List of Titles

American National Standard

ANSI/AAMI/ISO 10993-16:1997/(R)2003

Biological evaluation of medical devices— Part 16: Toxicokinetic study design for degradation products and leachables from medical devices

AAMI Association for the Advancement of Medical Instrumentation

American National Standard ANSI/AAMI/ISO 10993-16:1997/(R)2003

Biological evaluation of medical devices–Part 16: Toxicokinetic study design for degradation products and leachables

Approved 4 August 1997 by
Association for the Advancement of Medical Instrumentation

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Abstract: This standard 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.

Keywords: degradation, leachable, toxicokinetic study

List of Titles

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Committee representation

Association for the Advancement of Medical Instrumentation

The proposed adoption of ISO 10993-16:1997 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Degradation Working Group (U.S. Sub-TAG for ISO/TC 194/WG 2) and the AAMI Toxicokinetic Study Working Group (U.S. Sub-TAG for ISO/TC 194/WG 13), played an active part in developing the ISO standard.

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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 10993-16:1997

Toxicokinetic study design for degradation products and leachables

As indicated in the foreword to the main body of this document (page vi), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard, which was developed by ISO Technical Committee 194, *Biological evaluation of medical devices*, to fill a need for the global harmonization of test methods for biological aspects of medical devices.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation (AAMI). The U.S. TAG for ISO/TC 194 supports the international harmonization of methods used in evaluating the biocompatibility of medical devices in order to help reduce unnecessary repetition of testing.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI which gives the corresponding U.S. designation and the level of equivalency to the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

NOTE—Beginning with the ISO foreword on page vi, this American National Standard is identical to ISO 10993-16:1997.

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.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75% of the member bodies casting a vote.

International Standard ISO 10993 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

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

—*Part 1: Evaluation and testing*

—*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 cytotoxicity: in vitro methods*

—*Part 6: Tests for local effects after implantation*

—*Part 7: Ethylene oxide sterilization residuals*

—*Part 9: Framework for the identification and quantification of potential degradation products*

—*Part 10: Tests for irritation and sensitization*

—*Part 11: Tests for systemic toxicity*

—*Part 12*: *Sample preparation and reference materials*

—*Part 13: Identification and quantification of degradation products from polymers*

—*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*

Future parts will deal with other relevant aspects of biological testing.

Annex A forms an integral part of this part of ISO 10993. Annex B is for information only.

Introduction

This part of ISO 10993 provides guidance and requirements on the design and performance of toxicokinetic studies.

Toxicokinetics describes the absorption, distribution, metabolism and excretion of foreign compounds in the body with time. Essential to the evaluation of the safety of a medical device are consideration of the stability of the material(s) *in vivo* and the disposition of leachables and degradation products. Toxicokinetic studies may 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. 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.

The potential hazard posed by a medical device may be attributed to the interactions of its components or their metabolites with the biological system. Medical devices may 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 annex B). The methodologies and techniques utilized in such studies form the basis of the guidance in this standard. A rationale for the use of this part of ISO 10993 is given in annex A.

List of Titles

American National Standard ANSI/AAMI/ISO 10993-16:1997

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 reference

The following standard contains provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the edition indicated was valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent edition of the standard indicated below. Members of IEC and ISO maintain a register of currently valid International Standards.

ISO 10993-16:1992, *Biological evaluation of medical devices—Part 1: Guidance on selection of tests.*

3 Definitions

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

3.1 degradation product: Product of a material which is generated by the chemical breakdown or decomposition of the material.

3.2 leachable: Extractable component, such as an additive, monomeric or oligomeric constituent of polymeric material.

3.3 test substance: Degradation product or leachable used for toxicokinetic study.

3.4 absorption: Process by which a substance enters the blood and/or lymph system.

3.5 distribution: Process by which an absorbed substance and/or its metabolites circulate and partition within the body.

3.6 metabolism: Process by which an absorbed substance is structurally changed within the body by chemical and/or enzymatic reactions.

NOTE—The products of the initial reaction may subsequently be modified by either enzymatic or nonenzymatic reactions prior to excretion.

3.7 excretion: Process by which an absorbed substance and/or its metabolites are removed from the body.

3.8 bioavailability: Extent of systemic absorption of intact substance.

3.9 clearance: Rate of removal of a substance from the body by metabolism and/or excretion.

3.10 half-life ($t_{1/2}$): Time for the concentration of a particular molecular species to decrease to 50% of its initial value in the same body fluid or tissue.

