TECHNICAL SPECIFICATION

ISO/TS 20993

First edition
2006-08-01

Biological evaluation of medical devices — Guidance on a risk-management process

Évaluation biologique des dispositifs médicaux — Directives relatives à un processus d'évaluation du risque

Reference number
ISO/TS 20993:2006(E)

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Published in Switzerland

Foreword

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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 other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of normative document:

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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/TS 20993 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

Introduction

Risk management challenges the manufacturer to evaluate known and theoretical biological risks of the product, to develop the most appropriate methods for reducing the biological risks and to implement the appropriate test and analysis methods to demonstrate that the risks have been reduced. Material selection and evaluation of biological risk are integral components of the concept development and design processes for medical devices. This evaluation should be executed in line with the ISO 10993 series as a component of the risk management plan required in ISO 14971. This process encompasses identification of device and material hazards and the estimation and control of their associated risks.

Biological evaluation of medical devices — Guidance on a risk-management process

1 Scope

This Technical Specification describes a 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.

2 Risk management process

The evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. Information from various sources can be used in the performance of a biological risk assessment to identify areas of concern to be addressed by, in order of priority: literature review, clinical experience or testing. The risks posed by the identified biological hazards shall be evaluated. Testing strategy shall include a rationale for the selection and/or the waiving of tests. The rationale should be a clear, concise, logical and scientifically reasoned plan for evaluating biological safety, which demonstrates that biological hazards have been considered and relevant risks assessed and controlled.

Based on the risk management process described in ISO 14971, the biological evaluation of medical devices and their materials comprises the following elements.

a) Risk analysis:

   1) intended use/device characteristics;

   2) defining each material/device and its use;

   3) physically and chemically characterizing each material/device.

b) Biological hazard identification:

   1) identifying hazards in the materials, additives, processing aids, and potential other leachables;

   2) characterization of chemically-mediated hazards:

      i) review toxicology and other biological safety data;

      ii) toxicology data on component materials;

      iii) dose-response relationship;

      iv) nature of toxicity.

   3) characterization of non-chemically-mediated hazards.

c) Exposure assessment:

1) rate and pattern of leachable substance release;

2) physical form;

3) estimate patient exposure (total or clinically available amounts).

d) Risk estimation:

1) information on prior use of materials, additives, processing aids and other potential leachables;

2) data from biological evaluation;

3) data from clinical tests and clinical experience;

4) risk estimate from hazard identification and exposure assessment.

e) Risk evaluation:

1) evaluating the estimated risk against the acceptability criteria (predetermined in the risk management plan given in ISO 14971);

2) determining if risk control is necessary.

f) Risk control:

1) risk reduction;

2) option analysis including feasibility;

3) implementation of risk control measures;

4) residual risk evaluation and communication;

5) benefit assessment;

6) risk/benefit analysis;

7) other generated hazards — hazards generated by the control measures;

8) completeness of the risk control.

g) Overall residual risk evaluation:

1) evaluating the overall residual risk against the acceptability criteria (predetermined in the risk management plan given in ISO 14971);

2) overall risk acceptance.

h) Overall benefit evaluation:

1) benefit assessment.

i) Overall risk/benefit analysis;

j) Biological evaluation report;

k) Post-production information — post-production experience; review of risk management experience.

3 Testing and test reports

Following the logic of ISO 14971, if the evaluation of the biological risks concludes from the existing data that the identified risks are acceptable, no further testing is needed. Otherwise, additional information shall be obtained. Testing shall only be undertaken if the additional tests are judged likely to assist in reaching a conclusion, i.e. the rationale for testing shall be based on an analysis of the relevant risks from the existing data.

Test reports shall include descriptive evidence, an assessment of the findings, and a qualitative assessment of their acceptability.

4 Biological evaluation report

A full discussion of the factors leading to the conclusion with succinct and accurate rationales for each judgement and explanations for any uncertainties underlying each decision is essential and shall be provided. Expert assessors shall 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 shall:

— 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 shall be approved by the personnel assigned this responsibility and authority.

5 Conclusion

The use of the ISO 10993 series of tests (see Bibliography), 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.

Bibliography

[1] ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

[2] ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

[3] ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

[4] ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

[5] ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for* in vitro *cytotoxicity*

[6] ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

[7] ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

[8] ISO 10993-8, *Biological evaluation of medical devices — Part 8: Selection and qualification of reference materials for biological tests*

[9] ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

[10] ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and delayed-type hypersensitivity*

[11] ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

[12] ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

[13] ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

[14] ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

[15] ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

[16] ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

[17] ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

[18] ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

[19] ISO/TS 10993-19, *Biological evaluation of medical devices — Part 19: Physico-chemical, morphological and topographical characterization of materials*

[20] ISO/TS 10993-20, *Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices*

[21] ISO 14971:2000, *Medical devices — Application of risk management to medical devices*