INTERNATIONAL STANDARD

ISO 10993-16

Third edition
2017-05

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

Reference number
ISO 10993-16:2017(E)

ISO copyright office
Ch. de Blandonnet 8 • CP 401
CH-1214 Vernier, Geneva, Switzerland
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
copyright@iso.org
www.iso.org

Contents

Page

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*.

This third edition cancels and replaces the second edition (ISO 10993-16:2010), which has been technically revised with the following changes:

a) definition in 3.1 has been modified for clarification;

b) Clause 4 has been modified for clarification;

c) Clause 5 has been modified for clarification;

d) information regarding toxicokinetic studies on nano-objects have been added;

e) A.4 has been modified for clarification.

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

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, in which case, pharmaceutical legislation are to be considered. The need for and extent of toxicokinetic studies should be carefully considered based on the nature and duration of contact of the device with the body (see A.2). 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, etc.) 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 document. Annex A provides a rationale for the use of this document.

Biological evaluation of medical devices —

Part 16: Toxicokinetic study design for degradation products and leachables

1 Scope

This document provides principles on designing and performing toxicokinetic studies relevant to medical devices. Annex A describes the considerations for inclusion of toxicokinetic studies in the biological evaluation of medical devices.

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: Evaluation and testing within a risk management process*

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 http://www.electropedia.org/

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

3.1
absorption
process of uptake of substance into or across tissue, blood and/or lymph system

3.2
bioavailability
extent of systemic *absorption* (3.1) of specified substance

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* (3.14) and/or *excretion* (3.9)

3.6
c_{max}
maximum concentration of a specified substance in plasma

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* (3.15) 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* (3.11) 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* (3.9).

3.15
test substance
degradation product (3.7) or *leachable* (3.12) used for toxicokinetic study

3.16
t_{max}
time at which c_{max} (3.6) 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* (3.15) 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 ISO 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). Limit of detection/quantification shall be defined and justified.

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. Analyte recovery from the matrix shall be documented.

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*.

4.7 There should be sufficient data points with adequate time intervals to allow determination of kinetic parameters. In theory, this should cover several terminal half-lives; in practice, the constraints of the analytical method may necessitate a compromise.

5 Guidance on test methods

5.1 General considerations

5.1.1 The study should be performed on an appropriate sex and species; consider utilizing the same species used for the systemic toxicity studies. The animal welfare conditions should be as recommended in guidelines for the care and use of animals (see ISO 10993-2).

5.1.2 A non-radiolabelled test substance may be utilized provided that suitable validated assay procedures for the test substance in the relevant samples exist and the metabolism of the test substance is well characterized.

5.1.3 If necessary, the test substance should be radiolabelled in a metabolically stable position, preferably with ^{14}C or ^{3}H, and of suitable radiochemical purity (>97 %). When using ^{3}H, the possibility of tritium exchange should be considered. The specific activity and radiochemical purity of the test substance shall be known and reported.

5.1.4 The test substance should be administered by an appropriate route. This route should be relevant to the use of the medical device. The test substance should be prepared in a suitable vehicle taking into account the physicochemical properties of the test substance (leachable or degradation product) using appropriate route and dose of administration. The stability of the test substance in the vehicle shall be known and reported.

NOTE The study design might require the inclusion of other route(s) for comparison of percent absorption.

5.1.5 In dose balance studies, animals should be housed only in metabolism cages.

5.1.6 Urine and faeces should be collected in low temperature vessels (or in vessels containing preservative that does not interfere with the analysis) to prevent post-elimination microbial or spontaneous modification. Blood for whole-blood or plasma analysis should be collected in the presence of a suitable anticoagulant.

5.1.7 Controls should, wherever possible, be collected prior to dosing. In some studies, collection of controls (e.g. tissues) is not possible from the test animals and these should be obtained from a control group.

5.1.8 Collection times should be appropriate to the type of study being performed, and may be carried out, as necessary, over periods of minutes, hours, days, weeks or even months. For studies involving excreta, this is usually a 24 h period over at least 96 h. Where blood sampling is required, blood is collected according to a specified schedule ranging from minutes to hours over a period up to 72 h.

5.1.9 Toxicokinetic studies should be performed in accordance with good laboratory practice.

5.1.10 The study report shall include the following information, where relevant:

a) strain and source of animals, age, sex (if females indicate reproductive state), environmental conditions, diet;

b) test substance and sample, purity, stability, formulation, amount administered;

c) test conditions, including route of administration;

d) assay methods, extraction, detection, validation/qualification;

e) overall recovery of material;

f) tabulation of individual results at each time point;

g) quality standard or good laboratory practice compliance statement;

h) presentation and discussion of results;

i) interpretation of results.

5.2 Guidance on specific types of test

5.2.1 General

5.2.1.1 The study should be designed to provide the necessary information for risk assessment, and therefore it is usually not necessary to examine all aspects.

5.2.1.2 Absorption, distribution, metabolism and excretion studies are a range of studies capable of being performed either individually, examining one of these aspects, or collectively, examining several aspects in one study.

5.2.1.3 Depending on the design of the study, a number of kinetic parameters may be determined including absorption rate, area under the plasma concentration versus time curve, area under the first moment plasma concentration versus time curve, volume of distribution, c_{max}, t_{max}, half-life, mean residence time, elimination rate and clearance.

5.2.1.4 Kinetic parameters can only be determined for a particular molecular species and hence the assay needs to be specific and sensitive to this molecular species. True kinetic parameters of a relevant compound can only be determined following intravenous administration. It may therefore be necessary to include a limited intravenous administration study in the design of the kinetic parameter studies. This allows the fraction of the dose absorbed to be calculated and this serves as a correction in estimating parameters in other studies.

In some instances, intra-arterial administration should be considered as some compounds are known to be cleared through the pulmonary system.

5.2.1.5 The appropriate kinetic model should be used in determining the kinetic parameters. A number of computer programs exist for estimating kinetic parameters. The software should be validated prior to use and this validation should be documented. The assumptions entered into the program and the choices in modelling should be documented.

5.2.2 Absorption

Absorption depends on the route of administration, the physicochemical form of the test substance and the vehicle. It can be estimated from blood, serum, excreta and tissue concentrations. Bioavailability studies may be considered. The choice of the appropriate type of study depends on the other information required, availability of radiolabelled material and assay method. The absorption rate constant can be estimated reliably only if sufficient samples are taken in the absorption phase.

NOTE *In vitro* methods exist which can give important information on gastrointestinal and dermal absorption of chemicals.

5.2.3 Distribution

5.2.3.1 Distribution studies generally require radiolabelled compounds.

Studies may be

— quantitative, determining levels in dissected tissues,

— qualitative, using whole-body autoradiography (WBA), or

— semiquantitative, using graded WBA reference doses.

5.2.3.2 In general, sampling times in distribution studies may be based on kinetic data and will depend on test sample elimination. Multiple sampling times may be used. Sampling is normally more frequent in