

American National Standard



ANSI/AAMI/ ISO 10993-3: 2014/(R)2023

Biological evaluation of
medical devices—Part 3:
Tests for genotoxicity,
carcinogenicity and
reproductive toxicity

Biological evaluation of medical devices— Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity

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Abstract: specifies strategies for hazard identification and tests on medical devices for genotoxicity, carcinogenicity, and reproductive and developmental toxicity. Applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, or reproductive toxicity has been established

Keywords: biological evaluation, hazard identification, tests, genotoxicity, carcinogenicity, reproductive toxicity, developmental toxicity, toxicity

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Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. AAMI maintains a current list of each International Standard that has been adopted by AAMI (and ANSI). Available on the AAMI website at the address below, this list gives the corresponding U.S. designation and level of equivalency to the International Standard.

www.aami.org/standards/glossary.pdf

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 10993-3:2014 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) and the AAMI Mutagenicity, Carcinogenicity, and Reproductive Toxicity Working Group.

At the time this document was published, the **AAMI Biological Evaluation Committee** had the following members:

Co-chairs	Ronald P. Brown, FDA/CDRH Jon Cammack, PhD DABT, Medimmune LLC
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At the time this document was published, the **AAMI Mutagenicity, Carcinogenicity, and Reproductive Toxicity Working Group** had the following members:

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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 10993-3:2014

As indicated in the foreword to the main body of this document (page ix), 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.

ISO 10993-3:2014 was developed by Working Group (WG) 6, Mutagenicity, Carcinogenicity, and Reproductive Toxicity, of ISO Technical Committee (TC) 194, Biological Evaluation of Medical Devices, to specify specifies strategies for hazard identification and tests on medical devices for genotoxicity, carcinogenicity, and reproductive and developmental toxicity in accordance with one or more parts of the ISO 10993 series.

U.S. participation in ISO/TC 194/WG 06 is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation (AAMI) on behalf of the American National Standards Institute (ANSI). U.S. experts made a considerable contribution to this standard.

AAMI encourages its committees to harmonize their work with international standards as much as possible. Upon review of ISO 10993-3:2014, the AAMI Biological Evaluation Committee and the AAMI Mutagenicity, Carcinogenicity, and Reproductive Toxicity Working Group decided to adopt 10993-3, verbatim, as a revision of an American National Standard.

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 documents. 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 with the ISO standard.

The concepts incorporated into 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 comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 901 N. Glebe Rd., Suite 300, Arlington, VA 22203.

NOTE—Beginning with the ISO foreword on page ix, this American National Standard Amendment is identical to ISO 10993-3:2014.

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. 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.

The committee responsible for this document is ISO/TC 194.

The major technical changes are the following:

- a) test strategy changed by inclusion of a *in vivo* test and a follow-up evaluation;
- b) new Annex A "Guidance on selecting an appropriate sample preparation procedure in genotoxicity testing" included;
- c) Inclusion of further *in vitro* and *in vivo* test for evaluating the genotoxic potential of medical devices;
- d) new Annex B "Flowchart for follow-up evaluation" included;
- e) Annex E changed to "Considerations for carcinogenicity studies performed as implantation studies" and made normative;
- f) new Annex F "*In vitro* tests for embryo toxicity" included.

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 process*
- *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 skin sensitization*
- *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: 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]*

The following part is under preparation:

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

The following definitions apply in understanding how to implement an ISO International Standard and other normative ISO deliverables (TS, PAS, IWA):

- “shall” indicates a requirement;
- “should” indicates a recommendation;
- “may” is used to indicate that something is permitted;
- “can” is used to indicate that something is possible, for example, that an organization or individual is able to do something.

ISO/IEC Directives, Part 2 (sixth edition, 2011), 3.3.1, defines a requirement as an “expression in the content of a document conveying criteria to be fulfilled if compliance with the document is to be claimed and from which no deviation is permitted.”

ISO/IEC Directives, Part 2 (sixth edition, 2011), 3.3.2, defines a recommendation as an “expression in the content of a document conveying that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is deprecated but not prohibited.”

Introduction

The basis for biological evaluation of medical devices is often empirical and driven by the relevant concerns for human safety. The risk of serious and irreversible effects, such as cancer or second generation abnormalities, is of particular public concern. It is inherent in the provision of safe medical devices that such risks be minimized to the greatest extent feasible. The assessment of mutagenic, carcinogenic and reproductive hazards is an essential component of the control of these risks. Not all test methods for the assessment of genotoxicity, carcinogenicity or reproductive toxicity are equally well developed, nor is their validity well established for the testing of medical devices.

Significant issues with test sample size and preparation, scientific understanding of disease processes and test validation can be cited as limitations of available methods. For example, the biological significance of solid state carcinogenesis is poorly understood. It is expected that on-going scientific and medical advances will improve our understanding of and approaches to these important toxicological effects. At the time this document was prepared, the test methods proposed were those most acceptable. Scientifically sound alternatives to the proposed testing may be acceptable insofar as they address relevant matters of safety assessment.

In the selection of tests needed to evaluate a particular medical device, there is no substitute for a careful assessment of expected human uses and potential interactions of the medical device with various biological systems. These considerations will be particularly important in such areas as reproductive and developmental toxicology.

This part of ISO 10993 presents test methods for the detection of specific biological hazards, and strategies for the selection of tests, where appropriate, that will assist in hazard identification. Testing is not always necessary or helpful in managing toxicological risks associated with exposure to medical device materials but, where it is appropriate, it is important that maximum test sensitivity is achieved.

In the view of the multitude of possible outcomes and the importance of factors such as extent of exposure, species differences and mechanical or physical considerations, risk assessment have to be performed on a case-by-case basis.

Biological evaluation of medical devices— Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity

1 Scope

This part of ISO 10993 specifies strategies for risk estimation, selection of hazard identification tests and risk management, with respect to the possibility of the following potentially irreversible biological effects arising as a result of exposure to medical devices:

- genotoxicity;
- carcinogenicity;
- reproductive and developmental toxicity.

This part of ISO 10993 is applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, or reproductive toxicity has been established.

NOTE Guidance on selection of tests is provided in ISO 10993-1.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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*

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

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

OECD 414, *Prenatal Development Toxicity Study*

OECD 415, *One-Generation Reproduction Toxicity Study*

OECD 416, *Two-generation Reproduction Toxicity*

OECD 421, *Reproduction/Developmental Toxicity Screening Test*

OECD 451, *Carcinogenicity Studies*

OECD 453, *Combined Chronic Toxicity/Carcinogenicity Studies*

OECD 471, *Bacterial Reverse Mutation Test*

OECD 473, *In vitro Mammalian Chromosome Aberration Test*