Nanomaterials and medical device regulations

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By Royal Charter

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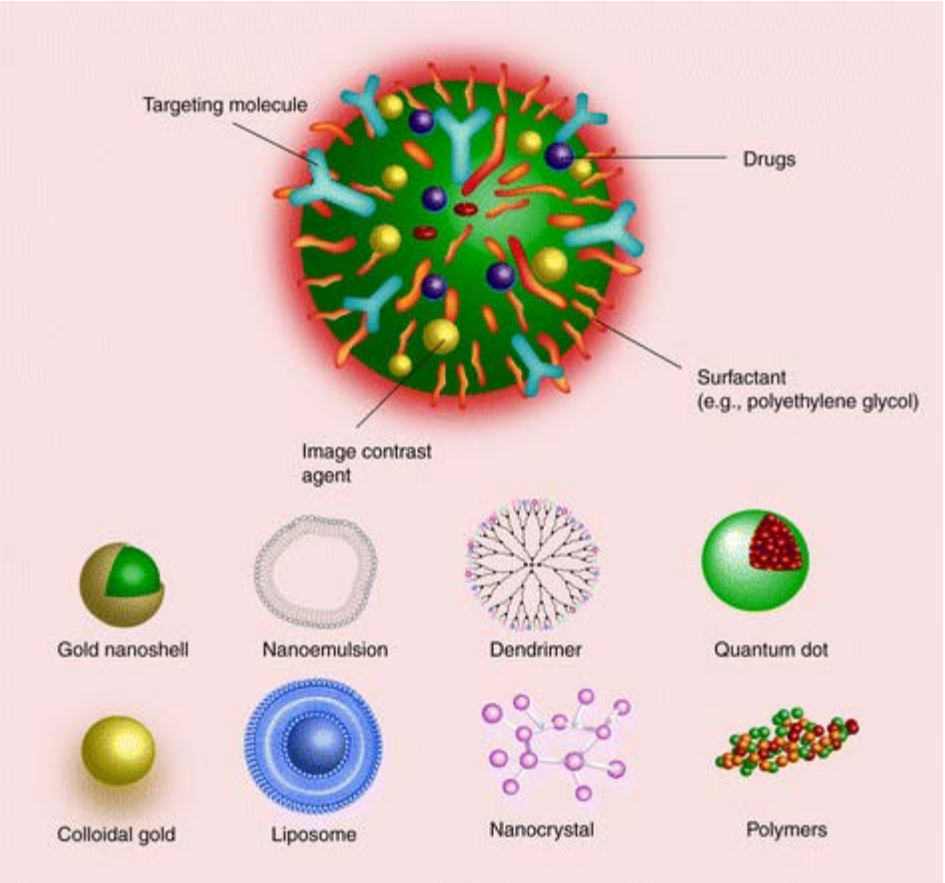
Nanomaterials

Outline

- What are nanomaterials
- The MDD and current EU guidance
- The future EU MDR
- Standards
    - ISO 10993-22
- FDA



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Introduction

Recommendation on the definition of a nanomaterial

2011/696/EU

A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

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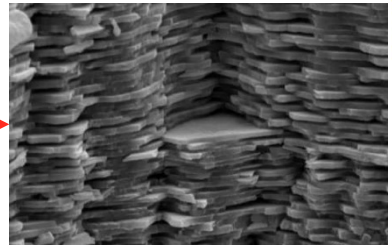
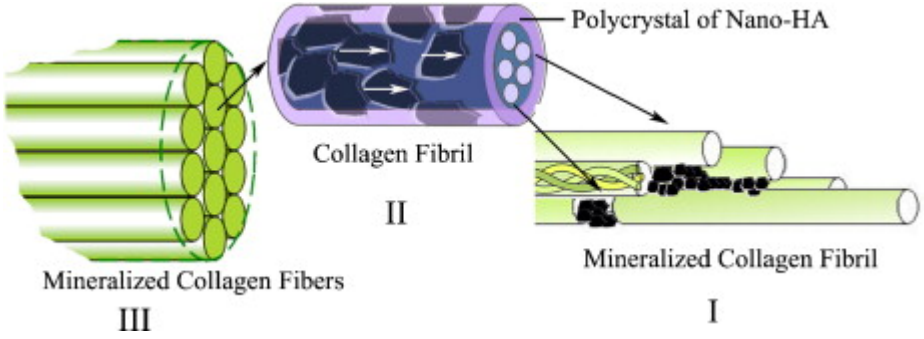
Examples of nanomaterials

