Singapore Standards Council

SS ISO 10993-5 : 2017
ISO 10993-5 : 2009, IDT
(ICS 11.100.20)

SINGAPORE STANDARD

Biological evaluation of medical devices

– Part 5 : Tests for in vitro cytotoxicity

Published by

Enterprise Singapore

SS ISO 10993-5 : 2017
ISO 10993-5 : 2009, IDT
(ICS 11.100.20)

SINGAPORE STANDARD

Biological evaluation of medical devices

– Part 5 : Tests for in vitro cytotoxicity

ISBN 978-981-47-8449-8

This Singapore Standard was approved by the Biomedical and Health Standards Committee on behalf of the Singapore Standards Council on 20 October 2017.

First published, 2018

The Biomedical and Health Standards Committee, appointed by the Standards Council, consists of the following members:

		Name	Capacity
Chairman	:	Dr Yong Chern Chet	*Individual Capacity*
Deputy Chairman 1	:	Ms Wong Woei Jiuang	*Health Sciences Authority*
Deputy Chairman 2		Mr Vincent Cheung	*Individual Capacity*
Deputy Chairman 3		Ms Selina Seah	*Changi General Hospital*
Advisor	:	Ms Jacqueline Monteiro	*Individual Capacity*
Secretary	:	Mr Choi Kwok Keong	*Singapore Manufacturing Federation – Standards Development Organisation*
Members	:	Prof Kishore Bhakoo	*Singapore Bioimaging Consortium*
		Mr Chung Kwong Yuew	*Temasek Polytechnic (BioMedical Engineering Faculty)*
		Ms Heidi Goh	*Singapore Manufacturing Federation (Medical Technology Industry Group)*
		Prof James Goh	*Biomedical Engineering Society (Singapore)*
		Dr Christopher Lam	*Health Sciences Authority (Medical Devices Branch)*
		Ms Audrey Lee	*Medtronic International Ltd*
		Assoc Prof Leo Hwa Liang	*National University of Singapore*
		Dr Lin Jianhua	*TUV SUD PSB Pte Ltd*
		Dr Leonard Loh	*Nanyang Polytechnic (BioMedical Engineering Hub)*
		Assoc Prof Eddie Ng Yin Kwee	*Nanyang Technological University*
		Dr Ong Siew Hwa	*Acumen Research Laboratories Pte Ltd*
		Mr Peh Ruey Feng	*Advent Access Pte Ltd*
		Mr Justine Phoon	*Biomedical Research Council*
		Dr Padmanabhan Saravanan	*Temasek Polytechnic (Centre of Innovation for Complementary Health Products)*
		Ms Celine Tan	*SPRING Singapore*
		Prof Tan Puay Hoon	*Singapore Health Services Pte Ltd*
		Ms Wang Dan	*Biosensors International Group*
		Ms Wong Shi Xuan	*Eu Yan Sang International Ltd*
		Dr Sidney Yee	*DxD Hub*

The National Mirror Working Group on ISO/TC 150 and 194, appointed by the Biomedical and Health Standards Committee to assist in the preparation of this standard, comprises the following experts who contribute in their *individual capacity*:

		Name
Convenor	:	Prof James Goh
Secretary	:	Mr Edwin Tan
Members	:	Assoc Prof Chew Sing Yan
		Mr Fan Mingwei
		Ms Heidi Goh
		Ms Ho Yuan Lu
		Prof James Hui Hoi Po
		Dr Lim Jing
		Dr Margam Chandrasekaran
		Assoc Prof Phan Toan-Thang
		Prof Seeram Ramakrishna
		Mr Tan Ming Jie
		Dr Tang Kin Fai
		Dr Ong Lee Lee

The organisations in which the experts of the National Mirror Working Group are involved are:

Biomedical Engineering Society (Singapore)
Cordlife Group Limited
Denova Sciences Pte Ltd
Edwards Lifesciences (Singapore) Pte Ltd
Emcero Pte Ltd
Health Sciences Authority
Institute of Material Research & Engineering
Nanyang Technological University
National University of Singapore
Osteopore International Pte Ltd
Wise Consultants and Services Pte Ltd

(blank page)

Contents

National Foreword

This Singapore Standard was prepared by the National Mirror Working Group for 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 10993-5 : 2009 "Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity" 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.

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 10993-5 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This third edition cancels and replaces the second edition (ISO 10993-5:1999) 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 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]

Introduction

Due to the general applicability of *in vitro* cytotoxicity tests and their widespread use in evaluating a large range of devices and materials, it is the purpose of this part of ISO 10993, rather than to specify a single test, to define a scheme for testing which requires decisions to be made in a series of steps. This should lead to the selection of the most appropriate test.

Three categories of test are listed: extract test, direct contact test, indirect contact test.

The choice of one or more of these categories depends upon the nature of the sample to be evaluated, the potential site of use and the nature of the use.

This choice then determines the details of the preparation of the samples to be tested, the preparation of the cultured cells, and the way in which the cells are exposed to the samples or their extracts.

At the end of the exposure time, the evaluation of the presence and extent of the cytotoxic effect is undertaken. It is the intention of this part of ISO 10993 to leave open the choice of type of evaluation. Such a strategy makes available a battery of tests, which reflects the approach of many groups that advocate *in vitro* biological tests.

The numerous methods used and endpoints measured in cytotoxicity determination can be grouped into the following categories of evaluation:

— assessments of cell damage by morphological means;

— measurements of cell damage;

— measurements of cell growth;

— measurements of specific aspects of cellular metabolism.

There are several means of producing results in each of these four categories. The investigator should be aware of the test categories and into which category a particular technique fits, in order that comparisons be able to be made with other results on similar devices or materials both at the intra- and interlaboratory level. Examples of quantitative test protocols are given in annexes. Guidance for the interpretation of the results is given in this part of ISO 10993.

Biological evaluation of medical devices —

Part 5:
Tests for *in vitro* cytotoxicity

1 Scope

This part of ISO 10993 describes test methods to assess the *in vitro* cytotoxicity of medical devices.

These methods specify the incubation of cultured cells in contact with a device and/or extracts of a device either directly or through diffusion.

These methods are designed to determine the biological response of mammalian cells *in vitro* using appropriate biological parameters.

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, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management system*

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