American National Standard

ANSI/AAMI/ISO 10993-2:2006

Biological evaluation of medical devices— Part 2: Animal welfare requirements

Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decision-making.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

INTERPRETATIONS OF AAMI STANDARDS AND RECOMMENDED PRACTICES

Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the Manager for Technical Development. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News.* The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News.*

American National Standard

ANSI/AAMI/ISO 10993-2:2006
(Revision of ANSI/AAMI/ISO 10993-2:1993/(R)2001)

Biological evaluation of medical devices—
Part 2: Animal welfare requirements

Approved 11 July 2006 by
Association for the Advancement of Medical Instrumentation

Registered 26 July 2006 by
American National Standards Institute

Abstract: 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.

Key words: animal welfare, animal testing

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing, or using products, processes, or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

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All AAMI standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

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International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard. NOTE: Documents are sorted by international designation.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1:2005	ANSI/AAMI ES60601-1:2005	Major technical variations
IEC 60601-1-2:2001 and Amendment 1:2004	ANSI/AAMI/IEC 60601-1-2:2001 and Amendment 1:2004	Identical
IEC 60601-2-04:2002	ANSI/AAMI DF80:2003	Major technical variations
IEC 60601-2-19:1990 and Amendment 1:1996	ANSI/AAMI II36:2004	Major technical variations
IEC 60601-2-20:1990 and Amendment 1:1996	ANSI/AAMI II51:2004	Major technical variations
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 and Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:2004	Major technical variations
IEC/TR 60878:2003	ANSI/AAMI/IEC TIR60878:2003	Identical
IEC/TR 62296:2003	ANSI/AAMI/IEC TIR62296:2003	Identical
IEC 62304:2006	ANSI/AAMI/IEC 62304:2006	Identical
IEC/TR 62348:2006	ANSI/AAMI/IEC TIR62348:2006	Identical
ISO 5840:2005	ANSI/AAMI/ISO 5840:2005	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001/(R)2004	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:2003	ANSI/AAMI/ISO 10993-1:2003	Identical
ISO 10993-2:2006	ANSI/AAMI/ISO 10993-2:2006	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003	Identical
ISO 10993-4:2002 and Amendment 1:2006	ANSI/AAMI/ISO 10993-4:2002 and Amendment 1:2006	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999/(R)2005	Identical
ISO 10993-10:2002 and Amendment 1:2006	ANSI/AAMI BE78:2002 ANSI/AAMI BE78:2002/A1:2006	Minor technical variations Identical
ISO 10993-11:2006	ANSI/AAMI/ISO 10993-11:2006	Identical
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999/(R)2004	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 10993-18:2005	ANSI/AAMI BE83:2006	Major technical variations
ISO/TS 10993-19:2006	ANSI/AAMI/ISO TIR10993-19:2006	Identical

International designation	U.S. designation	Equivalency
ISO/TS 10993-20:2006	ANSI/AAMI/ISO TIR10993-20:2006	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137-1:2006	ANSI/AAMI/ISO 11137-1:2006	Identical
ISO 11137-2:2006 (2006-08-01 corrected version)	ANSI/AAMI/ISO 11137-2:2006	Identical
ISO 11137-3:2006	ANSI/AAMI/ISO 11137-3:2006	Identical
ISO 11138-1: 2006	ANSI/AAMI/ISO 11138-1:2006	Identical
ISO 11138-2: 2006	ANSI/AAMI/ISO 11138-2:2006	Identical
ISO 11138-3: 2006	ANSI/AAMI/ISO 11138-3:2006	Identical
ISO 11138-4: 2006	ANSI/AAMI/ISO 11138-4:2006	Identical
ISO 11138-5: 2006	ANSI/AAMI/ISO 11138-5:2006	Identical
ISO/TS 11139:2006	ANSI/AAMI/ISO 11139:2006	Identical
ISO 11140-1:2005	ANSI/AAMI/ISO 11140-1:2005	Identical
ISO 11140-5:2000	ANSI/AAMI ST66:1999	Major technical variations
ISO 11607-1:2006	ANSI/AAMI/ISO 11607-1:2006	Identical
ISO 11607-2:2006	ANSI/AAMI/ISO 11607-2:2006	Identical
ISO 11737-1: 2006	ANSI/AAMI/ISO 11737-1:2006	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO 11737-3:2004	ANSI/AAMI/ISO 11737-3:2004	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161:2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO/TR 14969:2004	ANSI/AAMI/ISO TIR14969:2004	Identical
ISO 14971:2000 and A1:2003	ANSI/AAMI/ISO 14971:2000 and A1:2003	Identical
ISO 15223:2000, A1:2002, and A2:2004	ANSI/AAMI/ISO 15223:2000, A1:2001, and A2:2004	Identical
ISO 15225:2000 and A1:2004	ANSI/AAMI/ISO 15225:2000/(R)2006 and A1:2004/(R)2006	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO/TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO 15882:2003	ANSI/AAMI/ISO 15882:2003	Identical
ISO/TR 16142:2006	ANSI/AAMI/ISO TIR16142:2006	Identical
ISO 17664:2004	ANSI/AAMI ST81:2004	Major technical variations
ISO 17665-1:2006	ANSI/AAMI/ISO 17665-1:2006	Identical
ISO 18472:2006	ANSI/AAMI/ISO 18472:2006	Identical
ISO/TS 19218:2005	ANSI/AAMI/ISO 19218:2005	Identical
ISO 25539-1:2003 and A1:2005	ANSI/AAMI/ISO 25539-1:2003 and A1:2005	Identical