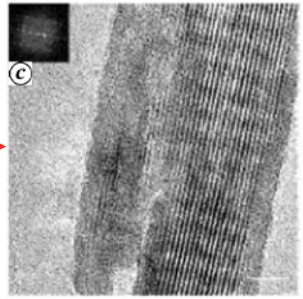
Nacre
$CaCO_3$
platelets



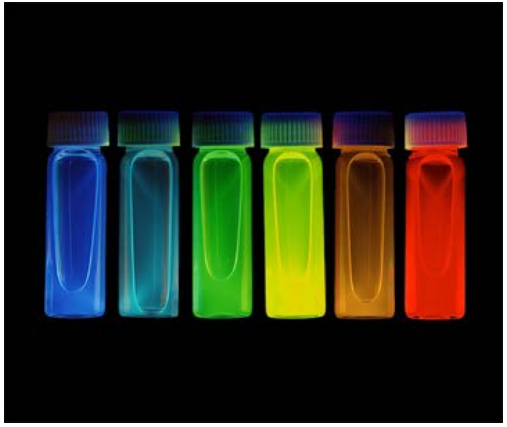


Bone (collagen and HA)

Steel
CNTs



Glass with
colloidal gold



Quantum
dots (CdSe)

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Nanomaterials

Pros and cons

Pros	Cons
Enhanced properties • Mechanical • Optical • Thermal • Biological • Chemical	Uncertainty over risk • Environmental • Biological • Toxicological • Exposure limits • Mode of action

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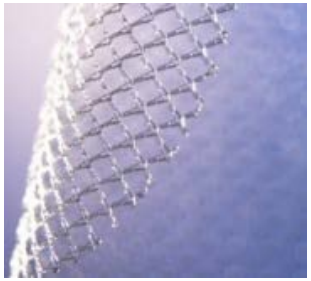
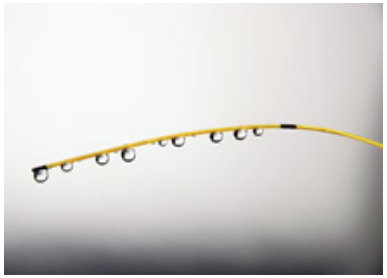
Examples of medical devices incorporating nanomaterials

Synthetic bone graft



Orthopaedic implants



Catheters

Wound care

In vivo imaging

AIMD

Dental fillers and composites

Dental crowns

IVD

Instruments

EU regulations and guidance

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Current EU MDD (93/42/EEC)

Annex I

- No explicit requirements in relation to nanomaterials

However:

All risks must be assessed and eliminated / reduced as far as possible

- ER 1
- ER 2
- ER 6

Material toxicity, compatibility, contaminants, residues, leachants must be evaluated

- ER 7.1
- ER 7.2
- ER 7.3
- ER 7.5

Risk of injury minimised in connection with physical features / dimensions

- ER 9.2

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Current EU AIMDD (90/385/EEC) & **IVDD (98/79/EC)**

Annex I

- No explicit requirements in relation to nanomaterials

However:

All risks must be assessed and eliminated / reduced as far as possible

- ER 1 / **A 1**
- ER 2 / **A 2**
- ER 5

Material toxicity, compatibility, contaminants, residues, leachants must be evaluated

- ER 9 / **B 1**

Risk of injury minimised in connection with physical features / dimensions

- ER 9.2 / **B 3.3**

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PUBLIC CONSULTATION ON THE DETERMINATION OF POTENTIAL HEALTH EFFECTS OF NANOMATERIALS USED IN MEDICAL DEVICES

SCENIHR report (January 2015)

In the field of medical devices, the alleged use of nanomaterials has been identified by Notified Bodies in the following applications:

- Carbon nanotubes in bone cements;
- Nanopaste hydroyapatite powder for bone void filling;
- Polymer setting material with nanoparticles in dental cements;
- Polycrystalline nanoceramics in dental restorative materials;
- Nanosilver or other nanomaterials used as coatings on implants and catheters;
- Nanosilver used as an antibacterial agent, for example in wound dressings;
- Iron-oxide nanoparticles being injected into tumour cells to be heated-up by radiation or an external magnetic field.

