INTERNATIONAL STANDARD

ISO 10993-11

First edition
1993-12-15

Biological evaluation of medical devices —

Part 11:
Tests for systemic toxicity

Évaluation biologique des dispositifs médicaux —

Partie 11: Essais de toxicité systémique

INTERNATIONAL ISO

Reference number
ISO 10993-11:1993(E)

Contents

International Organization for Standardization
Case Postale 56 • CH-1211 Genève 20 • Switzerland
Printed in Switzerland

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.

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.

International Standard ISO 10993-11 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Guidance on selection of tests*

— *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 cytotoxicity: in vitro methods*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 8: Clinical investigation*

— *Part 9: Degradation of materials related to biological testing* [Technical Report]

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymers*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from coated and uncoated metals and alloys*

— *Part 16: General guidance on toxicokinetic study design for degradation products and leachables from medical devices*

— *Part 17: Glutaraldehyde and formaldehyde residues*

Future parts will deal with other relevant aspects of biological testing.

Annex A of this part of ISO 10993 is for information only.

Introduction

When a device releases constituents into the body, the constituents may, in sufficiently large concentrations, lead to systemic toxicity. Clinical and experimental evidence of the systemic effects in this area is extremely sparse.

This part of ISO 10993 provides methodologies for the evaluation of the systemic toxicity potential of medical devices. In addition, it includes pyrogenicity testing.

Systemic toxicity is a developing experimental science and it is expected that each expert, in carrying out tests, will exercise judgement in the selection of a procedure from the lists of standards and documents quoted, thereby ensuring that the document that will best suit the needs of a particular device is chosen. It is assumed that, in selecting the most appropriate test method from the list, the individual method(s) may have to be adapted, to evaluate the device under test more appropriately.

It must be borne in mind that subchronic and/or chronic systemic toxicity testing is not always necessary for a risk assessment. Such assessment might be made on the basis of qualitative and quantitative analytical measurements to evaluate the exposure of possible leachables from the device.

This adaptation is intentional because of the developing nature of the science and because excessive rigidity or over-detailed specifications of methods could prevent application of more appropriate test methods. It is indeed intended that toxicological skill and judgement be applied during the course of study. However, it is equally necessary that, where changes from proposed methodologies are implemented, the rationale should be fully explained and supported scientifically. (See 6.4.)

It is essential, when evaluating the results of toxicological tests, to bear in mind the limitations and the potential variability of the tests. Similarly, it may not always be appropriate to extrapolate from animal studies to the human situation. While *in vivo* testing is designed to indicate possible health hazards, it does not eliminate the need for continuing monitoring and observation in humans.

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Biological evaluation of medical devices —

Part 11:
Tests for systemic toxicity

1 Scope

This part of ISO 10993 specifies methodologies for the evaluation of the systemic toxicity potential of medical devices which release constituents into the body. In addition, it includes pyrogenicity testing.

The test methods cited in this part of ISO 10993 are from International Standards, national standards, directives and regulations. This part of ISO 10993 is concerned with either the actual product or its leachables. It is intended that tests for extracts or leachables be conducted by choosing appropriate extraction vehicles to yield a maximum extraction of leachable materials, in order to conduct biological testing.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests.*

ISO 10993-2:1992, *Biological evaluation of medical devices — Part 2: Animal welfare requirements.*

ISO 10993-3:1992, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.*

ANSI/ADA No. 41, *Biological Evaluation of Dental Materials.*

ASTM F 619:1986, *Practice for Extraction of Medical Plastics*, Vol. 13.01.

ASTM F 750:1987, *Practice for Evaluating Material Extracts by Systemic Injection in the Mouse.*

BS 5736: Part 5:1982, *Evaluation of medical devices for biological hazards — Part 5: Method of test for systemic toxicity; assessment of pyrogenicity in rabbits of extracts from medical devices.*

SN 119 800, *Biological Evaluation of Dental Materials*, Swiss Association for Standardization.

European Pharmacopoeia XXII, 1990.

OECD — *Guidelines for Testing of Chemicals.*

Official Journal of the European Communities, 79/831.

Official Journal of the European Communities, 84/449.

Official Journal of the European Communities, 87/302.

US Code of Federal Regulation 1500.40: *Method of Testing Toxic Substances.*

US/EPA PB 86/108958.

US/EPA PB 89/124077.

US/FDA *Toxicological Principles for the Safety Assessment of Direct Food Additives*, 1982.

United States Pharmacopeia XXII: *Biological Reactivity Tests, In-Vivo*; The National Formulary XVII, Rockville, MD; Pharmacopeial Convention, 1990, pp. 1497-1500.

3 Definitions

For the purposes of this part of ISO 10993, the definitions in ISO 10993-1 and the following definitions apply.

3.1 extraction vehicle: Liquid for use in the extraction of leachables from a device.

3.2 extract liquid: Liquid which is tested for biological response after the device has been extracted within it.

3.3 specimen: Unit(s) of device placed into the extraction vehicle.

3.4 blank: Extraction vehicle not containing the specimen under test which is used for comparison with the extract liquid.

3.5 systemic toxicity: Toxicity involving the entire organism.

3.6 acute toxicity: Adverse effects occurring after administration of a single dose or multiple doses of a test sample given within 24 h.

3.7 subacute toxicity: Adverse effects occurring after administration of a single dose or multiple doses of a test sample per day given during a period of from 14 days to 28 days.

3.8 subchronic toxicity: Adverse effects occurring after administration of a single dose or multiple doses of a test sample per day given during a part of the lifespan (usually 90 days but not exceeding 10 % of lifespan).

