TECHNICAL REPORT

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Biological evaluation of medical devices — Guidance on the conduct of biological evaluation within a risk management process

Évaluation biologique des dispositifs médicaux — Directives relatives à la conduite d'une évaluation biologique au sein d'un procédé de management du risque

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In exceptional circumstances, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example), it may decide by a simple majority vote of its participating members to publish a Technical Report. A Technical Report is entirely informative in nature and does not have to be reviewed until the data it provides are considered to be no longer valid or useful.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TR 15499 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

Introduction

0.1 General

This Technical Report provides guidance on conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1. Although ISO 10993-1 provides a general framework for biological evaluation of medical devices, more detailed guidance can be helpful in the practical application of the standard. As a result, this Technical Report was developed to provide such guidance to users of ISO 10993-1. This guidance can be used to better understand the requirements of ISO 10993-1 and to illustrate some of the variety of methods and approaches available for meeting the requirements of ISO 10993-1.

Biological evaluation is a design verification activity which is set in the context of broader risk management processes. Therefore this Technical Report includes guidance on the application of ISO 10993-1 in the context of risk management processes conducted according to the requirements of ISO 14971. This Technical Report describes concepts and methods that can be considered in establishing and maintaining a risk management process for biological evaluation as part of the overall evaluation and development of a medical device.

As scientific knowledge advances our understanding of the basic mechanisms of tissue responses, biological evaluation may be based upon review of relevant established scientific data and upon chemical analysis and *in vitro* and *in vivo* testing where these are required. ISO 10993-1 specifies a framework in which to plan a biological evaluation which minimizes the number and exposure of test animals by giving preference to chemical constituent testing and *in vitro* models in situations where these methods yield equally relevant information to that obtained from *in vivo* models. The selection of which approach(es) are applicable to a particular medical device will depend on the nature of the device, the extent of available relevant scientific data and upon risk assessment.

When judging the applicability of the guidance in this Technical Report, applicable regulatory requirements and regulatory guidance should be considered.

An organization can voluntarily incorporate guidance from this Technical Report, wholly or in part, into its risk management process.

Guidance contained in this Technical Report can be useful as background information for those representing risk management process assessors, conformity assessment bodies and regulatory enforcement bodies.

0.2 Relationship with other standards, guidance documents and regulatory requirements

The relationship between ISO 10993-1, this Technical Report and the standards for biological evaluation of medical devices and general risk management is summarized as follows:

— this Technical Report provides guidance on the application of ISO 10993-1;

— biological evaluation is a component of risk management and this Technical Report includes guidance on the application of ISO 14971 to the conduct of biological evaluation.

Biological evaluation of medical devices — Guidance on the conduct of biological evaluation within a risk management process

1 Scope

This Technical Report is applicable to the conduct of biological evaluation of medical devices according to the requirements of ISO 10993-1. It does not add to, or otherwise change, the requirements of ISO 10993-1. This Technical Report does not include requirements to be used as the basis of regulatory inspection or certification assessment activities.

This guidance is applicable to all biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

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 10993-1:2009, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1 and the following apply.

3.1
biocompatibility
ability of a material to perform with an appropriate host response in a specific application

3.2
biological risk
potential for a substance to cause harm to health by virtue of its toxicity

3.3
biological safety
freedom from unacceptable biological risk

3.4
risk assessment
overall process comprising a risk analysis and a risk evaluation

[SOURCE: ISO/IEC Guide 51:1999, 3.12]

3.5
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO 14971:2007, 2.21]

3.6
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO 14971:2007, 2.22]

3.7
toxicological hazard
potential for a compound or material to cause an adverse biological reaction, taking into account the nature of the reaction and the dose required to elicit it

3.8
toxicological risk
probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure

3.9
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO 14971:2007, 2.17, modified]

4 Biological evaluation as a risk management practice

4.1 General

ISO 10993-1:2009, B.2.2.2 describes a continuous process by which a manufacturer can identify the biological hazards associated with medical devices, estimate and evaluate the risks, control these risks, and monitor the effectiveness of the control. Appropriate protection of the patient by weighing risks and benefits of medical devices is an essential element of this biological evaluation plan. Benefit to the patient from the use of medical devices entails the acceptance of potential risks. These risks will vary depending on the nature and intended use of the specific medical device. The level of risk which is acceptable for a specific device will depend upon the expected benefit provided by its use.

Consideration of biological (toxicological) risk is only one aspect of the risk assessment of a medical device, which should consider all aspects of risk. In some cases it can be specifically necessary to consider the relative benefits of materials of different biological safety profiles in the context of some other characteristic. For example it can be possible that the most biologically safe material available can have unacceptable mechanical strength, in which case it would be necessary to consider if an alternate stronger material is of *acceptable* biological safety. It is fundamental to the conduct of biological evaluation that it be undertaken as part of the overall risk management process required in the design and development of the medical device.

