

American National Standard

ANSI/AAMI BE78:2002/(R)2008

Biological evaluation of medical devices— Part 10: Tests for irritation and delayed-type hypersensitivity



The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the Manager for Technical Development. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News*. The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News*.

American National Standard

ANSI/AAMI BE78:2002/(R)2008
(Revision of ANSI/AAMI/ISO 10993-10:1995)

Biological evaluation of medical devices—Part 10: Tests for irritation and delayed-type hypersensitivity

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Association for the Advancement of Medical Instrumentation

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American National Standards Institute, Inc.

Abstract: This standard describes the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation and delayed-type hypersensitivity.

Keywords: biological evaluation, hypersensitivity, irritation, medical devices

AAMI Standard

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Glossary of equivalent standards

International Standards adopted in the United States may include normative references to other International Standards. For each International Standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the International Standard.

NOTE—Documents are sorted by international designation.

Other normatively referenced International Standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996/(R)2002	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:2002	ANSI/AAMI/ISO 10993-4:2002	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:1996	ANSI/AAMI/ISO/CEN 10993-12:1996	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997	Identical
ISO 10993-17:2002	ANSI/AAMI/ISO 10993-17:2002	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995 and Amdt 1:2001	ANSI/AAMI/ISO 11137:1994 and A1:2002	Identical

International designation	U.S. designation	Equivalency
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2002	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155:1996	ANSI/AAMI/ISO 14155:1996	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 10993-10:2002 (with a minor national deviation) as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Irritation and Sensitization Working Group (U.S. Sub-TAG for ISO/TC 194/WG 8), cochaired by Paul Upman of NAmSA and Katharine Merritt of the U.S. Food and Drug Administration/Center for Devices and Radiological Health, played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Biological Evaluation Committee** had the following members:

<i>Cochairs:</i>	Donald F. Gibbons, PhD Donald E. Marlowe
<i>Members:</i>	James M. Anderson, MD, PhD, Case Western Reserve University Sumner A. Barenberg, PhD, Bernard Technologies Eric R. Claussen, PhD, Becton Dickinson Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc. Donald F. Gibbons, PhD, 3M Lawrence H. Hecker, PhD, Abbott Laboratories Donald E. Marlowe, U.S. Food and Drug Administration/Center for Devices and Radiological Health Edward Mueller, Annapolis, MD Barry F. Page, Garner, NC Melvin E. Stratmeyer, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/OST Paul Upman, NAmSA
<i>Alternates:</i>	Raju G. Kammula, DVM, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health/ODE Sharon Northrup, PhD, U.S. Pharmacopeial Convention, Inc.

At the time this document was published, the **AAMI Irritation and Sensitization Working Group** had the following members:

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<i>Members:</i>	William C. Bradbury, PhD, Viromed Biosafety Laboratories Lee Ellis, Boston Scientific Corp. Mitchell B. Friedman, PhD, Abbott Laboratories Gloria Frost, PhD, Allegiance Healthcare Corporation Anita Kore, DVM, PhD, 3M Healthcare Howard Maibach, MD, University of California, San Francisco Katharine Merritt, PhD, U.S. Food and Drug Administration/Center for Devices and Radiological Health Anita Sawyer, Becton Dickinson Jeff Sturm, St. Jude Medical Inc. Paul J. Upman, PhD, NAmSA Randy White, PhD, Baxter Healthcare Corporation
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NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 10993-10:2002 and rationale for minor technical deviation

As indicated in the foreword to the main body of this document (page ix), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

International Standard ISO 10993-10 was developed by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, to provide guidance on the assessment of medical devices and their constituent materials with regard to their potential to produce irritation and delayed-type hypersensitivity.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation on behalf of the American National Standards Institute. The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of biological evaluation of medical devices as much as possible in order to help reduce unnecessary repetition of testing.

Upon review of ISO 10993-10, the AAMI Biological Evaluation Committee and AAMI Irritation and Sensitization Working Group decided to adopt ISO 10993-10:2002 with a minor technical deviation as a revision of ANSI/AAMI/ISO 10993-10:1995. The rationale for the deviation was to restore the text to its original text as voted on by the U.S. committee. A substantive change was introduced to ISO 10993-10:2002 that should not have been, and ANSI/AAMI BE78:2002 restores the original text (see below).

