GB

NATIONAL STANDARD OF THE

PEOPLE'S REPUBLIC OF CHINA

ICS 11.110

C 30

GB/T 16886.12-2005 / ISO 10993-12:2002

Replacing GB/T 16886.12-2000

Biological evaluation of medical devices -

Part 12: Sample preparation and reference materials

医疗器械生物学评价

第 12 部分：样品制备与参照样品

(ISO 10993-12:2002, IDT)

Issued on: March 23, 2005 **Implemented on: December 01, 2005**

Issued by: General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China;

Standardization Administration of the People's Republic of China.

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Foreword

This Part of GB/T 16886 equivalently adopts ISO 10993-12:2002 *Biological evaluation of medical devices - Part 12: Sample preparation and reference materials*.

After technical revision, this Part replaces GB/T 16886.12-2000. The main changes are as follows:

— Add terms “accelerated extraction”, “exaggerated extraction” and “stability of property values”;

— Change relevant contents and titles of Clause 4, Clause 5, Clause 6 and Clause 7 in 1st Edition;

— Change relevant contents and titles of Annex A, Annex B and Annex C in 1st Edition.

General title of GB/T 16886 is *Biological evaluation of medical devices.* It is consisted of following parts:

— Part 1: Evaluation and testing within a risk management process;

— 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: Test for in vitro cytotoxicity;

— Part 6: Tests for local effects after implantation;

— Part 7: Ethylene oxide sterilization residuals;

— Part 9: Framework for identification and quantification of potential degradation products;

— Part 10:Tests for irritation and delayed-type hypersensitivity;

— Part 11:Tests for systemic toxicity;

— Part 12:Sample preparation and reference materials;

— Part 13: Identification and quantification of degradation products from polymeric medical devices;

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

— Part 15: Identification and quantification of degradation products from metals and

Introduction

This Part of GB/T 16886 specifies methods of sample preparation and the selection of reference materials in the biological evaluation of medical devices. Because GB/T 16886 describes many different biological assay systems, the individual parts should be consulted to ascertain if these recommendations are appropriate for specific test systems.

Sample preparation methods should be appropriate for both the biological evaluation methods and the materials being evaluated. Each biological test method requires the selection of materials, extraction solvents and conditions.

This Part of GB/T 16886 is based on existing national and international specifications, regulations and standards wherever possible. They are periodically reviewed and revised.

Biological evaluation of medical devices -

Part 12: Sample preparation and reference materials

1 Scope

This Part of GB/T 16886 specifies requirements and gives guidance on the procedures to be followed in the preparation of samples and the selection of reference materials for medical devices testing in biological systems in accordance with one or more parts of the GB/T 16886 series.

Specifically, this Part addresses:

— test material selection;

— selection of representative portions from a device;

— test sample preparation;

— experimental controls;

— selection of and requirements for reference materials; and

— preparation of extracts.

The applicability of this Part to absorbable materials, materials that polymerize in situ, tissue-engineered medical products and materials of biological origin should be carefully evaluated.

2 Normative references

The articles contained in the following documents have become part of this Part of GB/T 16886 when they are quoted herein. For the dated documents so quoted, all the modifications (excluding corrigendum) or revisions made thereafter shall not be applicable to this Standard. For the undated documents so quoted, the latest editions shall be applicable to this Standard.

GB/T 16886.1 Biological evaluation of medical devices - Part 1: Evaluation and testing (GB/T 16886.1-2001, idt ISO 10993-1:1997)

YY/T 0316 Medical devices - Application of risk management to medical devices (YY/T 0316-2003, idt ISO 14971:2000)

3 Terms and definitions

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

[ISO Guide 30]

NOTE: For the purposes of this Part, a reference material is any well characterized material or substance, which 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.

3.11

simulated-use extraction

extraction of a test material or sample with an appropriate medium and under conditions that simulate product use, for the purpose of evaluating its potential hazard to the patient or user during its routine clinical use

3.12

stability of property values

ability of a material, when stored under specified conditions, to maintain a specific stated biological response, within specified limits, for a specific period of time

[ISO Guide 30]

3.13

test material

material, device, device portion, or component thereof subject to biological testing

3.14

test sample

test material or extract subject to biological testing

4 Experimental controls

Experimental controls shall be used in biological evaluations to validate a test procedure and/or to compare the results between materials. Depending on the biological test, negative controls, blanks and/or positive controls shall be used as is appropriate to the test.