3.11 mean residence time: Statistical moment related to half-life which provides a quantitative estimate of the persistence of a substance in the body.

3.12 c_{max}**:** Maximum concentration of a substance in plasma expressed in mass per unit volume.

NOTE—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.

3.13 t_{max}**:** Time at which c_{max} is observed.

3.14 AUC $_{0\text{-}t}$**:** Area under the plasma concentration versus time curve, from time zero to time *t* following a single dose of a substance.

NOTE—*t* is normally extrapolated to infinity.

3.15 AUMC $_{0\text{-}t}$**:** Area under the first moment plasma concentration versus time curve, from time zero to time *t* following a single dose of a substance.

NOTE—*t* is normally extrapolated to infinity.

3.16 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.

3.17 extract liquid: Liquid which is the result of the extraction process on the test material.

3.18 biodegradation: Alteration of a medical device or biomaterial involving loss of integrity and/or performance when exposed to a physiological or simulated environment.

3.19 bioresorption: Process by which a biomaterial is degraded in the physiological environment and the product(s) eliminated and/or absorbed.

4 Principles for design of toxicokinetic studies

4.1 Toxicokinetic studies should be designed on a case-by-case basis.

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 below and in clause 5.

4.3 The results of leaching studies 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 flowrate in the physiological milieu.

4.4 It is recommended to undertake toxicokinetic studies with a characterized leachable or degradation product which 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. They shall be fully described in the study report (see 5.1.11). Quantitative analytical methods shall be specific, sensitive and reproducible, and produce data which show linearity over the range of expected analyte concentrations. Validation of the assay method shall be presented in the report.

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*.

4.7 The study report should contain information on analyte binding in the sample (e.g. amount and affinity) and demonstrate that this does not lead to underestimation of analyte concentration.

4.8 There should be sufficient data points with adequate spacing 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 in an appropriate sex and species. Healthy young adult animals should be acclimatized to laboratory conditions for at least 7 days. They should be transferred to individual metabolism cages, when used, for an acclimatization period of at least 24 h. The environmental conditions should be as recommended in guidelines for the care and use of animals (see ISO 10993-2). During the study, conventional animal diets and drinking water should be freely available unless otherwise specified in the protocol. Animals should be randomly selected into groups for each time period studied; group sizes of at least three for small animals and at least two for larger species should be used. At the appropriate specified times, animals should be humanely killed.

5.1.2 A non-radiolabeled test substance may be utilized, providing 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 radiolabeled in a metabolically stable position, preferably with ^{14}C or ^{3}H, and of a suitable radiochemical purity (>97%). When using ^{3}H, the possibility of tritium exchange should be considered. The radiolabeled compound should be diluted, when appropriate, with non-radiolabeled substance.

5.1.4 When using a radiolabeled compound, the specific activity and radiochemical purity of the test substance shall be known.

5.1.5 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 sample appropriate to the route of dose administration. The stability of the sample under the proposed conditions of administration should be known and reported.

NOTE—The study design may require the inclusion of other route(s) for comparison.

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

5.1.7 Urine and feces should be collected in low temperature vessels (or in vessels containing preservative not interfering 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.

5.1.8 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.

5.1.9 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 24-h periods 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.

5.1.10 Toxicokinetic studies should be performed according to appropriate good laboratory practice.

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

a) strain and source of animals, environmental conditions, diet, age, sex;

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

c) test conditions, including route of administration;

d) assay methods, extraction, detection, validation;

e) overall recovery of material;

f) tabulation of individual results at each time point;

g) quality standard or good laboratory practice compliance statement;

h) discussion of results;

i) interpretation of results.

5.2 Guidance on specific types of test

5.2.1 General

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

5.2.1.1 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.

5.2.1.2 Depending on the design of the study, a number of kinetic parameters may be determined including absorption rate, elimination rate, AUC $_{0\text{-}t}$, AUMC $_{0\text{-}t}$, c_{max}, t_{max}, half-life, mean residence time, volume of distribution and clearance.

5.2.1.3 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.

5.2.1.4 The appropriate kinetic model should be used in determining the kinetic parameters. A number of computer programs exists 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 modeling 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. Complete bioavailability studies may be considered. The choice of the appropriate type of study depends on the other information required, availability of radiolabeled material and assay method. In a kinetic parameter study, the absorption rate constant can be estimated reliably only if sufficient samples are taken in the absorption phase.

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

5.2.3 Distribution

5.2.3.1 Distribution studies generally require radiolabeled compound. Studies may be

— quantitative, determining levels in dissected tissues,

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

— semiquantitative, using graded WBA standards.

