain or distress diagnosed by a qualified laboratory animal veterinarian that cannot be alleviated or justified as previously accepted by ethical review committee shall be promptly euthanized.

Death (other than as the result of euthanasia) is not required to meet the requirements of the ISO 10993 series and shall not be set as a required end point for animal tests to determine the biocompatibility of medical device materials.

Documentation shall be maintained providing details of animals found dead in the course of animal tests conducted to satisfy the requirements of the ISO 10993 series. In some instances, such occurrences can represent a failure to identify and implement all relevant refinement strategies.

4.7.2 Euthanasia

Methods of euthanasia employed at the termination of animal tests shall produce rapid irreversible loss of consciousness and subsequent death without evidence of pain or distress and negative effect to the animal.

The method of euthanasia selected and used shall be detailed and justified in documentation claiming compliance with this document.

Appropriate equipment shall be provided and properly maintained and the staff involved shall be adequately trained and technically competent.

4.8 Study documentation

The study documentation shall describe how the animal test requirements were determined and how the animal tests were conducted. It shall be submitted to the relevant body when compliance with this document is claimed.

The design of an animal test shall be specified and documented, prospectively, in a study protocol detailing the animal tests to be performed and containing, if appropriate and relevant, the following:

a) the specific requirements and the scientific objectives to be attained by the test specified in the ISO 10993 series;

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b) the available, relevant information about the composition and known properties of the material under investigation and its use or intended use;

c) the rationale and justification for using animals (see 4.2);

d) study documentation that shall include:

   1) the test strategy (see 4.5);

   2) the scientific justification for the species, stage of development, strain and numbers used, including group sizes and the need for positive and negative controls (see 4.2 and 4.4.1);

   3) the origin or source and health status of the animals to be used; specific justification should be provided for the use of non-purpose bred animals (see 4.6.1);

   4) details of the care and husbandry systems (see 4.6.1);

   5) a detailed description of the procedures to be applied and the data to be gathered (see 4.4.1, 4.4.2, 4.6.2 and 4.6.3);

   6) the observation schedules and humane end points to be implemented, and the contact details for key personnel (see 4.7);

   7) the method of euthanasia and the justification for the choice of method to be used (see 4.7.2);

   8) details of the analytical and statistical methods to be applied.

4.9 Validity of test results and mutual acceptance of data

Mutual acceptance of test data can significantly reduce animal test requirements, and facilitate timely and ethical regulatory decisions. Whenever possible, test methods shall be based on internationally recognized protocols and conducted in accordance with recognized quality assurance systems, for example, in accordance with the principles of good laboratory practice.

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Annex A
(informative)

Rationale for the development of this document

A.1 General

Ideally, the essential requirements of the ISO 10993 series should be met without recourse to animal tests.

Pending the development, validation and regulatory acceptance of suitable replacement test methods, the imperative of this document is to minimize any pain and distress caused by justifiable animal tests.

A.2 Principles of humane animal care and use

Those planning and performing animal tests should have an appropriate culture of care and endorse the principle that the best science and the best animal welfare are inseparable.

Specifically, good-faith efforts should be made both to reduce to the absolute minimum the justifiable pain and distress that can be caused during animal tests, and to identify and eliminate welfare costs associated with the production, care and use of animals for animal tests.

In many cases, expert judgement is required to balance conflicting considerations in order to determine the most refined and scientifically valid test strategy. Reduction and refinement strategies can have to be considered concurrently rather than consecutively in order to minimize the animal welfare costs.

At times, consideration must be given to the selection of the appropriate test method and protocol from a range of scientifically acceptable strategies. In some circumstances, the most refined option can use larger numbers of animals but more humane end points, or fewer animals of a more sentient species. The need for potential conflicts to be acknowledged and balanced on the basis of sound information and expert judgement has to be borne in mind when interpreting the provisions relating to reduction and refinement set out in the ISO 10993 series. The final decision can be a matter of expert judgement, but the imperative is to ensure scientific validity while minimizing the costs in terms of animal welfare.

For that reason, there should be transparency about the options considered, the factors weighed and the judgements exercised in demonstrating that appropriate decisions were taken. When exercising professional judgement, investigators should therefore be prepared to justify what is done, why it is done and how it is done, in the supporting documentation.

