

**SINGAPORE STANDARD**

# **Biological evaluation of medical devices**

– Part 3 : Tests for genotoxicity, carcinogenicity and reproductive toxicity

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**Biological evaluation of medical devices**

– Part 3 : Tests for genotoxicity, carcinogenicity and reproductive toxicity

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## National Foreword

This Singapore Standard was prepared by the National Mirror Working Group on ISO/TC 150 and 194 under the direction of the Biomedical and Health Standards Committee.

This Singapore Standard is an identical adoption of International Standard ISO 10993-3 : 2014 “Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity” published by the International Organization for Standardization.

Attention is drawn to the following:

1. Where appropriate, the words ‘International Standard’ shall be read as ‘Singapore Standard’.
2. The comma has been used throughout as a decimal marker whereas in Singapore Standards it is a practice to use a full point on the baseline as the decimal marker.
3. The references to International Standards shall be replaced by the following Singapore Standards:

International Standard	Corresponding Singapore Standard
ISO 10993-1	SS ISO 10993-1*
ISO 10993-3	SS ISO 10993-3
ISO 10993-4	SS ISO 10993-4*
ISO 10993-5	SS ISO 10993-5
ISO 10993-6	SS ISO 10993-6*
ISO 10993-10	SS ISO 10993-10
ISO 10993-11	SS ISO 10993-11*
ISO 10993-12	SS ISO 10993-12

\* Under development

Attention is drawn to the possibility that some of the elements of this Singapore Standard may be the subject of patent rights. Enterprise Singapore shall not be held responsible for identifying any or all of such patent rights.

### NOTE

1. *Singapore Standards (SSs) and Technical References (TRs) are reviewed periodically to keep abreast of technical changes, technological developments and industry practices. The changes are documented through the issue of either amendments or revisions.*
2. *An SS or TR is voluntary in nature except when it is made mandatory by a regulatory authority. It can also be cited in contracts making its application a business necessity. Users are advised to assess and determine whether the SS or TR is suitable for their intended use or purpose. If required, they should refer to the relevant professionals or experts for advice on the use of the document. Enterprise Singapore shall not be liable for any damages whether directly or indirectly suffered by anyone or any organisation as a result of the use of any SS or TR.*
3. *Compliance with a SS or TR does not exempt users from any legal obligations.*

## 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](http://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](http://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.

This third edition of ISO 10993-3 cancels and replaces the second edition (ISO 10993-3:2003), which has been technically revised.

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 minimised 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 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*