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SCENIHR report

This Guidance should take into account different categories of medical devices such as:

a. Non-invasive medical devices,

e.g. devices coming into contact with the intact skin,

b. Invasive devices (surgical or not), e.g.:

- Wound care materials,
- implantable medical devices,
- dental and bone fillings and cements,
- injectable nanomaterials.

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PUBLIC CONSULTATION ON THE DETERMINATION OF POTENTIAL HEALTH EFFECTS OF NANOMATERIALS USED IN MEDICAL DEVICES

SCENIHR report

In this assessment, where relevant, the SCENIHR is invited to differentiate between

- free,
- fixed, and
- embedded nanomaterials.

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PUBLIC CONSULTATION ON THE DETERMINATION OF POTENTIAL HEALTH EFFECTS OF NANOMATERIALS USED IN MEDICAL DEVICES

SCENIHR report

The Guidance should also differentiate the cases where the nanomaterial might

- inadvertently be released into the patient's or user's body and
- he cases where the nanomaterial is deliberately intended to be released into the human body.

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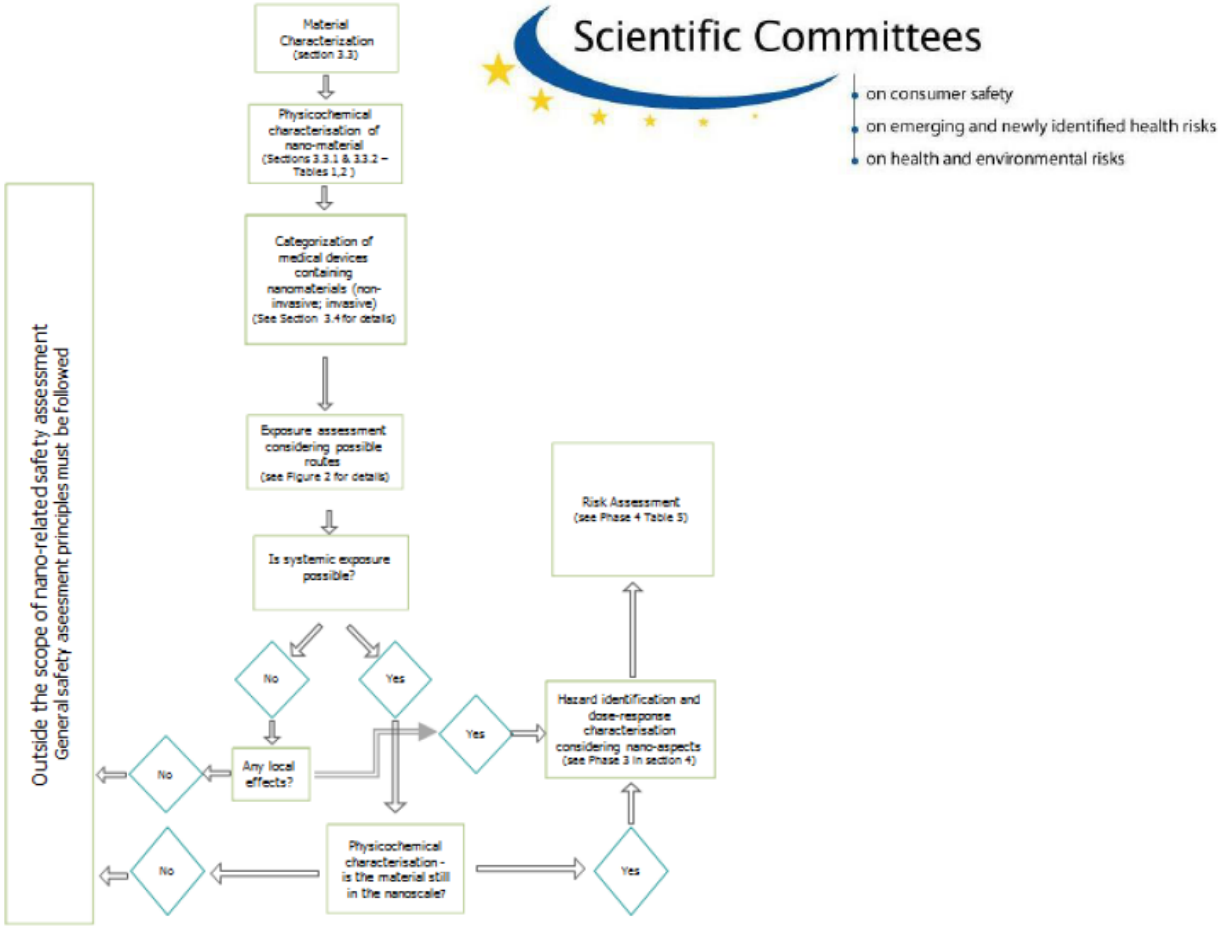
Safety assessment of nanomaterials used in medical devices