A.3 Replacement

A replacement alternative is generally accepted as any test method that replaces the use of living vertebrate animals with insentient alternatives. For many aspects of the biological evaluation of materials used in medical devices, validated replacement test methods are not currently available.

A.4 Reduction

Reduction is defined as reducing to the necessary minimum the number of animals to be used to meet a defined scientific objective. It includes strategies that eliminate the need for unnecessary testing (selection of only the appropriate animal tests and data-sharing to eliminate the need for duplicate testing). Both the testing strategy (the order in which tests are undertaken and evaluated) and the design of individual tests should be taken into account if this is to be realized in practice.

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The testing strategy should adopt a tiered or hierarchical approach. In vitro screening tests can at times be used to identify materials not suited for use in some forms of medical device, and such in vitro screening tests can obviate the need for confirmatory animal tests. In other circumstances, the evaluation of one biological property can be predictive of others (e.g. strong skin irritants are also likely to be ocular irritants), or the result of a pilot study can obviate the need for the use of additional animals (e.g. evidence of marked ocular irritancy in a single rabbit can be sufficient to characterize the test material).

The need for concurrent, as opposed to historical, control groups can be questioned. Where concurrent controls are justified, consideration should be given to reducing the numbers of animals used by testing a number of test materials against a common contemporary control group.

Experimental design, including the data-streams captured and the means of statistical analysis utilized, is a key reduction consideration when individual studies are planned and performed.

Animal numbers should not be reduced at the expense of compromising the scientific objective (thus risking false conclusions being drawn or necessitating the test being repeated with larger numbers). Nor should numbers be reduced if the consequential changes to the study design (e.g. more aggressive protocols and less humane end points) are likely to cause a disproportionate increase in the pain and distress that will be caused to the animals that are used.

On the other hand, numbers should not be set to provide maximum statistical precision when this is not appropriate.

A.5 Refinement

Refinement is considered to be the total measures taken to minimize the pain, suffering, distress or lasting harm to the animals that are used for animal tests. It can also be viewed more positively as those steps that are taken to improve the welfare of the animals that are used.

For some purposes, expert judgement is exercised in selecting the most appropriate test method from a range of scientifically valid test methods. Faced with a choice of reasonably and practically available test methods capable of producing scientifically satisfactory results, the selection should be made on the basis of which is the most refined. Custom and practice are not, of themselves, considered to be adequate justifications.

For some purposes, expert judgement is exercised in selecting the most appropriate species and stage of development. Faced with a choice of species or stages of development capable of producing scientifically satisfactory results, the species and stage of development of least neurophysiological sensitivity (in this context, the ability to experience pain and distress) should be selected. Custom and practice should not, of themselves, be considered adequate justification.

Good-faith efforts should be made to predict, when possible eliminate, recognize and manage the negative welfare consequences and adverse effects (such as the immediate result of the intervention, the later consequences or foreseeable complications) that can be encountered during an animal test.

Procedural training may minimize any stress caused when animal tests are subsequently performed. Surgical procedural training is essential. Good surgical technique includes asepsis, gentle tissue handling, minimal dissection of tissue, appropriate use of instruments, effective haemostasis, and correct use of suture materials and patterns. A laboratory animal veterinarian's inherent responsibility includes providing advice concerning surgical technique.

A number of disturbance indices and severity scoring systems have been developed and promoted to assist in recognizing, recording and interpreting signs of welfare problems arising during the course of animal tests. Consideration should be given to their use in animal tests performed to help evaluate materials used in medical devices. Examples are listed in Annex B.

Appropriate observation schedules, and staff trained and competent to rapidly detect the onset of problems and authorized to take appropriate and timely remedial action by a laboratory animal veterinarian, are key considerations.

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A.6 Humane end points

Humane end points is a phrase used to capture the minimization of animal suffering by ensuring that the earliest appropriate end points are applied. Sub-clinical end points shall be preferred to end points producing significant morbidity.

Humane end points are required to meet several eventualities, for example, when:

— the scientific objective has been realized;

— it is clear that the scientific objective cannot be realized (e.g. when some intercurrent problem has invalidated the data-stream);

— the welfare costs being encountered are more than can be justified by the need to undertake the test.

