INTERNATIONAL STANDARD

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Dentistry — Evaluation of biocompatibility of medical devices used in dentistry

Art dentaire — Évaluation de la biocompatibilité des dispositifs médicaux utilisés en art dentaire

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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 7405 was prepared by Technical Committee ISO/TC 106, *Dentistry*.

This second edition cancels and replaces the first edition (ISO 7405:1997) which has been technically revised. The following changes have been made:

a) addition of dentine barrier cytotoxicity test to Annex B;

b) improved description of test methods;

c) updated cross-references to ISO 10993 series.

Introduction

This International Standard concerns the evaluation of the biocompatibility of medical devices used in dentistry. It is to be used in conjunction with the ISO 10993 series of standards. This International Standard contains special tests, for which ample experience exists in dentistry and which acknowledge the special needs of dentistry.

Only test methods for which the members of the committee considered there was sufficient published data have been included. In recommending test methods, the need to minimize the use of animals was given a high priority. It is essential that the decision to undertake tests involving animals be reached only after a full and careful review of the evidence indicating that a similar outcome cannot be achieved by other types of test. In order to keep the number of animals required for tests to an absolute minimum, consistent with achieving the objective indicated, it can be appropriate to conduct more than one type of test on the same animal at the same time, e.g. pulp and dentin usage test and pulp capping test. However, in accordance with ISO 10993-2 these tests are performed both in an efficient and humane way. On all occasions when animal testing is undertaken, such tests are conducted empathetically and according to standardized procedures as described for each test.

This International Standard does not explicitly describe test methods for occupationally related risks.

Annexes B and C are included to encourage the development of *in vitro* and *ex vivo* test methods which will further reduce the use of animals in the evaluation of the biocompatibility of medical devices used in dentistry.

Dentistry — Evaluation of biocompatibility of medical devices used in dentistry

1 Scope

This International Standard specifies test methods for the evaluation of biological effects of medical devices used in dentistry. It includes testing of pharmacological agents that are an integral part of the device under test.

This International Standard does not cover testing of materials and devices that do not come into direct or indirect contact with the patient's body.

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 1942, *Dentistry — Vocabulary*

ISO 6344-1, *Coated abrasives — Grain size analysis — Part 1: Grain size distribution test*

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

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 10993-10[1)], *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-12:2007, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 14971, *Medical devices — Application of risk management to medical devices*

1) To be published.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 1942, ISO 10993-1, ISO 10993-12 and the following apply.

3.1
medical device
any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software necessary for its proper application intended by the manufacturer to be used for medical purposes for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

3.2
dental material
material and/or substance or combination of materials and/or substances specially formulated and prepared for use in the practice of dentistry and/or associated procedures

3.3
final product
medical device in its “as-used” state

NOTE Many dental materials are used in a freshly mixed state, and evaluation of the materials in both freshly mixed and set conditions should be considered.

3.4
positive control
positive control material
any well characterized material and/or substance that, when evaluated by a specific test method, demonstrates the suitability of the test system to yield a reproducible, appropriately positive or reactive response in the test system

3.5
negative control
negative control material
any well characterized material and/or substance that, when evaluated by a specific test method, demonstrates the suitability of the test system to yield a reproducible, appropriately negative, non-reactive or minimal response in the test system

NOTE In practice, negative controls include blanks, vehicles/solvents and reference materials.

3.6
reference material
material with one or more property values that are sufficiently reproducible and well established to enable use of the material or substance for the calibration of an apparatus, the assessment of a measurement method or for the assignment of values to materials

NOTE For the purpose of this document, a reference material is any well characterized material and/or substance that, when tested by the procedure described, demonstrates the suitability of the procedure to yield a reproducible, predictable response. The response may be negative or positive.

4 Categorization of medical devices

4.1 Categorization by nature of contact

4.1.1 General

For the purposes of this document, the classification of medical devices used in dentistry is derived from ISO 10993-1. If a device or material can be placed in more than one category, the more rigorous testing requirements shall apply. With multiple exposures the decision into which category a device is placed shall take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

NOTE In this context the term dentistry includes the oromaxillofacial environment.

4.1.2 Non-contact devices

These devices do not contact the patient's body directly or indirectly, and are not included in ISO 10993-1.

4.1.3 Surface-contacting devices

These devices include those that contact the surface of intact or breached or otherwise compromised skin, the surface of intact or breached or otherwise compromised oral mucosa, and those that contact the external surfaces of dental hard tissue, including enamel, dentine and cementum.

NOTE In some circumstances, dentine and cementum are considered as surfaces, e.g. after gingival recession.

4.1.4 External communicating devices

These devices include dental devices that penetrate and are in contact with oral mucosa, dental hard tissues, dental pulp tissue or bone, or any combination of these, and are exposed to the oral environment.

NOTE This group also includes any kind of lining or base material to be used under a restoration.

