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Biological evaluation of medical devices —

Part 22: Guidance on nanomaterials

Évaluation biologique des dispositifs médicaux —
Partie 22: Lignes directrices sur les nanomatériaux

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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).

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 on 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 the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

A list of all parts in the ISO 10993 series can be found on the ISO website.

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Introduction

This document is intended as guidance for the biological evaluation of medical devices that contain, generate or are composed of nanomaterials. Multiple definitions have been developed for the term nanomaterial. For the purposes of this document, the ISO definition will be used: A material is considered a nanomaterial when it has a size at the nanoscale including external and internal dimensions, i.e. when it has a size or is composed of structures with a length of approximately between 1 nm and 100 nm (ISO/TS 80004-1:2015). For regulatory purposes, it is advisable to check if specific national or regional regulatory definitions are applicable. It should be realized that other characteristics (e.g. nanospecific properties) might also be included in such definitions.

Morphological structures created on the surface of a medical device can also have sizes in the nanoscale. Therefore, possible effects of such structures on the biological response to the device also need to be considered.

Nano-objects having a length range from 1 nm to 100 nm can be generated during the life cycle of a medical device, so the evaluation of possible adverse effects due to the generation of nano-objects either from preparation, use, wear or degradation of medical devices needs to be addressed. This applies to medical devices manufactured using nanomaterials and medical devices that are manufactured not using nanomaterials but having the potential to generate nanoscale wear and/or degradation particles. For the biological evaluation of medical devices, knowledge on the potential generation and/or release of nano-objects from such materials is essential.

The procedures as described in the ISO 10993 series for the biological evaluation of medical devices can be used for the biological evaluation of those medical devices that contain nano-objects that are not released from such a device as they are an integrated part of the device. However, when release of the nano-objects is possible, a safety evaluation should also be performed on the released nano-objects. In addition to evaluating a medical device, nanomaterial components or constituents can also be separately evaluated.

This document provides trained professionals, in the context of medical device evaluation, a general approach to biological evaluation of nanomaterials and addresses how the other parts of the ISO 10993 series can be used when dealing with the evaluation of nanomaterials. It is likely that the various assays as described in the ISO 10993 series are not always appropriate as such in the testing of nanomaterials. Nanomaterials by themselves can be present as powders or colloid dispersions, but also can be present in medical devices while incorporated in a matrix, as nanostructured material or as surface structures on materials and/or medical devices. In general, nanomaterials themselves need to be evaluated instead of extracts as usually used when testing biomaterials or medical devices. Nanomaterials pose specific challenges when applying test systems commonly used for medical device evaluation and when interpreting test results.

The field of nanotechnology, development of nanomaterials and the evaluation of potential toxicity of such materials are emerging fields and this document represents only the knowledge at the time of writing. Although appropriate tools and methods for evaluation of nanomaterials are still under development, data on the characteristics and biological effects of nanomaterials should be provided in order to address safety issues in their application in the medical device field, taking into consideration a risk/benefit analysis.

This document provides guidance on how to perform a biological evaluation for those medical devices that contain, generate, or are composed of nanomaterials within a risk management process as described in ISO 10993.

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Biological evaluation of medical devices —

Part 22: Guidance on nanomaterials

1 Scope

This document describes considerations for the biological evaluation of medical devices that are composed of or contain nanomaterials. In addition, this guidance can also be used for the evaluation of nano-objects generated as products of degradation, wear, or from mechanical treatment processes (e.g. *in situ* grinding, polishing of medical devices) from (components of) medical devices that are manufactured not using nanomaterials.

This document includes considerations on the:

— characterization of nanomaterials;

— sample preparation for testing of nanomaterials;

— release of nano-objects from medical devices;

— toxicokinetics of nano-objects;

— biological evaluation of nanomaterials;

— presentation of results;

— risk assessment of nanomaterials in the context of medical device evaluation;

— biological evaluation report;

— nanostructures on the surface of a medical device, intentionally generated during the engineering, manufacturing or processing of a medical device.

The following are excluded from this document:

— natural and biological nanomaterials, as long as they have not been engineered, manufactured or processed for use in a medical device;

— intrinsic nanostructures in a bulk material;

— nanostructures on the surface of a medical device, generated as an unintentional by-product during the engineering, manufacturing or processing of a medical device.

NOTE Examples of unintentional nanostructures on the surface of a medical device are extrusion draw lines and machining/tool marks.

