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Medical Law

Biological evaluation of medical devices. Part I.

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Summary:

Biocompatibility is a biomedical science term, which refers to every biomaterial and medical device. Biocompatibility is essential for every medical device,Its evaluation and proper documentation is required by European standards and therefore also Polish ones. Twenty international standards ISO10993 constitute a set of normative documents, which describe recommended types of testing of new biomaterials and medical devices to be performed before introduction of these products to the market. Selection of the mandatory tests depends on the type of medical device, place, nature and duration of contact with the patient.

Key words: biocompatibility, biomaterial, medical device

1. Introduction

The concept of biocompatibility has significantly changed in the recent years. Currently, this term is applied in medicine in close association with biomaterials. It indicates not only the lack of cytotoxicity, but also the beneficial interaction with an organism of a patient in terms of biofunctionality of a given medical device. Biocompatibility refers to the interactions between biomaterials being part of medical devices and a tissue being a part of complex system, which remains in constant or temporary contact with a given medical device.

The definition of biocompatibility, introduced at the European Society for Biomaterials Consensus Conference I in 1991, states that biocompatibility is the ability of a material to perform with an appropriate host response in a specific application (Williams' definition). Unfortunately, this definition refers only to materials and not to medical devices, which in many cases are manufactured from more than one material. Usually, the majority of preclinical studies is conducted on particular biomaterials rather than on finished products. However, due to the technological advancement of current medical devices, on some stage of testing, trials on finished product (or its prototype) should be conducted, because the biocompatibility results of some tests may depend on the size and geometry of a given medical device. Since the scope of the abovementioned definition is very wide, scientists have tried to divide the general term of biocompatibility to the narrower subgroups in order to enable use of more detailed definitions. Selected subgroups and their definitions have been specified as follows:

1) **Biocompatibility of long-term implanted devices**
The biocompatibility of a long-term implantable medical device refers to the ability of the device to perform its intended function, without eliciting any undesirable local or systemic effects in the host.

2) **Biocompatibility of short–term implantable devices**
The biocompatibility of a medical device that is

intentionally placed within e.g. the cardiovascular system for transient diagnostic or therapeutic purposes refers to the ability of the device to carry out its intended function, with minimal interaction between device and blood that adversely affects device performance, and without inducing uncontrolled activation of cellular or plasma protein cascades.

3) **Biocompatibility of tissue-engineering products** The biocompatibility of a scaffold or matrix for a tissue-engineering products refers to the ability to perform as a substrate that will support the appropriate cellular activity, including the facilitation of molecular and mechanical signalling systems, without eliciting any undesirable effects in those cells, or inducing any undesirable local or systemic responses in the eventual host.

The notion of biocompatibility in the above mentioned definitions refers to the devices rather than to materials as compared to the general definition. Further discussion on the subject of biocompatibility took place at the conference in Sorrento in 2005 [2,3]. It was conceded that it is not possible to create one test which would define the biocompatibility of a material. In fact, the complexity of immunological response and repair processes of an organism reveal that a single test cannot be designated to determine the biocompatibility of various biomaterials and medical devices.

Biocompatibility tests constitute a group of analytical chemical methods and biological *in vitro* tests, which allow for tentative determination whether a given material (or rather biomedical device) is biocompatible. These tests do not explicitly indicate whether a material or device is biocompatible, but they constitute an important and necessary step towards animal testing and following clinical tests for biocompatibility of all materials from which the product is made in a particular application. Biocompatibility of medical device depends on a few factors including physicochemical properties of materials a device is made of, chosen method of sterilization, place of contact of the device with an organism i.e. the type of tissue which will be in direct contact with the device as well as the duration of the contact.

2. Standards for biocompatibility

The International Organization for Standardization (ISO) is an international, non-governmental body composed of representatives from various national standards organizations (in Poland it is the Polish Committee for Standardization), which develop worldwide proprietary industrial and commercial standards. ISO develops also documents concerning the notion of biocompatibility grouped in many standards with a general title 'Biological evaluation of medical devices' {ISO 10993) [4], which is a set of harmonized standards for the evaluation of biocompatibility of medical devices before clinical trials. The standards that have been approved by the European Union standards body – European Committee for Standardization (CEN) – automatically become the standards applicable in Europe (EN ISO).

Various parts of **ISO 10993 –** Biological evaluation of medical devices are listed below. Polish equivalent standards are listed in the brackets. At present, part 19 and 20 are not approved by Polish Committee for Standardization.

