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Pyrogenicity — Principles and methods for pyrogen testing of medical devices

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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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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.

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Introduction

At present, safety assessments of medical devices are guided by the toxicological and other studies recommended in the ISO 10993 series of standards.

Material-mediated pyrogenicity represents a systemic effect that is included in of ISO 10993-11:2017, Annex G, but efforts have been taken to generally address pyrogenicity testing in this document.

A pyrogenic response is the adverse effect of a chemical agent or other substance, such as microbial component to produce a febrile response. Tests for a pyrogenic response have been required to evaluate the safety of products that have direct or indirect contact to blood circulation and the lymphatic system, cerebrospinal fluid (CSF) and interact systemically with human body.

At present, the *in vivo* rabbit pyrogenicity test and the *in vitro* bacterial endotoxin test are available as accepted methods for evaluating the pyrogenicity of medical devices and their materials. Basic procedures, including sample preparation of each test article, are already established, internationally harmonized, and mentioned in the related guidelines and pharmacopoeias.

Recently, an *in vitro* pyrogen test using human immune cells, the human cell-based pyrogen test (HCPT), has been developed and applied for pyrogen testing of parenteral drugs. The concept of the application of pyrogen testing for medical devices is being considered due to the direct or indirect exposure to human blood cells (HCPT).

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Pyrogenicity — Principles and methods for pyrogen testing of medical devices

1 Scope

This document specifies the principles and methods for pyrogen testing of medical devices and their materials.

2 Normative references

There are no normative references in this document.

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:

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

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

3.1
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies.

[SOURCE: GHTF/SG1/N071:2012, 5.1]

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3.2
pyrogen
substance that causes fever

3.3
pyrogenicity
ability of a chemical agent or other substance to produce a febrile response

3.4
febrile response
temperature above the normal range due to an increase in the body's temperature set point

Note 1 to entry: It is also referred to as fever or pyrexia.

3.5
oxidative phosphorylation
metabolic pathway in most aerobic organisms, which uses enzymes to oxidise nutrients to release energy

4 Abbreviated terms

COX	Enzyme cyclooxygenase
CpG	Cytosine (C) next to guanine (G) in the DNA sequence, with the p indicating that C and G are connected by a phosphodiester bond.methyl group to the 5 position of the cytosine pyrimdine ring
ELISA	Enzyme llinked immunosorbent assay HCPT, e.g. monocyte activation test (MAT)
IKK	IkB kinase, an enzyme complex involved in propagating cellular response to inflammation
IRAK	Interleukin-1 receptor-associated kinase
LAL	Limulus amebocyte lysate
LPS	Lipopolysaccharide
MD-2	Molecule secreted glycoprotein that binds to extracellular domain of TLR4
MCP	Macrophage chemotactic protein
MIP	Macrophage inflammatory protein
NOD	Nucleotide-binding oligomerization domain
PGE_2	Prostaglandin E_2
RANTES	Regulated on activation, normal T-expressed and Secreted
RNA	Ribonucleic acid
SEA	Staphylococcal enterotoxin A
Spe C	Streptococcal pyrogenic exotoxin C
Spe F	Streptococcal pyrogenic exotoxin F
TBK	TANK binding kinase

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