

American National Standard

ANSI/AAMI/ISO 10993-3:2003/(R)2009



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



Association for the Advancement
of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the Manager for Technical Development. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News*. The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News*.



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

Approved 8 October 2003 and reaffirmed 10 August 2009 by
Association for the Advancement of Medical Instrumentation

Approved 23 October 2003 and reaffirmed 14 August 2009 by
American National Standards Institute, Inc.

Abstract: Specifies strategies for hazard identification and tests on medical devices for genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

Keywords: biological evaluation, genotoxicity, carcinogenicity, medical devices, reproductive and developmental toxicity

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing, or using products, processes, or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

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Glossary of equivalent standards

International standards adopted in the United States may include normative references to other international standards. For each international standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the international standard. (Note: Documents are sorted by international designation.)

Other normatively referenced international standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-04:2002	ANSI/AAMI DF80:2003	Major technical variations
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:2003	ANSI/AAMI/ISO 10993-1:2003	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:2003	ANSI/AAMI/ISO 10993-3:2003	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:2002	ANSI/AAMI/ISO 10993-12:2002	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997/(R)2003	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995 and Amdt 1:2001	ANSI/AAMI/ISO 11137:1994 and A1:2002	Identical

International designation	U.S. designation	Equivalency
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2003	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR13409:1996	Identical
ISO 13485:2003	ANSI/AAMI/ISO 13485:2003	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155-1:2003	ANSI/AAMI/ISO 14155-1:2003	Identical
ISO 14155-2:2003	ANSI/AAMI/ISO 14155-2:2003	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000 and A1:2003	ANSI/AAMI/ISO 14971:2000 and A1:2003	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical
ISO 25539-1:2003	ANSI/AAMI/ISO 25539-1:2003	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 10993-3:2003 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group (TAG) to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Genotoxicity, Carcinogenicity, and Reproductive Toxicity Working Group (U.S. Sub-TAG for ISO/TC 194/WG 6), chaired by Nirmal Mishra, DVM, PhD of the U.S. Food and Drug Administration and Robert Przygoda of Johnson & Johnson, played an active part in developing the ISO standard.

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

Cochairs: Donald E. Marlowe
Peter W. Urbanski

Members: James M. Anderson, MD, PhD, Case Western Reserve University
Eric R. Claussen, PhD, Becton Dickinson & Company
Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
Lawrence H. Hecker, PhD, Abbott Laboratories
Edward Mueller, MS, Annapolis, MD
Barry E. J. Page, Garner, NC
Melvin E. Stratmeyer, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/OST
Paul J. Upman, PhD, NAMSA
Peter W. Urbanski, Medtronic, Inc.

Alternates: Raju G. Kammula, DVM, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/ODE
Donald E. Marlowe, U.S. Food and Drug Administration/Center for Devices and Radiological Health
Sharon J. Northup, PhD, U.S. Pharmacopeial Convention, Inc.

At the time this document was published, the **AAMI Genotoxicity, Carcinogenicity, and Reproductive Toxicity Working Group** had the following members:

Cochairs: Nirmal Mishra, V, DVM, PhD
Robert Przygoda, PhD

Members: Joseph Carraway, NAMSA
Gloria H. Frost, PhD, Cardinal Health Medical Products and Services Group
Michelle A. Lee, Nelson Laboratories, Inc.
Nirmal Mishra, V, DVM, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health
Sharon J. Northup, PhD, U.S. Pharmacopeial Convention, Inc.
Lisa Olson, AppTec Laboratory Services
Robert T. Przygoda, PhD, Johnson & Johnson
Edward Reverdy, PhD, Boston Scientific Corporation
Anita Y. Sawyer, Becton Dickinson & Company
Brenda Seidman, PhD, Independent Expert
Kenneth R. St John, PhD, Independent Expert
Jeff M. Sturm, St Jude Medical, Inc.
Randy D. White, PhD, Baxter Healthcare Corporation

Alternates: William C. Bradbury, PhD, AppTec Laboratory Services
Lee Ellis, Boston Scientific Corporation
Chandramallika (Molly) Ghosh, PhD, NAMSA
Lawrence H. Hecker, PhD, Abbott Laboratories
Katharine Merritt, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health
David Porter, PhD, U.S. Pharmacopeial Convention, Inc.
Chad Summers, Nelson Laboratories, Inc.

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 10993-3:2003

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

International standard ISO 10993-3 was developed by Technical Committee ISO/TC 194, Biological evaluation of medical devices, to specify strategies for hazard identification and tests on medical devices for genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

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) on behalf of the American National Standards Institute (ANSI). The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of biological evaluation of medical devices as much as possible. Upon review of ISO 10993-3, the AAMI Biological Evaluation Committee and the AAMI Genotoxicity, Carcinogenicity, and Reproductive Toxicity Working Group proposed the adoption of 10993-3:2003 verbatim as a revision of ANSI/AAMI/ISO 10993-3:1993.

This edition of ISO 10993-3 is different from the 1992 edition in that it changes the recommendations for sample preparation. The new edition provides options for genotoxicity testing and provides additional guidance for deciding when to perform genotoxicity, carcinogenicity, or reproductive tests. Also, the references were updated in the bibliography and several informative annexes were added.

AAMI and ANSI procedure require that American National Standards be reviewed and, if necessary, revised within five years to confirm currency or reflect technological advances that have occurred since publication, as appropriate.

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 with the ISO standard.

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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 comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page viii, this American National Standard is identical to ISO 10993-3:2003.

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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. 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.

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.

ISO 10993-3 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-3:1992), which has been technically revised.

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 in vitro cytotoxicity*
- Part 6: *Tests for local effects after implantation*
- Part 7: *Ethylene oxide sterilization residuals*
- Part 8: *Selection and qualification of reference materials for biological tests*
- Part 9: *Framework for the 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: *Establishment of allowable limits for leachable substances*
- Part 18: *Chemical characterization of materials*

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

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 in 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 ongoing scientific and medical advances will alter our understanding of and approaches to these important toxicity test methods. At the time this part of ISO 10993 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 hazard identification but, where it is appropriate, it is important that maximum test sensitivity be achieved. Most tests included in this part of ISO 10993 refer to Guidelines for Testing of Chemicals, prepared by the Organization for Economic Cooperation and Development (OECD).

The interpretation of findings and their implications for human health effects are beyond the scope of this part of ISO 10993. Because 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 has to be performed on a case-by-case basis.

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

1 Scope

This part of ISO 10993 specifies strategies for hazard identification and tests on medical devices for the following biological aspects:

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

This part of ISO 10993 is applicable for evaluation of a medical device whose potential for genotoxicity, carcinogenicity, or reproductive toxicity has been identified.

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

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 10993-1:1997, *Biological evaluation of medical devices—Part 1: Evaluation and testing*

ISO 10993-2:1992, *Biological evaluation of medical devices—Part 2: Animal welfare requirements*

ISO 10993-6:1994, *Biological evaluation of medical devices—Part 6: Tests for local effects after implantation*

ISO 10993-12:2002, *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 414¹⁾, *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*

OECD 476, *In vitro Mammalian Cell Gene Mutation Test*

¹⁾ Organization for Economic Cooperation and Development.