- EN ISO 10993-1:2009 Part 1: Evaluation and testing (PN-EN ISO 10993-1:2010 Część 1: Ocena i badanie)
- EN ISO 10993-2:2006 Part 2: Animal welfare requirements (PN-EN ISO 10993-2:2006 Część 2: Wymagania dotyczące postępowania ze zwierzętami)
- EN ISO 10993-3:2009 Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (PN-EN ISO 10993-3:2009 Część 3: Badania genotoksyczności, rakotwórczości i toksyczności reprodukcyjnej)
- EN ISO 10993-4:2009 Part 4: Selection of tests for interactions with blood (PN-EN ISO 10993-4:2009 Część 4: Wybór badań dla interakcji z krwią).
- EN ISO 10993-5:2009 Part 5: Tests for in vitro cytotoxicity (PN-EN ISO 10993-5:2009 Część 5: Badania cytotoksyczności in vitro).
- EN ISO 10993-6:2009 Part 6: Tests for local effects after implantation (PN-EN ISO 10993-6:2009 Część 6: Badania miejscowej reakcji po implantacji).
- EN ISO 10993-7:2008 Part 7: Ethylene oxide sterilization residuals (PN-EN ISO 10993-7:2009 Część 7: Pozostałości po sterylizacji tlenkiem etylenu).
- EN ISO 10993-9:2009 Part 9: Framework for identification and quantification of potential degradation products (PN-EN ISO 10993-9:2010 Część 9: Ramowy plan identyfikacji i oznaczania ilościowego potencjalnych produktów degradacji).
- EN ISO 10993-10:2010 Part 10: Tests for irritation and skin sensitization (PN-EN ISO 10993-10:2011 Część 10: Badania działania

drażniącego i działania uczulającego na skórę).

- EN ISO 10993-11:2009 Part 11: Tests for systemic toxicity (PN-EN ISO 10993-11:2009 Część 11: Badania toksyczności układowej).
- EN ISO 10993-12:2009 Part 12: Sample preparation and reference materials (PN-EN ISO 10993-12:2009 Część 12: Przygotowanie próbki i materiały odniesienia).
- EN ISO 10993-13:2010 Part 13: Identification and quantification of degradation products from polymeric medical devices (PN-EN ISO 10993-13:2010 Część 13: Identyfikacja i oznaczanie ilościowe produktów degradacji wyrobów medycznych z polimerów).
- EN ISO 10993-14:2009 Part 14: Identification and quantification of degradation products from ceramics (PN-EN ISO 10993-14:2009 Część 14: Identyfikacja i oznaczanie ilościowe produktów degradacji ceramiki).
- EN ISO 10993-15:2009 Part 15: Identification and quantification of degradation products from metals and alloys (PN-EN ISO 10993-15:2009 Część 15: Identyfikacja i oznaczanie ilościowe produktów degradacji metali i stopów).
- EN ISO 10993-16:2010 Part 16: Toxicokinetic study design for degradation products and leachables (PN-EN ISO 10993-16:2010 Część 16: Projektowanie badań toksykokinetycznych produktów degradacji i substancji wymywalnych).
- EN ISO 10993-17:2009 Part 17: Establishment of allowable limits for leachable substances (PN-EN ISO 10993-17:2009 Część 17: Ustalenie dozwolonych granic dotyczących substancji wymywalnych).
- EN ISO 10993-18:2009 Part 18: Chemical characterization of materials (PN-EN ISO 10993-18:2009 Część 18: Charakterystyka chemiczna materiałów).
- ISO/TS 10993-19:2006 Part 19: Physico-chemical, morphological and topographical characterization of materials.
- ethods for immunotoxicology testing of medical devices.

3. Biocompatibility

Biocompatibility is a specific requirement for products used in healthcare. However, individual tests, which are essential to confirm the biocompatibility of the medical device may vary depending on the way of placing it within organism, duration of contact with a tissue and type of sterilisation.

When selecting the materials used to manufacture medical devices, the usefulness of a given material for a specified goal should be taken into consideration with regard to the characteristics and properties of this material, in particular involving the chemical, toxicological, physical, electrical, morphological and mechanical properties. In addition, other issues in the overall evaluation of the biological of a material and suitability for a given application should be considered.

Among these parameters, the attention should be directed to:

1) substrates used in the biomaterial manufacturing,
2) intended additives, process contaminants and residues from the manufacturing process,
3) leachable substances,
4) degradation products,
5) other components and their interactions in the final product,
6) properties and characteristics of the final product.

