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BSI Standards Publication

Biological evaluation of medical devices

Part 22: Guidance on nanomaterials

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National foreword

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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).

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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.

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.

TECHNICAL REPORT **ISO/TR 10993-22:2017(E)**

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.