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BSI Standards Publication

Biological evaluation of medical devices

Part 10: Tests for irritation and skin sensitization (ISO 10993-10:2010)

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National foreword

This British Standard is the UK implementation of EN ISO 10993-10:2010. It supersedes BS EN ISO 10993-10:2009 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/194, Biological evaluation of medical devices.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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Compliance with a British Standard cannot confer immunity from legal obligations.

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Évaluation biologique des dispositifs médicaux - Partie 10: Essais d'irritation et de sensibilisation cutanée (ISO 10993-10:2010)

Biologische Beurteilung von Medizinprodukten - Teil 10: Prüfung auf Irritation und Hautsensibilisierung (ISO 10993-10:2010)

This European Standard was approved by CEN on 23 July 2010.

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Foreword

This document (EN ISO 10993-10:2010) has been prepared by Technical Committee ISO/TC 194 "Biological evaluation of medical devices" in collaboration Technical Committee CEN/TC 206 “Biological evaluation of medical devices” the secretariat of which is held by NEN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2011, and conflicting national standards shall be withdrawn at the latest by February 2011.

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

This document supersedes EN ISO 10993-10:2009.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annex ZA and ZB, which are integral parts of this document.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Endorsement notice

The text of ISO 10993-10:2010 has been approved by CEN as a EN ISO 10993-10:2010 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on Medical Devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this International Standard given in Table ZA.1 confers, within the limits of the scope of this European Standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC on medical devices

Clause(s)/sub-clause(s) of this European Standard	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4, 5, 6, 7, 8, Annexes A, B and C	7.1, 7.2, 7.5	Within the limits of the Scope of this standard.
6.5 and Annex C	6a	Subclause 6.5 and Annex C contain requirements that are relevant to clinical investigations according to section 2 of Annex X, as referred to in essential requirement 6a of Directive 93/42/EEC.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on Active Implantable Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on active Implantable Medical Devices.

Once this Standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this International Standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB.1 — Correspondence between this European Standard and Directive 90/385/EEC on Active Implantable Medical Devices

Clause(s)/sub-clause(s) of this European Standard	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4, 5, 6, 7, 8, Annexes A, B and C	9 (first and second indents only)	Within the limits of the Scope of this standard.
6.5 and Annex C	5a	Subclause 6.5 and Annex C contain requirements that are relevant to clinical investigations according to section 2 of Annex 7, as referred to in essential requirement 5a of Directive 90/385/EEC.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Biological evaluation of medical devices —

Part 10:
Tests for irritation and skin sensitization

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 skin sensitization.

This part of ISO 10993 includes:

a) pretest considerations for irritation, including *in silico* and *in vitro* methods for dermal exposure;

b) details of *in vivo* (irritation and sensitization) test procedures;

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. In Annex B several special irritation tests are described for application of medical devices in areas other than skin.

2 Normative references

The following referenced documents are indispensable for the application of this document. 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*

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 document, the terms and definitions given in ISO 10993-1 and the following apply.

3.1
allergen
sensitizer
substance or material that is capable of inducing a specific hypersensitivity reaction upon repeated contact with that substance or material

3.2
blank
extraction vehicle not containing the test material, retained in a vessel identical to that which holds the test material and subjected to identical conditions to which the test material is subjected during its extraction

NOTE The purpose of the blank control is to evaluate possible confounding effects due to the extraction vessel, vehicle and extraction process.

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
dose
dosage
amount of test sample administered (e.g. mass, volume) expressed per unit of body weight or surface area

NOTE The terms are often used interchangeably (more commonly dosage).

3.5
erythema
reddening of the skin or mucous membrane

3.6
eschar
scab or discoloured slough of skin

3.7
extract
liquid or suspension that results from exposing a test or control material to a solvent under controlled conditions

3.8
induction
process that leads to the *de novo* generation of an enhanced state of immunological activity in an individual, to a specific material

3.9
irritant
agent that produces irritation

3.10
irritation
localized non-specific inflammatory response to single, repeated or continuous application of a substance/material

NOTE Skin irritation is a reversible reaction and is mainly characterized by local erythema (redness) of the skin.