Medical devices are an unusual subject of research in the analysis of toxicity. Very often, the medical device is a complex unit and the potential toxicity of materials is associated with both physical and chemical properties. The knowledge of potential toxicity of materials is required, however the majority of classic toxicological tests were designed for pure chemical substances that is they may be inapplicable in case of biocompatibility tests for medical devices. Since the toxicological information for the substrates and their precise chemical composition is usually unavailable, the possible interaction between the components of the device in contact with the organism is poorly known.

Risks caused by toxicity of a substance being a part of medical device may emerge not until direct contact with a tissue of the patient. Therefore, the risk, which may posed by actual or potential adverse effects of the material, is a function of the possible toxicity of the organism and exposure time to it. The safety of each of leachable compounds contained in the medical device or on its surface shall be evaluated by: determination of the overall level of potentially harmful substances, estimation of the amount, which may come into contact with the issues of the patient, assessment of the exposure risk and performing analysis comparing the potential risks with the benefits for patient after approval of given medical device. After possible evaluation of potential adverse effects, which may occur in case of using a given biomaterial (based on biocompatibility tests), possible risk should be estimated in comparison with

other material and/or tests for evaluation of its safety and effectiveness.

4. General principles applying to biological evaluation of medical devices

The composition of the materials, character, degree, frequency and duration of contact of a device or its components should be taken into account in the tests for biological evaluation and during the interpretation of the results. Following these principles, medical devices are classified in order to facilitate the selection of relevant studies.

The range of potential biological hazards is wide and may include:

1) short-term effects (e.g. acute toxicity, irritation to the skin, eyes and mucosal surfaces, sensitisation, haemolysis and thrombogenicity);
2) long-term or specific toxic effects (e.g. subchronic and chronic toxic effects, sensitisation, genotoxicity, carcinogenicity and effects on reproduction).

All potential biological hazards should be considered for every material being a part of a medical device, and the same final product. It does not simultaneously imply, that conducting tests for all potential hazards will be necessary and practical.

The materials or final product shall be considered for biological re-evaluation if any of the following occurs:

1) any change in the source (e.g. change of supplier) or in the specification of the materials used in the manufacture of the product;
2) any change in the formulation, processing, primary packaging or sterilization of the product;
3) any change in the final product during storage;
4) any change in the intended use of the product;
5) any evidence that the product may produce adverse effects when used in humans.

Biological evaluation performed in accordance to ISO 10993 should be considered in conjunction with the nature and possible mobility of the ingredients used to manufacture the device and other available data such as results of preclinical and clinical studies, data obtained from users of similar products or biomaterials.

5. Classification of medical devices

Medical devices are subjected to classification according to the nature and duration of body contact. Some products may belong to more than one category, therefore the tests recommended for the relevant categories should be taken into consideration while planning biocompatibility tests. Tests of any individual product, which does not belong to any of the stipulated categories should be consistent with the general principles contained in relevant parts of ISO 10993. Therefore, medical devices are classified according to the following general principles, what facilitates the selection of research most relevant to the product:

5.1. Classification according to the type of contact

1) **Non-contact devices** – e.g. diagnostic apparatus *in vitro*, specialist computer software. They are not included in the scope of ISO 10993.

2) **Surface-contacting devices**. These include medical devices in contact with the following surfaces:

a) skin: devices that contact intact skin surfaces only; examples include electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types;

b) mucosal membranes: devices that contact intact mucosal membranes; examples include contact lenses, urinary catheters, intravaginal devices, devices used in gastroscopy and colonoscopy, endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices and intrauterine devices;

c) breached or compromised surfaces: devices that contact breached or otherwise compromised body surfaces aiming at healing the tissues – examples include examples include dressings, healing devices and occlusive patches for ulcers, burns, etc.

3) **External communicating devices** include medical devices in contact with the tissue, that can be classified further according to the following application or a location of a contact:

a) blood path, indirect: devices that contact the blood path at one point and serve as a conduit for entry into the vascular system; examples include solution administration sets,, transfusion sets and blood administration sets, etc.;

b) tissues / bones / dentin: devices coming into contact with these tissues, examples include laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials and skin staples;

c) circulating blood: devices that contact circulating blood; examples include. catheters, temporary pacemaker electrodes, oxygenators, dialysers, dialysis tubing and accessories, immunoadsorbents, etc.

4) **Implant devices** – medical devices in contact with a tissue in the following application sites:

a) tissue / bone: device mainly intended for contact with bone, examples include orthopedic devices, such as orthopaedic pins, plates,

replacement joints, bone prostheses, bone cements and intraosseous devices, etc.; devices mainly intended for contact with soft tissue and tissue fluid, examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, artificial larynxes, subperiostal implants and ligation clips, etc.;

b) **blood**: devices principally contacting blood; examples include pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices., etc.