SCENIHR report



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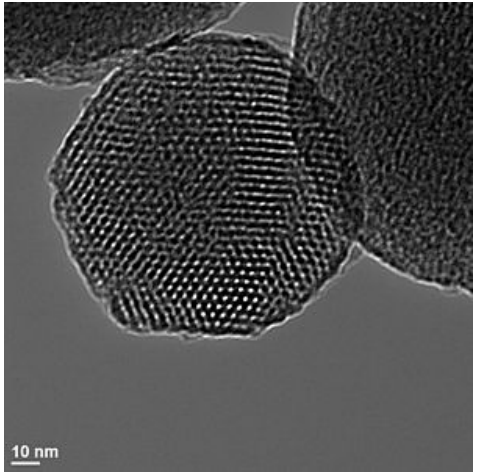
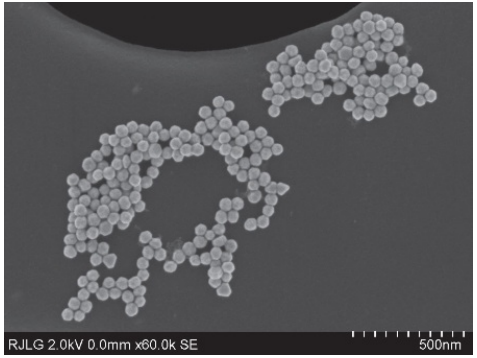
Physicochemical characterisation of nanomaterials

Chemical composition	• MS, AAS, ICP-MS, FTIR, NMR, UVVis, HPLC, GC/LC-MS, XRD, Raman spectroscopy
Particle size	• FFF, HDC, HPLC, AUC, CLS disc centrifugation, TEM, SEM, STEM, HRTEM, STM, AFM, DLS, DMA, NTA
Particle and mass concentration	• UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS
Specific surface area	• BET
Surface chemistry	• LDE, SPM, XPS, MS, RS, FTIR, NMR, AUC (for surface composition), GE, SPM, LDE, Nano SIMS, SERS





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Physicochemical characterisation of nanomaterials

Surface charge	• PALS
Redox potential	• Potentiometric methods, X-ray absorption spectroscopy
Solubility and partition properties	• Solubility/ dissolution rate in water and other solvents
pH	• pH in aqueous media
Viscosity	• OECD 114

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Physicochemical characterisation of nanomaterials

Density and pore density	• DIN ISO 697, EN/ISO 60
Dustiness	• EN 15051:2006, DIN 33897-2.
Chemical reactivity/ catalytic activity	• Kinetic measurements of chemical, biochemical and/or catalyzed reactions
Photocatalytic activity	• TEM, UV, X-ray topography

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Examples of methods for size analysis

SEM (STEM)	• above 50-100 nm
TEM	• Few nm
STM	• Not stated
HRTEM	• below 0.2 nm
AFM	• Scanned area is limited
SAXS	• 5-25 nm
DLS & NTA	• (1-2000 nm) & (10-15000 nm)

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Release of nanomaterials from medical devices

Highest potential for release of nanomaterials from medical devices is associated with devices:

