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Biological evaluation of medical devices —

Part 10: Tests for skin sensitization

Évaluation biologique des dispositifs médicaux —

Partie 10: Essais de sensibilisation cutanée

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194 *Biological and clinical evaluation of medical devices,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 10993-10:2010), which has been technically revised.

The main changes compared to the previous edition are as follows:

— this document now contains a description of skin sensitization testing only;

— Annex C on non-animal methods for skin sensitization (formerly Annex D) has been updated;

— the testing for irritation is now described in ISO 10993-23.

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document assesses possible contact hazards from chemicals released from medical devices, which may produce skin sensitization.

Some materials that are included in medical devices have been tested, and their skin sensitization potential has been documented. Especially for dental materials, sensitizing properties were reported —see Reference [51]. Other materials and their chemical components have not been tested and may induce adverse effects when in contact with human tissue. 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 (background information is provided in Annex D). Since 2015, several in chemico and in vitro assays have been validated and Organization for Economic Co-operation and Development (OECD) test guidelines released to assess the skin sentization potential of chemicals.[75][79][104] An overview of available alternative skin sensitization tests for neat chemicals is given in Annex C. These test methods, each developed to address a specific key event, can possibly not be sufficient alone to conclude on the presence or absence of skin sensitization potential of chemicals and should be considered in the context of integrated approaches such as integrated approaches to testing and assessment (IATA), combining them with other complementary information. Note that the in vitro and in chemico tests for skin sensitization in Annex C have thus far been validated only for neat chemicals and not for medical devices. To confirm that they are applicable for evaluation of the skin sensitization potential of medical devices, their assays need to be assessed and validated.

Where appropriate, the preliminary use of in vitro methods is encouraged for screening purposes prior to animal testing. To reduce the number of animals used, this document presents a step-wise approach, with review and analysis of test results at each stage. It is intended that, for regulatory submission, skin sensitization studies be conducted using GLP or ISO/IEC 17025 as applicable to the respective country and comply with regulations related to animal welfare. Statistical analyses of data are recommended and used whenever appropriate. This document includes important tools for the development of safe products and is intended for use by professionals, appropriately qualified by training and experience, who can interpret its requirements and judge the outcomes of the evaluation for each medical device, taking into consideration all the factors relevant to the device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.

This document is based on numerous standards and guidelines, including OECD Guidelines, US Pharmacopoeia and the European Pharmacopoeia. It is intended to be the basic document for the selection and conduct of tests enabling the evaluation of dermal sensitization responses relevant to the safety of medical materials and devices.

Biological evaluation of medical devices —

Part 10:
Tests for skin sensitization

1 Scope

This document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to induce skin sensitization.

This document includes:

— details of in vivo skin sensitization test procedures;

— key factors for the interpretation of the results.

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

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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, *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 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

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
allergic contact dermatitis
clinical diagnosis based on an observed immunologically-mediated cutaneous reaction to a substance

3.3
blank
extraction *vehicle* (3.17) not containing the *test material* (3.15), 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 1 to entry: The purpose of the blank control is to evaluate possible confounding effects due to the extraction vessel, vehicle and extraction process.

3.4
challenge
process following the *induction* (3.8) phase, in which the immunological effects of subsequent exposures in an individual to the inducing material are examined

3.5
elicitation
immunological reaction to exposure to a sensitizer in a previously sensitized individual

3.6
erythema
reddening of the skin or mucous membrane

3.7
extract
liquid that results from extraction of the *test sample* (3.16) or control

[SOURCE: ISO 10993-12:2021, 3.6]

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

3.9
irritant
agent that produces *irritation* (3.10)

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

Note 1 to entry: Skin irritation is a reversible reaction and is mainly characterized by symptoms like local *erythema* (3.6) (redness), swelling, itching, peeling, cracking and scaling of the skin.

3.11
negative control
well-characterized material or substance that, when evaluated by a specific test method, demonstrates the suitability of the procedure to yield a reproducible, appropriately negative, non-reactive or minimal response in the test system

Note 1 to entry: In practice, negative controls include *blanks* (3.3), *vehicles* (3.17)/solvents and reference materials.

[SOURCE: ISO 10993-12:2021, 3.10, modified — Note 1 to entry has been replaced.]

