SLOVENSKI STANDARD
oSIST prEN ISO 10993-16:2016

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Biološko ovrednotenje medicinskih pripomočkov - 16. del: Načrt toksikokinetičnih raziskav razgradnih produktov in izlužnin (ISO/DIS 10993-16:2016)

Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables (ISO/DIS 10993-16:2016)

Biologische Beurteilung von Medizinprodukten - Teil 16: Entwurf und Auslegung toxikokinetischer Untersuchungen hinsichtlich Abbauprodukten und herauslösbaren Bestandteilen (ISO/DIS 10993-16:2016)

Évaluation biologique des dispositifs médicaux - Partie 16: Conception des études toxicocinétiques des produits de dégradation et des substances relargables (ISO/DIS 10993-16:2016)

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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 16:
Toxicokinetic study design for degradation products and leachables

Évaluation biologique des dispositifs médicaux —

Partie 16: Conception des études toxicocinétiques des produits de dégradation et des substances relargables

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 (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 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 third edition cancels and replaces the second edition (ISO 10993-16:2010), of which it constitutes a major revision with the following technical changes:

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]

— Part 33: Guidance on tests to evaluate genotoxicity -- Supplement to ISO 10993-3 [Technical Report]

Introduction

Toxicokinetics describe the absorption, distribution, metabolism and excretion, with time, of foreign compounds in the body. Essential to the evaluation of the safety of a medical device is consideration of the stability of the material(s) *in vivo* and the disposition of intended and unintended leachables and degradation products. Toxicokinetic studies can be of value in assessing the safety of materials used in the development of a medical device or in elucidating the mechanism of observed adverse reactions. Toxicokinetic studies can also be applicable to medical devices containing active ingredients. The need for and extent of such studies should be carefully considered based on the nature and duration of contact of the device with the body (see Annex A). Existing toxicological literature and toxicokinetic data can be sufficient for this consideration.

The potential hazard posed by a medical device can be attributed to the interactions of its components or their metabolites with the biological system. Medical devices can release leachables (e.g. residual catalysts, processing aids, residual monomers, fillers, antioxidants, plasticizers) and/or degradation products which migrate from the material and have the potential to cause adverse effects in the body.

A considerable body of published literature exists on the use of toxicokinetic methods to study the fate of chemicals in the body (see Bibliography). The methodologies and techniques utilized in such studies form the basis of the guidance in this part of ISO 10993. Annex A provides a rationale for the use of this part of ISO 10993.

Biological evaluation of medical devices —

Part 16: Toxicokinetic study design for degradation products and leachables

1 Scope

This part of ISO 10993 gives principles on how toxicokinetic studies relevant to medical devices should be designed and performed. Annex A describes the considerations for inclusion of toxicokinetic studies in the biological evaluation of medical devices.

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 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-1:2010, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process; Technical Corrigendum 1*

ISO 10993-2:2006, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-12:2012, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17:2002, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 10993-18:2005, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

ISO/TR 10993-22:2016, *Biological evaluation of medical devices — Part 22: Guidance on nanomaterials*[1)]

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

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
absorption
process by which a substance enters the blood and/or lymph system

3.2
bioavailability
extent of systemic absorption of specified substance

1) Under preparation

3.3
biodegradation
degradation due to the biological environment

Note 1 to entry: Biodegradation might be modelled by *in vitro* tests.

3.4
bioresorption
process by which a biomaterial is degraded in the physiological environment and the product(s) eliminated and/or absorbed

3.5
clearance
rate of removal of a specified substance from the body or parts of the body by metabolism and/or excretion

3.6
$\mathbf{c_{max}}$
maximum concentration of a specified substance in plasma expressed in mass per unit volume

Note 1 to entry: When the maximum concentration in fluid or tissue is being referred to, it should have an appropriate identifier, e.g. c_{max}, liver, and be expressed in mass per unit volume or mass.

3.7
degradation product
product of a material which is derived from the chemical breakdown of the original material

3.8
distribution
process by which an absorbed substance and/or its metabolites circulate and partition within the body

3.9
excretion
process by which an absorbed substance and/or its metabolites are removed from the body

3.10
extract
liquid that results from extraction of the test substance or control

3.11
half-life
$t_{1/2}$
time for the concentration of a specified substance to decrease to 50 % of its initial value in the same body fluid or tissue

3.12
leachable
chemical that can migrate from a device or component under storage conditions or conditions of use

Note 1 to entry: A leachable (e.g. additives, monomeric or oligomeric constituent of polymeric material) can be extracted under laboratory conditions that simulate normal conditions of exposure.

3.13
mean residence time
statistical moment related to half-life which provides a quantitative estimate of the persistence of a specified substance in the body

3.14
metabolism
process by which an absorbed substance is structurally changed within the body by enzymatic and/or non-enzymatic reactions

Note 1 to entry: The products of the initial reaction can subsequently be modified by either enzymatic or non-enzymatic reactions prior to excretion.

3.15
test substance
degradation product or leachable used for toxicokinetic study

3.16
t_{max}
time at which c_{max} is observed

3.17
volume of distribution
V_d
parameter for a single-compartment model describing the apparent volume which would contain the amount of test substance in the body if it were uniformly distributed

4 Principles for design of toxicokinetic studies

4.1 Toxicokinetic studies should be designed on a case-by-case basis, see Annex A.

4.2 A study protocol shall be written prior to commencement of the study. The study design, including methods, shall be defined in this protocol. Details of areas to be defined are given in 4.3 to 4.7 and in Clause 5.

4.3 The results of extraction studies (see ISO 10993-12 and ISO 10993-18) should be considered in order to determine the methods to be used for toxicokinetic studies. Information on the chemical and physicochemical properties, surface morphology of the material and biochemical properties of any leachable should also be considered.

NOTE The extent and rate of release of leachables depend on the concentration at the surface, migration to the surface within the material, solubility and flow rate in the physiological milieu.

4.4 It is recommended to undertake toxicokinetic studies with a characterized leachable or degradation product that has the potential of being toxic. However, the performance of toxicokinetic studies on mixtures is possible under certain conditions. An extract liquid (see lSO 10993-12), or a ground or powdered form of the material or device, may be used in exceptional circumstances and shall be justified in the study design.

4.5 Analytical methods shall be able to detect and characterize degradation products, leachables and metabolites in biological fluids and tissues. For analytical methods, other parts of ISO 10993 shall be used as relevant. The methods shall be fully described in the study report (see 5.1.10). Quantitative analytical methods shall be specific, sensitive and reproducible (see ISO 10993-18).

Validation/qualification of the method shall be performed.

4.6 The study design shall state the physiological fluid, tissue or excreta in which analyte levels will be determined.

NOTE Blood is convenient to sample and thus is often the fluid of choice for kinetic parameter and absorption studies. It is necessary to specify whether analysis is on whole blood, serum or plasma and to provide validation of this choice. Binding to circulating proteins or red cells can be determined *in vitro*. Analyte recovery from the matrix shall be documented.