NOTE: The same type of control may be applicable to different tests and may allow cross-reference to other established materials and test methods. Additional guidance on the selection of experimental controls is given in Annex A. Use of positive controls for in vivo testing may be affected by animal welfare

considered. Tools used for cutting medical devices into representative portions for testing shall be clean to prevent contamination.

9 Selection of representative portions from a device

9.1 If a device cannot be tested as a whole, each individual material in the final product shall be represented proportionally in the test sample.

9.1.1 The test sample of devices with surface coatings shall include both coating material and the substrate.

9.1.2 The test sample shall include a representative portion of the joint and/or seal if adhesives, radio frequency (RF) seals, or solvent seals are used in the manufacture of a portion of the device which contacts patients.

9.2 Composite materials shall be tested as finished materials.

9.3 When different materials are present in a single device, the potential for synergies and interactions shall be considered in the choice of test sample.

9.4 The test sample shall be chosen to maximize the exposure of the test system to the components of a device that are known to have a potential for a biological response.

10 Preparation of extracts of samples

10.1 General

If extracts of the device are required for a test procedure, the extraction media and conditions of extraction used shall be appropriate to the nature and use of the final product and to the purpose of the test, e.g. hazard identification, risk estimation, or risk assessment. The physicochemical properties of the device materials, leachable substances, or residues shall be considered when choosing the extraction conditions.

NOTE: For additional guidance on the extraction of samples, see Annex C.

10.2 Containers for extraction

10.2.1 The extraction shall be performed in clean, chemically inert, closed containers with minimum headspace.

10.2.2 To ensure that the extraction vessels do not adulterate the extract of the test materials, the extraction vessels shall be:

a) borosilicate glass tubes with caps having an inert liner [e.g. poly (tetrafluoroethylene)];

b) other inert extraction vessels as required for specific materials and/or extraction procedures.

conditions is considered to be appropriate, the method shall be justified, specified and reported.

10.3.6 Liquid extracts shall, if possible, be used immediately after preparation to prevent sorption onto the extraction container or other changes in composition. If an extract is stored longer than 24 h, then the stability and homogeneity of the extract under the conditions of storage shall be verified.

10.3.7 Extract pH shall not be adjusted unless a rationale is provided.

10.3.8 The extract shall not routinely be processed by filtration, centrifugation or other methods to remove suspended particulates. However, if such processing is necessary, the rationale shall be documented.

10.3.9 For hazard identification exaggerated extraction conditions shall be considered to increase the exposure dose of leachables. The solvent and conditions of extraction shall be selected on the basis of physicochemical properties of the material and/or predicted low molecular mass chemicals that might be extracted.

10.3.10 Any solvents used in the extraction of a polymeric material or device shall not cause dissolution of the polymer formulation. No more than a slight softening of the polymeric material shall occur in the presence of the volatile solvent (e.g. less than 10 % dissolution). The solvent shall be removed (prior to use in a bioassay) to the extent that any residues do not adversely affect the biological assay (e.g. cause protein denaturation or skin irritation).

10.4 Extraction conditions for hazard identification and risk estimation in exaggerated-use condition

10.4.1 Hazards that arise from changes in the manufacturing process or insufficient control of the manufacturing process shall be considered in the design and preparation of samples for test and preparation of extracts of those devices, in accordance with YY/T 0316 / ISO 14971:2000. Particular attention shall be given to residues, e.g. trace elements and cleaning and disinfection agents, of those manufacturing processes.

10.4.2 Where the toxic potential is shown to be within the requirement for a product tested by exaggerated extraction, there shall be no need to further challenge the device by simulated-use extraction.

10.4.3 The test samples for materials that cure in situ (e.g. cements, adhesives and pre-polymer mixtures) shall represent the curing point at which the material is placed in situ and the maximum curing time during use in situ (i.e. simulate the minimum and maximum cures during clinical use).

Where extracts are used in the test methods for evaluation of materials that cure in situ, initiation of the extraction shall occur from the point in the cure at which the material is placed in situ.

For test methods that use these materials directly, e.g. direct-contact or agar overlay cytotoxicity, implantation, some genotoxicity tests, and direct-contact hemolysis, the material shall be used as in clinical use, with in situ cure in the test system.

NOTE: Modification of the clinical delivery system may be appropriate, so that the designated dimensions or mass of the material is delivered for testing.