3.12
oedema
swelling due to abnormal infiltration of fluid into the tissues

3.13
positive control
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

3.14
skin sensitization
T-cell mediated delayed-type hypersensitivity reaction induced by low molecular weight reactive chemicals (allergens) comprising two phases, induction and elicitation

Note 1 to entry: In humans, the responses can be characterized by pruritis, *erythema* (3.6), *oedema* (3.12), papules, vesicles, bullae or a combination of these. In other species, the reactions can differ and only erythema and oedema can be seen.

3.15
test material
material, device, device portion or component thereof that is sampled for biological or chemical testing

3.16
test sample
material, device, device portion, component, *extract* (3.7) or portion thereof that is subjected to biological or chemical testing or evaluation

3.17
vehicle
liquid used to moisten, dilute, suspend, *extract* (3.7) or dissolve the test substance/material

4 General principles — Step-wise approach

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

This document requires a step-wise approach, considering that any stage can result in the conclusion that further testing for skin sensitization is not necessary:

a) literature and supplier information review, including chemical and physical properties, and information on the skin sensitization potential of any medical device constituent as well as structurally-related chemicals and materials; refer to ISO 10993-1 for details; conduct risk assessment based on existing information to determine whether skin sensitization risk is acceptable or whether further testing is necessary;

b) additional characterization and risk assessment, if needed, of the device material, involving chemical characterization and analysis of the test sample according to the general principles described in ISO 10993-18;

c) in vitro tests shall be considered in preference to in vivo tests in accordance with ISO 10993-2, and the replacement of the latter as new in vitro tests are scientifically validated and become reasonably and practicably available;

NOTE There are currently a number of internationally validated and accepted in vitro tests to detect the skin sensitization potential of chemicals; however, these in vitro tests are not yet validated for medical devices. Work is ongoing for some of these tests to qualify them for use with medical devices.

d) in vivo animal tests are only 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).

5 Pretest considerations

5.1 General

It is important to emphasize that pretest considerations can result in the conclusion that testing for skin sensitization is not necessary.

The requirements given in ISO 10993-1:2018, Clause 5, and the following apply.

In vivo, non-sterile samples shall be investigated by topical investigation only, as the possibility of microbial contamination of the test sample can confound the final assay interpretation. In cases where the sterility of a test sample cannot be guaranteed, but the sample is still considered to be free from microbial contamination, intradermal administration may be justified.

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 mould-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 components pose a risk depends on the leaching or degradation characteristics of the finished products. Those chemical components which have skin sensitization potential shall be identified.

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

The chemical composition of these materials is typically more complex than those in 5.2.2. A number of reaction products/impurities/additives/residual catalyst can be present and the degree or extent of polymerization can vary.

5.2.4 Biologically derived materials

These materials are inherently complex in their composition. They often also contain process residues, for example, cross-linkers and anti-microbial agents. Biological materials can be inconsistent from sample to sample.

The methods in this document have not been designed for testing of biologically derived materials and can therefore be less adequate. For example, the tests in this document 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. Quantitative data on the chemical composition shall also be obtained. If quantitative data are 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 (e.g. mould-release agents) shall also be obtained from appropriate members of the manufacturing chain, including converters and component manufacturers.

If information on composition is incomplete, a literature study to establish the likely nature of the starting material and any additives is recommended, so as to assist in the selection of the most appropriate methods of analysis for the material concerned.

The chemical composition of finalized products shall be determined in accordance with ISO 10993-18.

NOTE The composition of ceramics, metals and alloys can be specified in accordance with ISO or ASTM international standards and/or can be specified by the user. However, in order to obtain full qualitative and quantitative details on composition, it can 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.

6 Skin sensitization tests

6.1 Choice of test methods

In vitro and in chemico alternative approaches have been developed for neat chemicals using a combination of different assays to identify skin sensitizers. Several of these methods have been included in the OECD test guidelines (TG 442C[75], TG 442D[79] and TG 442E[104]) or in the OECD test guideline program[121] (see Annex C).

Together, the assays described in these test guidelines cover three key events of the now identified adverse outcome pathway (AOP) for skin sensitization, including the molecular initiating event (protein binding), induction of inflammation, and activation of dendritic cells. These test methods developed to address a specific key event can possibly not alone be sufficient to conclude on the presence or absence of skin sensitization potential of chemicals and should be considered in the context of integrated approaches such as IATA, combining them with other complementary information.