5.2. Classification by the duration of contact.

Medical devices are subjected to classification according to the duration of contact of the devices with the organism as follows:

- limited exposure (A): devices whose single or multiple use or contact is likely to be up to 24 h;
- prolonged exposure (B): devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 days;
- permanent exposure (C): devices whose single, multiple or long-term use or contact exceeds 30 days.

If a material or device may be placed in more than one duration category, the more rigorous testing requirements shall apply. With multiple exposures to the device, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

6. Biocompatibility testing

In addition to general principles, the following rules should be applied to the testing of medical devices. Tests should be performed on the final product or representative samples from the final product or from materials processed in the same manner as the final product. The choice of test procedures shall take into account:

a) the nature, degree, duration, frequency and conditions of exposure to or contact of humans with the device in the normal intended use;
b) the chemical and physical nature of the final product;
c) the toxicological activity of the chemical elements or compounds in the formulation of the final product;
d) that certain tests (e.g. those designed to assess systemic effects) may not be applicable where the presence of leachable materials has been excluded, or where leachables have a known and acceptable toxicity profile;
e) the relationship of device surface area to recipient body size;
f) the existing information based on the literature, data from preclinical studies and experience in the use of similar products;

The protection of humans is the primary goal of this procedure, a secondary goal being to ensure animal welfare and to minimize the number and exposure of test animals.

It should be noted that despite the favourable results of in vitro and in vivo there may still a risk of adverse effects on the body of the product. Therefore, patients being in the next stage i.e. clinical trials should be thoroughly observed.

The basic rule known and used during the biomaterials testing is the principle that biocompatibility cannot be determined by one type of test. It is highly unlikely that only one parameter could affect and determine the biocompatibility of the device. Therefore, it is necessary to analyze many parameters of biocompatibility. ISO10993-1 standard specifies the type of test that should be considered to have the best knowledge of the biocompatibility of the tested product.

Tests in specific categories proposed in the standards are presented in Table 1 and Table 2.

6.1. Initial evaluation tests

6.1.1. Cytotoxicity

Cytotoxicity tests are described in ISO 10993-5. With the use of cell culture techniques, these tests determine the lysis of cells (cell death), the inhibition of cell growth and other effects on cells caused by medical devices, materials and/or their extracts.

6.1.2. Sensitization

Tests that examine the sensitization are described in ISO10993-10. They are performed on the animal or human model and enable the evaluation of the capacity of medical devices, materials and/or their extracts to induce allergies. These tests are particularly important, because exposure or contact to even minute amounts of potential leachables can result in allergic or sensitization reactions.

6.1.3. Irritation

Specific tests that can be used to satisfy these requirements are provided in ISO 10993-10. They determine the likelihood of a material, device, or their extract to cause irritation in sites vulnerable

to irritations by a given device such as skin, eyes and mucosal membrane. These tests should be performed on a suitable animal or human model. Tested factor should be in contact with the corresponding tissue or tissue fluids (skin, eyes, mucosal membranes) for an appropriate time to determine the irritancy of the tested device or material and the potential leachables.

6.1.4. Intracutaneous reactivity

Specific tests that can be used to satisfy these requirements are provided in ISO 10993-10. They evaluate the reaction of tissue to medical device extracts. These tests are applicable where determination of irritation by dermal or mucosal tests are inappropriate for the use of the device (e.g. medical devices having access to the blood path).

6.1.5. Systemic toxicity – acute toxicity

These tests 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. These tests are appropriate where contact allows potential absorption of toxic leachables and degradation products.

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.

6.1.6. Subacute and subchronic toxicity

Performing tests of subacute and subchronic toxicity shall be planned on the basis of ISO 10993-11. These tests determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts, adverse effects of constant or multiple exposure may occur as a result of accumulation of chemical substances in the tissues or as a result of other mechanisms, which should be determined by performing long-term testing (subacute, subchronic and chronic). Tests of systemic toxicity conducted with multiple exposure method provide detailed information about the toxic effects, target organs, the reversibility of these effects and may serve as a basis for safety assessment.

6.1.7. Genotoxicity

Genotoxicity testing is described in ISO10993-3. These tests use mammalian or non-mammalian cell culture such as bacteria, yeast, fungi in order 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.

6.1.8. Implantation

The intent of implantation tests described in ISO 10993-6 is 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 in a tissue appropriate to the intended application (e.g., dental examinations). If the effects on the whole organism are determined, these tests are equal to subchronic systemic toxicity testing. Therefore, implantation test protocols may be expanded to include systemic toxicity tests, subacute and subchronic toxicity tests, and chronic toxicity tests.

