SLOVENSKI STANDARD
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Biološko ovrednotenje medicinskih pripomočkov - 11. del: Preskusi sistemske toksičnosti (ISO/DIS 10993-11:2025)

Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO/DIS 10993-11:2025)

Biologische Beurteilung von Medizinprodukten - Teil 11: Prüfungen auf systemische Toxizität (ISO/DIS 10993-11:2025)

Évaluation biologique des dispositifs médicaux - Partie 11: Essais de toxicité systémique (ISO/DIS 10993-11:2025)

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Biological evaluation of medical devices —

Part 11: Tests for systemic toxicity

Évaluation biologique des dispositifs médicaux —
Partie 11: Essais de toxicité systémique

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194 *Biological and clinical evaluation of medical devices*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 10993-11:2017), which has been technically revised with the following changes:

a) emphasized risk assessment based on available data as a first step;

b) added rabbits to Table 1 for group sizes;

c) provided guidance on exaggeration of the human dose for toxicity studies;

d) provided additional examples of clinical signs and observations in Annex C;

e) provided clarification on study duration for studies described in Annex H;

f) the Bibliography was updated.

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Systemic toxicity is a potential adverse effect of the use of medical devices. Generalized effects, as well as organ and organ system effects can result from absorption, distribution and metabolism of constituents from the device or its materials to parts of the body with which they are not in direct contact. This document addresses the evaluation of generalized systemic toxicity, not specific target organ or organ system toxicity, even though these effects may result from the systemic absorption and distribution of toxicants.

Because of the broad range of medical devices, and their materials and intended uses, this document is not overly prescriptive. While it addresses specific methodological aspects to be considered in the design of systemic toxicity tests, proper study design has to be uniquely tailored to the nature of the device's materials and its intended clinical application.

Other elements of this document are prescriptive in nature, including those aspects that address compliance with good laboratory practices and elements for inclusion in reporting.

While some toxicity tests (e.g., long term implantation or dermal toxicity studies) can be designed to study systemic effects as well as local, carcinogenic or reproductive effects, this document focuses only on those aspects of such studies, which are intended to address systemic effects. Studies which are intended to address other toxicological end points are addressed in ISO 10993-3, ISO 10993-5, ISO 10993-6, ISO 10993-10, ISO 10993-23, and ISO/TS 10993-20.

Prior to conducting a systemic toxicity study, all reasonably available data and scientifically sound methods in the planning and refinement of the systemic toxicity study design should be reviewed. This includes the suitability of use of existing toxicological data, chemistry data and/or other biological test data (including from *in vitro* tests and less invasive *in vivo* tests) for the refinement of study design (dose selection, and/or selection of pathological end points). For the repeated exposure systemic toxicity study in particular, the use of scientifically sound study design, the use of pilot studies and statistical study design and the use of unbiased, quantitative end points/methods in the pathological assessment (including clinical pathology, gross pathology and histopathology) are important so as to obtain data which have sufficient scientific validity.

The outcome of any single test should not be the sole basis for making a determination of whether a device is safe for its intended use.

Biological evaluation of medical devices —

Part 11:
Tests for systemic toxicity

1 Scope

This document specifies requirements and gives guidance on procedures to be followed in the evaluation of the potential for medical device materials to cause adverse systemic reactions.

2 Normative references

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

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 10993-11, *Biological evaluation of medical devices - Part 11: Tests for systemic toxicity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

3 Terms and definitions

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

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

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

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

3.1
dose
dosage
amount of test sample administered (e.g., mass, volume) expressed per unit of body weight or surface area

3.2
dose-effect
relationship between the dosage and the magnitude of a defined biological effect either in an individual or in a population sample

3.3
dose-response
relationship of dosage to the spectrum of effects related to the exposure either in an individual or in a population of individuals to a range of doses

3.4
leachable substance
chemical released from a device or material by the action of solvents related to the use of the device

Note 1 to entry: Examples of leachable substances are additives, sterilant residues, process residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers.