One major change to the previous edition was made. Annex B describes the very important intracutaneous reactivity test. Historically, this was in the normative section and it is now informative.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of equivalent standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and level of equivalency with the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page ix, this American National Standard is identical to ISO 10993-10:2002 with the exception of the national deviation to subclause 7.5.4.3.1 (see below).

ANSI/AAMI deviation from ISO 10993-10:2002

Subclause 7.5.4.3.1 Induction phase

The third sentence has been changed from “Repeat this procedure three times a week for three weeks” to “Repeat this procedure **one to** three times a week for three weeks.”

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 3.

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.

Attention is drawn to the possibility that some of the elements of this part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-10 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-10:1995), which has been technically revised.

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

- *Part 1: Evaluation and testing*
- *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 8: Selection and qualification of reference materials for biological tests*
- *Part 9: Framework for the identification and quantification of potential degradation products*
- *Part 10: Tests for irritation and delayed-type hypersensitivity*
- *Part 11: Tests for systemic toxicity*
- *Part 12: Sample preparation and reference materials*
- *Part 13: Identification and quantification of degradation products from polymeric medical devices*
- *Part 14: Identification and quantification of degradation products from ceramics*
- *Part 15: Identification and quantification of degradation products from metals and 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*

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

This part of ISO 10993 is a harmonization of numerous standards and guidelines, including BS 5736, OECD Guidelines, U.S. Pharmacopoeia, and the European Pharmacopoeia. It is intended to be the basic document for the selection and conduct of tests enabling evaluation of irritation and dermal sensitization responses relevant to safety of medical materials and devices.

Annex A forms a normative part of this part of ISO 10993. Annexes B and C are for information only.

Introduction

This part of ISO 10993 assesses possible contact hazards from chemicals released from medical devices that may produce skin and mucosal irritation, eye irritation, and delayed contact hypersensitivity.

Some materials that are included in medical devices have been tested, and their skin or mucosal irritation or sensitization potential has been documented. Other materials and their chemical components have not been tested and may induce adverse effects when in contact with biological tissues. The manufacturer is thus obliged to evaluate each device for potential adverse effects prior to marketing.

Traditionally, small animal tests are performed prior to testing on humans to help predict human response. More recently, *in vitro* tests and human tests have been added as alternatives. Despite progress and considerable effort in this direction, a review of findings suggests that currently no satisfactory *in vitro* test has been devised to eliminate the requirement for *in vivo* testing. Where appropriate, the preliminary use of *in vitro* methods is encouraged for screening purposes prior to animal testing. In order to reduce the number of animals used, this part of ISO 10993 presents a step-wise approach, with review and analysis of test results at each stage. An animal test is usually required prior to human testing.

It is intended that these studies be conducted using Good Laboratory Practice and comply with regulations related to animal welfare. Statistical analysis of data is recommended and should be used whenever appropriate.

The tests included in this part of ISO 10993 are important tools for development of safe products, provided that these are executed and interpreted by trained personnel.

Biological evaluation of medical devices—Part 10: Tests for irritation and delayed-type hypersensitivity

1 Scope

This part of ISO 10993 describes the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation and delayed-type hypersensitivity.

This part of ISO 10993 includes

- a) pretest considerations,
- b) details of the test procedures, and
- c) key factors for the interpretation of the results.

Instructions are given in annex A for the preparation of materials specifically in relation to the above tests.

Supplementary tests which are required specifically for devices used intradermally in the ocular, oral, rectal, penile, and vaginal areas are given in annex B.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 10993-1:1997, *Biological evaluation of medical devices—Part 1: Evaluation and testing*.

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

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

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

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

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

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

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

ISO 14155-1, *Clinical investigation of medical devices for human subjects—Part 1: General requirements*.

ISO 14155-2, *Clinical investigation of medical devices for human subjects—Part 2: Clinical investigation plans*.

3 Terms and definitions

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

3.1 allergen (sensitizer): Substance/material which is capable of inducing specific hypersensitivity such that, on subsequent exposure to the same substance/material characteristic, allergic effects are produced.

3.2 blank liquid: Solvent portion treated in the same manner as the identical solvent used for the preparation of test samples but without test material, and which is intended for the determination of a background response of the solvent.

3.3 challenge, elicitation: Process following the induction phase in which the immunological effects of subsequent exposures in an individual to the inducing material are examined.

3.4 corrosion: Slow destruction of the texture or material of a tissue.

