

Specjalistyczne metody badań materiałów, 2014

Biologiczna ocena wyrobów medycznych

Normy prawne regulujące badanie
biozgodności materiałów

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Biomateriał to każda substancja inna niż lek albo kombinacja substancji syntetycznych lub naturalnych, która może być użyta w dowolnym czasie, a której zadaniem jest **uzupełnianie** lub **zastąpienie** tkanek narządu lub jego części **w celu spełnienia ich funkcji.**

A Consensus Development Conference on the Clinical Applications of Biomaterials, National Institute of Health, Bethesda, Maryland, 1982

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Toksyczność materiału lub produktów jego degradacji
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ICS 11.100.20;

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Wprowadza
EN ISO 10993-1:2009 , IDT

ISO 10993-1:2009, IDT

Zastępuje
PN-EN ISO 10993-1:2009

Biologiczna ocena wyrobów medycznych -- Część 1: Ocena i badanie w procesie zarządzania ryzykiem

EUROPEAN STANDARD
NORME EUROPÉENNE
EUROPÄISCHE NORM

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English Version

Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009)

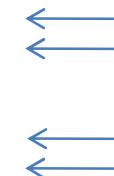
Évaluation biologique des dispositifs médicaux - Partie 1:
Évaluation et essais au sein d'un processus de gestion du
risque (ISO 10993-1:2009)

Biologische Beurteilung von Medizinprodukten - Teil 1:
Beurteilung und Prüfungen im Rahmen eines
Risikomanagementsystems (ISO 10993-1:2009)

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

- *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: Tests 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 skin sensitization*
- *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 alloys*

- *Part 16: Toxicokinetic study design for degradation products and leachables*
- *Part 17: Establishment of allowable limits for leachable substances*
- *Part 18: Chemical characterization of materials*
- *Part 19: Physico-chemical, morphological and topographical characterization of materials (Technical Specification)*
- *Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical Specification)*

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

Część 1 dotyczy ogólnego opisu procesów testowania urządzeń medycznych i oceny zagrożeń.

Biological evaluation of medical devices —

Part 1:

Evaluation and testing within a risk management process

1 Scope

This part of ISO 10993 describes:

- the general principles governing the biological evaluation of medical devices within a risk management process;
- the general categorization of devices based on the nature and duration of their contact with the body;
- the evaluation of existing relevant data from all sources;
- the identification of gaps in the available data set on the basis of a risk analysis;
- the identification of additional data sets necessary to analyse the biological safety of the medical device;
- the assessment of the biological safety of the medical device.

This part of ISO 10993 does not cover testing of materials and devices that do not come into direct or indirect contact with the patient's body, nor does it cover biological hazards arising from any mechanical failure. Other parts of ISO 10993 cover specific tests, as indicated in the Foreword.

Do urzędzeń medycznych zalicza się także materiały medyczne

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1

medical device

any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body,

and which does not achieve its primary 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

NOTE 1 This definition has been developed by the Global Harmonization Task Force (GHTF).

NOTE 2 Products which might be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach, are:

- 1) aids for disabled/handicapped people;
- 2) devices for the treatment/diagnosis of diseases and injuries in animals;
- 3) accessories for medical devices (see Note 4);
- 4) disinfection substances;
- 5) devices incorporating animal and human tissues, which might meet the requirements of the above definition but are subject to different controls.

NOTE 3 Accessories intended specifically by manufacturers to be used together with a "parent" medical device to enable that medical device to achieve its intended purpose, should be subject to ISO 10993.

NOTE 4 Medical devices are different from drugs/biologics, and their biological evaluation requires a different approach.

NOTE 5 Medical devices can include dental devices.

Definicja materiału:

3.2

material

any synthetic or natural polymer, metal, alloy, ceramic or other non-viable substance, including tissue rendered non-viable, used as a medical device or any part thereof

3.3

final product

medical device in its "as-used" state, as defined by the manufacturer's specification or labelling

3.4

chemical constituent

any synthetic or natural substance that is used in a process for manufacturing materials and/or medical devices, such as additives (antioxidants, UV stabilizers, dyestuff, etc.), processing aids (solvents, lubricants, antifoaming agents, etc.)

