List of Titles

American National Standard

ANSI/AAMI/ISO 10993-8:2000

Biological evaluation of medical devices—Part 8: Selection and qualification of reference materials for biological tests

AAMI Association for the Advancement of Medical Instrumentation

American National Standard ANSI/AAMI/ISO 10993-8:2000

Biological evaluation of medical devices—Part 8: Selection and qualification of reference materials for biological tests

Approved 16 October 2000 by
Association for the Advancement of Medical Instrumentation

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American National Standards Institute, Inc.

Abstract: This part of ISO 10993 gives guidance on procedures to be followed in the preparation of samples of medical devices for testing in biological systems in accordance with one or more parts of the ISO 10993 series.

Keywords: medical devices, biological evaluation, reference materials

List of Titles

AAMI Standard

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List of Titles

Contents

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 60601-2-21:1994 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 VP20:1994	Major technical variations
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:1992	ANSI/AAMI/ISO 10993-4:1993	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:1995	ANSI/AAMI/ISO 10993-10:1995	Identical
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:1996	ANSI/AAMI/ISO/CEN 10993-12:1996	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-15:2000 [1]	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995	ANSI/AAMI/ISO 11137:1994	Identical
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 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:200x [1]	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 TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155:1996	ANSI/AAMI/ISO 14155:1996	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 200x [1]	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:200x [1]	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:200x [1]	ANSI/AAMI/ISO 14971:2000	Identical

International designation	U.S. designation	Equivalency
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR 15844:1998	Identical

[1] FDIS approved; being prepared for publication.

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 10993-8:2000 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also serves as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Sample Preparation and Reference Materials Working Group (U.S. Sub-TAG for ISO/TC 194/WG 12), cochaired by Donald E. Marlowe of the FDA Center for Devices and Radiological Health and Sharon Northup, PhD, representing U.S. Pharmacopeial Convention, Inc., played an active part in developing the ISO standard. Mr. Marlowe also chairs the responsible ISO working group, ISO/TC 194/WG 12, Sample preparation and reference materials.

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

Cochairs:	Donald F. Gibbons, PhD
	Donald E. Marlowe
Members:	James M. Anderson, MD, PhD, Case Western Reserve University
	Eric R. Claussen, PhD, Cobe Laboratories, Inc.
	Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
	Donald F. Gibbons, PhD, 3M
	Jean A. Goggins, PhD, Consultant, San Diego, CA
	Donald E. Marlowe, FDA Center for Devices and Radiological Health
	Daniel E. McLain, PhD, Becton Dickinson
	Edward Mueller, Bernard Technologies
	Barry F. Page, Consultant, Garner, NC
	Harold Stanley, DDS, American Dental Association
	Paul Upman, North American Science Associates, Inc.
Alternates:	Sumner A. Barenberg, PhD, Bernard Technologies
	Sharon Northup, PhD, U.S. Pharmacopeial Convention, Inc.
	Mel Stratmeyer, PhD, FDA Center for Devices and Radiological Health

At the time this document was balloted, the **AAMI Sample Preparation and Reference Materials Working Group** had the following members:

Cochairs:	Donald E. Marlowe
	Sharon Northup, PhD
Members:	Wiliam Bradbury, PhD, Viromed Biosafety Labs
	Gloria Frost, PhD, Allegiance Healthcare Corp.
	Donald F. Gibbons, PhD, 3M
	Lawrence H. Hecker, PhD, Abbott Labs
	Emanuel Horowitz, PhD, Johns Hopkins University
	Dennis Jenke, PhD, Baxter Healthcare Corporation
	Michelle Lee, Nelson Laboratories, Inc.
	Donald E. Marlowe, FDA Center for Devices and Radiological Health
	Daniel McLain, PhD, Becton Dickinson
	Ed Mueller, Bernard Technologies
	Sharon Northup, PhD, U.S. Pharmacopeial Convention, Inc.
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	Eric Claussen, Becton Dickinson
	Joel Gorski, PhD, North American Science Associates, Inc.
	Raju Kammula, DVM, PhD, FDA Center for Devices and Radiological Health
	Randy White, Baxter Healthcare Corporation

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 10993-8:2000

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 10993-8 was developed by Technical Committee ISO/TC 194, Biological evaluation of medical devices, to specify requirements on the use of reference materials used to determine the biological response of a material.

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 on behalf of the American National Standards Institute. 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 in order to help reduce unnecessary repetition of testing. Upon review of ISO 10993-8 the AAMI Biological Evaluation Committee and the AAMI Sample Preparation and Reference Materials Working Group decided to adopt ISO 10993-8 verbatim as a new 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 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.

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, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the foreword on page viii, this American National Standard is identical to ISO 10993-8:2000.

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 3.

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 part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 10993-8 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical device*s.

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

— *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 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 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 using health-based risk assessment*

— *Part 18: Chemical characterization of materials*

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

Introduction

The information given in this part of ISO 10993 should be considered as a supplement to ISO 10993-12 which specifies requirements and gives guidance on procedures to be followed in the preparation of samples of medical devices for testing in biological systems in accordance with one or more parts of the ISO 10993 series. In clause 4 of ISO 10993-12:1996, there is a discussion of the use of reference materials as experimental controls. Annex A of ISO 10993-12:1996 provides specific information regarding current sources of commercially available reference materials.