4.1.5 Implant devices used in dentistry

These devices include dental implants and other dental devices that are partially or fully embedded in one or more of the following:

a) soft tissue, e.g. subperiosteal implants and subdermal implants;

b) bone, e.g. endosteal implants and bone substitutes;

c) pulpodentinal system of the tooth, e.g. endodontic materials;

d) any combination of these, e.g. transosteal implants.

4.2 Categorization by duration of contact

4.2.1 General

For the purposes of this document, medical devices used in dentistry are classified by duration of contact as described in ISO 10993-1 and listed in 4.2.2 to 4.2.4.

4.2.2 Limited exposure devices

Devices whose single or multiple use or contact is likely to be up to 24 h.

4.2.3 Prolonged exposure devices

Devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 d.

4.2.4 Permanent contact devices

Devices whose single, multiple or long-term use or contact exceeds 30 d.

NOTE 1 The definition of the term “permanent” is meant to be applied solely for the use of this document. It is consistent with the definition given in ISO 10993-1.

NOTE 2 With multiple exposures to the device, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

5 Biological evaluation process

5.1 General

Each medical device used in dentistry shall be subjected to a structured biological evaluation programme within a risk management process (see ISO 10993-1). Guidance on the implementation of this programme is provided in ISO 14971 and ISO 10993-1. The biological evaluation programme shall include the review of data sets concerning the biological properties of each medical device used in dentistry. When this part of the biological evaluation programme indicates that one or more data sets are incomplete and that further testing is necessary, the tests should be selected from the methods described in the ISO 10993 series of standards or in this International Standard, or in both. If tests that are not included in these International Standards are selected, a statement shall be made that indicates that the tests described in these International Standards have been considered and shall include a justification for the selection of other tests.

For combination products the final product should be evaluated according to this document in conjunction with any applicable standards.

NOTE 1 In this context, combination products are dental devices of any kind that incorporate, or are intended to incorporate, as an integral part, a substance that:

a) if used separately, would be a medicine or a biological product;

b) is liable to affect the patient’s body by an ancillary action.

An example would be a bone filling/augmentation device containing a growth factor (i.e. a biological product).

NOTE 2 For combination products, where the device and pharmacological components are packaged separately, it may be informative to test the device components alone.

5.2 Selection of tests and overall assessment

The selection of tests and the overall assessment of the results shall be carried out by an expert who has the appropriate chemical, physical and biological data concerning the device and who is aware of the intended conditions of use.

5.3 Selection of test methods

The selection of test methods shall be based upon consideration of:

a) the intended use of the medical device;

b) the tissue(s) which the medical device may contact;

c) the duration of the contact.

If a test selected is not included in the International Standards, a justification for the choice of the methods shall be included in the test report for each device. If more than one test method in the same category is recommended by the standards, the selection of one test over the others should be justified.

5.4 Types of test

According to the categorization of the device, tests shall be considered for use as summarised in Table A.1. This table indicates which types of test method shall be considered, but not that they are necessarily required to be carried out. A decision not to carry out a type of test identified in Table A.1 shall be justified in the test report on each device. The types of test listed are regarded as a framework for the evaluation of the biocompatibility of medical devices used in dentistry. For most types of test, particular methods are identified, although for some devices it is recognized that alternative methods not included in the International Standards listed may be more appropriate.

For convenience, the types of test have been listed in three groups.

a) Group I

This group comprises *in vitro* tests of cytotoxicity. General guidance for *in vitro* cytotoxicity tests is presented in ISO 10993-5 and shall be followed. Detailed test protocols for the agar or agarose diffusion and filter diffusion methods, appropriate to dental materials, are included in this International Standard. The *in vitro* cytotoxicity methods include:

1) agar diffusion test (see 6.2);

2) filter diffusion test (see 6.3);

3) direct contact or extract tests in accordance with ISO 10993-5;

4) dentine barrier cytotoxicity test (see Annex B);

5) tooth slice model.

NOTE 1 The order of listing does not indicate any preference for one method over another.

NOTE 2 This list does not indicate that all cytotoxicity tests mentioned have to be performed for each medical device under consideration.

NOTE 3 The use of the dentine barrier cytotoxicity test is encouraged and a description of the test is presented in Annex B. Another approach is the tooth slice model. References to this test are presented in the Bibliography.

b) Group II

This group comprises tests in accordance with the 10993 series of standards and particular tests, where appropriate, are identified:

1) acute systemic toxicity — oral application — in accordance with ISO 10993-11;

2) acute systemic toxicity — application by inhalation — in accordance with ISO 10993-11;

3) subacute and subchronic systemic toxicity — oral application — in accordance with ISO 10993-11;

4) skin irritation and intracutaneous reactivity in accordance with ISO 10993-10;

5) delayed-type hypersensitivity in accordance with ISO 10993-10;

6) genotoxicity in accordance with ISO 10993-3;

7) local effects after implantation in accordance with ISO 10993-6.