3.11
necrosis
cell death as a direct result of irreversible changes caused by injury or disease

NOTE One should be aware that tissue repair will occur either resulting in complete functional restoration or resulting in scar formation.

3.12
negative control
any well-characterized material or substance that, when tested by a specific procedure, demonstrates the suitability of the procedure to yield a reproducible, appropriately negative, non-reactive or minimal response in the test system

NOTE In practice, negative controls include blanks, vehicles/solvents and reference materials.

3.13
oedema
swelling due to abnormal infiltration of fluid into the tissues

3.14
positive control
any well-characterized material or substance that, when evaluated by a specific test method, demonstrates the suitability of the test system to yield a reproducible, appropriately positive or reactive response in the test system

3.15
skin corrosion
production of irreversible damage to the skin, manifested as visible necrosis through the epidermis and into the dermis, following application of a test sample

EXAMPLE The action of a compound/chemical/test sample resulting in **ulceration** of skin (see 3.19).

3.16
skin sensitization
allergic contact dermatitis
immunologically mediated cutaneous reaction to a substance

NOTE In the human, the responses can be characterized by pruritis, erythema, oedema, papules, vesicles, bullae or a combination of these. In other species the reactions can differ and only erythema and oedema can be seen.

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

3.18
test sample
material, device, device portion, component, extract or portion thereof that is subjected to biological or chemical testing or evaluation

3.19
ulceration
open sore representing loss of superficial tissue

3.20
vehicle
liquid used to moisten, dilute, suspend, extract or dissolve the test substance/material

4 General principles — Step-wise approach

The available methods for testing irritation and sensitization were developed specifically to detect skin and mucous membrane irritation and skin sensitization potential. Other types of adverse effect are generally not predicted by these tests. For medical devices that are used as implants or external communicating devices, intradermal testing is more relevant in approaching the application and so for detection of irritation activity, intracutaneous testing shall be used as described in 6.4.

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) in accordance with ISO 10993-2, *in vitro* tests in preference to *in vivo* tests shall be considered, and replacement of the latter as new *in vitro* tests are scientifically validated and become reasonably and practicably available. For the evaluation of skin irritation and corrosion, *in vitro* alternatives are available for chemicals; there are currently no internationally validated and accepted *in vitro* tests to detect sensitizers;

d) *in vivo* animal tests: in order to ensure reproducibility and sensitivity, a test of a positive-control substance for irritation and skin sensitization shall be included in each assay by the testing laboratory in order to validate the test system and demonstrate a positive response; for guinea pig sensitization assays, however, when consistency has been demonstrated over a six month or more extended period, a positive control does not need to be included in every assay, but may be run at regular intervals which shall not exceed six months.

NOTE 1 Sensitization can at the moment only be determined by an *in vivo* assay. This can be accomplished by using the local lymph node assay (LLNA) in mice, the occluded patch test in guinea pigs or the guinea pig maximization test (GPMT). For single chemicals the LLNA is now the preferred assay for determining the sensitizing potential. See References [69] [88] [90].

NOTE 2 *In vivo* animal tests are appropriate when test materials cannot be characterized and risk assessments cannot be undertaken using information obtained by the means set out in a), b) and c).

NOTE 3 For sensitization assays in guinea pigs, ten animals are normally used for positive control once every six months. Fewer guinea pigs can be used when an assay with a positive control substance is performed more frequently than once every six months. At least five test animals with a positive substance and five control animals should be used.

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.

Clinical studies in accordance with ISO 14155-1, ISO 14155-2 and to ethics principles shall not be performed before the results of the other evaluations in a) to d) are known.

5 Pretest considerations

5.1 General

It is important to emphasise 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 10993-1:2009 and the following apply.