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Biological evaluation of medical devices — Requirements for interlaboratory studies to demonstrate the applicability of validated in vitro methods to assess the skin sensitization of medical devices

~~DTS stage~~

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Contents

Foreword

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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).~~.

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

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Introduction

International Standards can be used to demonstrate the safety and compliance of medical devices. ISO 10993-10 specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to induce skin sensitization (Type IV hypersensitivity reaction). The methods included in ISO 10993-10 are based on animal or human testing, with an ~~informative~~ annex on in vitro and in chemico tests for skin sensitization that have been validated for neat chemicals. The effort to reduce or replace the use of animals in toxicity testing has led to the development of many new non-animal methods. The ~~OECD~~ test guidelines in ~~the 442 series~~References [56] and [57] include alternatives to animal testing methods for skin sensitization that have been previously validated to confirm their equivalence/superiority to the current in vivo methods. However, currently, none of the OECD test guideline methods are considered sufficient stand-alone replacements for in vivo tests that assess the skin sensitization potential of chemicals~~.~~[1].

Current OECD test guideline methods are validated with neat chemicals and not with more complex mixtures such as medical devices or medical devices extracts. In order to use these methods in the specific context of medical devices, an evaluation is needed to verify their applicability for assessing skin sensitization of medical devices. Given the number of candidate test methods and the time that is required to assess them, it is important to ensure that the same science-based evaluation process and criteria are consistently applied to any new candidate test method. The purpose of this document is to provide a framework for the conduct of prevalidation and interlaboratory studies to assess the applicability of candidate test methods for assessing one or more key events related to OECD's adverse outcome pathway (AOP) for skin sensitization when evaluating medical devices~~.~~[2].

~~NOTE For a candidate test method evaluated per this document to be considered for inclusion in ISO 10993-10, the test report can be submitted to ISO/TC 194/WG 8.~~

Biological evaluation of medical devices — Requirements for interlaboratory studies to demonstrate the applicability of validated in vitro methods to assess the skin sensitization of medical devices

1 Scope

This document specifies the framework and the methodology to evaluate and demonstrate the applicability of a validated non-animal method from an OECD test guideline to assess the skin sensitizing potential of a medical device or a medical device material. This document addresses:

— database of reference chemical skin sensitizers and non -sensitizers;

— reference materials;

— feasibility testing of candidate test methods, including any method optimization for use with extracts of medical devices;

— prevalidation of candidate test methods;

— interlaboratory study:

  — sample preparation and coding;

  — spiking of the extracts of negative control medical device material;

  — collection of the data;

  — statistical analysis to assess reliability and reproducibility.

The use of the approaches described in this document to assess the applicability of a candidate test method does not imply that the candidate test method can be used as stand-alone test for the evaluation of skin sensitization potential of medical devices. For certain candidate test methods, integrated approaches and/or defined approaches ~~may be~~are needed~~.~~.[1] The evaluation of skin sensitization potential of a medical device is described in ISO 10993~~-~~10.

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 10993-12~~:2021~~, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain ~~terminological~~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**~~
candidate test method
test method for in vitro sensitization testing of medical devices that is under evaluation

3.4~~3~~
interlaboratory study
~~**round robin study**~~
ILS
organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories ~~in accordance with~~according to predetermined conditions

3.4
interlaboratory reproducibility
between-laboratory reproducibility
measure of the extent to which different qualified laboratories, using the same protocol and testing the same substances, can produce qualitatively and quantitatively similar results

Note 1 to entry: Interlaboratory reproducibility is determined during the prevalidation and validation processes, and indicates the extent to which a test can be successfully transferred between laboratories.[29]

3.5
intralaboratory ~~study~~reproducibility
~~organization, performance and evaluation~~within-laboratory reproducibility
determination of ~~measurements or tests on~~ the ~~same or similar items~~extent that qualified people within the same laboratory ~~in accordance with predetermined conditions~~can successfully replicate results using a specific protocol at different times

3.6
prevalidation
PRE
initial phase of a *validation* ~~study;~~(3.10) small-scale study intended to obtain preliminary information on the relevance and reliability of a *candidate test method* (3.2)

3.7

test article
material (e.g~~,~~ a final finished device or a reference material) that is to be used to generate a *test sample* (3.8) (e.g~~,~~ using extraction)

3.8
test sample
sample (e.g~~,~~ a test article extract or spiked extract vehicle) that in its present form can be evaluated by a candidate test method

3.9
test system
system (e.g~~,~~ in vivo animal model, in vitro cellular model~~,~~ and in-silico computational models) that is used for hazard identification as part of a test method

3.10
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[SOURCE: ISO 9000:2015, 3.8.13, modified ~~—Note~~— Notes 1, 2 and 3 to entry ~~has~~have been deleted.]

4 Consideration on the process for demonstration of the applicability domain

The process for evaluating the applicability of a candidate test method for sensitization testing of medical devices shall include feasibility, prevalidation~~,~~ and interlaboratory studies (see Figure 1).

Prior to conducting a prevalidation study, a feasibility study may be needed to determine if any modification of the OECD TG protocols (e.g. dilution, solvents, incubation times, volume of test sample, stimulation index value) is necessary for the evaluation of medical devices.

Protocols for feasibility studies are not described in this document as the design of these studies should be specific to the OECD TG method.

If the candidate test method protocols planned for the prevalidation and interlaboratory studies deviate from the OECD TG protocol, the number and nature of the modifications as well as the data and documentation available (e.g. from a feasibility study) to support the modifications shall be provided. A scientific rationale for the impact of these changes on the acceptance of the method for assessing the sensitizing potential of sample tests should be provided to justify that the method used remains equivalent to the original OECD method.

The same candidate test method and protocols shall be used for both the prevalidation study and the interlaboratory study.

As the non-animal methods considered are already validated with single chemicals (but not with mixtures such as medical devices extracts) and integrated in OECD test guidelines (e.g~~., OECD 442 series~~, see Reference [91] and ~~OECD guideline 497~~Reference [1] on defined approaches for sensitization) with historical data of chemicals assessment, the prevalidation step shall be conducted to:

a) prepare the standard operating procedures (SOPs), so that they can be readily used by other laboratories;

b) generate preliminary data on the reliability and relevance of the candidate test method for assessing skin sensitization of medical devices.

During the prevalidation and interlaboratory phases, evaluation of the performance of non-animal methods shall be performed with positive and negative control test samples (in accordance with Clause 5) that are representative of medical devices extracts. The accuracy, sensitivity, specificity and reproducibility shall be calculated and compared to the targeted performance values in Clause 7 and Clause 8.

If the prevalidation study does not achieve the performance criteria in accordance with Clause 7, then additional feasibility testing may be needed to optimize the assay protocol for increased accuracy, specificity, and/or intralaboratory reproducibility prior to conducting a repeat prevalidation study. If the prevalidation study meets the performance criteria in accordance with Clause 7, then an interlaboratory study can be considered.