3.5

data set

information from a variety of sources necessary to characterize the biological response of a device

4 General principles applying to biological evaluation of medical devices

- 4.1 The biological evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation programme within a risk management process in accordance with ISO 14971, as set out in Figure 1. Annex B provides guidance on this process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals. See Annex C for how to perform a literature review of existing data. ←

The risk management plan should identify aspects of the biological evaluation requiring specific technical competencies and shall identify the person(s) responsible for the biological safety evaluation.

The evaluation programme shall include documented, informed decisions that assess the advantages/disadvantages and relevance of:

- a) the physical and chemical characteristics of the various candidate materials;

NOTE Where this information is already documented within the risk management for the device it can be included by reference.

- b) any history of clinical use or human exposure data;

- c) any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites;

- d) test procedures.

- Evaluation may include both a study of relevant preclinical and clinical experience and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design.

→ **4.2** In the selection of materials to be used in device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties.

→ **4.3** The following shall be taken into account for their relevance to the overall biological evaluation of the device:

- a) the material(s) of manufacture;
- b) intended additives, process contaminants and residues (see ISO 10993-7 for ethylene oxide residues);
- c) leachable substances (see ISO 10993-17);
- d) degradation products (see ISO 10993-9, for general principles and 10993-13, 10993-14 and 10993-15 for degradation products from polymers, ceramics and metals, respectively);
- e) other components and their interactions in the final product;
- f) the performance and characteristics of the final product;
- g) physical characteristics of the final product, including but not limited to, porosity, particle size, shape and surface morphology.

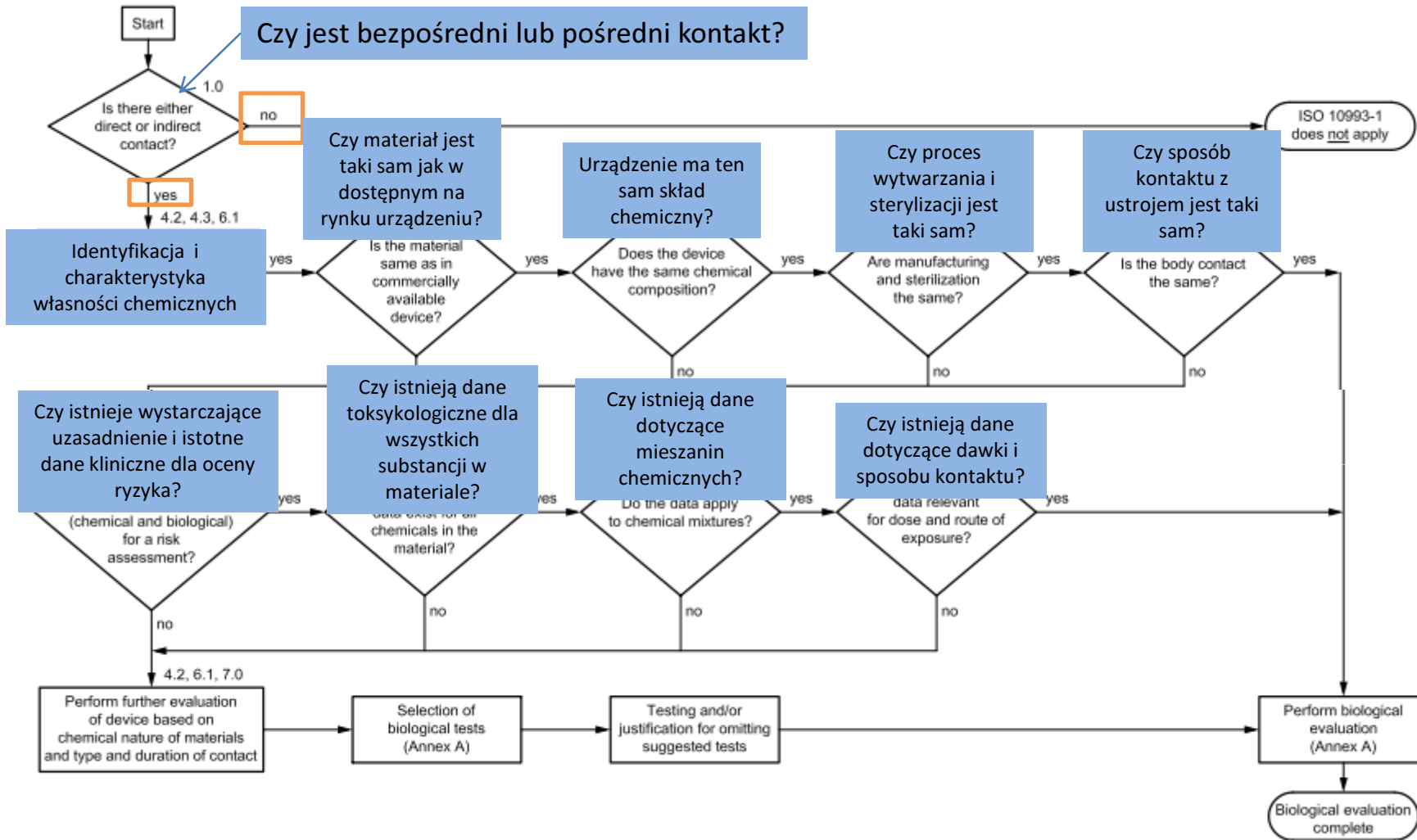
Identification of material chemical constituents and consideration of chemical characterization (see ISO 10993-18) shall precede any biological testing (see Figure 1).

