SLOVENSKI STANDARD
oSIST prEN ISO 10993-11:2016

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Biološko ovrednotenje medicinskih pripomočkov - 11. del: Preskusi sistemske toksičnosti (ISO/DIS 10993-11:2015)

Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO/DIS 10993-11:2015)

Biologische Beurteilung von Medizinprodukten — Teil 11: Prüfungen auf systemische Toxizität (ISO/DIS 10993-11:2015)

Évaluation biologique des dispositifs médicaux - Partie 11: Essais de toxicité systémique (ISO/DIS 10993-11:2015)

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ICS:

11.100.20	Biološko ovrednotenje medicinskih pripomočkov	Biological evaluation of medical devices

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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

ICS: 11.100.20

ISO/CEN PARALLEL PROCESSING

This draft has been developed within the International Organization for Standardization (ISO), and processed under the **ISO lead** mode of collaboration as defined in the Vienna Agreement.

This draft is hereby submitted to the ISO member bodies and to the CEN member bodies for a parallel five month enquiry.

Should this draft be accepted, a final draft, established on the basis of comments received, will be submitted to a parallel two-month approval vote in ISO and formal vote in CEN.

To expedite distribution, this document is circulated as received from the committee secretariat. ISO Central Secretariat work of editing and text composition will be undertaken at publication stage.

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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 (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 meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 194 "Biological and clinical evaluation of medical devices"

This second edition cancels and replaces the first edition (2006).

The major technical changes are the following:

a) Reduction in group size for chronic toxicity testing in Table 1;

b) new Annex F (informative);

c) original Annex F moved to Annex G;

d) new Annex H (informative);

e) bibliography updated.

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

Part 1: *Evaluation and testing within a risk management system*

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: *Method for the establishment of allowable limits for leachable substances*

Part 18: *Chemical characterization of materials*

Part 19: *Physico-chemical, morphological and topographical characterization of materials [Technical specification]*

Part 20: *Principles and methods for immunotoxicology testing of medical devices [Technical specification]*

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 leachates from the device or its materials to parts of the body with which they are not in direct contact. This part of ISO 10993 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 part of ISO 10993 is not overly prescriptive. Whilst it addresses specific methodological aspects to be considered in the design of systemic toxicity tests, proper study design must be uniquely tailored to the nature of the device's materials and its intended clinical application.

Other elements of this part of ISO 10993 are prescriptive in nature, including those aspects that address compliance with good laboratory practices and elements for inclusion in reporting.

While some systemic 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 endpoints are addressed in ISO 10993-3, ISO 10993-6, ISO 10993-10 and ISO/TS 10993-20.

Finally, toxicology is an imperfect science. 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 — Tests for systemic toxicity

1 Scope

This part of ISO 10993 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 referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

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

3 Terms and definitions

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

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

Note 1 to entry: There are two types of dose-response relationships. The first type is the response of an individual to a range of doses. The second type is the distribution of responses of a population of individuals to a range of doses.

3.4
leachable substance
chemical removed from a device or material by the action of water or other liquids 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.

3.5
limit test
use of a single group treated at a suitable dosage of test sample in order to delineate the presence or absence of a toxic hazard

3.6
systemic toxicity
toxicity that is not limited to adverse effects at the site of contact between the body and the device

Note 1 to entry: Systemic toxicity requires absorption and distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced.

3.7
acute systemic toxicity
adverse effects occurring at any time after single, multiple or continuous exposures of a test sample within 24 h

3.8
subacute systemic toxicity
adverse effects occurring after multiple or continuous exposure 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 intravenous studies are generally defined as treatment durations of > 24 h but < 14 d.

3.9
subchronic systemic toxicity
adverse effects occurring after the repeated or continuous administration of a test sample for a part of the lifespan

Note 1 to entry: Subchronic toxicity studies are usually 90 d in rodents but not exceeding 10 % of the lifespan of other species. Subchronic intravenous studies are generally defined as treatment durations of 14 d to 28 d for rodents and nonrodents, respectively.

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 6 months to 12 months.

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

4 General considerations

4.1 General

Selection of the appropriate test(s) for a device shall be in accordance with ISO 10993-1, giving due consideration to mode and duration of contact.

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 deviations are necessary, they shall be recorded in the test report, together with their justification. For hazard identification purposes, it may be necessary to exaggerate exposure to the test samples.

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, to satisfy the provisions of ISO 10993-2, all reasonably and practically available replacement, reduction and refinement alternatives should be identified and implemented. For *in vivo* acute toxicity testing, *in vitro* cytotoxicity data are useful in estimating starting doses [9].

4.2 Selection of animal species

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 the mouse or rat is preferred with the option of the rabbit in the case of dermal and implantation studies. 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 is used when a series of systemic toxicity studies of different durations are performed, e.g. acute, subacute, subchronic and/or chronic systemic toxicity. This controls 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 $\pm$ 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 conform to accepted animal husbandry guidelines. 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 necessary for meaningful 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 purpose of the study.