6.1.9. Haemocompatibility

Specific tests that can be used to satisfy these requirements are provided in ISO 10993-4. These tests are designed for evaluation of the effect of the exposure of medical devices indented for contact with blood or its components. Specific haemocompatibility tests may also be designed to simulate the geometry, contact conditions and flow dynamics of the device or material during clinical applications.

6.2. Supplementary evaluation tests

6.2.1. Chronic toxicity

Chronic toxicity tests are described in ISO 10993-11. These tests determine the effects of either single or multiple exposures to medical devices, materials and/or their extracts during the major portion of life-span. Chronic toxicity tests usually lasts from 6 to 12 months.

6.2.2. Carcinogenicity

Carcinogenicity tests are described in ISO 10993-3. These tests determine the tumorigenic potential of medical devices, materials and/or their extracts from either single or multiple exposures or contacts during the major portion of the life-span of the test animal. These tests may be designed in order to examine both chronic toxicity and carcinogenicity in a single experimental study. Carcinogenicity tests should be conducted only if there are suggestive data from other sources.

6.2.3. Reproductive and developmental toxicity

Reproductive and developmental toxicity tests are described in ISO 10993-3. These tests evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embry-

Table 1: Initial tests used in biocompatibility evaluation of medical devices according to category of the device, the nature and duration of body contact (in accordance with EN ISO10993-1).

Medical device categorization by			**Biological effect**							
Category of the device	Nature of body contact	Contact duration: **A** – Limited (< 24 h) **B** – prolonged (24 h to 30 days) **C** – permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemictoxicity (acute)	Subacute and subchronictoxicity	Genotoxicity	Implantation	Haemocompatibility
Surface devices	Skin	A	X	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 body surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X	X	X
	Tissues, bones, dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	X
		C	X	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
Implants	Tissues, bones	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

onic development (teratogenicity), and prenatal and early postnatal development. Reproductive/ developmental toxicity tests or bioassays should only be conducted when the device has potential impact on the reproductive potential of the subject. The application site of the device should be considered.

6.2.4. Biodegradation

Biodegradation tests are described in ISO 10993-9. These testsare particularlyrecommended whenthere is anylikelihood ofresorptionand/ordegradation ofthe materialsincluded in themedical device.Corresponding tests may determine the processes of absorption, distribution, biotransformation and elimi-

Table 2: Supplementary tests used for biological evaluation of medical devices according to category of the device, the nature and duration of body contact (in accordance with EN ISO10993-1)

Medical device categorization by			**Biological effect**			
Category of the device	Nature of body contact	Contact duration: **A** – limited (< 24 h) **B** – prolonged (24 h to 30 days) **C** – permanent (> 30 days)	Chronic toxicity	Carcinogenicity	Reproductive/ Developmental toxicity	Biodegradation
Surface devices	Skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C				
	Breached body surface	A				
		B				
		C				
External communicating device	Blood path	A				
		B				
		C	X	X		
	Tissues, bones, dentin	A				
		B				
		C	X	X		
	Circulating blood	A				
		B				
		C	X	X		
Implants	Tissues, bones	A				
		B				
		C	X	X		
	Blood	A				
		B				
		C	X	X		

nation of leachables and degradation products. In particular, these studies carried outforbiodegradable or bioresorbable polymers

6.2.5. Pharmacokinetics

Pharmacokinetic studies determine metabolic processes of absorption, distribution, biotransformation and elimination of leachables and degradation products of the materials or their extracts.

The evaluation of biocompatibility shall include a study of relevant experience and actual testing. The assessment of available information concerning tested material or device may result in the conclusion that no testing is needed if the material has a

demonstrable history of use in a specified role that is equivalent to that of the device under design. Due to the diversity of medical devices, it is recognized that not all tests identified in a category will be necessary for a given device.
The test methods used in the biological evaluation shall be sensitive, precise and accurate. The test results should be reproducible (interlaboratory) as well as repeatable (intralaboratory).

Currently, biological testing relies on animal models. However, as scientific knowledge advances our understanding of basic mechanisms, preference should be given to in vitro models in situations where properly-validated andgive equivalent results with in vivostudies. EU directive 86/609/ECC states that, no animal testing shall be conducted, if another scientifi-callysatisfactory methodfor obtaining the results is rational and available. Obviously, it should be noted that in vitro testing differ from animal testing. It is only a model restricted for testing specific types of cells such as e.g. cytotoxicity tested on a cell culture, which is a screening assay of toxicity evaluation.

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