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ISO/FDIS 7405

Dentistry — Evaluation of biocompatibility of medical devices used in dentistry

Médecine bucco-dentaire — Évaluation de la biocompatibilité des dispositifs médicaux utilisés en médecine bucco-dentaire

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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Foreword

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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 document 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).

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This document was prepared by Technical Committee ISO/TC 106, *Dentistry*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 55, *Dentistry*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces ISO 7405:2018 which has been technically revised.

The main changes compared to the previous edition are as follows:

— update on normative references (e.g. replacement of ISO 6344-1 with ISO 6344-3);

— clarification on text of definitions and addition of definition for dentine barrier (3.8);

— for the agar diffusion test (6.2) the criteria for assessment of decolorization zone (Table 1) and qualitative morphological/lysis index (Table 2) were harmonized with ISO 10993-5;

— addition of Annex D with an antioxidant responsive element (ARE) reporter assay cytotoxicity test.

— addition of Annex E “Margin of safety (MoS) for medical devices used in dentistry”.

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

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

Only the 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 number and exposure of test 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 dentine 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 in accordance with standardized procedures as described for each test.

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

Annex B is 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. Annex C is based on and replaces ISO/TS 22911.

Dentistry — Evaluation of biocompatibility of medical devices used in dentistry

1 Scope

This document 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 document 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 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 1942, *Dentistry — Vocabulary*

ISO 6344-3, *Coated abrasives — Determination and designation of grain size distribution — Part 3: Microgrit sizes P240 to P5000*

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 10993-5:2009, *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, *Biological evaluation of medical devices — Part 10: Tests for skin sensitization*

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

ISO 10993-12:2021, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17:2023, *Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents*

ISO 10993-18:2020, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

ISO/TS 10993-19, *Biological evaluation of medical devices — Part 19: Physico-chemical, morphological and topographical characterization of materials*

ISO 10993-23, *Biological evaluation of medical devices — Part 23: Tests for irritation*

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

ISO 16443, *Dentistry — Vocabulary for dental implants systems and related procedure*

CIE S 017, *ILV: International Lighting Vocabulary*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 1942, ISO 10993-1, ISO 10993-12, ISO 10993-17, ISO 10993-18, ISO 16443, CIE S 017 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
dental material
substance or combination of substances specially formulated and prepared for use in the practice of dentistry and/or associated procedures

Note 1 to entry: Material is included within substance in this definition.

[SOURCE: ISO 1942: 2020, 3.1.4.8, modified — Note 1 to entry has been added]

3.2
final product
medical device or device component that includes all manufacturing processes for the "to be marketed" device including packaging and sterilization, if applicable, and that includes processes prior to intended use, such as mixing, preconditioning and preparation

[SOURCE: ISO 10993-1:2018, 3.8, modified — Wording from "and that includes processes prior to intended use…" has been added.]

3.3
positive control material
well characterized material 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

3.4
negative control material
well characterized material 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 1 to entry: In practice, negative control materials include blanks, vehicles or solvents and *reference materials* (3.5).

3.5
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 1 to entry: For the purpose of this document, a reference material is any well characterized material or substance that, when tested by the procedure described, demonstrates the suitability of the procedure to yield a reproducible, predictable response. The response can be negative or positive.

3.6
in vitro pulp chamber
device that holds a thin slice of dentine between two chambers and allows fluid and molecules to filter or to diffuse across the *dentine barrier* (3.8)

3.7
diffusion
establishment of passive movement of solutes (solubilized constituents) by means of a diffusion gradient through the *dentine barrier* (3.8)

3.8
dentine barrier
barrier made out of a slice of dentine from human or animal origin

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 For the purposes of this document, 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 1 This group also includes any kind of lining or base material to be used under a restoration.

NOTE 2 This group does not include implant devices used in dentistry (see 4.1.5).

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.

With multiple exposures to the device, 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 When calculating the duration of exposure for contact categorization of repeat use devices, the total exposure period in days between the first and last use of the medical device can be considered. For instance, the same device can be reused intermittently over a number of days, or replacement devices can be used over a number of days. If the treatment intervals are expected to be long relative to the elimination time of any leachable toxins from the body, this infrequent use can be considered as for a single treatment episode.

4.2.2 Limited exposure devices

Devices whose cumulative sum of single, multiple or repeated duration of contact is up to 24 h.

4.2.3 Prolonged exposure devices

Devices whose cumulative sum of single, multiple or repeated duration of contact time is likely to exceed 24 h but not 30 days.

4.2.4 Long-term exposure devices

Devices whose cumulative sum of single, multiple or repeated contact time exceeds 30 days.

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). The implementation of this programme shall be in accordance with 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 shall be selected from the methods described in the ISO 10993 series, in this document 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 shall be evaluated in accordance with 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.

EXAMPLE A bone filling/augmentation device containing a growth factor (i.e. a biological product).

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

All tests shall be conducted in accordance with recognized current/valid best laboratory/quality practices, where applicable.

NOTE 2 Examples of relevant guidance include the principles of Good Laboratory Practice or ISO/IEC 17025.

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 more than one test method in the same category is recommended by the standards mentioned in 5.1, the selection of one test over the others shall be justified.