NOTE—The action of a strong irritant.

3.5 delayed-type hypersensitization: Induction of specific T-cell mediated immunological memory for an allergen to which an individual is exposed, resulting in a delayed-type hypersensitivity reaction after secondary contact with the allergen.

3.6 dose: Quantity to be administered to the test system at one time.

3.7 edema: Swelling due to abnormal infiltration of fluid into the tissues.

3.8 erythema: Reddening of the skin or mucous membrane.

3.9 eschar: Scab or discolored slough of skin.

3.10 induction: Process that leads to the *de novo* generation of an altered state of immunological reactivity in an individual to a specific material.

3.11 irritant: Agent that produces irritation.

3.12 irritation: Localized non-specific inflammatory response to single, repeated, or continuous application of a substance/material.

3.13 necrosis: Death of one or more cells, or portion of tissue or organ, resulting in irreversible damage.

3.14 negative control: Material or substance which, when tested by the procedure described, demonstrates the suitability of the procedure to yield a reproducible, appropriate negative, nonreactive, or background response in the test system.

3.15 positive control: Material or substance which, when tested by the procedure described, demonstrates the suitability of the procedure to yield a reproducible, appropriate positive, or reactive response in the test system.

3.16 solvent: Material or substance used to moisten, dilute, suspend, extract, or dissolve the test substance material. Examples: Chemical, vehicle, medium, etc.

3.17 test material: Material, device, device portion, or component thereof that is sampled for biological or chemical testing.

3.18 test sample: Extract or portion of the test material that is subjected to biological or chemical testing.

3.19 ulceration: Open sore representing loss of superficial tissue.

4 General principles—Step-wise approach

The available methods for testing irritation and sensitization were developed specifically to detect skin irritation and sensitization potential. Other types of adverse affects are generally not predicted by these tests.

This part of ISO 10993 requires a step-wise approach, which shall include one or more of the following:

- a) characterization of test material, involving chemical characterization and analysis of the test sample according to the general principles described in ISO 10993-9, ISO 10993-13, ISO 10993-14, ISO 10993-15, and ISO 10993-18;
- b) literature review, including an evaluation of chemical and physical properties, and information on the irritation and sensitization potential of any product constituent as well as structurally related chemicals and materials;
- c) consideration of *in vitro* tests in preference to *in vivo* tests, and replacement of the latter as new *in vitro* methods become available and validated; at the present time, there are no validated *in vitro* tests (other than simple screens) to detect irritants or sensitizers;

- d) *in vivo* animal tests;

NOTE—Acute *in vivo* animal studies are undertaken to test for materials not already classified as severe irritants or strong sensitizers by step a) or b). Materials that do not demonstrate an acute dermal irritation at single exposure may then be further evaluated following repeated exposure.

A test of a positive-control substance for skin sensitization [7] shall be run at least every six months by the testing laboratory to validate the test system and demonstrate a positive response.

- e) non-invasive human tests/clinical trials.

If the material has been demonstrated not to be an irritant, a sensitizer, or toxic in animals, studies on skin irritation may then be considered in humans.

5 Pretest considerations

5.1 General

It is important to emphasize that pretest considerations may result in the conclusion that testing for irritation and/or sensitization is not necessary.

The requirements given in clause 5 of ISO 10993-1:1997 and the subclauses below apply.

5.2 Types of material

5.2.1 Initial considerations

It shall be taken into consideration that, during manufacture and assembly of medical devices, additional chemical components may be used as processing aids, e.g., lubricants or mold-release agents. In addition to the chemical components of the starting material and manufacturing process aids, adhesive/solvent residues from assembly and also sterilant residues or reaction products resulting from the sterilization process may be present in a finished product. Whether these compounds pose a health hazard/risk depends on the leakage or degradation characteristics of the finished products.

5.2.2 Ceramics, metals, and alloys

These materials are normally less complex than polymers and biologically derived materials in terms of the number of chemical constituents.

5.2.3 Polymers

These materials are normally chemically more complex than those in 5.2.2 in terms of composition. A number of additives may be present and the completeness of polymerization may vary.

5.2.4 Biologically derived materials

These materials are inherently complex in their composition. They often also contain process residues, e.g., cross-linkers and anti-microbial agents. Biological materials may not be consistent from sample to sample.

The methods in this part of ISO 10993 have not been designed for testing of biologically derived materials and may therefore be less adequate. For example, the tests in this part of ISO 10993 do not consider cross-species sensitization.

