INTERNATIONAL STANDARD

ISO 10993-23

First edition
2021-01

Biological evaluation of medical devices —

Part 23: Tests for irritation

Évaluation biologique des dispositifs médicaux —
Partie 23: Essais d'irritation

Reference number
ISO 10993-23:2021(E)

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Published in Switzerland

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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).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of 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 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).

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 medical devices, which can produce irritation.

Some materials that are included in medical devices have been tested, and their skin or mucosal irritation potential has been demonstrated. Other materials and their chemical components have not been tested and can 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.

The irritation potential of a medical device or its components can be predicted either by an *in vivo* animal irritation test or by an *in vitro* irritation test if qualified for use with medical devices.

ISO 10993-2 describes animal welfare aspects for performing animal studies for the biological evaluation of medical devices thereby also emphasizing the 3R's for replacement, reduction, and refinement of animal studies. This document describes tests to determine the irritancy of medical devices, materials or their extracts either by *in vitro* tests or *in vivo* tests. *In vitro* tests have preference over *in vivo* tests when appropriately validated and providing equally relevant information to that obtained from *in vivo* tests (see ISO 10993-1 and ISO 10993-2).

Traditionally, tests in small animals have been performed prior to testing on humans to help predict human responses. More recently, *in vitro* tests as well as human tests have been added as adjuncts or alternatives. For skin irritation testing of neat chemicals *in vitro* tests were developed using reconstructed human epidermis (RhE) models[31]. The method was adapted for detection of irritant chemicals in medical device extracts. The results of a large round robin study that tested two types of RhE models showed that these models can also be used to detect the presence of irritant chemicals extracted from polymeric materials [polyvinylchloride (PVC) and silicone] commonly used in the manufacture of medical devices[6]. This method was found to be equally sensitive in the detection of low concentrations of some strong irritant compounds when compared to the human patch testing and intracutaneous rabbit test[14]. Therefore, a stepwise approach for irritant testing can start with the *in vitro* RhE model.

The developed and validated RhE models are appropriate to predict skin tissue irritation response. It is recommended to explore the use of other alternative *in vitro* models to assess the irritation potential for mucosal or eye epithelial applications.

It is intended that, for regulatory submission, these studies be conducted using GLP or ISO/IEC 17025 as applicable to the respective country and comply with regulations related to animal welfare. Statistical analysis of data is recommended and can be used whenever appropriate.

This document is intended for use by professionals, appropriately qualified by training and experience, who are able to 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.

The tests included in this document are important tools for the development of safe products, provided that they are executed and interpreted by trained personnel.

This document is based on numerous standards and guidelines, including OECD Test Guidelines (TG), U.S. Pharmacopoeia[40] and the European Pharmacopoeia[39]. It is intended to be the basic document for the selection and conduct of tests enabling evaluation of irritation responses relevant to the safety of medical materials and devices.

Instructions are given in normative Annex A for the preparation of materials specifically in relation to the above tests. In normative Annex D several special *in vivo* irritation tests are described for application of medical devices in areas other than skin. In addition, normative Annex E provides information for conducting human skin irritation testing.

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. 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.

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.

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 10993-9, *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 medical device materials within a risk management process*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

OECD 404, *Acute Dermal Irritation/Corrosion*

OECD 439, *In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method*