Physical effects of the device shall be considered if they impact the biocompatibility (see ISO/TS 10993-19).

For implanted devices, in addition to systemic effects, local effects should also be considered for risk evaluation.

- **4.4** The choice of tests and the data required in a biological evaluation, and their interpretation, shall take into account the chemical composition of the materials, including the conditions of exposure as well as the nature, degree, frequency and duration of exposure of the medical device or its constituents to the body, enabling the categorization of devices to facilitate the selection of appropriate tests (see Clause 5). The rigour necessary in the biological evaluation is principally determined by the nature, degree, duration and frequency of the exposure and the hazards identified for the material.
- **4.5** All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical (see Clauses 5 and 6). Test results cannot guarantee freedom from potential biological hazards, thus biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the device.
- The range of possible biological hazards is wide and can include short-term effects such as acute toxicity, irritation to the skin, eye and mucosal surfaces, haemolysis and thrombogenicity, as well as long-term or specific toxic effects such as subchronic and chronic toxic effects, sensitization, allergy, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction including teratogenicity.

Schemat postępowania w ocenie urządzeń medycznych



Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

4.6 Selection of any *in vitro* or *in vivo* tests shall be based on end-use applications. All tests shall be conducted according to recognised current/valid best laboratory/quality practices, for example Good Laboratory Practice (GLP) or ISO/IEC 17025, where applicable, and the data shall be evaluated by competent, informed professionals.

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible shall be considered for use in preference to *in vivo* tests. Whenever possible, *in vitro* screening shall be carried out before *in vivo* tests are commenced. Test data, complete to the extent that an independent analysis could be made, shall be retained.

4.7 The materials or final product shall be re-evaluated if any of the following occurs:

- a) any change in the source or in the specification of the materials used in the manufacture of the product;
- b) any change in the formulation, processing, primary packaging or sterilization of the product;
- c) any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport;
- d) any change in the intended use of the product;
- e) any evidence that the product may produce adverse effects when used in humans.

4.8 The biological evaluation shall take into account the nature and mobility of the chemical constituents in the materials used to manufacture the device and other information, other non-clinical tests, clinical studies, and post-market experience for an overall assessment.

Kategoryzacja postępowania ze względu na rodzaj kontaktu z organizmem:

5.2 Categorization by nature of body contact

5.2.1 Surface-contacting devices

These include medical devices in contact with the following.

a) Skin **skóra**

— devices that contact intact skin surfaces only.

EXAMPLES Electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types.

b) Mucosal membranes **błony śluzowe**

— devices that contact intact mucosal membranes.

EXAMPLES Contact lenses, urinary catheters, intravaginal and intra-intestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, some dental prostheses and orthodontic devices.

c) Breached or compromised surfaces **naruszone powierzchnie i powłoki**

— devices that contact breached or otherwise compromised body surfaces.

EXAMPLES Dressings or healing devices and occlusive patches, for ulcers, burns and granulation tissue.