In many contexts, therefore, humane end points are not reserved only for animals that are moribund or have other clinical signs indicative of severe welfare problems. A procedure shall be in place to provide for emergency veterinary care. A laboratory animal veterinarian or veterinary care trained staff shall be available to expeditiously assess the animal condition, treat the animal, investigate an unexpected death, or advise on euthanasia. In the case of a pressing health problem, if the researcher and veterinary care staff cannot reach consensus on treatment or euthanasia, the laboratory animal veterinarian shall have the authority.

Appropriate supportive, symptomatic and specific treatments to manage welfare problems arising in the course of an animal test should be pre-determined and deployed.

Death (other than as the result of euthanasia) is not required as an end point for animal tests to determine the biocompatibility of medical device materials. Deaths of animals in the course of such tests shall be clearly recorded in documentation claiming compliance with the ISO 10993 series and can in some cases represent a failure to implement all reasonable and appropriate refinement opportunities.

A.7 Animal accommodation

A.7.1 Accommodation and care

Ideally the accommodation and care of animals in laboratories would enable them to meet their physical needs and satisfy their behavioural drives.

A number of factors relating to accommodation and care can impair the welfare of test animals and/or compromise the validity of data obtained from animal tests. In general, the standard of accommodation and care should minimize any stresses contingent upon animals being unable to meet their physical needs or satisfy their behavioural drives.

Justification is required for any departures from contemporary best practice, as is an explanation of how such departures (e.g. single housing of social species, failure to provide environmental enrichment) can affect the scientific validity of the animal test.

A number of nationally and internationally recognized guidelines on accommodation and care have been produced and some examples are listed in References [1], [6], [8] and [19].

A.7.2 Environmental conditions

A number of environmental factors can impair the welfare of test animals and/or compromise the validity of data obtained from animal tests.

Environmental factors (e.g. temperature, humidity, air quality) that can compromise the validity of the data collected, or how it can be interpreted, should be considered when animal tests are planned. These

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should be monitored and recorded while the tests are in progress, and acknowledged and taken into account when the results are evaluated.

In general, to ensure the validity and reproducibility of the tests, animals should be maintained at a stable temperature and provided with suitable substrates to manipulate and control their microenvironment. Extremes of humidity should be avoided.

Good air quality should be maintained regardless of the air-change rate. Reference [8] provides informative reference material on this topic.

A.8 Ethical review

The decision to use animals in biological evaluation of medical devices requires critical thought, judgment, and analysis. Although the primary responsibility for ethical care and use is shouldered on the researchers, the ethical review committee (or equivalent institutional committee) shall ensure the ethical conduct of animal usage. The ethical review committee membership shall include, a qualified laboratory animal veterinarian, at least one researcher experienced in animal testing of medical devices, a person with a non-scientific background and a public member to represent the general community. All committee members should have appropriate training and education in ethical care and use of animals for biological evaluation of medical devices.

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Annex B
(informative)

Further suggestions for replacing, reducing and refining animal tests

B.1 General

Suggestions to reduce the number of animals used, to refine the test methods to reduce or eliminate pain or distress in animals, and to replace animal tests by other scientifically valid means not requiring animal tests, are set out in Clauses B.2 to B.6.

This Annex is intended to highlight and address some of the current limitations and obstacles to the application of the principles of humane experimental technique to animal tests.

References [1], [6], [8] and [19] provide further information on the issues covered in this document.

B.2 Alternative methods

Priority should be given by competent authorities, funding agencies and scientists to the development, validation and incorporation into testing practice of appropriate alternative methods that replace, reduce or refine animal tests.

B.3 Data-sharing for prevention of unnecessary duplication

Those who regulate or undertake animal tests are encouraged to make full use of all existing mechanisms and to establish further means of facilitating or requiring data-sharing in order to prevent unnecessary duplication and to enable appropriate materials to be used in medical devices as quickly and as ethically as possible.

B.4 Databases

As an aid to minimizing unnecessary repetition, international databases of test methods, their scope and limitations and the known biological properties and clinical uses of materials used in medical devices, should be established, maintained and publicized.

B.5 Minimization of animal usage

Only the minimum number of the most refined and justified animal tests should be performed in order to yield meaningful data to facilitate sound risk assessments and not to insist upon maximum statistical precision when this is not appropriate.

B.6 Publication

Investigators conducting animal tests to establish the biocompatibility of medical device materials, and those who own the data generated, are encouraged to publish their test methods and results in internationally referenced journals.

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