11 Records

Documentation of the sample and its preparation shall include, but not be limited to:

a) type and, if known, composition of material, source of material, device, device portion or component;

   NOTE: A written description, drawing, photograph or other methods can achieve all or part of this requirement.

b) lot or batch number, where appropriate;

c) description of processing, cleaning or sterilization treatments, if appropriate; and

d) extraction techniques, as appropriate, including documentation of extraction medium, extraction ratios, the conditions for extraction, means of agitation, as well as any deviations from the conditions specified in this Part, such as filtration of the extract or extraction media.

Annex B
(Informative)
General principles and practices of test material preparation and sample selection

The material used in the biological assay shall be representative of the composition and surface characteristics of the final product and of the processes used in its manufacture. See 7.1 and 5.1 a of GB/T 16886.1-2001).

Documentation of the composition of plastic and rubber materials shall include identification of the resin, polymer and any additives. The formulation description shall specify the history of the material, e.g. information on thermal processing, and whether it is virgin or regrind and, if regrind, the specification for the maximum allowable regrind.

Materials that may be re-sterilized by the same or alternative methods shall be tested after treatment by the multiple sterilizations. For example, a material that is sterilized by radiation and re-sterilized by ethylene oxide shall be tested after

a) irradiation, and

b) irradiation plus ethylene oxide.

If a “worst-case” exposure can be identified with appropriate justification, testing may be performed after exposure to this treatment.

Ideally, all biological tests which use a material cut from a device, a device component itself as the test material, or extract prepared from either, shall be performed with the surface of the material exposed to the test systems’ cellular/biological environment. An alternative method to cutting the surface is fabrication of miniatures of the device using the same process (extrusion, dipping, etc.), temperatures, time, atmosphere, release agents, annealing, curing, cleaning, sterilization, etc., processes used in the manufacture of the device. This assists in evaluating any effects related to surface area, surface characteristics, concentration of leachables and the material's surface and shape.

Metals used in biological tests shall be from the same stock material used to fabricate the device and using the same machining, grinding, polishing, cleaning, passivation, surface treatment and sterilization used in the manufacture of the final product.

Ceramic materials used in biological tests shall be manufactured from the same powder stock using the same casting, investing, moulding, sintering, surface finishing and sterilization processes used to manufacture the device.

Bioprosthetic, i.e. animal-tissue-derived, materials shall be tested after they have been preserved under the manufacturer's maximum and minimum allowable fixation times to allow for varying penetration of the fixative.

Annex C
(Informative)
Principles of test material extraction

WARNING — Application of GB/T 16886 test methods to device materials comprising proteins shall be made with great care.

C.1 The purpose of extraction of a medical device is to provide a suitable test sample for determining the biological reactivity of any leachables in the biological system, to demonstrate the hazard potential (hazard identification) of the leachable and for use in conducting human health risk assessments of the leachable. If extracts of the device are prepared, the medium and conditions of extraction used shall be appropriate to the nature and use of the final product as well as to the predictability (such as test purpose, rationale, sensitivity, etc.) of the test method. Extraction conditions and application of the extract to test systems, therefore, shall ideally reflect not only actual in-use conditions of the products but also the purpose and predictability of the tests.

Biological tests are carried out in order to identify hazards and estimate risks of the hazards in exaggerated- use and/or in actual-use conditions. Extractions differ for various test purposes:

a) exaggerated extraction is appropriate for hazard identification, and

b) simulated-use extraction is applicable for generation of a safety factor for use in human health risk assessments.

C.2 This Part assumes that the amount of extractable substance(s) is related to the period of extraction, the temperature, the ratio of surface-area-of-material to volume-of-extractant and the nature of the extractant.

C.3 The period of extraction shall be sufficient to maximize the amount of material extracted. In practice, use of these standard conditions of time and temperature for extraction are recommended in lieu of other unvalidated or non-standard conditions.

C.4 An alternative practice is repeated extraction followed by concentration to obtain sufficient extractable substance(s). This practice is applicable for the purposes of hazard identification.

C.5 Extraction temperatures can vary for the different materials to be tested. Extraction shall not initiate significant degradation of the material. The extraction temperature is dependent upon the physicochemical characteristics of the device material(s). The extraction temperature chosen for polymers, for example, shall be below the glass transition temperature. If the glass transition temperature is below the use temperature, the extraction temperature shall be below the melting temperature. Recommended

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