Note 2 to entry: Leachable substances related to the use of gas pathway devices can be evaluated according to the ISO 18562 series.

3.5
limit test
use of a single group treated at a suitably high dosage of test sample in order to delineate the presence or absence of a toxic hazard; if not toxic at this high dose, further testing at higher dosages is generally not necessary

3.6
systemic toxicity
harm that occurs in an organ or system other than at the contact site

3.7
acute systemic toxicity
adverse effects occurring within at least 72 h following a single or repeated administration of a test sample for a period of up to 24 h

3.8
subacute systemic toxicity
adverse effects occurring after single or repeated exposure of a test sample between 24 h and 28 d

Note 1 to entry: Since this term is semantically incorrect, the adverse effects occurring within the specified time period may also be described as a short-term repeated exposure systemic toxicity study. The selection of time intervals between 14 d and 28 d is consistent with most international regulatory guidelines and considered a reasonable approach. Subacute repeated intravenous and intraperitoneal studies are generally defined as exposure durations of ≤14 d for rodents.

3.9
subchronic systemic toxicity
adverse effects occurring after repeated administration or continuous exposure of a test sample for a period of up to 10 % of the lifespan of the species

Note 1 to entry: Subchronic toxicity studies are usually 90 d in rodents or rabbits but not exceeding 10 % of the lifespan of other species. Subchronic repeated dose intravenous and intraperitoneal studies are generally defined as treatment durations of 28 d for rodents.

3.10
chronic systemic toxicity
adverse effects occurring after the repeated or continuous administration of a test sample for a major part of the life span

Note 1 to entry: Chronic toxicity studies usually have a duration of at least 6 months in rodents or exceeding 10 % of the lifespan of other species.

3.11
test sample
material, device, device portion, component, chemical, extract or portion thereof subjected to biological or chemical testing or evaluation

4 General considerations

4.1 General

Before a decision to perform a systemic toxicity test is made, a biological evaluation as described in ISO 10993-1 shall be conducted. To evaluate potential toxicological risks of medical devices, first, consideration of applicability of chemical characterization and toxicological risk assessment should be given before pursuing systemic toxicity testing using an animal model. Only when there is not sufficient data to assess the risk of systemic toxicity using the chemical characterization and toxicological risk assessment or when this cannot be adequately performed due to the nature of the device, the in vivo toxicity studies should be considered.

Some devices contain such low concentrations of extractable constituents that adverse effects are unlikely to be observed in a systemic toxicity test. Chemical analysis of test sample extracts can provide information on whether in vivo systemic toxicity testing is potentially useful to the overall biological evaluation.

EXAMPLE 1 The analytical results from a water extract can provide a reasonable estimate of the composition and concentration of device constituents in the saline extract used for dosing an in vivo study, if:

— extraction conditions are comparable and

— identification and quantitation are adequate.

EXAMPLE 2 The analytical results from all extracts in an exhaustive extraction study can provide a reasonable estimate of the potential systemic exposure from a systemic toxicity study performed using implantation as the route of exposure.

If available, such information shall be considered when designing a systemic toxicity study. Where constituent concentrations are less than approximately 0,015 – 0,15 mg/kg/day, in vivo effects are unlikely to be observed. Particularly, chemical information should inform whether the study will be useful for the overall biological evaluation[11].

Testing shall be performed on the final product and/or representative component samples of the final product and/or materials. Test samples shall reflect the conditions under which the device is normally manufactured and processed. If modifications to the manufacturing and processing conditions are necessary, or deviations to the protocol occurred, they shall be recorded in the test report, together with their justification. For hazard identification purposes, it could be necessary to exaggerate exposure to the test samples. It could also be necessary to determine the dose for implantation-based systemic toxicity studies, including but not limited to calculation of dose based on animal weight and worst-case clinical use per the intended use, and accounting for a safety factor.