In accordance with ISO 10993-2, such integrated approaches shall be taken into consideration for assessing skin sensitization potential of neat chemicals. Whether these approaches are also applicable for medical devices or medical device extracts is not yet known. An overview of available alternative skin sensitization tests for neat chemicals is presented in Annex C.

There are currently three animal assays available for the determination of the skin sensitizing potential of chemicals. These include two guinea pig assays and one murine assay. The two guinea pig assays are the guinea pig maximization test (GPMT) and the closed-patch test (Buehler test). Of these two assays, the maximization test is the most sensitive method. See Reference [9]. The closed-patch test is suitable for topical products.

The murine local lymph node assay (LLNA) was internationally accepted as an OECD test guideline in 2010[33] for testing single chemicals as a stand-alone alternative to the guinea pig assays, and is now the preferred in vivo assay for chemicals. See References [19] and [32]. In some instances, guinea pig assays can be necessary for the evaluation of the sensitizing potential of certain test samples. Such can be true for certain metals (see Reference [44]) that can give false negative findings in the LLNA or skin

irritants that can give false positive findings, as well as high molecular weight substances, which do not penetrate the skin or substances that are not soluble in the recommended vehicles.

NOTE All three animal assays were developed for the detection of skin sensitizing potential of chemicals, i.e. contact dermatitis, delayed type (type IV) hypersensitivity.

In view of the provisions laid down in ISO 10993-2 on animal welfare requirements, when an in vivo assay is performed, the LLNA shall be taken into consideration. In addition to animal welfare considerations, the LLNA has the advantage of providing objective quantitative data.

6.2 Murine local lymph node assay

6.2.1 Principle

Following topical treatment of a test sample on the dorsum of the ears, the extent of lymphocyte proliferation is measured in the lymph nodes that drain the sites of application (ears). A response in cellular proliferation of threefold or more compared with the activity of the controls is the threshold for designating a test material as a sensitizer.

The LLNA shall be performed using a dose response approach when substances are used. For final products/medical devices, it can be sufficient to test only the undiluted extract.

NOTE References [15] to [44] contain representative LLNA publications. Laboratories conducting this assay are encouraged to review these and other relevant publications available.

6.2.2 Test sample preparation

The test sample shall be a liquid, suspension, gel or paste such that it can be applied to the ears of the mice. Where possible, a series of doses (dilutions) shall be investigated. Otherwise, the highest concentration prepared as a chemical solution or suspension or as an extract should be used. When a strong response in the LLNA is detected with an extract, a follow-up study evaluating multiple doses may be necessary to evaluate the possible skin sensitization potency of the extract. Systemic toxicity and excessive local skin irritation can invalidate the test results; these reactions should therefore be avoided. In certain circumstances, pre-testing can be necessary.

A commonly used vehicle for substances/chemicals is an acetone olive oil (AOO) 4:1 mixture. Liquid samples that are hydrophilic and/or do not adequately adhere to the skin of the ear should be modified to adhere to the test site. This can be obtained by adding a thickening agent like carboxy methyl cellulose or hydroxyethyl cellulose (with a density of 0,5 %) or by a surfactant such as Pluronic® L92[1)] with a volume fraction of 1 %. For water soluble chemicals, dimethyl sulfoxide (DMSO) or dimethyl formamide (DMF) are preferred above the surfactant Pluronic® L92. See Reference [34]. Alternatively, other extract vehicles can be used, as mentioned. See Reference [33]. The effect of additions to the extract media and/or changes in vehicle composition shall be validated and documented. This can be done by experiments using weak to moderate skin sensitizers as commonly used as positive controls. In addition, spiking of the test sample with a positive control can be performed in order to demonstrate that the LLNA is still able to detect the presence of potential skin sensitizers in the prepared extract. Other fundamental aspects of test article extraction are specified in ISO 10993-12.

A separate extract shall be prepared for each daily application.

NOTE For polymeric materials, an optional extraction method is given in Annex B.