5.2.3.2 In general, sampling times in distribution studies should be t_{max}, 24 h and 168 h or longer, depending on test substance elimination. Intermediate times may be used when these additional data are required. Sampling is normally more frequent in the early phase of absorption and elimination; however, samples need to be obtained over as much of the elimination phase as possible (ideally 3 to 4 half-lives) to provide the best estimates of kinetic parameters. The major determinant is often assay sensitivity.

5.2.4 Metabolism and excretion

5.2.4.1 Metabolism cages should permit separate collection of urine and feces throughout the study. For studies of up to 14 days, the urine and feces should be individually collected at 24 h and then every 24 h until the end of the experiment. In some study designs, animals may be sacrificed at intermediate times. Samples may be collected prior to 24 h when it is probable that the test substance or its metabolites will be rapidly excreted. For studies of longer duration, sampling over the initial period should occur as for the short-term studies. Thereafter, samples should be obtained for a continuous 24 h period per assessment period.

NOTE—The use of metabolism cages for prolonged periods may be detrimental to animal welfare. Therefore, at the longer times, representative discontinuous samples may be collected and these results extrapolated to continuous sampling.

5.2.4.2 The carcasses and/or target organs of the individual animals should be retained for analysis, and blood collected for analysis of plasma and whole-blood concentrations. After collection of the samples from the metabolism cages at the sacrifice time, the cages and their traps should be washed with an appropriate solvent. The resulting washes can be pooled and a representative fraction retained for analysis.

5.2.4.3 The recovery or calculated recovery of test substance should ideally be (100±10)% when a radiolabeled compound is used (see the note below). The amount of test substance in each fraction should be analyzed by suitably validated procedures for either radiolabeled or non-radiolabeled compound in the appropriate milieu. Where a radiolabeled compound is used, both parent compound and metabolites are assessed, unless a specific assay is used. If the radiolabeled compound cannot be sufficiently recovered in the excreta (feces and/or urine) or in the body, collection of expired air should be considered.

NOTE—The recovery range specified may not be achievable in all cases, and reasons for any deviation should be stated and discussed in the report.

5.2.4.4 Levels of radioactivity in the biological milieu should be determined, for example by liquid scintillation counting; however, it must be stressed that this represents a mixed concentration of compound and metabolites, and no kinetic parameters can be derived from it. Where isolation of metabolites is considered necessary, this may involve a number of extractions and chromatographic procedures (e.g. high-pressure liquid chromatography, thin layer chromatography, gas-liquid chromatography), and the resulting material should be characterized by chemical methods and a variety of physical chemistry techniques (e.g. mass spectrometry, nuclear magnetic resonance spectroscopy).

NOTE—The use of tissues, cells, homogenates and isolated enzymes for the study of metabolism *in vitro* is well documented. These methods identify potential metabolism which may not occur *in vivo* unless the compound is available at the appropriate site. The extents and rates of metabolism *in vitro* compared to *in vivo* will often differ.

Annex A
(normative)

Circumstances in which toxicokinetic studies shall be considered

A.1 Potential hazards exist in the use of most medical devices. However, it is neither necessary nor practical to conduct toxicokinetic studies for all identifiable degradation products and leachables, nor for all medical devices.

A.2 The need for toxicokinetic studies as part of the biological evaluation of a medical device shall be considered taking into account the final product and its constituent chemicals, including potential and designed degradation products, and leachables in combination with the intended use of the device.

A.3 Where appropriate, theoretical degradation processes should be investigated prior to toxicokinetic studies by means of *in vitro* experiments (e.g. tissue homogenates or cells), not only for animal welfare reasons as given in ISO 10993-2, but also to determine probable rather than possible degradation products.

A.4 Toxicokinetic studies shall be considered if

a) the device is designed to be bioresorbable, or

b) the device is a permanent contact implant, and biodegradation or significant corrosion is known or likely, and/or migration of leachables from the device occurs, or

c) substantial quantities of potentially toxic or reactive degradation products and leachables are likely or known to be released from a medical device into the body during clinical use.

NOTE—The meaning of the term “substantial quantities” is dependent on the properties of the chemicals in question.

A.5 Toxicokinetic studies are not required to be considered if

a) the achieved or expected rates of release of degradation products and leachables from a particular device or material have been adjudged to provide safe levels of clinical exposure following reference to significant historical experience, or

b) sufficient toxicological data or toxicokinetic data relevant to the degradation products and leachables already exist.