Kategoryzacja postępowania ze względu na rodzaj kontaktu z organizmem:

5.2.2 External communicating devices

External communicating devices shall be categorized according to their contact with the following application sites:

a) Blood path, indirect

punktowy kontakt z krwią

- devices that contact the blood path at one point and serve as a conduit for entry into the vascular system.

EXAMPLES Solution administration sets, extension sets, transfer sets and blood administration sets.

b) Tissue/bone/dentin

tkanki

- devices that contact tissue, bone or pulp/dentin systems.

EXAMPLES Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples.

c) Circulating blood

krw w przepływie

- devices that contact circulating blood.

EXAMPLES Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

Kategoryzacja postępowania ze względu na rodzaj kontaktu z organizmem:

5.2.3 Implant devices

Implant devices shall be categorized according to their contact with the following application sites:

a) Tissue/bone

tkanki

- devices principally contacting bone.

EXAMPLES Orthopaedic pins, plates, replacement joints, bone prostheses, bone cements and intra-osseous devices.

- devices principally contacting tissue and tissue fluid.

EXAMPLES Pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips and intra-uterine devices.

b) Blood

kontakt z krwią

- devices principally contacting blood.

EXAMPLES Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices.

Kategoryzacja postępowania ze względu na czas trwania kontaktu:

5.3 Categorization by duration of contact

Medical devices shall be categorized according to the anticipated duration of contact as follows.

- a) Limited exposure (A) – devices whose cumulative single, multiple or repeated use or contact is up to 24 h.
- b) Prolonged exposure (B) – devices whose cumulative single, multiple or repeated long-term use or contact is likely to exceed 24 h but not 30 d.
- c) Permanent contact (C) – devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 d.

If a material or device can be placed in more than one duration category, the more rigorous testing and/or evaluation considerations shall apply. 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. If a device is intended to change during its lifetime, as those that are polymerized and/or biodegraded *in situ*, separate evaluations shall be conducted for the different device states. For example, for a biodegradable glue intended to polymerize *in situ*, the different device states would include starting components, intermediate reaction products, the fully polymerized material and degradation products.

Charakterystyka materiału jest pierwszym etapem w procesie oceny właściwości biologicznych

6.1 Material characterization

Material characterization is a crucial first step in the biological evaluation process. The extent of chemical characterization required depends on what pre-clinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device; but, as a minimum, the characterization shall address the constituent chemicals of the device and possible residual process aids or additives used in its manufacture. Material characterization is described in ISO 10993-18 and ISO/TS 10993-19.

Figure 1 indicates how the different steps in the chemical characterization process link to the overall biological evaluation decision points.

If the combination of all materials, chemicals and processes has an established history of safe use in the intended application, then further characterization and biological evaluation might not be necessary.

The identity and quantity of novel materials and chemicals present should be established or measured.

For device extractables and leachables that have known toxicological data relevant to the intended dose and for which route and frequency of exposure that indicate adequate safety margins exist, the need for further testing is likely to be minimal or non-existent. For devices that have known leachable chemical mixtures, potential synergies of the leachable chemicals should be considered.

The results of the risk assessment can lead to the conclusion that additional material characterization is necessary, for example, where the margin of safety is not considered adequate if the entire amount of a particular chemical were to leach out. In such cases, appropriate extraction testing, simulating clinical exposure, can be used to estimate the degree of clinical exposure to the chemical constituent. The acceptability of the level of leachables shall be established in accordance with ISO 10993-17.

Where the potential for degradation exists under the conditions of manufacture, sterilization, transport, storage, and use of the device, the presence and nature of degradation products shall be characterized in accordance with ISO 10993-9, ISO 10993-13, ISO 10993-14, and ISO 10993-15.

6.2.1 General

Assess all reasonably and practicably available information and compare to the data set(s) needed to assess the biological safety of the device (see Annex A and Clause 4). Identify any additional data or testing needed to complete the data sets required to perform the risk assessment.

ISO 10993-2 applies to any *in vivo* testing being considered. Additional *in vivo* testing shall not be carried out where:

- 1) results are available from relevant studies that have been carried out previously

or

- 2) the existing pre-clinical and clinical data, including history of safe use, meet the requirements of biological evaluation and therefore further animal testing would be unethical. In assessing the relevance of data, on prior use of a material, to the biological evaluation, the level of confidence in the historical data should be taken into account. ISO 10993-18:2005, Annex C, gives some informative principles for judging toxicological equivalence.

