Technical Information Report

AAMI/ISO TIR15499: 2017

Biological evaluation of medical devices—Guidance on the conduct of biological evaluation within a risk management process

AAMI
Advancing Safety in Healthcare Technology

Biological evaluation of medical devices—Guidance on the conduct of biological evaluation within a risk management process

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Abstract: Provide guidance applicable to the conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1 and is applicable to all biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

Keywords: biological evaluation, risk management, risk assessment, biological testing, material characterization, chemical characterization, biological safety assessment

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AAMI Technical Information Report

A technical information report (TIR) is a publication of the Association for the Advancement of Medical Instrumentation (AAMI) Standards Board that addresses a particular aspect of medical technology.

Although the material presented in a TIR may need further evaluation by experts, releasing the information is valuable because the industry and the professions have an immediate need for it.

A TIR differs markedly from a standard or recommended practice, and readers should understand the differences between these documents.

Standards and recommended practices are subject to a formal process of committee approval, public review, and resolution of all comments. This process of consensus is supervised by the AAMI Standards Board and, in the case of American National Standards, by the American National Standards Institute.

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ANSI Registration

Publication of this Technical Report that has been registered with ANSI has been approved by the Accredited Standards Developer (AAMI, 4301 N. Fairfax Drive, Suite 301, Arlington, VA 22203-1633). This document is registered as a Technical Report according to the Procedures for the Registration of Technical Reports with ANSI. This document is not an American National Standard and the material contained herein is not normative in nature.

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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. The code in the US column, "(R)20xx" indicates the year the document was officially reaffirmed by AAMI. E.g., ANSI/AAMI/ISO 10993-4:2002/(R)2009 indicates that 10993-4, originally approved and published in 2002, was reaffirmed without change in 2009.

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

www.aami.org/standards/glossary.pdf

Committee representation

Association for the Advancement of Medical Instrumentation

Strategic Approach to Biological Assessment Working Group

The adoption of ISO TR 15499 as an AAMI Technical Information Report was initiated by the AAMI Strategic Approach to Biological Assessment Working Group (BE/WG 15). AAMI BE/WG 15 functions as the U.S. consensus body to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from AAMI BE/WG 15 played a very active part in developing the ISO Technical Report.

At the time this document was published, the **AAMI Strategic Approach to Biological Assessment Working Group** had the following members:

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Background of AAMI adoption of ISO/TR 15499:2016

As indicated in the foreword to the main body of this document (page x), 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 and clinical evaluation of medical devices*, provides guidance on the conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1. This document is a revision and replacement of ISO/TR 15499:2012. Revisions focused on clarified definitions; and substantiation of risk evaluation, risk control, and compensation/adjustment of pH and osmolality.

U.S. participation in ISO/TC 194 is organized through the U.S. Technical Advisory Group to ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation. Experts from the United States made a considerable contribution to this standard.

AAMI/ISO TIR 15499 was registered with the American National Standards Institute (ANSI) on 27 August 2017.

AAMI procedures recommend that technical information reports be reviewed every three years and, if necessary, revised to reflect technological advances that may have occurred since publication.

AAMI (and ANSI) have adopted other ISO standards and technical reports. 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.

As used within the context of this document, “shall” indicates requirements strictly to be followed to conform to the recommended practice. “Should” indicates 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 should be avoided but is not prohibited.

“May” is used to indicate that a course of action is permissible within the limits of the recommended practice. “Can” is used as a statement of possibility and capability. Finally, “must” is used only to describe “unavoidable” situations, including those mandated by government regulation.

NOTE Users of this technical information report are advised that this document is an AAMI identical adoption of an ISO document and that the following international conventions have been carried over to the AAMI publication:

- British English spelling (e.g. colour instead of color)
- Use of SI units (e.g. metres instead of feet, Celsius instead of Fahrenheit, etc.)
- Decimal comma instead of a decimal point (e.g. 1 000,15 instead of 1,000.15)

The concepts incorporated in this technical information report should not be considered inflexible or static. This technical information report, 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 technical information report are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 4301 N. Fairfax Dr, Suite 301, Arlington, VA 22203-1633.

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 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.

The committee responsible for this document is ISO/TC 194, *Biological and clinical evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO/TR 15499:2012), which has been technically revised with the following major changes:

— definitions have been clarified;

— risk evaluation and risk control have been substantiated;

— compensation/adjustment of pH and osmolality has been substantiated.

Introduction

General

This document provides guidance on the conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1. Although ISO 10993-1 provides a general framework for biological evaluation of medical devices, more detailed guidance can be helpful in the practical application of the standard. As a result, this document was developed to provide such guidance to users of ISO 10993-1. This guidance can be used to better understand the requirements of ISO 10993-1 and to illustrate some of the variety of methods and approaches available for meeting the requirements of ISO 10993-1.

Biological evaluation is a design verification activity which is set in the context of broader risk management processes. Therefore, this document includes guidance on the application of ISO 10993-1 in the context of risk management processes conducted according to the requirements of ISO 14971. This document describes concepts and methods that can be considered in establishing and maintaining a risk management process for biological evaluation as part of the overall evaluation and development of a medical device.

As scientific knowledge advances our understanding of the basic mechanisms of tissue responses, biological evaluation may be based upon review of relevant established scientific data and upon chemical analysis and *in vitro* and *in vivo* testing where these are required. ISO 10993-1 specifies a framework in which to plan a biological evaluation which minimizes the number and exposure of test animals by giving preference to chemical constituent testing and *in vitro* models in situations where these methods yield equally relevant information to that obtained from *in vivo* models. The selection of which approach(es) are applicable to a particular medical device will depend on the nature of the device, the extent of available relevant scientific data and upon risk assessment.

When judging the applicability of the guidance in this document, applicable regulatory requirements and regulatory guidance should be considered.

An organization can voluntarily incorporate guidance from this document, wholly or in part, into its risk management process.

Guidance contained in this document can be useful as background information for those representing risk management process assessors, conformity assessment bodies and regulatory enforcement bodies.

Relationship with other standards, guidance documents and regulatory requirements

The relationship between ISO 10993-1, this document and the standards for biological evaluation of medical devices and general risk management is summarized as follows:

— this document provides guidance on the application of ISO 10993-1;

— biological evaluation is a component of risk management and this document includes guidance on the application of ISO 14971 to the conduct of biological evaluation.

Biological evaluation of medical devices—Guidance on the conduct of biological evaluation within a risk management process

1 Scope

This document is applicable to the conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1. It does not add to, or otherwise change, the requirements of ISO 10993-1. This document does not include requirements to be used as the basis of regulatory inspection or certification assessment activities.

This guidance is applicable to all biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

2 Normative references

There are no normative references in this document.

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
biocompatibility
ability of a medical device or material to perform with an appropriate host response in a specific application

3.2
biological risk
probability of harm to health occurring as a result of medical device or material interactions

3.3
biological safety
freedom from unacceptable biological risk

3.4
risk assessment
overall process comprising a risk analysis and a risk evaluation

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.5
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

