TECHNICAL REPORT

ISO/TR 15499

Second edition
2016-12-01

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

Évaluation biologique des dispositifs médicaux — Directives relatives à la conduite d'une évaluation biologique au sein d'un procédé de management du risque

Reference number
ISO/TR 15499:2016(E)

ISO copyright office
Ch. de Blandonnet 8 • CP 401
CH-1214 Vernier, Geneva, Switzerland
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
copyright@iso.org
www.iso.org

Contents

Page

Foreword ..... **iv**
Introduction ..... **v**
1 Scope **1**
2 Normative references **1**
3 Terms and definitions **1**
4 Biological evaluation as a risk management practice **2**
4.1 General 2
4.2 The biological evaluation plan 3
5 Guidance on risk management **6**
5.1 Risk assessment 6
5.1.1 Introduction 6
5.1.2 Risk analysis 6
5.1.3 Risk estimation 7
5.1.4 Risk evaluation 7
5.1.5 Risk control 8
5.2 Evaluation of residual risk acceptability 8
5.3 Post production monitoring 8
6 Guidance on specific aspects of biological evaluation **8**
6.1 Material characterization 8
6.1.1 Chemical characterization 8
6.1.2 Use of chemical characterization data in a biological evaluation 8
6.1.3 Proprietary materials formulations 9
6.1.4 Effects of manufacturing processes 9
6.2 Biological evaluation 10
6.2.1 Determining the acceptability of the level of leachable (allowable limit) according to ISO 10993-17 10
6.2.2 pH and osmolality compensation for absorbable materials 10
6.3 Device testing considerations 10
6.3.1 Tiered approaches to biological testing 10
6.3.2 When to do long-term testing (chronic toxicity, reproductive toxicity, biodegradation and carcinogenicity studies) 10
6.4 Biological safety assessment 11
6.4.1 Thresholds of Toxicological Concern (TTC) 11
6.4.2 What constitutes sufficient justification and/or clinically relevant data for a risk assessment 11
6.4.3 Guidance on mixtures in risk assessment 11
6.4.4 What constitutes “sufficient toxicology data” including dose and route relevance 12
6.4.5 What to include in the biological safety assessment report 12
6.5 General guidance 12
6.5.1 Changes which can require re-evaluation of biological safety 12
6.5.2 Good laboratory practice 13
Bibliography **14**

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

[SOURCE: ISO 14971:2007, 2.21]