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Dentistry — Preclinical evaluation of dental implant systems — Animal test methods

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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.

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).

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For an explanation on 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.

The committee responsible for this document is ISO/TC 106, *Dentistry*, Subcommittee SC 8, *Dental implants*.

This second edition cancels and replaces the first edition (ISO/TS 22911:2005), which has been technically revised.

Introduction

This Technical Specification concerns animal tests relevant to the functional testing of dental implant systems.

Many dental implants currently available consist of a main component, the dental implant body, which is endosseous, and one or more other components that penetrate through the oral mucous membranes into the oral cavity.

That portion that penetrates into the oral cavity may support a dental prosthesis, which transfers functional stress to the dental implant during mastication and other oral activities. This functional stress may influence the host responses to the dental implant.

The biocompatibility of a dental implant system and its constituent materials can be evaluated to a large extent by following the guidance and methods described in ISO 10993 (all parts) and ISO 7405 [1]. However, to evaluate the influence of functional stress upon the host responses to a dental implant system, an animal usage test may also be helpful.

Dentistry — Preclinical evaluation of dental implant systems — Animal test methods

1 Scope

This Technical Specification concerns animal tests relevant to the functional assessment of dental implant systems, using both macroscopic and microscopic parameters. It is intended for use only when risk analysis indicates a need for additional information that only animal testing can provide.

This Technical Specification is not intended to provide information on the mechanical strength of implantable materials themselves, but rather a qualitative evaluation of the implant-bone interface.

NOTE Mechanical properties of dental implant systems are described in ISO 14801[3].

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

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

3 Terms and definitions

For the purpose of this document, the terms and definitions given in ISO 1942 and ISO 16443 apply.

4 Test method

4.1 Test protocol

Before testing each particular dental implant system, the manufacturer or sponsor is responsible for preparing a detailed test protocol, which should include, at least, full details of the following:

a) the aim of the study;

b) the rationale and justification for an animal test and such other information as may be required to satisfy ISO 10993-2;

c) the dental implant system to be tested, including its chemical composition and physical structure (including surface modification, if present), its recommended mode of clinical insertion and use, and the controls to be used;

d) the animal species chosen, their husbandry and a justification for the choice;

e) the test protocol to be followed, including the number of animals and test specimens, the time intervals chosen and a justification for their use;

f) the methods of assessment to be employed, both clinically and in the laboratory, and a justification for their use;

g) the methods of analysis of the clinical and laboratory data to be employed and the criteria to be used in determining the outcome of the study;

h) the information to be included in the test report.

NOTE Because there is wide variation in the design and clinical procedures associated with the use of different dental implant systems, it is not possible to formulate a single detailed test protocol. However, this Technical Specification provides guidance for some of the fundamental features of a test method, which should be common to all protocols. A list of references for test protocols in non-human species is presented in the Bibliography.

4.2 Animals and animal welfare

4.2.1 Animal welfare

Animal welfare shall be in accordance with ISO 10993-2 and applicable regulatory requirements for test animals.

Users should be aware that national regulatory requirements in the field of animal welfare may apply.

4.2.2 Test animals

No particular animal model of a usage test for dental implant systems has yet been validated as relevant to the human situation. It is recommended, therefore, that an animal species be chosen which meets the following criteria:

a) oral hygiene can be maintained, either naturally or artificially;

b) the jaws are of sufficient size to allow normal surgical access and to accommodate the dental implant system in its form intended for use in humans;

c) the site into which the dental implant system is to be placed should have opposing teeth;

d) the animals should be skeletally mature if appropriate for its intended use;

e) animals having an omnivorous pattern of masticatory jaw movement are preferable.

4.2.3 Number of animals

The number of animals should be justified and should be the minimum necessary for determining the stated objectives of the study.

4.3 Test procedure

4.3.1 Test specimens

Use supplied dental implant systems as intended for human clinical use. If dental implants that differ in any way from those intended for clinical use are included in the study, a justification for this decision should be included.

4.3.2 Control specimens

Use a suitable control unless data from comparable studies are available. It is possible that data from a previously published study may be acceptable if the experimental conditions in the two studies are strictly comparable. If a dental implant system control is needed, either a dental implant system for which peer-reviewed clinical data are available or a dental implant similar to the test implant, but unloaded, may be appropriate.

4.3.3 Surgical preparation of sites for the placement of the dental implant and control

Where necessary, create an area of edentulous jaw prior to the insertion of the dental implant.

When this is necessary, the animals must be anaesthetised as determined and directed by appropriate laboratory practice conditions, using a recognized anaesthesia technique prior to any surgical procedures. All surgery should be carried out under aseptic conditions. Extract the number of teeth required to provide the site(s) needed for the placement of the dental implant(s), using appropriate methods. The animals may require appropriate medical treatment to prevent infections under clinical conditions to best simulate human conditions. Further, the animals should be placed on an appropriate soft diet for a period postoperatively to minimize the risk of damage to the healing tissues. If the test implant is not intended for immediate implantation or delayed immediate implantation but for delayed implantation, the implant should be placed after an appropriate healing period.