NOTE 1 In order to allow use of the latest edition of the referenced document only, an undated cross-reference is possible. An indication of the appropriate clause and subclause is only possible for dated references. Therefore, the user of this International Standard is requested to check the referenced documents for the appropriate clause numbers.

NOTE 2 Information regarding acute toxicity testing is presented in Annex C.

NOTE 3 In the evaluation of materials following local implantation involving mineralized tissues in accordance with ISO 10993-6, examination of undemineralized sections, in addition to routine demineralized sections, is recommended.

c) Group III

This group comprises tests, specific for medical devices used in dentistry, not referred to in the 10993 series of standards:

1) pulp and dentine usage test (see 6.4);

2) pulp capping test (see 6.5);

3) endodontic usage test (see 6.6).

NOTE Dental implant system usage test in accordance with ISO/TS 22911 can also be considered, if applicable.

5.5 Re-evaluation of biocompatibility

In accordance with ISO 10993-1, a device shall be considered for re-evaluation of its biocompatibility as described in 5.4 when revisions or modifications to the formula, quality and/or performance specifications are made.

6 Test procedures specific to dental materials

6.1 Recommendations for sample preparation

6.1.1 General

These recommendations have been designed for *in vitro* testing, but can also be used for other purposes, if suitable.

6.1.2 General recommendations for sample preparation

For the preparation of test samples, consult the respective product standards and/or the manufacturer's instructions, and follow those descriptions as closely as possible. Justify any deviation from the manufacturer's instructions. A detailed description of the sample preparation shall be included in the test report. Take the following (e.g. environmental) factors into account, considering the final use of the device:

a) **temperature**;

b) **humidity**;

c) **light exposure**: samples of photosensitive materials should be produced under the condition that ambient light does not activate them;

d) **material of sample mould**: ensure that the material of the sample mould and eventual lubricant used do not interfere with the setting process of the material;

NOTE Suitable materials can be semitranslucent or white plastic materials such as polyethylene or polytetrafluoroethylene (PTFE).

e) **oxygen exposure**: for materials that produce an oxygen inhibited layer during hardening ensure that the sample mould is properly sealed during hardening;

f) **sterilization**: samples should either be produced under aseptic conditions or be sterilized by the method appropriate to the material, if necessary and possible; ensure that sterilization does not affect the material (e.g. sterilization shall not elute substances from material);

g) **ratio of sample surface area versus cell layer surface or cell culture medium**: document the ratio of sample surface area versus cell layer surface or cell culture medium; justify the selection of shape and sample surface area and the applied ratio of sample surface area versus cell layer surface or cell culture medium;

h) **extracts**: if extracts are required for a test procedure, prepare extract samples in accordance with ISO 10993-12:2007, Clause 10.

6.1.3 Specific recommendations for light curing materials

Take the following factors into account, considering the final use of the light curing material:

a) **material of sample mould**: the reflection coefficient of materials used for sample moulds should be as close as possible to that of dentin in order to simulate the clinical situation;

NOTE Suitable materials can be semitranslucent or white plastic materials such as polyethylene or PTFE.

b) **light exposure**: light curing should be done to simulate clinical usage as closely as possible. The manufacturer's instructions for use should be followed to provide the same level of curing as would be the case in actual usage. This will often require curing from one side only but will sometimes entail a two-sided cure. The cure method is material and/or process specific. Where fully cured test samples are required for testing, it is important to ensure that the test samples are homogeneous after removal from the mould. In the case of one-component materials, there should be no voids, clefts or air-bubbles present when viewed without magnification. Reference should be made to the light source used (light intensity, curing time, spectral distribution of curing light and type of curing light should be documented). Care shall be taken to ensure that the light source is recommended for the materials to be tested and that it is in a satisfactory operating condition;

c) **oxygen exposure**: for materials that produce an oxygen inhibited layer during light curing, both ends of the mould should be covered with transparent oxygen barrier materials (e.g. a polyester film) during light curing. If the material is recommended by the manufacturer for surface finishing after curing, the sample surfaces should be ground and polished using the recommended clinical procedures. If there are no such instructions and if required for testing, the samples should be ground on both ends, with a P2 000 paper in accordance with ISO 6344-1, after first being set against the transparent oxygen barrier material.

6.1.4 Specific recommendations for chemically setting materials

Take the following factors into account, considering the final use of the chemically setting materials:

a) **mixing**: mix sufficient material to ensure that the preparation of each test sample is completed from one batch. Prepare a fresh mix for each test sample. The mixing shall be performed in accordance with the respective product standards, if applicable;

b) **oxygen exposure**: for materials that produce an oxygen inhibited layer during chemical curing, both ends of the mould should be covered with oxygen barrier materials (e.g. a polyester film) during curing. If the material is recommended by the manufacturer for surface finishing after curing, the sample surfaces should be ground and polished using the recommended clinical procedures. If there are no such instructions and if required for testing, the samples should be ground on both ends, with a P2 000 paper in accordance with ISO 6344-1, after first being set against the oxygen barrier material.