5.3 Information on chemical composition

5.3.1 General

Full qualitative data on the chemical constituents of the material shall be established. Where relevant to biological safety, quantitative data shall also be obtained. If quantitative data is not obtained, the rationale shall be documented and justified.

5.3.2 Existing data sources

Qualitative and quantitative information on the composition shall be obtained where possible from the supplier of the starting material.

For polymers, this often requires access to proprietary information; provision should be made for the transfer and use of such confidential information.

Qualitative information about any additional processing additives (for example, mold-release agents) shall also be obtained from appropriate members of the manufacturing chain, including converters and component manufacturers.

In the absence of any data on composition, a literature study to establish the likely nature of the starting material and any additives is recommended to assist in the selection of the most appropriate methods of analysis for the material concerned.

NOTE—The composition of ceramics, metals, and alloys may be in accordance with ISO or American Society of Testing Materials (ASTM) standards and/or may be specified by the user. However, in order to obtain full qualitative and quantitative details on composition, it may be necessary to request these from the supplier or manufacturer of the starting material and also from component manufacturers to ensure that processing aids are also identified. Material master files held by regulatory authorities are another source of data, where they are accessible.

5.4 Material characterization

When details of composition are unavailable, or only qualitative information is available, or new or unknown substances may be expected to develop during the manufacturing process, it may be necessary to undertake analysis of a material.

Analytical methods appropriate for the material under investigation shall be used. All analytical techniques shall be justified, validated, and reported and, if not already known, the pH of the material (chemical solutions) shall be measured prior to any *in vivo* or *in vitro* testing when possible. Chemical analysis (qualitative as well as quantitative) of extracts may give useful information. In this context, it should also be emphasized that chemical analysis of the extract may give results that make testing for irritation and sensitization unnecessary, as information on irritation and sensitization potential of the compounds present in the extract solution may already be available.

6 Irritation tests

6.1 *In vitro* irritation tests

Two *in vitro* methods, the rat skin Transcutaneous Electrical Resistance (TER) test and the EPISKIN test, have been internationally validated as alternative tests to assess the skin corrosivity of chemicals. However, no validated methods to assess skin irritancy yet exist.

National and international organizations continue work to develop and validate *in vitro* tests for skin irritancy in parallel with the search for alternative methods; others have been developing methods to quantify the responses of animals and humans in order to better define endpoints using non-invasive techniques. See C.1.

6.2 Factors to be considered in design and selection of *in vivo* tests

Irritation testing of medical devices can be performed with the finished product and/or extracts thereof.

Factors affecting the results of irritation studies include:

- a) the nature of the device used in a patch test;
- b) the dose of the test material;
- c) the method of application of the test material;
- d) the degree of occlusion;
- e) the application site;
- f) the duration and number of exposures; and
- g) the techniques used in evaluating the test.

Additional background information is provided in annex C.

While increased flexibility allows the investigator to enhance the sensitivity of the test to suit conditions of use and population exposure, consistency in procedure contributes to comparability of test results with different materials and from different laboratories.

Provisions have been included in the test procedures for evaluation of devices and materials that will have repeated and/or prolonged exposure. The study shall be designed to exaggerate the anticipated contact (time and/or concentration) in the clinical situation. This shall be born in mind during interpretation of the result.

If the pH of the test sample is less than or equal to 2 or equal to or greater than 11.5, the material shall be declared an irritant and no further testing is required. However, experimental evidence suggests that acidity and alkalinity of the test material are not the only factors to be considered in relation to the capacity of a material to produce severe injury. The concentration of the test material, its period of contact, and many other physical and chemical properties are also important.

NOTE—For products intended to be used extensively on normal and compromised skin, no substantial risk is normally accepted; however, many products, in spite of a potential to irritate, are fully acceptable because of their inherent benefit or intended biological activity.

6.3 Animal skin irritation test

6.3.1 Principle

An assessment is made of the potential of the material under test to produce dermal irritation in a relevant animal model.

The rabbit is the preferred test animal.

6.3.2 Test material

If the test material is either a solid or a liquid, it shall be prepared as specified in annex A.

In order to demonstrate the sensitivity of the assay, it is advisable to include, in addition to the negative control, a positive control on each animal. As there are two test sites and two control sites on each animal, a maximum of two test materials may be applied together with the control materials, provided that the same vehicle is used.