6.2.3 Animals and husbandry

Healthy female non-pregnant mice of the CBA/Ca, CBA/J or BALB/c strain shall be used, unless another strain is validated. See References [33], [41] and [42]. Several mouse strains have been reported as

1) Pluronic® L92 is an example of a suitable product available commercially. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of this product.

acceptable (DBA/2, B6C3F1). See Reference [35]. The mice shall be 7 weeks to 12 weeks of age; the mice in each study shall be matched in age (within a one-week age range).

Husbandry and selection of animals shall be in accordance with ISO 10993-2. The mice, routinely acclimatized to the laboratory, shall be individually identified. For certain test samples, individual housing can be necessary. This shall be justified and documented.

Animals shall be uniquely identified by methods not to include ear punches or ear tags.

When group housing is performed, cross contamination and unwanted oral intake should be taken into consideration.

6.2.4 Test procedure

For chemicals, the LLNA is generally performed in a dose-response manner. For solid medical devices, samples to be tested shall be extracts. In these cases, only a single dose is available for testing. In general, the extract can be investigated undiluted. However, when the extract contains highly toxic components, this can result in a negative response in the LLNA due to toxicity. It is therefore recommended, to perform the LLNA in a dose-response manner and to dilute the extract when investigating cytotoxic extracts (see ISO 10993-5). In addition, when a strong response is detected in the LLNA, a dose response follow up can be conducted to evaluate the possible sensitization potency of the extract.

To ensure reproducibility and sensitivity, a test of a positive-control substance for skin sensitization shall be included by the testing laboratory in order to validate the test system and demonstrate a positive response. Well-known weak to moderate contact allergens (e.g. mercaptobenzothiazole, hexyl cinnamic aldehyde, or benzocaine), shall be used as positive control. The examples mentioned can possibly not be suitable for each vehicle used for sample preparation (e.g. water-based vehicle); in such cases, another positive control can be selected. ASTM F2148 indicates that in such circumstances formalin and 2,4-dinitrochlorobenzene (DNCB) should be used as positive controls. This shall be justified and documented.

While inclusion of a concurrent positive control group is recommended, there may be situations in which only periodic testing (i.e. at intervals ≤ 6 months) of the positive control test substance can be adequate. This is the case for laboratories that conduct the LLNA regularly (i.e. conduct the LLNA at a frequency of no less than once per month) and have an established historical positive control database that demonstrates the laboratory's ability to obtain reproducible and accurate results with positive controls. Adequate proficiency with the LLNA can be successfully demonstrated by generating consistent positive results with the positive control in at least 10 independent tests conducted within a reasonable period of time (i.e. less than one year).

The individual body weights shall be recorded at initiation and at the end of the study. In order to detect potential toxicity of the test sample, clinical observation shall be performed and recorded during the study.

Using a positive control only once every six months can have consequences for the results obtained in the previous six months period when this positive control shows a negative outcome. Reference [33] states that periodic testing (i.e. at intervals ≤ 6 months) of the positive control substance can be considered in laboratories that conduct the LLNA regularly (i.e. conduct the LLNA at a frequency of no less than once per month), and that have a history and a documented proficiency for obtaining consistent results with positive controls. It is important to realize that the decision to only include a positive control periodically instead of concurrently can have ramifications on the adequacy and acceptability of negative study results generated without a concurrent positive control during the interval between each periodic positive control study. For example, if a false-negative result is obtained in the periodic positive control test, all negative test substance results obtained in the interval between the last acceptable periodic positive control test and the unacceptable periodic positive control test can be questioned. In order to demonstrate that the prior negative test substance results are acceptable, a laboratory can be expected to repeat all negative tests, which requires additional expenses and increased animal use.

6.2.5 Treatment groups

When the LLNA is performed, the data of a minimum of five mice per group shall be available for evaluation. Lymph node responses may be determined either by individual measurement or by measurement of pooled lymph node samples. For statistical analysis, individual measurement is preferred.

When only a single dose is available for evaluation, for example, an extract, a minimum of five mice shall be used for each group, when individual responses are measured.

Treatment groups shall be assigned to:

— blank of each type of vehicle employed (see Annex A);

— when appropriate, positive control for each vehicle employed;

— test groups for each extract vehicle employed.

When testing a single chemical or substance, the LLNA shall be performed in a dose-response manner. For other types of test and sample-like extracts, a dose-response evaluation can possibly not be feasible. When only one test group is employed, this shall be justified and documented.

