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**Biological evaluation of medical  
devices —**

**Part 11:  
Tests for systemic toxicity**

*Évaluation biologique des dispositifs médicaux —  
Partie 11: Essais de toxicité systémique*



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# Contents

Page

<b>Foreword</b>	<b>v</b>
<b>Introduction</b>	<b>vi</b>
<b>1 Scope</b>	<b>1</b>
<b>2 Normative references</b>	<b>1</b>
<b>3 Terms and definitions</b>	<b>1</b>
<b>4 General considerations</b>	<b>3</b>
4.1 General	3
4.2 Selection of animal species	3
4.3 Animal status	3
4.4 Animal care and husbandry	3
4.5 Size and number of groups	4
4.5.1 Size of groups	4
4.5.2 Number of groups	4
4.5.3 Treatment controls	4
4.6 Route of exposure	5
4.7 Sample preparation	5
4.8 Dosing	5
4.8.1 Test sample administration	5
4.8.2 Dosage volumes	5
4.8.3 Dosage frequency	6
4.9 Body weight and food/water consumption	6
4.10 Clinical observations	6
4.11 Clinical pathology	6
4.12 Anatomic pathology	7
4.13 Study designs	7
4.14 Quality of investigation	7
<b>5 Acute systemic toxicity</b>	<b>7</b>
5.1 General	7
5.2 Study design	8
5.2.1 Preparations	8
5.2.2 Experimental animals	8
5.2.3 Test conditions	8
5.2.4 Body weights	9
5.2.5 Clinical observations	9
5.2.6 Pathology	9
5.3 Evaluation criteria	10
5.3.1 General	10
5.3.2 Evaluation of results	10
5.4 Final report	10
<b>6 Repeated exposure systemic toxicity (subacute, subchronic and chronic systemic toxicity)</b>	<b>12</b>
6.1 General	12
6.2 Study design	12
6.2.1 Preparations	12
6.2.2 Experimental animals	12
6.2.3 Test conditions	13
6.2.4 Body weights	13
6.2.5 Clinical observations	13
6.2.6 Pathology	13
6.3 Evaluation criteria	14
6.3.1 General	14
6.3.2 Evaluation of results	14

6.4	Final report .....	15
<b>Annex A</b>	<b>(informative) Routes of administration .....</b>	<b>16</b>
<b>Annex B</b>	<b>(informative) Dosage volumes .....</b>	<b>18</b>
<b>Annex C</b>	<b>(informative) Common clinical signs and observations .....</b>	<b>19</b>
<b>Annex D</b>	<b>(informative) Suggested haematology, clinical chemistry and urinalysis measurements .....</b>	<b>20</b>
<b>Annex E</b>	<b>(informative) Suggested organ list for histopathological evaluation .....</b>	<b>22</b>
<b>Annex F</b>	<b>(informative) Organ list for limited histopathology for medical devices subjected to systemic toxicity testing .....</b>	<b>24</b>
<b>Annex G</b>	<b>(informative) Information on material-mediated pyrogens .....</b>	<b>25</b>
<b>Annex H</b>	<b>(informative) Subchronic rat — Dual routes of parenteral administration .....</b>	<b>26</b>
<b>Bibliography</b>	<b>.....</b>	<b>28</b>

## 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](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 (see [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.

For an explanation on the voluntary nature of standards, 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](http://www.iso.org/iso/foreword.html).

This document was prepared by Technical Committee ISO/TC 194 *Biological and clinical evaluation of medical devices*.

This third edition cancels and replaces the second edition (ISO 10993-11:2006), which has been technically revised with the following changes:

- a) reduction in group size for chronic toxicity testing in [Table 1](#);
- b) a new [Annex F](#) was added;
- c) the original [Annex F](#) was moved to [Annex G](#);
- d) a new [Annex H](#) was added;
- e) the Bibliography was updated.

A list of all parts in the ISO 10993 series can be found on the ISO website.

## Introduction

Systemic toxicity is a potential adverse effect of the use of medical devices. Generalized effects, as well as organ and organ system effects can result from absorption, distribution and metabolism of leachates from the device or its materials to parts of the body with which they are not in direct contact. This document addresses the evaluation of generalized systemic toxicity, not specific target organ or organ system toxicity, even though these effects may result from the systemic absorption and distribution of toxicants.

Because of the broad range of medical devices, and their materials and intended uses, this document is not overly prescriptive. While it addresses specific methodological aspects to be considered in the design of systemic toxicity tests, proper study design has to be uniquely tailored to the nature of the device's materials and its intended clinical application.

Other elements of this document are prescriptive in nature, including those aspects that address compliance with good laboratory practices and elements for inclusion in reporting.

While some systemic toxicity tests (e.g. long term implantation or dermal toxicity studies) can be designed to study systemic effects as well as local, carcinogenic or reproductive effects, this document focuses only on those aspects of such studies, which are intended to address systemic effects. Studies which are intended to address other toxicological end points are addressed in ISO 10993-3, ISO 10993-6, ISO 10993-10 and ISO/TS 10993-20.

Prior to conducting a systemic toxicity study, all reasonably available data and scientifically sound methods in the planning and refinement of the systemic toxicity study design should be reviewed. This includes the suitability of use of input data such as existing toxicological data, data from chemical characterization studies and/or other biological tests (including *in vitro* tests and less invasive *in vivo* tests) for the refinement of study design, dose selection, and/or selection of pathological end points to cover in the evaluation of a study. For the repeated exposure systemic toxicity study in particular, the use of scientifically sound study design, the use of pilot studies and statistical study design and the use of unbiased, quantitative end points/methods in the pathological (including histopathological) and clinical chemistry methods are important so as to obtain data which have sufficient scientific validity.

Finally, toxicology is an imperfect science. The outcome of any single test should not be the sole basis for making a determination of whether a device is safe for its intended use.

# Biological evaluation of medical devices —

## Part 11: Tests for systemic toxicity

### 1 Scope

This document specifies requirements and gives guidance on procedures to be followed in the evaluation of the potential for medical device materials to cause adverse systemic reactions.

### 2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

### 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

##### **dose**

##### **dosage**

amount of test sample administered (e.g. mass, volume) expressed per unit of body weight or surface area

#### 3.2

##### **dose-effect**

relationship between the dosage and the magnitude of a defined biological effect either in an individual or in a population sample

#### 3.3

##### **dose-response**

relationship of dosage to the spectrum of effects related to the exposure

Note 1 to entry: There are two types of dose-response relationships. The first type is the response of an individual to a range of doses. The second type is the distribution of responses of a population of individuals to a range of doses.