- in which the nanomaterial is intended to be released,
- that are composed of free nanomaterials
- containing free nanomaterials
- release/loosening of nanomaterials present as coatings on medical devices
- chemical breakdown or wear-and-tear processes due to (bio)degradation of medical devices
- grinded, polished or shaped during application,

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Exposure routes to nanomaterials released from medical devices

For patients, the following exposure routes may be applicable:

- inhalation exposure
- dermal exposure
- mucosal exposure
- oral exposure
- parenteral exposure
- ocular exposure

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Estimation of exposure for risk assessment

			Type of application of nanomaterials External exposure/internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	Type of contact	Duration of contact		Weak (physisorb)	Strong (chemisorb)	In degradable materials*	In non-degradable materials
Surface device	Intact skin	≤ 24 h	H/N	M/N	M/N	L/N	N/N
		>24 h to 30 d	H/N	M/N	M/N	M/N	N/N
		>30 d	H/N	M/N	M/N	H/N	N/N
	Intact mucosal membrane	≤ 24 h	H/L	M/L	M/N	L/L	N/N
		>24 h to 30 d	H/M	M/M	M/L	M/M	N/N
		>30 d	H/M	M/M	M/L	H/M	N/N
	Breached or compromised surface	≤ 24 h	H/H	M/M	M/L	L/M	N/N
		24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		30 d	H/H	M/M	M/L	H/M	N/N
External Communicating device	Blood path, indirect **	≤ 24 h	na	M/M	M/L	L/L	N/N
		>24 h to 30 d	na	M/M	M/L	M/M	N/N
		>30 d	na	M/M	M/L	H/M	N/N
	Tissue/bone/dentin	≤ 24 h	H/H	M/M	M/L	L/L	N/N
		>24 h to 30 d	H/H	M/M	M/L	M/M	N/N
		>30 d	H/H	M/M	M/L	H/H	N/N
	Circulating blood***	≤ 24 h	na	H/H	H/H	L/L	N/N
		>24 h to 30 d	na	H/H	H/H	M/M	N/N
		>30 d	na	H/H	H/H	H/H	N/N
Implant device	Tissue/bone	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N
	Blood	≤ 24 h	H/H	H/H	H/L	L/L	N/N
		>24 h to 30 d	H/H	H/H	H/L	M/M	N/N
		>30 d	H/H	H/H	H/L	H/H	N/N

H - high
M - medium
L - low
N - negligible
N/A – not applicable

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Safety assessment of nanomaterials used in medical devices

SCENIHR report

- Summary of methods and literature:
  - Toxicokinetics
  - Cytotoxicity
  - Acute toxicity
  - Irritation
  - Delayed-type hypersensitivity
  - Genotoxocity
  - Haemocompatibility
  - Repeated-dose toxicity
  - Implantation
  - Chronic toxicity / carcinogenicity
  - Reproductive and developmental toxicity

Testing proposed	Non-invasive short term use	Non-invasive long term use	Invasive short term use	Invasive long term use
Low exposure	Phys: chem data	Phys: chem data	Phys: chem data	Phys: chem data
	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*
	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*
	Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity
		Genotoxicity *in vitro*		Genotoxicity *in vitro*
				General Immuno toxicity testing
Medium exposure Additional tests		Genotoxicity *in vivo*	Other *in vitro* plus *in silico* testing*	28/90 day *in vivo* toxicity test
		Immuno toxicity at location site	Genotoxicity *in vitro* and *in vivo*	*In vitro* and *in vivo* (repeated dose) genotoxicity testing
		Persistence /accumulation studies at location site only		ADME including persistence /accumulation studies
High exposure Additional tests	Selected *in vivo* acute toxicity tests focussed on location site(s)	Selected *in vivo* chronic toxicity tests focussed on location site(s)	*In vivo* acute toxicity tests	*In vivo* chronic toxicity tests may include reprotox depending on patient group.