3.9 test sample: Device or extract thereof used for systemic toxicity testing.

4 Test sample requirements and recommendations

4.1 General

The patient may be exposed to a variety of conditions or states of the device. Test samples shall be selected primarily for the conditions under which the device is normally used. If deviations are necessary, they shall be recorded in the test report, together with their justification.

Testing should be performed on the final product, and/or representative component samples of the final product and/or materials. In some cases it may be advisable also to test the individual components separately or immediately after the final product has been assembled.

4.2 Use of mould

If a mould is used for the preparation of samples, it shall not interact with or negatively influence the sample material. If appropriate a suitable insulation medium should be used.

4.3 Polished materials

If the final device is habitually polished, then the sample surface shall be similarly treated. The polishing medium shall be carefully and completely removed. Sharp edges should be rounded as appropriate for the application.

4.4 Production conditions

The component or device used in the sample preparation shall be exposed to the same conditions and substances as it would encounter during production, such as washing, packaging and sterilization.

4.5 Sterilization

Devices which are intended for sterilization shall be used after sterilization by the intended procedures.

4.6 Physical state of sample

4.6.1 Materials which are conducive to direct application (e.g. liquid, paste or gel) may be tested without modification in dermal and oral studies.

4.6.2 Powders (e.g. products classed as superabsorbents) may be tested by direct deposition or by making a paste in an appropriate solvent or liquid dispersant and then applying it.

4.6.3 Liquids may be tested by direct deposition or after dilution.

For liquid materials such as sprays or inks which will be used by the end-user in a dried form, thin layers are prepared on slides, dried and then extracted.

4.6.4 Solid materials may be used directly on the skin. If it is considered necessary, the solid may be pulverized or moistened sufficiently with water or a suitable non-irritating vehicle to ensure good contact with the tissues. Appropriate solvents are listed in 5.4.

5 Method for extraction from medical devices

5.1 Rationale

5.1.1 The following procedure outlines the basis to obtain extracts from medical devices for testing. This procedure may supplement but does not supersede methods contained in specific study protocols.

5.1.2 Extraction conditions may attempt to exaggerate the clinical-use conditions so as to define the potential toxicological hazard without causing significant changes in the material pieces, which would not be experienced in actual practice, e.g. solidification or melting. Alternatively, because of well-defined clinical exposure and actual commercial product-processing parameters, it may be more appropriate for product testing to simulate in-use exposure time and temperature.

5.2 Specimen preparation

The specimen may be prepared by subdividing it into portions; it may also be tested as a whole entity, if appropriate.

For materials that cannot be subdivided without loss of specimen character, identity or integrity, and for which the calculated volume of extraction solvent will not cover the entire specimen (i.e. complex devices, metal objects, interiors of bags, etc.), use the minimum amount of extraction vehicle which will cover the test surfaces. When individual devices are small, it may be necessary to extract multiple units to provide enough sample for necessary testing. Depending on the type of sample, designate either the mass (to the nearest 0,1 g) or the exposed surface area (to the nearest 1 cm^2) extracted. Record the volume of extract.

5.3 Specimen requirements

5.3.1 The recommended ratio of sample surface area to volume of extraction vehicle is given in table 1. In many cases, however, other ratios may be appropriate.

NOTE 1 Additional explanations are given in ISO 10993-12.

5.3.2 Specimens shall be of such dimensions as to fit conveniently within the extraction container and their total surface area shall be completely covered by the extraction vehicle.

5.3.3 The majority of devices are provided sterile and/or cleanly packaged. Extra manipulations and exposure to the drying temperatures are not usually warranted and, in fact, may adversely affect the outcome of some studies.

Table 1

Form of material area	Thickness mm	Ratio: surface/extraction vehicle
a) Film or sheet (separate or coated on glass slides)	< 0,5	6 cm^2 per 1 ml [1]
	0,5 to 1	3 cm^2 per 1 ml [1]
b) Tubing	< 0,5 (wall)	6 cm^2 per 1 ml [2]
	0,5 to 1 (wall)	3 cm^2 per 1 ml [2]
c) Slabs, tubing and moulded items	> 1	3 cm^2 per 1 ml [3]
d) Irregular shapes (powders, pellets, etc.)	—	0,2 g sample per 1 ml

1) Both sides combined.
2) Sum of internal and external surfaces.
3) All exposed surfaces combined.

5.3.4 Conduct rinsing and drying procedures when the specimen to be extracted does not appear free of surface contaminants or when otherwise required. Rinse the material using purified water or water for injection. Repeat rinsing if necessary and dry prior to extraction if required for extraction vehicle compatibility. Omission of the rinsing procedure is recommended for apparently clean specimens as it may permit a more realistic evaluation of the manufacturing process and material.

5.3.5 Ensure that the extraction vessels do not adulterate the extract of the test materials.

5.4 Extraction vehicle

Use an extraction vehicle representative of the extremes of the solubility spectrum for extracting substances from materials (recommended in 5.4.1 to 5.4.3).

NOTE 2 Pay special attention to the biocompatibility of the extraction vehicle.

5.4.1 Polar extraction vehicle: physiological saline.

5.4.2 Non-polar extraction vehicle: Oleum neutrale (e.g. DAC, Fract. Coconut, BP 73) or vegetable oil (e.g. cottonseed oil or sesame oil, EP or USP) are deemed acceptable for the following procedure.

Sesame oil or cottonseed oil should, if possible, be freshly refined oil.