Physical and chemical properties of the test sample including, for example, pH, stability, viscosity, osmolality, buffering capacity, solubility and sterility, are some factors to consider when designing the study.

When animal tests are considered, all reasonably and practically available replacement, reduction and refinement (3Rs) alternatives should be identified and implemented to satisfy the provisions of ISO 10993-2.

4.2 Selection of animal model

There is no absolute criterion for selecting a particular animal species for systemic toxicity testing of medical devices. However, the species used shall be scientifically justified and in line with the provisions of ISO 10993-2. For acute oral, intravenous, dermal and inhalation studies of medical devices, rodents (mouse or rat) are preferred. Rabbit (lagomorph) is an option in dermal studies and preferred in the case of implantation studies where a large model is needed due to the size of the implant. Other non-rodent species may also need to be considered for testing, recognizing that a number of factors might dictate the number or choice of species for study.

It is preferred that a single animal species and strain are used when a series of systemic toxicity studies of different durations are performed, e.g. acute, subacute, subchronic and/or chronic systemic toxicity. This minimizes the variability between species and strains and facilitates an evaluation related solely to study duration. Should multiple species or strains be used, justification for their selection shall be documented.

4.3 Animal status

Generally, healthy purpose-bred young adult animals of known origin and with defined microbiological health status should be used. At the commencement of the study, the weight variation of animals used within a sex should not exceed ±20 % of the mean weight. When females are used, they should be nulliparous and non-pregnant. Animal selection shall be justified.

4.4 Animal care and husbandry

Care and handling of animals shall be in accordance with the animal care guidelines of the country in which the test facility is located. Animals shall be acclimatized to the laboratory conditions prior to treatment and the period of time documented. Control of environmental conditions and proper animal care techniques are essential to animal well-being, minimization of stress-related physiological responses and the quality of the results. Dietary constituents and bedding materials that are known to produce or influence toxicity should be properly characterized and their potential to influence test results taken into account.

4.5 Size and number of groups

4.5.1 Size of groups

The precision of the systemic toxicity test is dependent to a large extent on the number of animals used per dose level. The degree of precision needed and, in turn, the number of animals per dose group needed depends on the study design.

Group sizes should logically increase with the duration of treatment, such that at the end of the study sufficient animals in every group are available to help meet the objectives of the study. Group sizes shall meet both ISO 10993-11 and ISO 10993-6 requirements on the group size when the testing is designed to address both implantation and systemic toxicity endpoints, otherwise, additional justification shall be provided and documented. The study should use the least number of animals to detect meaningful differences in biological responses and provide meaningful interpretation of the data (see ISO 10993-2). Recommended minimum group sizes, with all routes of test sample administration considered, are given in Table 1.

Table 1 — Recommended minimum group sizes[a]

Study type	Rodent	Rabbit	Non-rodent
Acute	5	3	3
Subacute	10 (5 per sex)	6 (3 per sex)	6 (3 per sex)
Subchronic	20 (10 per sex)	8 (4 per sex)	8 (4 per sex)
Chronic	30 (15 per sex) [b]	12 (6 per sex)	[c]

[a] Testing in a single sex is typical for acute and pharmacopeia-type testing. When a device is intended for use in only one sex, testing should be done in that sex.

[b] The recommendation for rodents refers to one dose-level group testing. Where additional exaggerated dose groups are included the recommended group size may be reduced to 10 per sex.

[c] Expert statistical consultation for chronic study non-rodent group size is recommended. The number of animals tested should be based on the minimum required to provide meaningful data. Enough animals shall remain at the termination of the study to ensure proper statistical evaluation of the results.

4.5.2 Number of groups

One dose group treated at a suitable dosage of test sample in a single species could delineate the presence or absence of a hazard (i.e., limit test). However, other multi-dose or dose response studies require multiple groups to delineate the toxic response.