5.4 Types of test

5.4.1 General

In accordance with the categorization of the device, tests shall be considered for use as summarized 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 can be more appropriate.

5.4.2 Physical and chemical characterization

Material characterization of the medical device or component (see Table A.1) is a crucial first step in biological evaluation. Material characterization, if performed, shall be conducted in accordance with ISO 10993-18 and ISO/TS 10993-19. For nanomaterials, see ISO/TR 10993-22.

The types of biological tests are listed in three groups.

Toxicological risk assessment of chemical constituents should be performed according to ISO 10993-17. The margin of safety (MoS) should be considered within the toxicological risk assessment. For guidance on the MoS, see Annex E.

5.4.3 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 document. The in vitro cytotoxicity methods include:

a) agar diffusion test (see 6.2);

b) filter diffusion test (see 6.3);

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

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

e) antioxidant responsive element (ARE) reporter assay cytotoxicity test (see Annex D).

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 need 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. See References [21] to [23] and [29] to [32].

NOTE 4 The use of ARE reporter assay cytotoxicity test is encouraged, if measurement of the oxidative stress of cells after exposure to test and control materials via metabolic activity is either applicable or justified or both.

5.4.4 Group II

This group comprises tests in accordance with the ISO 10993 series and particular tests, which shall be considered, where appropriate:

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

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

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

d) skin sensitization in accordance with ISO 10993-10;

e) genotoxicity in accordance with ISO 10993-3;

f) local effects after implantation in accordance with ISO 10993-6;

g) irritation in accordance with ISO 10993-23.

When evaluating materials following local implantation with mineralized tissues in accordance with ISO 10993-6, it is recommended to examine undemineralized sections, in addition to routine demineralized sections.

NOTE If appropriate, the local effects after implantation are evaluated in accordance with the endosseous dental implant usage test instead of ISO 10993-6 [see 5.4.5, d)].

5.4.5 Group III

This group comprises tests that are specific for medical devices used in dentistry and that are not referred to in the ISO 10993 series:

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

b) pulp capping test (see 6.5);

c) endodontic usage test (see 6.6);

d) endosseous dental implant usage test (see Annex C).

The endosseous dental implant usage test is not required but is recommended 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, the quality or the performance specifications, or combination of them, are made.

NOTE See also ISO 10993-1:2018, B.4.5.1, which provides indications on when to commence a re-evaluation.

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 either the respective product standards or the manufacturer's instructions, or both, 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 shall 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 sample mould materials can be semitranslucent or white plastic materials such as polyethylene or polytetrafluoroethylene (PTFE).

e) Oxygen exposure: For materials that produce an oxygen inhibition layer during hardening, ensure that the sample mould is properly sealed during hardening.

f) Sterilization: Samples shall 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 10993-12:2021, 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 dentine in order to simulate the clinical situation.

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

b) Light exposure: Light curing shall be done to simulate clinical usage as closely as possible. The manufacturer's instructions for use shall be followed to provide the same level of curing as would be the case in actual usage. This often requires curing from one side only but sometimes entails a two-sided cure. The cure method is either material- or process-specific, or both. 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 shall be no voids, clefts or air-bubbles present when viewed without magnification. The light source characteristics used shall be documented, e.g. irradiance at material surface, spectral distribution of irradiance or radiant flux, curing time and

type of curing light. The light source and operating condition shall conform to the instructions for use of the material and light source manufacturer.

c) Oxygen exposure: For materials that produce an oxygen inhibition layer during light curing, both ends of the mould shall 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 shall be ground and polished using the recommended clinical procedures. If there are no such instructions and if required for testing, the samples shall be ground on both ends, with a P2 000 paper in accordance with ISO 6344-3, 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 inhibition layer during chemical curing, both ends of the mould shall 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 shall be ground and polished using the recommended clinical procedures. If there are no such instructions and if required for testing, the samples shall be ground on both ends, with a P2 000 paper in accordance with ISO 6344-3, after first being set against the oxygen barrier material.

6.1.5 Positive control material

For in vitro tests and certain in vivo tests (e.g. pulp and dentine usage test), it is recommended to include a standard positive control material, which is handled and processed like the test materials (i.e. being plastic after mixing and then setting) and which is based on freely available chemicals or materials.

Such a positive control material for in vitro testing of plastic filling materials is described in Table B.1. The use of this specific positive control material is optional. Other materials with a validated history and other well characterized positive control materials with reproducible data on toxicity can be used instead.

6.2 Agar diffusion test

6.2.1 Objective

This test is designed to demonstrate the nonspecific cytotoxicity of test materials after diffusion through agar or agarose. This test method is not appropriate for leachables that interact with the agar or agarose.

6.2.2 Cell line

Use an established fibroblast or epithelial cell line, which is readily available (e.g. from the American Type Culture Collection (ATCC), see https://www.atcc.org)[1)]. In the report, specify the identification number of the cell line, if applicable, the description and designation of the cell line used and a justification for its selection. See also ISO 10993-5.

6.2.3 Culture medium, reagents and equipment

Use the culture medium specified for the selected cell line. Sterilize by filtration. For the preparation of 3 % agar or 3 % agarose, thawed, tempered and sterilized by autoclaving, mix 1:1 with the culture medium.

1) This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.