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Biological Evaluation of Medical Devices – Part 23: Tests for Irritation

(ISO 10993-23:2021, IDT)

医疗器械生物学评价 第 23 部分：刺激试验

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Foreword

This Document was drafted as per the rules specified in GB/T 1.1-2020 *Directives for Standardization – Part 1: Rules for the Structure and Drafting of Standardizing Documents*.

This Document is Part 23 of GB/T (Z) 16886 *Biological Evaluation of Medical Devices*. GB/T (Z) 16886 consists of the following parts:

--- Part 1: Evaluation and testing within a risk management process;

--- 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 9: Framework for identification and quantification of potential degradation products;

--- Part 10: Tests for irritation and skin sensitization;

--- 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 leachable;

--- Part 17: Establishment of allowable limits for leachable substances;

--- Part 18: Chemical characterization of medical device materials within a risk management process;

--- Part 19: Physio-chemical, morphological and topographical characterization of materials;

--- Part 20: Principles and methods for immunotoxicology testing of medical devices;

Biological Evaluation of Medical Devices – Part 23: Tests for Irritation

1 Scope

This Document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation. This Document includes:

--- pre-test considerations for irritation, including in silico and in vitro methods for dermal exposure;

--- details of in vitro and in vivo irritation test procedures;

--- key factors for the interpretation of the results.

The tests are designed to predict and classify the irritation potential of medical devices, materials or their extracts according to ISO 10993-1 and ISO 10993-2.

2 Normative References

The provisions in following documents become the essential provisions of this Document through reference in this Document. For the dated documents, only the versions with the dates indicated are applicable to this Document; for the undated documents, only the latest version (including all the amendments) is applicable to this Document.

GB/T 16886.1-2022 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, IDT)

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

NOTE: GB/T 16886.2-2011 Biological evaluation of medical devices - Part 2: Animal welfare requirements (ISO 10993-2:2006, IDT)

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

of the assay to detect irritant activity of these forms of materials prior to testing.

6.2.2 Principle of the method

Endpoints: cell viability determination is based on cellular reduction of MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) and subsequent conversion to a purple formazan salt that is quantitatively measured after extraction from the tissues. The cell viability in treated tissues is expressed as a percentage of the negative control. The percent reduction in viability is used to predict the irritation potential.

NOTE 1: Reduced tissue survival can be accompanied by IL-1α release. Tissue culture media from the exposure can be collected and kept frozen at ≤-20 °C for possible analysis of cytokines.

Brief procedure: studies performed with polymeric biomaterials specifically manufactured to contain irritant chemicals at low concentrations indicated that a prolonged exposure is needed compared to the OECD 439 protocol for neat chemicals. An incubation period of no less than 18 h up to 24 h exposure at 37 °C for exposure to potentially low concentrations of irritants in extracts from biomaterials is sufficient for predicting irritation in vitro by reduction of tissue viability below 50 %. Both 18 h and 24 h exposure showed similar results in both RhE models evaluated in the round robin study using medical device extracts.

Tissues are incubated at 37 °C, 5 % CO_2 in a humidified incubator following the addition of the test and control extracts.

Exposure to the test sample extract is terminated by rinsing with Dulbecco's phosphate buffered saline (DPBS), or PBS without Ca^{2+} and Mg^{2+}. After washing, the tissues are manually dried. The viability is assessed by incubating the tissues for 3 h with MTT solution in a 24-well plate (1 mg/ml; 300 µl per well). The formazan crystals are extracted using an appropriate amount (depending on the RhE model used) of isopropanol for at least 2 h at room temperature. Two or three aliquots (depending on the instructions of the supplier) per tissue of extracted formazan is then added to 96-well plates (200 µ1/ well) and quantified spectrophotometrically at 570 nm.

For direct inoculation assays, a solution with a 1 % volume fraction of sodium dodecyl sulfate (SDS, see 6.4.4) in saline solution of NaCl 0.9 % can be used as positive controls (PCs) and DPBS or PBS without Ca^{2+} and Mg^{2+} treated epidermis are used as the negative control, respectively. For extracted assays, a verified irritant infused control extracted in sesame oil and in saline solutions of NaCl 0.9 % can be used as positive controls.

NOTE 2: Aliquots of culture media collected after 18 h or 24 h exposure can be stored frozen (at a minimum of -20 °C) for potential cytokine (IL-1α) measurements as a complementary endpoint to cell viability. IL-1α measurement determines the inflammation component to the assessment of skin irritation in addition to the cell damage component determined indirectly by the MTT test for cell viability.

Vehicle controls shall include saline (NaCl 0.9 %) solution and sesame oil that have undergone the ISO 10993-12 medical device extraction procedure. For each treated tissue the viability is expressed as a percent relative to negative DPBS or PBS treated control tissues (mean).

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