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Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

Évaluation biologique des dispositifs médicaux — Application du seuil de préoccupation toxicologique (TTC) pour évaluer la biocompatibilité des substances extractibles des dispositifs médicaux

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Contents

Page

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).

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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*.

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.

Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

1 Scope

This document describes the basis for, selection of, and general applicability of a threshold of toxicological concern (TTC) value for a constituent present in/on a medical device or released from a medical device. The TTC values in this document can be used for:

— comparing to a maximum concentration of an identified or unidentified constituent in an extract (see ISO 10993-18);

— supporting toxicological equivalence;

— comparing to a maximum exposure dose estimate of an identified constituent (see ISO 10993-17).

NOTE Constituent is defined in 3.1.

ISO 10993-18 specifies how to convert TTC (µg/d) into a concentration (µg/ml).

TTC is not applicable to constituents with adequate toxicity data for deriving a tolerable intake (TI) value (see ISO 10993-17).

The TTC values established in this document are protective for carcinogens, systemic toxicants, and reproductive toxicants (see Clause 5). This document does not include TTC values for other biological endpoints assessed as part of the biological evaluation of a medical device, per ISO 10993-1, for example:

— cytotoxicity;

— irritation;

— sensitization;

— hemocompatibility;

— material mediated pyrogenicity;

— local effects that occur in tissues at the site of contact between a medical device and the body (e.g. the observations from implantation studies).

The TTC values in this document do not apply to potential exposure via gas pathways of medical devices. For application of TTC for constituents present/released from these devices, see the ISO 18562 series.

The TTC values presented in this document are not applicable for the safety assessment of cohort of concern (see 5.3).

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 10993-1:2018, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

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

3 Terms and definitions

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

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

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

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

3.1
constituent
chemical or compound present in or on a finished medical device or material(s) of construction

Note 1 to entry: Constituents may be intentionally present (e.g. an additive such as an antioxidant) or unintentionally present (e.g. an impurity).

Note 2 to entry: When applying TTC to an extractable or leachable, the identity of the extractable/leachable represents a constituent to which individual(s) are potentially exposed due to medical device use.

3.2
extractable
constituent released when the medical device or material of construction is extracted using laboratory extraction conditions and vehicles

Note 1 to entry: When applying TTC to an extractable, the extracted amount is assumed to potentially contact the individual(s) to whom the medical device contacts during clinical use, see ISO 10993-17.

3.3
identified constituent
constituent assigned a full chemical structure

3.4
leachable
constituent released from a medical device and potentially contacts the individual(s) during its clinical use

Note 1 to entry: When applying TTC to a leachable, the leached amount is assumed to potentially contact the user(s) of the medical device during its clinical use, see ISO 10993-17.

3.5
threshold of toxicological concern
TTC
level of exposure for constituents, below which there would be no appreciable risk to human health[1]

4 Background

4.1 General

The Threshold of Toxicological Concern (TTC) was originally developed for evaluating the toxicological risk of impurities present at low levels when impurity toxicity data are not available[2]. The concept was developed to address impurities present in food contact materials, and was then adapted for impurities in pharmaceutical products[3]to[16][20][21]. The TTC concept can be used to evaluate constituents present, or released, at low amounts from a medical device.