This document is intended to provide a general framework and highlights important aspects which need to be considered when assessing the safety of medical devices composed of, containing and/or generating nano-objects. Additionally, the document identifies several common pitfalls and obstacles which have been identified when testing nanomaterials compared to bulk materials or small molecule chemical species. As a technical report (TR), this document represents the current technical knowledge related to nanomaterials. No detailed testing protocols are outlined or provided. This document can serve as a basis for future documents containing detailed protocols with a focus on nanomaterial testing.

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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 (all parts), *Biological evaluation of medical devices*

ISO/TR 13014, *Nanotechnologies — Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment*

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993 (all parts), ISO/TR 13014 and ISO 14971 and the following apply.

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

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

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

3.1
aggregate
particle comprising strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of calculated surface areas of the individual components

Note 1 to entry: The forces holding an aggregate together are strong forces, for example, covalent bonds, or those resulting from sintering or complex physical entanglement.

Note 2 to entry: Aggregates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO/TS 80004-2:2015, 3.5, modified — definition and Note 1 to entry changed]

3.2
agglomerate
collection of weakly bound particles or *aggregates* (3.1) or mixtures of the two where the resulting external surface area is similar to the sum of the surface areas of the individual components

Note 1 to entry: The forces holding an agglomerate together are weak forces, for example van der Waals forces, or simple physical entanglement.

Note 2 to entry: Agglomerates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO/TS 80004-2:2015, 3.4]

3.3
engineered nanomaterial
nanomaterial (3.7) designed for a specific purpose or function

[SOURCE: ISO/TS 80004-1:2015, 2.8]

3.4
incidental nanomaterial
nanomaterial (3.7) generated as an unintentional by-product of a process

Note 1 to entry: The process includes manufacturing, bio-technological or other processes.

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Note 2 to entry: See “ultrafine particle” in ISO/TR 27628:2007, 2.21.

[SOURCE: ISO/TS 80004-1:2015, 2.10]

3.5
manufactured nanomaterial
nanomaterial (3.7) intentionally produced to have selected properties or composition

[SOURCE: ISO/TS 80004-1:2015, 2.9]

3.6
nanofibre
nano-object (3.8) with two similar external dimensions in the *nanoscale* (3.12) and the third dimension significantly larger

Note 1 to entry: A nanofibre can be flexible or rigid.

Note 2 to entry: The two similar external dimensions are considered to differ in size by less than three times and the significantly larger external dimension is considered to differ from the other two by more than three times.

Note 3 to entry: The largest external dimension is not necessarily in the nanoscale.

[SOURCE: ISO/TS 80004-6:2013, 2.6]

3.7
nanomaterial
material with any external dimension in the *nanoscale* (3.12) or having internal structure or surface structure in the nanoscale

Note 1 to entry: This generic term is inclusive of *nano-object* (3.8) and *nanostructured material* (3.17).

Note 2 to entry: See also 3.3 to 3.5.

Note 3 to entry: For regulatory purposes, it is advisable to check if specific national or regional regulatory definitions are applicable. It should be realized that different size ranges or other properties might be included in such definitions.

[SOURCE: ISO/TS 80004-1:2015, 2.4, modified — Note 2 to entry modified and Note 3 to entry added]

3.8
nano-object
discrete piece of material with one, two or three external dimensions in the *nanoscale* (3.12)

Note 1 to entry: The second and third external dimensions are orthogonal to the first dimension and to each other.

[SOURCE: ISO/TS 80004-1:2015, 2.5]

3.9
nanoparticle
nano-object (3.8) with all external dimensions at the *nanoscale* (3.12) where the length of the longest and the shortest axes of the nano-object do not differ significantly

Note 1 to entry: If the dimensions differ significantly (typically by more than 3 times), terms such as *nanofibre* or *nanoplate* may be preferred to the term nanoparticle.

[SOURCE: ISO/TS 80004-2:2015, 4.4]

3.10
nanoplate
nano-object (3.8) with one external dimension in the *nanoscale* (3.12) and the two other external dimensions significantly larger

Note 1 to entry: The smallest external dimension is the thickness of the nanoplate.

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Note 2 to entry: The two significantly larger dimensions are considered to differ from the nanoscale dimension by more than three times.

Note 3 to entry: The larger external dimensions are not necessarily in the nanoscale.

[SOURCE: ISO/TS 80004-6:2013, 2.4]

3.11
nanorod
solid *nanofibre* (3.6)

[SOURCE: ISO/TS 80004-2:2015, 4.7]

3.12
nanoscale
length range approximately from 1 nm to 100 nm

Note 1 to entry: Properties that are not extrapolations from larger sizes are predominantly exhibited in this length range.