In addition to the general principles given in Clause 4, the following shall apply when biological testing of medical devices is considered necessary as part of the overall risk management process.

- a) Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization).
- b) The choice of test procedures shall take into account:
 - 1) the nature, degree, duration, frequency and conditions of exposure to or contact of humans with the device in the normal intended use;
 - 2) the chemical and physical nature of the final product;
 - 3) the toxicological activity of the chemicals in the formulation of the final product;

- 4) that certain tests (e.g. those designed to assess systemic effects) might not be applicable where the presence of leachable chemicals has been excluded, or where chemicals have a known and acceptable toxicity profile, allowing the safe use by evaluation in accordance with ISO 10993-17 and risk assessment in accordance with ISO 14971;
 - 5) the relationship of device surface area to recipient body size;
 - 6) the existing information based on the literature, previous experience and non-clinical tests;
 - 7) the sensitivity and specificity of the test being considered in relation to the relevant biological evaluation data set;
 - 8) that the protection of humans is the primary goal of this part of ISO 10993; a secondary goal is to ensure animal welfare and to minimize the number and exposure of the test animals.
- c) If extracts of the devices are prepared, the solvents and conditions of extraction used should be appropriate to the nature and use of the final product, as well as to the predictability (such as test purpose, rationale, sensitivity, specificity, etc.) of the test method (see ISO 10993-12).
- d) Positive and negative controls should be used where appropriate.

The test methods used in the biological evaluation tests shall be sensitive, precise and accurate. All tests shall be conducted in compliance with current/valid best laboratory/quality practices, for example GLP or ISO/IEC 17025, where applicable.

The test results should be reproducible (intralaboratory) as well as repeatable (interlaboratory) and robust.

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2 Test descriptions

6.2.2.1 General

The evaluation tests described in 6.2.2.2 to 6.2.2.15 shall be considered and carried out where necessary to complete the data sets needed for the biological evaluation of the particular medical device. Where the existing data are adequate, additional testing is not required (see Annex A).

Due to the diversity of medical devices, it is recognised that not all tests identified in a category will be necessary or practicable (see ISO 14971) for a given device. It is indispensable for testing that each device be considered on its own merits.

Additional tests not indicated in the table may be necessary (e.g. bio-degradation and toxicokinetics).

6.2.2.2 Cytotoxicity

Cytotoxicity tests employing cell culture techniques shall be used to determine the lysis of cells (cell death), the inhibition of cell growth, colony formation, and other effects on cells caused by medical devices, materials and/or their extracts (see ISO 10993-5).

6.2.2.3 Delayed-type hypersensitivity

Hypersensitivity tests shall be used to estimate the potential for contact sensitization by medical devices, materials and/or their extracts, using an appropriate animal model (see ISO 10993-10).

These tests are important because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions.

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2.4 Irritation (including intracutaneous reactivity)

Irritation tests shall be used to estimate the irritation potential of medical devices, materials and/or their extracts, using an appropriate site for application such as skin, eye and mucous membrane in a suitable model. The test(s) performed shall be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact (see ISO 10993-10).

The intracutaneous reactivity test shall be used to assess the localized reaction of tissue to medical device extracts. This test is applicable where the determination of irritation by dermal or mucosal tests is inappropriate (e.g. where medical devices are implanted or have blood contact).

This test might also be useful where extractables are hydrophobic (see ISO 10993-10).

6.2.2.5 Systemic toxicity (acute)

Acute systemic toxicity tests shall be used where contact allows potential absorption of toxic leachables and degradation products, to estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to medical devices, materials and/or their extracts in an animal model (see ISO 10993-11).

Pyrogenicity tests are included to detect material-mediated pyrogenic reactions of extracts of medical devices or materials. No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination.

If feasible, acute systemic toxicity tests may be combined with subacute and subchronic toxicity and implantation test protocols.

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2.6 Subacute and subchronic toxicity

Subacute and subchronic toxicity tests shall be carried out to determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts for a period not less than 24 h to a period not greater than 10 % of the total life-span of the test animal (e.g. up to 13 weeks in rats).