[1]In production Last updated 10/12/2006

[2]Final approval pending

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation of Medical Devices Committee

The adoption of ISO 10993-2:2006 as an American National Standard was initiated by the AAMI Biological Evaluation of Medical Devices Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Animal Protection Aspects Working Group (U.S. Sub-TAG for ISO/TC 194/WG 3), played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Biological Evaluation of Medical Devices Committee** had the following members:

Cochairs:	Donald E. Marlowe
	Peter William Urbanskic
Members:	James M. Anderson, MD, PhD, Case Western Reserve University (Independent Expert)
	Joseph Carraway, DVM, NAMSA
	Lawrence H. Hecker, PhD, Hospira Inc
	John G. Miller, DVM, AAALAC International
	Barry F.J. Page, Barry Page Consulting (Independent Expert)
	Anita Y. Sawyer, Becton Dickinson & Company
	Melvin E. Stratmeyer, PhD, FDA/CDRH
	Peter William Urbanski, Medtronic Inc
Alternates:	Raju G. Kammula, DVM, PhD, FDA/CDRH
	Donald E. Marlowe, FDA/CDRH
	Michael F. Wolf, Medtronic Inc

At the time this document was published, the **AAMI Animal Protection Aspects Working Group** had the following members:

Cochairs:	Leticia Medina, Abbott Laboratories
	John G. Miller, DVM
Members:	Richard W. Bianco, University of Minnesota
	Stephanie Board, St. Jude Medical, Inc.
	Joseph Carraway, DVM, NAMSA
	W. Jean Dodds, DVM, Independent Expert
	Lawrence H. Hecker, PhD, Hospira Inc
	Leticia Medina, Abbott Laboratories
	John G. Miller, DVM, AAALAC
	Lisa Olson, AppTec
	Anita Y. Sawyer, Becton Dickinson & Company
	Christine Schultz, Kimberly-Clark Corporation
	Melvin E. Stratmeyer, PhD, FDA/CDRH
Alternates:	Mary Cao, Kimberly-Clark Corporation
	Kelli Young, DVM, NAMSA

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 10993-2:2006

As indicated in the foreword to the main body of this document (page viii), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

ISO 10993-2:2006 was developed by Working Group (WG) 3, Animal Protection Aspects, of ISO Technical Committee (TC) 194, *Biological evaluation of medical devices*, to specify 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.

U.S. participation in ISO/TC 194/WG 3 is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation (AAMI) on behalf of the American National Standards Institute (ANSI). U.S. experts made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with international standards as much as possible. Upon review of ISO 10993-2, the AAMI Biological Evaluation of Medical Devices Committee and the AAMI Animal Protection Aspects Working Group decided to adopt 10993-2, verbatim, as a revision of ANSI/AAMI/ISO 10993-2:1993/(R)2001.

This edition of ISO 10993-2 has been expounded upon. It includes new definitions and new clauses covering justification of animal tests, humane endpoints, study documentation, validation of test results, and mutual acceptance of data. It also contains new annexes on rationale and further suggestions for replacing, reducing, and refining animal tests.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO documents. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

The concepts incorporated into this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page viii, this American National Standard is identical to ISO 10993-2:2006.

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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 10993-2 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-2:1992), which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and delayed-type hypersensitivity*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices*

Introduction

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

This part of ISO 10993 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 part of ISO 10993 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. It 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 also 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.

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

It 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 referenced documents are indispensable for the application 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 10993-1:2003, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

3 Terms and definitions

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

3.1
alternative method
any test method that replaces an animal test, reduces the numbers of animals used, or refines the procedures applied

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

3.3
animal test
any use of an animal for scientific purposes

NOTE 1 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.