Biological evaluation of medical devices—Part 8: Selection and qualification of reference materials for biological tests

1 Scope

This part of ISO 10993 specifies requirements on the use of reference materials or certified reference materials used to determine the biological response of a material. It specifies the selection and qualification of reference materials for biological tests and the characteristics of reference materials for the use of reference materials as experimental controls.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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

ISO Guide 30:1992, *Terms and definitions used in connection with reference materials.*

3 Terms and definitions

For the purposes of this part of ISO 10993, the terms and definitions given in ISO 10993-12, ISO Guide 30, and the following apply.

3.1 certified reference material (CRM): Reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence. [ISO Guide 30:1992, 2.2]

NOTE—Standard reference material (SRM) is a trademark-protected certification supplied by the National Institutes for Standards and Technology, Gaithersburg, MD, USA.

3.2 reference material (RM): Material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials. [ISO Guide 30:1992, 2.1]

3.3 homogeneous: Condition of being of uniform structure or composition with respect to the biological endpoint under study.

NOTE 1—The RM is said to be homogeneous if the biological response to a specific test is found to lie within the specified uncertainty limits of the test, irrespective of the site in the batch or lot of material from where the test sample is taken.

NOTE 2—Adapted from ISO Guide 30:1992, 2.6.

3.4 reference method: Thoroughly investigated test method that clearly and exactly describes the necessary conditions and procedures for the evaluation of a specific biological endpoint, has been shown to have accuracy and precision commensurate with its intended use and can, therefore, be used to characterize an RM.

NOTE—Adapted from ISO Guide 30:1992, 3.10.

3.5 stability of property values: Ability of a material, when stored under specified conditions, to maintain the stated biological response, within specified limits, for a specific period of time.

NOTE—Adapted from ISO Guide 30:1992, 2.7.

4 Use of certified reference materials or reference materials

Reference materials (RM) or certified reference materials (CRM) shall be used in biological tests as control materials to qualify in-house tests and control materials. They demonstrate the suitability of the procedure to yield a reproducible, predictable response, e.g., positive or negative. Use of a reference material in this way will ensure the comparability of the response between laboratories.

The property values of any material used in this way shall be characterized with each biological test procedure for which the use of the material is desired. A material characterized and then certified for one reference test method or response, e.g., sensitization [6], shall not be used as a reference material for another, e.g., cytotoxicity [5], without additional characterization.

5 Characteristics of reference materials

5.1 One or more property values

RMs or CRMs used to determine the biological response of a material shall be evaluated with each biological test procedure for which the use of the material is desired. It is not sufficient to qualify a material for one type of reference test method or response, e.g., sensitization [6], and declare it a reference material for another, e.g., cytotoxicity [5], without additional qualification testing.

5.2 Long-term availability of the reference material

To ensure the long-term availability of a reference material for determination of biological response, the user of the material should obtain a commitment as long as possible, preferably not less than five years, from the supplier of the RMs or CRMs.

A second, but less desirable, option is the publication by the reference material supplier of an “open formulation” for the material, i.e., publication of the source materials and details of the processing needed to ensure uniform batches of RM.

5.3 Certification of reference materials for biological safety testing

The biological response of the certified reference material under specific test conditions shall be established through interlaboratory studies.

6 Use of reference materials as experimental controls

6.1 Material screening versus biocompatibility of medical devices

The use of the reference materials described in ISO 10993-12 and elsewhere in this part of ISO 10993 are limited to biological screening of the materials intended for use in the manufacture of medical devices. However, while not intended for the purpose**,** they are often used in the performance assessment of the finished medical device. The vertical standard for the device, when available, shall address the biological testing of the product in the performance environment of the device. Biological testing described in the vertical product standard takes precedence over testing performed to screen the materials for suitability.

6.2 Misuse of CRMs

The attention of the users of this part of ISO 10993 is directed to the discussion of “proper use” and “misuse” of CRMs in the introduction to ISO Guide 33. This discussion points out areas of potential under- and over-utilization of RMs and CRMs.

Users of this part of ISO 10993 shall note that the use of calibration materials to evaluate the biological response of materials under investigation within a single laboratory is acceptable.

Bibliography

The ISO Guides listed below provide material which will enable the reader to place the discussion in this International Standard into context.

[1] ISO Guide 31:1981, *Contents of certificates of reference materials.*

[2] ISO Guide 33:1989, *Uses of certified reference materials.*

[3] ISO Guide 35:1989, Certification of reference materials—General and statistical principles.

[4] ISO/IEC Directives, Part 2:1992, *Methodology for the development of International Standards.*[1)]

The following International Standards contain additional information on biological evaluation procedures for specific biological endpoints.

[5] ISO 10993-5:1999, *Biological evaluation of medical devices—Part 5: Tests for in vitro cytotoxicity.*

[6] ISO 10993-10:1995, *Biological evaluation of medical devices—Part 10: Tests for irritation and sensitization*.

[1)] At present under revision. It is anticipated that the contents will be divided between the revision of Part 1 and a new Part 2 comprising mainly the revision of present Part 3.