Material selection and risk analysis are integral components of the design process for medical devices. The selection of materials plays a crucial role in evaluating the biological safety and, when approached in a systematic way, allows the collection of relevant data. In line with ISO 9001 and ISO 14971, criteria to define the acceptable biological (toxicological) risk should be established at the start of the design process. Because starting material, formulation and processing variations could impact final product biocompatibility, these considerations should also be incorporated into the risk assessment. The biological safety evaluation should be designed and performed to demonstrate the achievement of specified criteria for safety. This evaluation is a component of the risk management plan encompassing identification of all hazards and the estimation of associated risks. Adequate risk assessment requires characterization of toxicological hazards and exposures.

A major component in hazard identification is material characterization. The following steps can be identified:

— define and characterize each material, including suitable alternative materials;

— identify hazards in materials, additives, processing aids, etc.;

— identify the potential effect of downstream processing (e.g. chemical interactions between material components, or final product sterilization) on chemicals present in final product;

— identify the chemicals that could be released during product use (e.g. intermediate or final degradation products from a degradable implant);

— estimate exposure (total or clinically available amounts);

— review toxicology and other biological safety data (published/available).

Information on biological safety to be reviewed can include:

— toxicology data on relevant component materials/compounds;

— information on prior use of relevant component materials/compounds;

— data from biological safety tests.

The risks posed by the identified hazards should then be evaluated. At this stage it should be possible to determine whether there is an undue toxicological risk from the material.

If it can be concluded from existing data that risks are acceptable then no additional toxicity testing is needed. Testing is also unwarranted if risks are found to be unacceptable. When existing data are insufficient, additional information should be obtained. The purpose of testing is to obtain additional data which can assist in reaching a conclusion. A rationale for testing should therefore be based on an analysis of the relevant risks which are indicated from the existing data.

The results of any tests should be assessed. Test reports should include descriptive evidence, an assessment of the findings and qualitative assessment of their acceptability.

The assessor 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 including the rationale for any decisions and the impact of test results and other information on the assessment.

The evaluation indicates the identity and significance of all relevant evidence and highlights the scientific basis of the overall conclusions in an accurate, clear and transparent manner. It is very important that the factors leading to the conclusion are fully discussed with succinct and accurate rationales for each judgment and identification and discussion of any uncertainties underlying each decision.

The components of risk management are summarized in Figure 1 (taken from ISO 14971). The different elements of a biological evaluation process can be considered in terms of the elements of the overall risk management process.

In summary, biological evaluation should be seen as an element of risk management practice and therefore the conduct of a biological evaluation of a medical device should aim to meet both the requirements of ISO 10993-1 and ISO 14971.

4.2 The biological evaluation plan

Subclause 3.4 of ISO 14971:2007 requires that risk management activities be planned in advance. Since biological evaluation is a risk management activity, a Biological Evaluation Plan is required, and this forms part of the Risk Management Plan. It is emphasized that simply planning to conduct testing against all of the aspects of toxicology identified in Table A.1 of ISO 10993-1:2009 does not meet the requirements of ISO 14971 or ISO 10993-1. The biological evaluation plan should be drawn up by a knowledgeable and experienced team and include as a minimum:

— arrangements for gathering of applicable information from the published literature (including information sources and search strategies), in house and supplier data and other sources in order to conduct risk analysis;

— arrangements for conducting the evaluation, including the requirement for any specific technical competencies relevant to the specific device application;

— arrangements for review and approval of the plan as part of the overall design control process;

— arrangements for review of the final conclusions of the evaluation and the approval of any additional testing programme required;

— arrangements for the final review and approval of the outcomes of the biological risk assessment, including the risk control measures applied and the documentation of any residual risks and the disclosure of residual risks through means such as product labelling.