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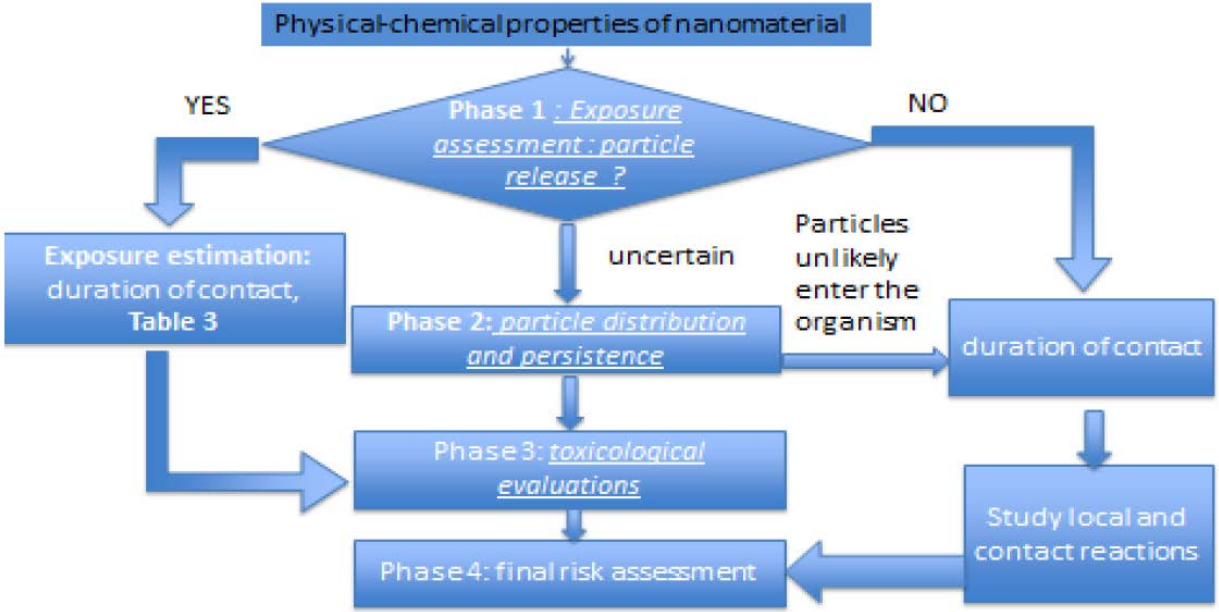
RISK EVALUATION

SCENIHR report



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RISK EVALUATION

SCENIHR report

Release of nanoparticles	Non-invasive		Invasive Lung		Invasive Other	
	Short exposure	Long exposure	Short exposure	Long exposure	Short exposure	Long exposure
Low/insignificant	N/VL*	L/F**	L	F	L	F
Medium	L/F	L/F	L/F	F	L/F	F
High	L/F	L/F	F	F	F	F

Assessment:
F – full
L – limited
VL – very limited
N – none

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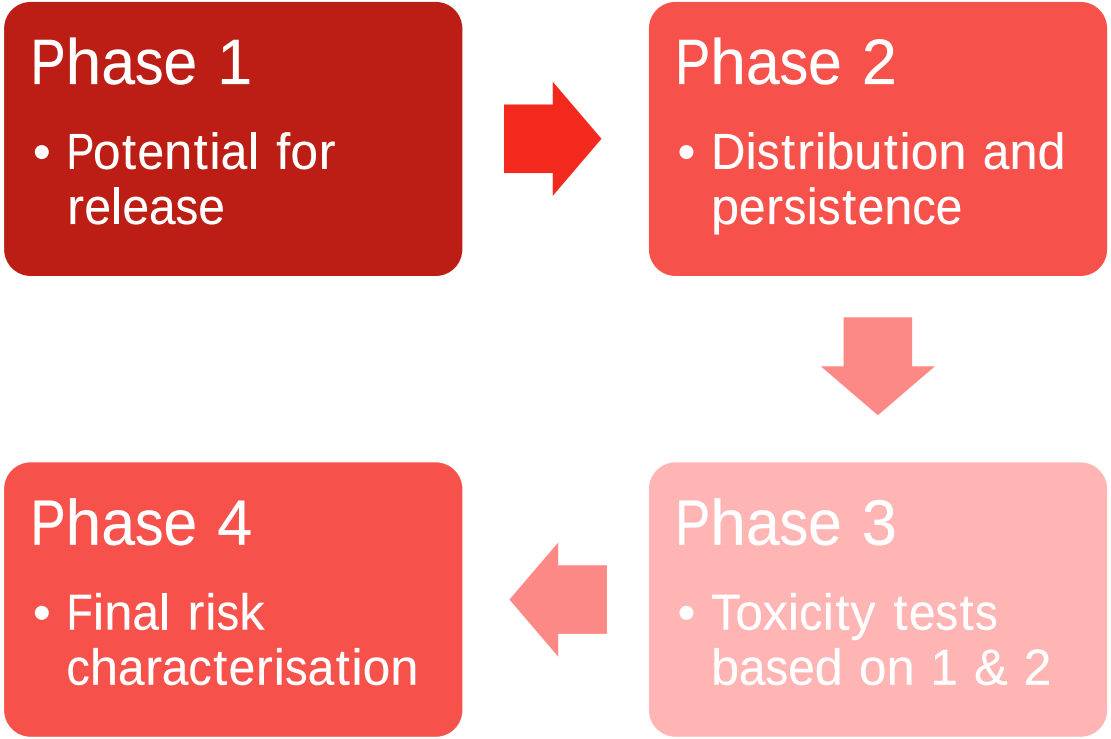
RISK EVALUATION