4.3.4 Placement of dental implant systems

Carry out the surgical procedures for the placement of dental implants and associated implant component(s) aseptically and follow precisely the test protocol. Procedures should be carried out under appropriate anaesthesia. The dental prosthesis should be completed according to the test protocol. Post-operative care regimens should reflect the purpose of the study and recognized procedures of aftercare.

4.3.5 Test periods

Assess the dental implant system and the host responses to it after time intervals that are appropriate to the objectives of the study. Where the objective of the study is to assess the appropriateness of using the dental implant system clinically, then at least three test periods, including baseline and appropriate follow-up periods after loading, are recommended. The start point for these follow-up periods should reflect any postoperative intervals during which the animal was not on a normal diet. Unless otherwise required, only the last period would emphasize surgical removal and microscopic analyses. If evaluation of bone resorption and/or implant loosening is an objective, an appropriate long-term period should be assessed.

NOTE For time periods of implants in tissue, see also ISO 10993-6[2].

4.3.6 Dental plaque control

If necessary, give the animals regular dental plaque control procedures, and include full details in the test protocol.

4.3.7 Clinical and radiographic examination

Record the status of the health of the gingival and periodontal tissues at appropriate intervals. In addition to a visual examination of the gingival tissues, it is recommended that, whenever possible, the status of oral hygiene, dental plaque and gingival inflammation are recorded, using recognized clinical indices. Make particular note of the stability or degree of mobility of the device, the presence of inflammation in the surrounding tissues and any evidence of local infection.

Take standardized radiographs of the dental implant site, the adjacent and occluding teeth and the supporting bone on prescheduled occasions when the animals are anaesthetised, so that a series of preoperative and postoperative images are obtained up to the time of termination of the study.

4.3.8 Termination of the test period

Carry out animal euthanasia, if necessary, at the termination of the test period, according to the guidelines in ISO 10993-2.

4.4 Evaluation

Evaluate the tissue responses by clinical, radiographic, histopathological, statistical and other methods of analysis as may be necessary for the study. Unless otherwise required for the purposes of the study, surgical removal of the dental implant and histopathological evaluation of the tissue responses around it should be restricted to only the longest or last follow-up period.

4.4.1 Clinical evaluation

Provide relevant details of the general health of the animals during the study, including body weight. The health of the soft tissues around the test and control dental implant systems and around the adjacent and occluding teeth and of both the whole jaws and associated muscular tissue should be evaluated to determine if these structures have changed over the period of the study. Record any changes to implant superstructure including associated artificial teeth.

NOTE Any failed implants and mode of failure.

4.4.2 Radiographic assessment

Evaluate the radiographic appearance of the test and control dental implant systems, including the bone surrounding them and the adjacent and occluding teeth, to determine if those osseous structures have changed over the period of the study.

4.4.3 Specimen retrieval

Retrieve, if necessary, following the termination of the test, blocks of tissue representative of the whole jaw and associated muscular tissue and also specifically blocks of tissue containing the test dental implant systems and the control, together with the adjacent teeth, bone and oral soft tissues *in situ*, for histopathological and/or other examinations. Depending upon the particular aims of the study, it might be necessary to retrieve other blocks of tissue and/or to examine them by other techniques.

4.4.4 Specimen preparation for histopathological examination

If blocks of tissue have been retrieved, process them for histopathological examination as appropriate. According to the particular parameters of histopathological assessment to be undertaken, both undemineralized and demineralized sections may be necessary. Microscopic examination of hard, plastic-embedded, undemineralized specimens is recommended for the evaluation of the implant/tissue and implant/oral cavity interfaces.

4.4.5 Microscopic assessment

Examine a sufficient number of sections to assess the nature of the interaction between the surrounding hard and soft tissues and the dental implant system or the control. Particular attention should be paid to quality and quantity, of, at least, the following:

a) areas of direct bone/implant contact;

b) new bone and/or fibrous tissue;

c) bone resorption;

d) inflammation, infection, abscess formation and necrosis;

e) any changes in the jaws and associated muscular tissue mass;

f) where possible, any changes to the dental implant.

A sufficient number of sections from the blocks of the adjacent and occluding teeth should be examined to determine their status and that of their surrounding tissues.

4.4.6 Statistical analysis

There are many International Standards covering the field of statistical analysis. Cite the relevant International Standard, if used, or if not, specify the analytical techniques to be employed.

5 Test report

Prepare a test report containing, at least, the following:

a) all details of the study protocol as indicated in 4.1 and any deviations from the original protocol;

b) all details of the clinical and laboratory observations and measurements and the appropriate analyses, as indicated in 4.4;

c) an overall analysis of the data obtained from the study, including a comparison to controls, with conclusions relating to the extent to which the aim(s) of the study have been met, in particular concerning the biocompatibility of the dental implant system tested.

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