6.3.3 Animals and husbandry

Healthy young adult albino rabbits of either sex from a single strain, weighing not less than 2 kg, shall be used.

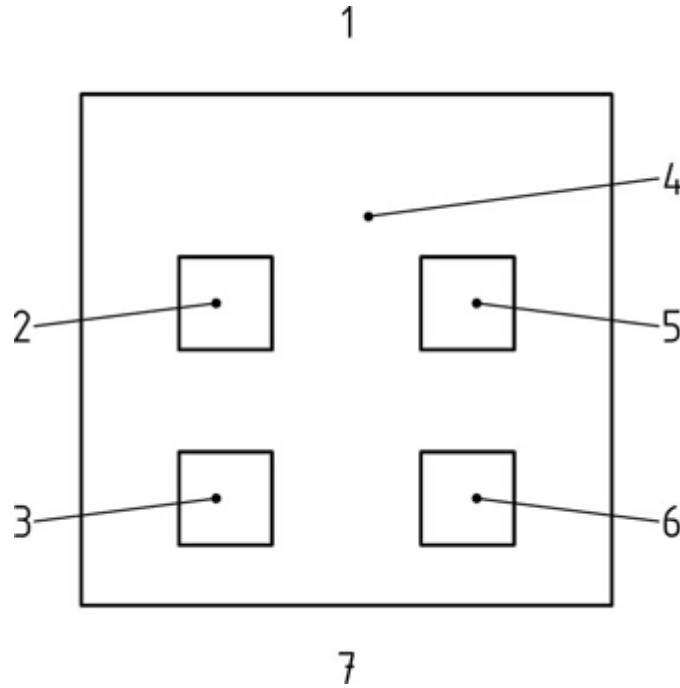
The animals shall be acclimatized and cared for as specified in ISO 10993-2.

If irritation is anticipated, consideration shall be given to testing in one animal first. Unless a well-defined positive response (score greater than 2 for either erythema or edema; see Table 1) is observed, a minimum of two further animals shall be used. If no response is expected, initial testing may be conducted using three animals. If the response in the test using the minimum of three animals is equivocal, further testing shall be considered.

6.3.4 Test procedure

6.3.4.1 Preparation of animals

The condition of the skin is a critical factor. Use only animals with healthy intact skin. Fur is generally clipped within 24 h to 4 h of testing on the backs of the animals a sufficient distance on both sides of the spine for application and observation of all test sites (approximately 10 cm × 15 cm). Fur may be re-clipped to facilitate observation and/or to accommodate repeated exposures. Depilatories may be used by trained technicians, if the process has been validated at the testing facility. If repeated exposure is required, follow the procedures in 6.3.4.2, 6.3.4.3, or 6.3.4.4, repeated for a maximum of 21 days.



Key

- 1 Cranial end
- 2 Test site
- 3 Control site
- 4 Clipped dorsal region
- 5 Control site
- 6 Test site
- 7 Caudal end

Figure 1—Location of skin application sites

6.3.4.2 Application of powder or liquid sample

Apply 0.5 g or 0.5 mL of the test material directly to each test skin site as shown in Figure 1. For solid and hydrophobic materials, there is no need for moistening. If the material is a powder, it should be slightly moistened with water or other suitable solvent before application (see annex A).

Cover the application sites with a 2.5 cm × 2.5 cm non-occlusive dressing (such as an absorbent gauze patch) and then wrap the application site with a bandage (semi-occlusive or occlusive) for a minimum of 4 h. At the end of the contact time, remove the dressings and mark the positions of the sites with permanent ink. Remove residual test material by appropriate means, such as washing with lukewarm water or other suitable non-irritating solvent and careful drying.

6.3.4.3 Application of extracts and extract vehicle

Apply the appropriate extract(s) to the 2.5 cm × 2.5 cm absorbent gauze patches. Use a volume of extract sufficient to saturate the gauze; generally 0.5 mL per patch. Apply one patch on each side of the animal as shown in Figure 1. Apply a control patch of gauze moistened with the extract vehicle as indicated in Figure 1.

Cover the application sites with a bandage (semi-occlusive or occlusive) for a minimum of 4 h. At the end of the contact time, remove the dressings and mark the positions of the sites with permanent ink. Remove residual test material by appropriate means, such as washing with lukewarm water or other suitable non-irritating solvent and careful drying.