These tests shall be waived if available data for the chronic toxicity of the relevant materials are sufficient to allow the subacute and subchronic toxicity to be evaluated. The reason for waiving of the tests shall be included in the overall biological evaluation report. These tests shall be appropriate for the route and duration of contact.

Subacute and subchronic toxicity tests are given in ISO 10993-11.

If feasible, subacute and subchronic systemic toxicity test protocols may be expanded to include implantation test protocols to evaluate subacute and subchronic systemic and local effects.

6.2.2.7 Genotoxicity

A battery of *in vitro* genotoxicity tests employing mammalian or non-mammalian cell culture or other techniques shall be used to determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials and/or their extracts.

If any of the *in vitro* tests are positive, either *in vivo* mutagenicity tests shall be performed or the presumption shall be made that the material is mutagenic (see ISO 10993-3).

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2.8 Implantation

Implantation tests shall be used to assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or tissue appropriate to the intended application (e.g. special dental usage tests). These tests shall be appropriate for the route and duration of contact.

If feasible, implantation test protocols may be expanded to evaluate both local and systemic effects to meet acute, subacute, subchronic, and chronic toxicity testing requirements (see ISO 10993-6).

6.2.2.9 Haemocompatibility

Haemocompatibility tests shall be used to evaluate, using an appropriate model or system, the effects of blood-contacting medical devices or materials on blood or blood components.

One haemocompatibility test, haemolysis, determines the degree of red cell lysis and the release of haemoglobin caused by medical devices, materials, and/or their extracts *in vitro*.

Other specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications and determine blood/material/device interactions (see ISO 10993-4).

6.2.2.10 Chronic toxicity

Chronic toxicity tests shall be used to determine the effects of either single or multiple exposures to medical devices, materials and/or their extracts during a major period of the life-span of the test animal (e.g. usually 6 months in rats). These tests shall be appropriate for the route and duration of exposure or contact (see ISO 10993-11).

If feasible, chronic systemic toxicity test protocol may be expanded to include an implantation test protocol to evaluate both chronic systemic and local effects.

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2.11 Carcinogenicity

If there is no information from other sources, testing the potential carcinogenicity of the material/device shall be considered. However, it is rare for carcinogenicity tests to be considered appropriate for medical devices (see ISO 10993-3). Carcinogenicity tests shall be used to determine the tumorigenic potential of medical devices, materials and/or their extracts from either single or multiple exposures or contacts over a period of the major portion of life-span of the test animal. Carcinogenicity tests should be appropriate for the route and duration of exposure or contact; lifetime studies or transgenic models may be appropriate. These tests may be designed to examine both chronic toxicity and tumorigenicity in a single experimental study.

6.2.2.12 Reproductive and developmental toxicity

Reproductive and developmental toxicity tests shall be used to evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development. Reproductive/developmental toxicity tests or bio-assays shall only be conducted when the device has potential impact on the reproductive potential of the subject. In addition, such tests should be considered for devices/materials used during pregnancy. The application site of the device is the primary criterion when considering carrying out the tests. Reproductive and developmental toxicity tests are described in ISO 10993-3.

6.2.2.13 Biodegradation

Biodegradation tests shall be considered if

a) the device is designed to be biodegradable

or

b) the device is intended to be implanted for longer than 30 d

or

c) an informed consideration of the material(s) system indicates that toxic substances might be released during body contact.

Parameters that affect the rate of degradation shall be described and documented.

The mechanisms of biodegradation should be described. These mechanisms should be simulated *in vitro* to determine the rates of degradation and release of potentially toxic chemicals to estimate the exposure. *In vivo* tests may be required to assess biodegradation of a material.

Biodegradation tests might not be necessary if the probable products of degradation are in the predicted quantities, and produced at a rate similar to those that have a history of safe clinical use; and/or if particulate, they are present in a physical state, i.e. size distribution and shape, similar to those with a history of safe clinical use or sufficient degradation data relevant to the substances and degradation products in the intended use already exists.

A general framework for biodegradation tests is given in ISO 10993-9.

Specific *in vitro* biodegradation tests for polymers, ceramics and metals are described in ISO 10993-13, ISO 10993-14 and ISO 10993-15 respectively.