A.6 The release of leachables and degradation products from metals, alloys and ceramics is usually too low to justify toxicokinetic studies.

Annex B
(informative)

Bibliography

[1] ISO 10993-2:1992, Biological evaluation of medical devices—Part 2: Animal welfare requirements.

[2] ISO 10993-12:1996, Biological evaluation of medical devices—Part 12: Sample preparation and reference materials.

[3] ANDERSEN, M.E, CLEWELL, H.J. III, GARGAS, M.L., SMITH, F.A. and REITZ, R.H. Physiologically-based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol. Appl. Pharmacol. **54**:100-116, 1987.

[4] BOGEN, D.K. Simulation software for the Macintosh. Science. **24**:138-142, 1989.

[5] U.S. Food and Drug Administration. Guidelines for the format and content of the human pharmacokinetics and bioavailability section of an application. Department of Health and Human Services. Washington DC.

[6] HATTIS, D., WHITE, P., MAMORSTEIN, L. and KOCH, P. Uncertainties in pharmacokinetic modelling for perchloroethylene. 1. Comparison of model structure, parameters and predictions for low-dose metabolism rates derived by different authors. Risk Analysis. **10**:449-458, 1990.

[7] International Programme on Chemical Safety (IPCS). Principles of toxicokinetic studies. Environmental Health Criteria. **57,** World Health Organization, Geneva, 1986.

[8] ISO/TR 10993-9:1994, Biological evaluation of medical devices—Part 9: Degradation of materials related to biological testing.

[9] JOLLOW, D.J., ROBERTS, S., PRICE, V., LONGACRE, S. and SMITH, C. Pharmacokinetic considerations in toxicity testing. Drug Metab. Rev. **13**:983-1007, 1982.

[10] KATZPER, M. The use of visual programming for pharmacokinetic and pharmacodynamic simulation. Center for Drug Evaluation and Research, FDA, Rockville, MD.

[11] LIN, C.S., SHOAF, S.E. and GRIFFITHS, J.C. Pharmacokinetic data in the evaluation of the safety of food and colour additives. Reg. Toxicol. Pharmacol. **15**:62-72, 1992.

[12] MONRO, A.M. Interspecies comparisons in toxicology: The utility and futility of plasma concentrations of the test substance. Reg. Toxicol. Pharmacol. **12**:137-160, 1990.

[13] Organization for Economic Cooperation and Development (OECD). Guidelines for testing of chemicals—No 417. Toxicokinetics. OECD Publications, Paris.

[14] REITZ, R. Distribution, persistence and elimination of toxic agents. In: Progress in Predictive Toxicology. Clayson, D.B. et al. (eds.), Elsevier, New York, 1990.

[15] ROWLAND, M. and TOZER, T.N. Clinical Pharmacokinetics: Concepts and Applications (2nd edition). Lea and Febigerm, Philadelphia, 1989.

[16] SMITH, D.A., HUMPHREY, M.J. and CHARUEL, C. Design of toxicokinetic studies. Xenobiotica. **20**:1187-1199, 1990.

[17] SPEID, L.H., LUMLEY, C.E. and WALKER, S.R. Harmonization of guidelines for toxicity testing of pharmaceuticals by 1992. Reg. Toxicol. Pharmacol. **12**:179-211, 1990.

[18] TRAVIS, C.B. Pharmacokinetics. In: Carcinogen risk analysis. Traves C.B. (ed). Contemporary Issues in Risk Analysis, vol. 3, Plenum Press, New York, 1988.

[19] WAGNER J.G. Pharmacokinetics for Pharmaceutical Scientists. Technomic Publishing Co. Inc., Lancaster, PA, 1994.

[20] WARTAK. A modern approach to individualised drug therapy. Clinical Pharmacology and Therapeutics Series, Vol. 2. Praeger Publishers CBS Educational and Professional Publishing, 1983.

[21] WEISSINGER J. Nonclinical pharmacologic and toxicologic considerations for evaluating biologic products. Reg. Toxicol. Pharmacol. **10:**255-263,1989.

[22] WELLING P.G. Pharmacokinetic Processes and Mathematics. ACS Monograph 185. American Chemical Society, Washington DC, 1986.

[23] WELLING, P.G. and DE LA IGLESIA, F.A. Drug Toxicokinetics. Marcel Dekker, Inc., New York, 1993.

[24] YACOBI, A., SKELLY, J.P. and BATRA, V.K. Toxicokinetics and New Drug Development, Pergamon Press, New York, 1989.