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Biological evaluation of medical devices —

Part 33: Guidance on tests to evaluate genotoxicity — Supplement to ISO 10993-3

Évaluation biologique des dispositifs médicaux —

Partie 33: Directives sur les essais pour évaluer la génotoxicité — Supplément à l'ISO 10993-3

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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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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT), see the following URL: Foreword — Supplementary information.

The committee responsible for this document is ISO/TC 194, *Biological and clinical evaluation of medical devices*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *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 delayed-type hypersensitivity*

— *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 leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

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— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials (Technical specification)*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical specification)*

— *Part 33: Guidance on tests to evaluate genotoxicity - Supplement to ISO 10993-3 (Technical Report)*

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Introduction

Genotoxicity tests are designed to detect compounds which induce genetic damage directly or indirectly by various mechanisms. These tests should enable hazard identification with respect to genetic damages. Expression of gene mutations, large scale chromosomal damage, recombination, and numerical changes are generally considered to be essential for heritable effects and the multi-step carcinogenesis. A positive genotoxicity test provides an indication that further testing can be warranted to determine the carcinogenic potential of the compound. Because the relationship between exposure to particular chemicals and carcinogenesis is established for man, while a similar relationship has been difficult to prove for heritable diseases, genotoxicity tests have been used mainly for the prediction of carcinogenicity. Nevertheless, because germ line mutations are clearly associated with human disease, the suspicion that a compound can induce heritable effects is considered to be just as serious as the suspicion that a compound can induce cancer. In addition, the outcome of such tests can be valuable for the interpretation of carcinogenicity studies.

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Biological evaluation of medical devices —

Part 33:
Guidance on tests to evaluate genotoxicity — Supplement to ISO 10993-3

1 Scope

There are differences between the views of regulatory bodies on the subject of genotoxicity testing. The purpose of this Technical Report is to provide background information to facilitate the selection of tests and guidance on the performance of tests.

2 Selection of tests

Since chemicals can induce genetic damage by different mechanisms, a battery of tests sensitive to different types of genetic damage are thought to provide the best assurance for detecting genotoxic hazard. The tests selected usually include tests to detect point mutations and tests to detect chromosomal aberrations. Both bacterial cells and cultured mammalian cells are used to detect genotoxic agents. *in vivo* tests are sometimes incorporated into these test batteries. These tests are sometimes included in the initial test battery or are used to clarify results from *in vitro* tests, see Reference [13].

3 Recommended tests

Although there are some variations in details, the same genotoxicity tests are commonly recommended by most regulatory agencies. The following are commonly recommended tests:

— bacterial reverse mutation test (see OECD 471[1] and Clause 6);

— *in vitro* mammalian chromosome aberration test (see OECD 473[2] and Clause 7);

— *in vitro mammalian micronucleus test* (see OECD 487[6] and Clause 8);

— *in vitro* mammalian cell gene mutation test using mouse lymphoma (L5178Y) cells (see OECD 475[4] and Clause 9);

— *in vivo* mammalian erythrocyte micronucleus test (see OECD 474[3] and Clause 10);

— *in vivo* chromosome aberration test (see OECD 475[5] and Clause 11).

For medical devices, a battery of tests is commonly used for genotoxicity evaluations. The general strategy identified in ISO 10993-3 is as follows:

a) test for gene mutations in bacteria. Bacterial Reverse Mutation Assay, OECD 471[1] technically modified for medical devices to allow, for example, testing with extracts from devices (see Clause 6);

and either

b) an *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells, Chromosome aberration test, OECD 473[2] technically modified for medical devices (see Clause 7), or

c) an *in vitro* mouse lymphoma tk assay, OECD 476[5] technically modified for medical devices (see Clause 8) including detection of small (slow growing) and large colonies, or

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