6.2.2.14 Toxicokinetic studies

The purpose of conducting toxicokinetic studies is to evaluate the absorption, distribution, metabolism and excretion (ADME) of a chemical that is known to be toxic or whose toxicity is unknown. These studies will also serve to determine the delivered dose to the target organ(s) in order to assess any health hazards using the physiologically based pharmacokinetic (PBPK) modelling. The extrapolation of test results across gender, age, species and doses/exposure may be possible, but requires critical expert judgement to be exercised and explained.

The need for *in vivo* toxicokinetic studies, to determine the processes of absorption, distribution, metabolism and elimination of leachables and degradation products of medical devices, materials and/or their extracts (see 6.2.2.13 and ISO 10993-16), shall be considered in the light of results from the *in vitro* biodegradation studies.

When deciding whether or not to conduct toxicokinetic studies as part of the biological evaluation of a medical device, the final product and its chemical constituents, including potential and designed degradation products and leachables in combination with the intended use of the device, shall all be taken into account (see 6.2.2.13).

Where appropriate, theoretical degradation processes shall be investigated prior to toxicokinetic studies by means of *in vitro* experiments (e.g. tissue, homogenates or cells), not only for animal welfare reasons as given in ISO 10993-2, but also to determine probable rather than possible degradation products.

Toxicokinetic studies shall be considered if

a) the device is designed to be bioresorbable

or

b) the device is a permanent contact implant, and biodegradation or significant corrosion is known or likely, and/or migration of leachables from the device occurs

or

c) substantial quantities of potentially toxic or reactive degradation products and leachables are likely or known to be released from a medical device into the body during clinical use.

Toxicokinetic studies are not required if the achieved or expected rates of release of degradation products and leachables from a particular device or material have been judged to provide safe levels of clinical exposure following reference to significant historical experience, or if sufficient toxicological data or toxicokinetic data relevant to the degradation products and leachables already exist.

The release of leachables and degradation products from metals, alloys and ceramics is usually too low to justify toxicokinetic studies, unless the material is designed to biodegrade.

Toxicokinetic study design for degradation products and leachables is given in ISO 10993-16.

Opisy testów i odwołanie do poszczególnych części normy:

6.2.2.15 Immunotoxicology

ISO/TS 10993-20 provides an overview of immunotoxicology with particular reference to the potential immunotoxicity of medical devices. Immunotoxicity testing shall be considered based on the chemical nature of the materials of manufacture and data from sources that are suggestive of immunotoxicological effects or if the immunogenic potential of any of the chemicals is unknown.

Analiza wyników biologicznej oceny:

7 Interpretation of biological evaluation data and overall biological safety assessment

Expert assessors who have the necessary knowledge and experience shall determine and document:

- a) the strategy and programme content for the biological evaluation of the medical device;
- b) the criteria for determining the acceptability of the material for the intended purpose, in line with the risk management plan;
- c) the adequacy of the material characterization;
- d) the rationale for selection and/or waiving of tests;
- e) the interpretation of existing data and results of testing;
- f) the need for any additional data to complete the biological evaluation;
- g) overall biological safety conclusions for the medical device.

Annex A gives the general evaluation tests that should be considered for each device and duration category.

Due to the diversity of medical devices, it is recognised that not all tests identified in a category will be necessary or practical for any given device. It is indispensable for testing that each device be considered on its own merits.

Table A.1 — Evaluation tests for consideration

Medical device categorization by			Biological effect							
Category	nature of body contact (see 5.2) Contact	contact duration (see 5.3) A – limited ($<$ 24 h) B – prolonged ($>$ 24 h to 30 d) C – permanent ($>$ 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device		A	X ^a	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

^a The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

B.4 Biological evaluation report

Expert assessors should determine if the available information is sufficient to meet the purpose of the evaluation of biological safety and if so, document how the conclusion on safety was reached.

The biological evaluation report should:

- contain a summary of the results of the overall evaluation;
- confirm that the risk analysis and risk control have been completed.

The risk management report should be approved by the personnel assigned this responsibility and authority.

B.5 Conclusion

The use of the ISO 10993 series of tests, as part of the appropriate risk management process, offers scientific validity to the process of biological response evaluation, makes proper provisions for the ethical use of animals, and offers greater reassurance to the public regarding the biological safety of medical devices.