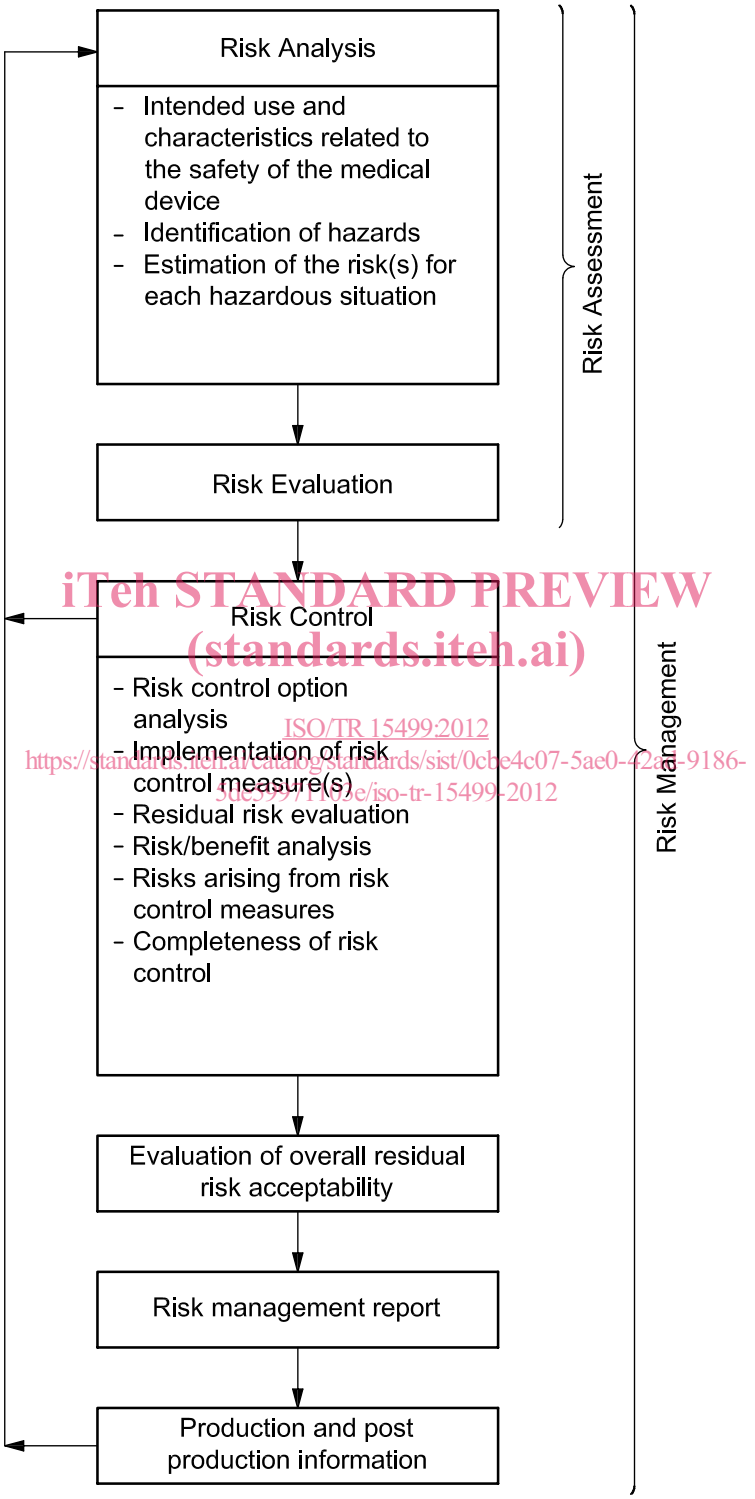

Figure 1 — A schematic representation of the risk management process (from ISO 14971)

5 Guidance on risk management

5.1 Risk assessment

5.1.1 Introduction

Risk assessment is the combination of the processes of risk analysis in which risks are identified and estimated and risk evaluation in which risks are evaluated to identify those which require mitigation (risk control).

5.1.2 Risk analysis

Risk analysis is the process of identifying the specific hazards and assessing their significance. In a biological evaluation this equates to consideration of the potential toxicity of materials components and their route of exposure. Risk analysis should be methodically conducted by means of estimation of risks from each material/component for each route of exposure and toxicological effect.

Risk analysis therefore begins with identification and characterization of the indirect and direct patient-contacting materials and components of the device. This should be done based on the final form of the device in its manufactured state, taking into account the presence of any manufacturing additives, processing aids or other potential contaminants such as sterilant residues. Effects of processing on materials composition and chemistry (including both bulk and surface effects) should also be considered. In particular, where reactive or hazardous ingredients have been used in, or can be formed by, the production, processing, storage or degradation of a material, the possibility of the presence of toxic residues should be considered. The potential for interactions with or introduction of contaminants from packaging materials should also be considered.

Physical and chemical material properties are relevant to biological safety and will need to be identified at this stage. These can include one or more of the following:

— wear, load, fatigue, e.g. especially in load bearing devices such as total joint prostheses and the associated production of particulates or materials degradation;

— friction and associated irritation, e.g. in applications such as catheters;

— interactions between material combinations (chemical interactions), e.g. different flexibility, galvanic corrosion, abrasion;

— heat (e.g. thermal degradation or other thermally induced material changes);

— manufacturing processes, e.g. internal stresses produced can promote environmental stress cracking (ESC), morphological changes, or degradation);

— environmental interactions, e.g. endoscope (stomach acids), dressings (external environment), UV-light, detergents, decontamination and sterilization processes;

— electricity, e.g. short circuits, degradation, heating, muscle stimulation;

— potential interactions between components;

— effect of physical form, e.g. particulates.

Materials information can be obtained through review of literature, vendor data, in house data or comparison with existing products on the market where the manufacturing processes and formulations are known and the same as in the device under evaluation.

NOTE 1 Annex C of ISO 10993-1:2009 provides guidance on conduct of literature review.

This initial characterization is then followed by consideration of the toxicology of the known material components. This specific nature of the toxic effect(s) and the dose-response relationship should be considered.