NOTE When sufficient data have been collected to demonstrate consistency for the dose response of the positive control, a single dose can be included to demonstrate the sensitivity of the assay. See Reference [32].

The appropriate sample shall be applied to the dorsal side of both ears of designated mice at a dose of 25 µl/d for three consecutive days. Each day, observe the ears for signs of irritation that can interfere with interpreting results. See References [23], [27] and [29].

6.2.6 Determination of cellular proliferation and tissue preparation

The proliferating cells in the draining lymph nodes can be labelled by either a radioactive or fluorescent label. Radiolabels commonly used are ^{3}H-methyl thymidine and ^{125}I-iododeoxyuridine, while for fluorescence, fluorodeoxyuridine can be used.

At (72 ± 2) h after the last treatment, record individual mouse weights and administer intravenously the label for cell proliferation. Inject 0,25 ml of phosphate buffered saline (PBS) containing 740 KBq (20 µCi) units of radioactivity of ^{3}H-methyl thymidine into all test and control mice via the tail vein. For ^{125}I-iododexyuridine, inject 0,25 ml PBS containing 74 KBq (2 µCi), and for fluorodeoxyuridine inject 0,25 ml containing 10^{-5} mol/l into the tail vein. See Reference [33].

Other alternative procedures not requiring radiolabelling are available and should be considered [e.g. adenosine triphosphate (ATP) (OECD TG 442A [122]) determination (DA method), bromodeoxyuridide BrdU (OECD TG 442B [123]) determination (ELISA or FCM method)].

NOTE 1 For more information, see References [33], [36], [42], [43] and [49].

Euthanize the mice (5 ± 0,75) h after the administration of the labelling solution according to ISO 10993-2. Remove the draining auricular lymph node. Care shall be taken to avoid cross contamination of the tissue samples. The lymph nodes of each group may be pooled, or pairs of lymph nodes of each individual animal may be pooled. Data from each individual animal is preferred as it provides the variability between each animal in a group. Single cell preparations are prepared by gently pressing the lymph nodes through a 200 µm stainless steel wire mesh or nylon mesh over a container. Rinse the strainer with chilled PBS into the container to remove cells from the mesh filter. The container now contains the cell preparation. Cell preparations are washed twice by centrifugation and resuspended in PBS. Cells are precipitated with 5 % trichloroacetic acid (TCA) at (4 ± 2) °C for (18 ± 1) h. After a final centrifugation step, pellets are resuspended in 1 ml of TCA and transferred to scintillation vials

containing 10 ml of scintillation fluid for ^{3}H-counting, or transferred directly to a gamma counter for ^{125}I-counting. See References [21], [35] and [36].

NOTE 2 Alternatively, labelling and determination of cellular proliferation can be performed ex vivo. See References [37] and [38].

6.2.7 Results and interpretation

Measure the level of radioactivity in the lymph node cells in counts per minute per mouse (cpm/mouse). Convert counts per minute (cpm) to disintegration per minute (dpm). Calculate the mean and standard deviation of dpm for at least three counts for each animal or each group of mice. Subtract the background value from each result.

When using the individual sampling method continue to calculate the mean and standard deviation of the dpm for each group of five mice. Determine the stimulation index (SI) by dividing the mean test dpm by the blank dpm. An SI of three or more (≥3,0) shall be considered positive for designating a test sample as a sensitizer. See Reference [16].

Positive control samples shall produce an SI that is greater than or equal to 3,0.

For a valid study, the positive control shall be conducted either concurrently or within the previous six months. See Reference [33].

6.2.8 Test report

The test report shall include:

a) a description of the test material(s) or device;

b) the intended use/application of the test sample or material;

c) the International Standard used (including its year of publication);

d) a detailed description of the method employed in preparing the test sample or test material or device;

e) a description of the test animals;

f) the method of application to the ears;

g) a description of the method for determining cellular proliferation;

h) any deviations from the procedure;

i) records of the observations, including clinical and body weight observations;

j) an assessment of the results, including positive control;

k) the date of the test.

6.3 Guinea pig assays for the detection of skin sensitization

6.3.1 Principle

The two guinea pig assays currently used for the detection of sensitizing activity of chemicals and medical devices are the Buehler assay and the GPMT. Both assays consist of an induction and challenge phase, thus covering all stages of hypersensitivity.