Note 2 to entry: Properties impacting biocompatibility can also occur at larger sizes, e.g. between 100 nm and 1 um.

[SOURCE: ISO/TS 80004-1:2015, 2.1, modified — Note 2 to entry was added]

3.13
nanoscale phenomenon
effect attributable to the presence of *nano-objects* (3.8) or *nanoscale* (3.12) regions

[SOURCE: ISO/TS 80004-1:2015, 2.13]

3.14
nanoscale property
characteristic of a *nano-object* (3.8) or *nanoscale* (3.12) region

[SOURCE: ISO/TS 80004-1:2015, 2.14]

3.15
nanoscience
study, discovery and understanding of matter, where size- and structure-dependent properties and phenomena manifest, predominantly in the *nanoscale* (3.12), distinct from those associated with individual atoms or molecules, or extrapolation from larger sizes of the same material

[SOURCE: ISO/TS 80004-1:2015, 2.2]

3.16
nanostructure
composition of inter-related constituent parts in which one or more of those parts is a *nanoscale* (3.12) region

Note 1 to entry: A region is defined by a boundary representing a discontinuity in properties.

[SOURCE: ISO/TS 80004-1:2015, 2.6]

3.17
nanostructured material
material having internal *nanostructure* (3.16) or surface nanostructure

Note 1 to entry: This definition does not exclude the possibility for a *nano-object* (3.8) to have internal structure or surface structure. If external dimension(s) are in the *nanoscale* (3.12), the term nano-object is recommended.

[SOURCE: ISO/TS 80004-1:2015, 2.7]

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3.18
nanotechnology
application of scientific knowledge to manipulate and control matter predominantly in the *nanoscale* (3.12) to make use of size- and structure-dependent properties and phenomena distinct from those associated with individual atoms or molecules, or extrapolation from larger sizes of the same material

Note 1 to entry: Manipulation and control includes material synthesis.

[SOURCE: ISO/TS 80004-1:2015, 2.3]

3.19
nanotube
hollow *nanofibre* (3.6)

[SOURCE: ISO/TS 80004-2:2015, 4.8]

3.20
representative test material
RTM
material, which is sufficiently homogenous and stable with respect to one or more specified properties, and is implicitly assumed to be fit for its intended use in the development of measurement and test methods that target properties other than those for which homogeneity and stability have been demonstrated

[SOURCE: ISO/TS 16195:2013; 3.1, modified — Notes 1 and 2 to entry deleted]

4 General principles

4.1 General considerations

Nanomaterials are manufactured and used because of the specific properties that can be associated with the decrease in size accompanied by an increase of surface area. Also, materials with dimensions in the size range >100 nm or <1 micron can elicit properties different from those in the macroscale (>1 micron). For these types of particulate materials, it might be considered to perform an assessment similar to nanomaterials in the size range between 1 nm and 100 nm.

The biological evaluation of any material or medical device intended for use in humans should form part of a structured biological evaluation program within a risk management process in accordance with ISO 14971 and ISO 10993-1. The risk management process is applicable to devices that contain or are composed of nanomaterials. The risk management process is also applicable to devices that generate nano-objects as products of degradation, wear, or from mechanical treatment processes (e.g. *in situ* grinding, polishing of medical devices). Similarly, if there is release of nano-objects, there are specific challenges in the safety evaluation of such products. The safety evaluation and risk assessment of nanomaterials requires a special focus as various nanomaterials consisting of the same chemical substance can have a different toxicological risk profile depending on a number of variables, including size, surface chemistry, physicochemical properties and intended application. For medical devices that are composed of or that contain nanomaterials, the safety evaluation program should specifically address issues related to the safety evaluation of nanomaterials. The ISO 10993 series, ISO/TR 13014, ISO 14971, and References [5],[14],[15],[16],[21],[23],[24],[28],[46],[47] and [49] deal with biological evaluation of medical devices and various aspects of nanomaterials.

Nanomaterials have sizes similar to structures at subcellular levels including DNA, and thus (theoretically) can reach and interact with such structures. Also, medical devices utilizing materials with nanoscale internal structures or with surface nanoscale features associated with coatings, functionalization, or with other topographical features on the nanoscale, that are intended as part of the functionality of the device, can have specific and unique properties that might need to be addressed in the biological evaluation. For example, it has been shown that nanoscale surface topography can influence cell alignment, cell morphology, cell signalling, gene expression and extracellular matrix [52] [53] [54].

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