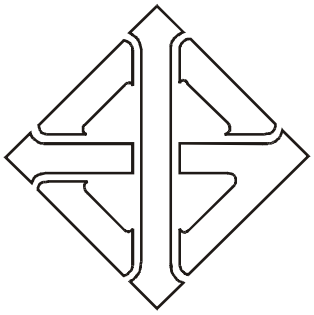

มาตรฐานผลิตภัณฑ์อุตสาหกรรม

THAI INDUSTRIAL STANDARD

มอก. 2395 เล่ม 2–2551

ISO 10993-2 : 2006

การประเมินทางชีวภาพของเครื่องมือแพทย์

เล่ม 2 : ข้อกำหนดสวัสดิภาพของสัตว์

BIOLOGICAL EVALUATION OF MEDICAL DEVICES -

PART 2 : ANIMAL WELFARE REQUIREMENTS

สำนักงานมาตรฐานผลิตภัณฑ์อุตสาหกรรม

กระทรวงอุตสาหกรรม

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มาตรฐานผลิตภัณฑ์อุตสาหกรรม
การประเมินทางชีวภาพของเครื่องมือแพทย์
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สำนักงานมาตรฐานผลิตภัณฑ์อุตสาหกรรม
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ประกาศในราชกิจจานุเบกษา ฉบับประกาศและงานทั่วไป เล่ม 126 ตอนพิเศษ 21ง
วันที่ 10 กุมภาพันธ์ พุทธศักราช 2552

คณะกรรมการวิชาการคณะที่ 687

มาตรฐานการทดสอบทางชีวภาพของวัสดุอุปกรณ์ทางการแพทย์และทันตกรรม

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กรรมการ

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–	คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
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กรรมการและเลขานุการ

นางสาวศุลีพร ศรีพัฒนะพิพัฒน์	สำนักงานมาตรฐานผลิตภัณฑ์อุตสาหกรรม

เนื่องจากมีการนำสัตว์จำนวนมากมาใช้ในการทดสอบเพื่อประเมินผลทางชีวภาพของเครื่องมือแพทย์และวัสดุที่ใช้ทำ ถึงแม้ว่าปัจจุบันจะมีการใช้วิธีทดสอบอื่นมาทดแทนการใช้สัตว์ แต่การทดสอบหลายอย่างก็ยังมีความจำเป็นที่ต้องใช้สัตว์ในการทดสอบ เพราะให้ผลที่ถูกต้อง ดังนั้นเพื่อให้ผู้ที่เกี่ยวข้องได้ตระหนักถึงการมีจริยธรรมในการใช้สัตว์และถูกต้องเหมาะสมตามหลักวิทยาศาสตร์ จึงกำหนดมาตรฐานผลิตภัณฑ์อุตสาหกรรม การประเมินทางชีวภาพของเครื่องมือแพทย์ เล่ม 2 : ข้อกำหนดสวัสดิภาพของสัตว์ ขึ้น

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดขึ้นโดยรับ ISO 10993-2 : 2006 Biological evaluation of medical devices-Part 2 : Animal welfare requirements มาใช้ในระดับเหมือนกันทุกประการ (identical) โดยใช้ ISO ฉบับภาษาอังกฤษเป็นหลัก

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดขึ้นเพื่อให้ทันกับความต้องการของผู้ใช้ และจักได้แปลเป็นภาษาไทยในโอกาสอันควร หากมีข้อสงสัยโปรดติดต่อสอบถามที่สำนักงานมาตรฐานผลิตภัณฑ์อุตสาหกรรม

คณะกรรมการมาตรฐานผลิตภัณฑ์อุตสาหกรรมได้พิจารณามาตรฐานนี้แล้ว เห็นสมควรเสนอรัฐมนตรีประกาศตามมาตรา 15 แห่งพระราชบัญญัติมาตรฐานผลิตภัณฑ์อุตสาหกรรม พ.ศ. 2511

ประกาศกระทรวงอุตสาหกรรม

ฉบับที่ 3892 (พ.ศ. 2551)

ออกตามความในพระราชบัญญัติมาตรฐานผลิตภัณฑ์อุตสาหกรรม

พ.ศ. 2511

เรื่อง กำหนดมาตรฐานผลิตภัณฑ์อุตสาหกรรม

การประเมินทางชีวภาพของเครื่องมือแพทย์

เล่ม 2 : ข้อกำหนดสวัสดิภาพของสัตว์

อาศัยอำนาจตามความในมาตรา 15 แห่งพระราชบัญญัติมาตรฐานผลิตภัณฑ์อุตสาหกรรม พ.ศ.2511 รัฐมนตรีว่าการกระทรวงอุตสาหกรรมออกประกาศกำหนดมาตรฐานผลิตภัณฑ์อุตสาหกรรม การประเมินทางชีวภาพของเครื่องมือแพทย์ เล่ม 2 : ข้อกำหนดสวัสดิภาพของสัตว์ มาตรฐานเลขที่ มอก. 2395 เล่ม 2-2551 ไว้ดังมีรายการละเอียดต่อท้ายประกาศนี้

ประกาศ ณ วันที่ 23 กรกฎาคม พ.ศ. 2551

สุวิทย์ คุณกิตติ

รัฐมนตรีว่าการกระทรวงอุตสาหกรรม

มาตรฐานผลิตภัณฑ์อุตสาหกรรม
การประเมินทางชีวภาพของเครื่องมือแพทย์
เล่ม 2 : ข้อกำหนดสวัสดิภาพของสัตว์

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดขึ้นโดยรับ ISO 10993-2 : 2006 Biological evaluation of medical devices-Part 2 : Animal welfare requirements มาใช้ในระดับเหมือนกันทุกประการ (identical) โดยใช้ ISO ฉบับภาษาอังกฤษเป็นหลัก

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดข้อเสนอแนะและข้อแนะนำเพื่อให้เกิดการลดจำนวนสัตว์ที่ใช้ทดสอบ ให้มีวิธีทดสอบที่ลดความเจ็บปวดและความทรมานที่สัตว์ได้รับ และการใช้วิธีทดสอบอื่นแทนวิธีทดสอบโดยใช้สัตว์ โดยกำหนดข้อกำหนดต่างๆ สำหรับการทดสอบโดยใช้สัตว์ ได้แก่ ข้อกำหนดทั่วไป เหตุผลที่ให้มีการทดสอบโดยใช้สัตว์ ความสามารถของบุคลากรที่เกี่ยวข้องกับการทดสอบ การวางแผนและการดำเนินการทดสอบ ลำดับการทดสอบโดยต้องทดสอบภายนอกร่างกาย (*in vitro* test) ก่อนการทดสอบในสัตว์ (animal test) การดูแลสัตว์และการจัดการสถานที่เลี้ยง จริยธรรมในการใช้สัตว์ การจัดทำเอกสารศึกษาเกี่ยวกับการทดสอบ การตรวจสอบความใช้ได้และการยอมรับร่วมของผลทดสอบ

รายละเอียดให้เป็นไปตาม ISO 10993-2 : 2006

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 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, 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

2

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 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 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 judgements 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 judgement 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 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 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 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.

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 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.

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 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) 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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