NOTE 2 The prevention of pain, suffering, distress or lasting harm by the effective use of anesthesia 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 anesthetics, 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, or the breeding and supply of purpose-bred animals for use on such tests, within the scope of this part of ISO 10993

3.5
euthanasia
humane killing of an animal by a method causing a minimum of physical and mental suffering

3.6
humane endpoints
pre-determined, specific criteria and measures to be implemented to minimize or terminate pain, suffering or distress caused by animal tests as soon as the scientific objectives have been met, or when it is realized they cannot be met, or when the animal welfare problems being encountered are greater than can be justified by the importance, potential benefits, objectives and nature of the study

3.7
procedural training
prior training and acclimatizing of animals to the interventions to be performed during an animal test, with a view to minimizing stress to the animal when animal tests are conducted

3.8
protocol
documentation prepared in advance of animal tests being undertaken setting out the justification, rationale and test method (including scientific and humane endpoints) for the animal tests

3.9
purpose-bred animal
any animal bred with the intention that it be used in animal tests or for other experimental or scientific purposes

3.10
reduction
reducing to the essential minimum the number of animals used in an animal test to meet a defined scientific objective

3.11
refinement
sum total of measures taken to safeguard the welfare of the test animals by minimizing any resulting pain, suffering, distress, or lasting harm to the animals that are used

3.12
replacement
any scientifically valid and reasonably and practically available test method that either completely or partially replaces the use of living vertebrate animals with test methods that have not the potential to cause pain or distress to animals

3.13
test animal
any animal used in *in vivo* animal tests, or used to provide tissue for *ex vivo* or *in vitro* tests

3.14
validation
formal process by which the reliability and relevance of a test method is established for a particular purpose

4 Requirements

4.1 General

This part of ISO 10993 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 part of ISO 10993 focuses on the need to demonstrate that animal welfare is properly considered when expert judgment 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 part of ISO 10993 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 part of ISO 10993 sets out essential requirements that safeguard animal welfare by minimizing the pain and distress caused when animal tests are considered or undertaken by:

a) 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;

b) 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;

c) 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;

d) 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.

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 judgments and implementing these measures does not comply with the essential requirements of this part of ISO 10993.

NOTE These principles, and the essential requirements of this part of ISO 10993, can also be relevant to animal tests conducted on medical device materials and medical devices, in other contexts.

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:

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

b) 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;

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

d) 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 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 Although this part of ISO 10993 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.”

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 whilst minimizing the pain, suffering, distress or lasting harm that might be produced to the test animals.

As stated 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 of International Standards 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 might 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 were considered and met.

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 might 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 provenance 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, 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, might 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.

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 to minimize the incidence of intra-operative sepsis. The incidence of surgical sepsis shall be documented.

Proper provision 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. The regimens followed shall be documented.

4.7 Humane endpoints

4.7.1 General

Humane endpoints 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. 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 veterinarian. The provision of such treatments and/or the rationale for withholding such treatments shall be documented.

Animals experiencing severe pain or distress that cannot be alleviated shall be promptly euthanized.

Death (other than as the result of euthanasia) is not required to meet the requirements of the ISO 10993 series of International Standards, and shall not be set as a required endpoint 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 of International Standards. 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.

The method of euthanasia selected and used shall be detailed and justified in documentation claiming compliance with this part of ISO 10993.

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 part of ISO 10993 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 ISO 10993 series requirements and the scientific objectives to be attained by the test;

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 provenance 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 endpoints 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.

Annex A
(informative)

Rationale for the development of this part of ISO 10993

A.1 General

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

Pending the development, validation and regulatory acceptance of suitable replacement test methods, the imperative of this part of ISO 10993 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 might 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 judgment is required to balance conflicting considerations in order to determine the most refined and scientifically valid test strategy. Reduction and refinement strategies may have to be considered concurrently rather than consecutively in order to minimize the animal welfare costs.

At times, consideration may have to be given to selecting the appropriate test method and protocol from a range of scientifically acceptable strategies. In some circumstances the most refined option can be that which uses larger numbers of animals but more humane endpoints, or lower numbers of animals of a more sentient species. The need for potential conflicts to be acknowledged and balanced on the basis of sound information and expert judgment 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 judgment, but the imperative is to ensure scientific validity whilst minimizing the costs in terms of animal welfare.

For that reason, there should be transparency about the options considered, the factors weighed, and the judgments exercised in demonstrating that appropriate decisions were taken. When exercising professional judgment, 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.

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 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 might 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 endpoints) 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 sum total of 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 judgment 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 judgment 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.

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, are key considerations.

A.6 Humane endpoints

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

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

a) the scientific objective has been realized;

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

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

In many contexts, therefore, humane endpoints are not reserved only for animals that are moribund or have other clinical signs indicative of severe welfare problems.

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 endpoint 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 behavioral 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 behavioral 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) might 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 the Bibliography.

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 might compromise the validity of the data collected, or how it might be interpreted, should be considered when animal tests are planned. These should be monitored and recorded whilst 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. The Bibliography provides informative reference material.

A.8 Ethical review

The requirements set out in this part of ISO 10993 are intended to complement and inform, not supersede, local or national provisions for animal tests to be subjected to independent ethical review.

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 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.

The Bibliography identifies some relevant publications providing further information on the issues covered in this part of the ISO 10993 series.

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

ISO member bodies, notified bodies and 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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