SCENIHR report



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The future EU MDR

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The future MDR

Current text

Whereas

(15) There is scientific uncertainty about the risks and benefits of nanomaterials used for medical devices… manufacturers should take special care when using nanoparticles for which there is a high or medium potential for internal exposure, those devices should be subject to the most severe conformity assessment procedure.

Article 2 – definitions

(18) Taken from 2011/696/EU

Article 3

NM definition may be amended based on technical and scientific progress.

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Article 2

Definitions

(19) ‘particle’

for the purposes of the definition of nanomaterial in point (18), means a minute piece of matter with defined physical boundaries;

(20) ‘agglomerate’

for the purposes of the definition of nanomaterial in point (18), means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components;

(21) ‘aggregate’

for the purposes of the definition of nanomaterial in point (18), means a particle comprising of strongly bound or fused particles;

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ANNEX I

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Chapter II Requirements regarding design and manufacture

- 10. Chemical, physical and biological properties
  - 10.6.
    - Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.

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Annex VIII

CLASSIFICATION RULES

Chapter III. CLASSIFICATION RULES

- 3. SPECIAL RULES
  - 6.7. Rule 19
    - All devices incorporating or consisting of nanomaterial are:
      - in class III if they present a high or medium potential for internal exposure;
      - in class IIb if they present a low potential for internal exposure;
      - in class IIa if they present a negligible potential for internal exposure.

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Class III (and IIb implants)

Conformity assessment procedures – Article 51

Annex IX - **CONFORMITY ASSESSMENT BASED ON A QUALITY MANAGEMENT SYSTEM AND ON ASSESSMENT OF TECHNICAL DOCUMENTATION**

Similar to current Annex II.3 (FQA) + II.4 (DE)

Annex X - **CONFORMITY ASSESSEMENT BASED ON TYPE EXAMINATION**

Annex XI - **CONFORMITY ASSESSEMENT BASED ON PRODUCT CONFORMITY VERIFICATION**

Similar to current Annex III (TE) + V (PQA)

Article 52.4 - class IIb implantable devices, except sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors shall also be subject to the assessment of the technical documentation as specified in Section 4 of Annex IX (similar to current design examination).

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Annex X

For class III implantable devices, and for Class IIb active devices intended to administer and/or remove a medicinal product

NB prepare a clinical evaluation assessment report and submits to expert panel at EC

Scientific opinion within 60 days – NB gives due consideration

Standards

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Standards and guidance

Publically available standards

PAS 71:2011	•Vocabulary – Nanoparticles
PAS 130:2007	•Guidance on the labelling of manufactured nanoparticles and products containing manufactured nanoparticles
PAS 131:2007	•Terminology for medical, health and personal care applications of nanotechnology
PAS 132:2007	•Terminology for the bio-nano interface
PAS 136:2007	•Terminology for nanomaterials
PAS 137:2013	•Nanomaterials and nanotechnology-based products - Guide to regulation and standards
PAS 138:2012	•Disposal of manufacturing process waste containing manufactured nano-objects. Guide
PAS 139:2012	•Detection and characterization of manufactured nano-objects in complex matrices. Guide

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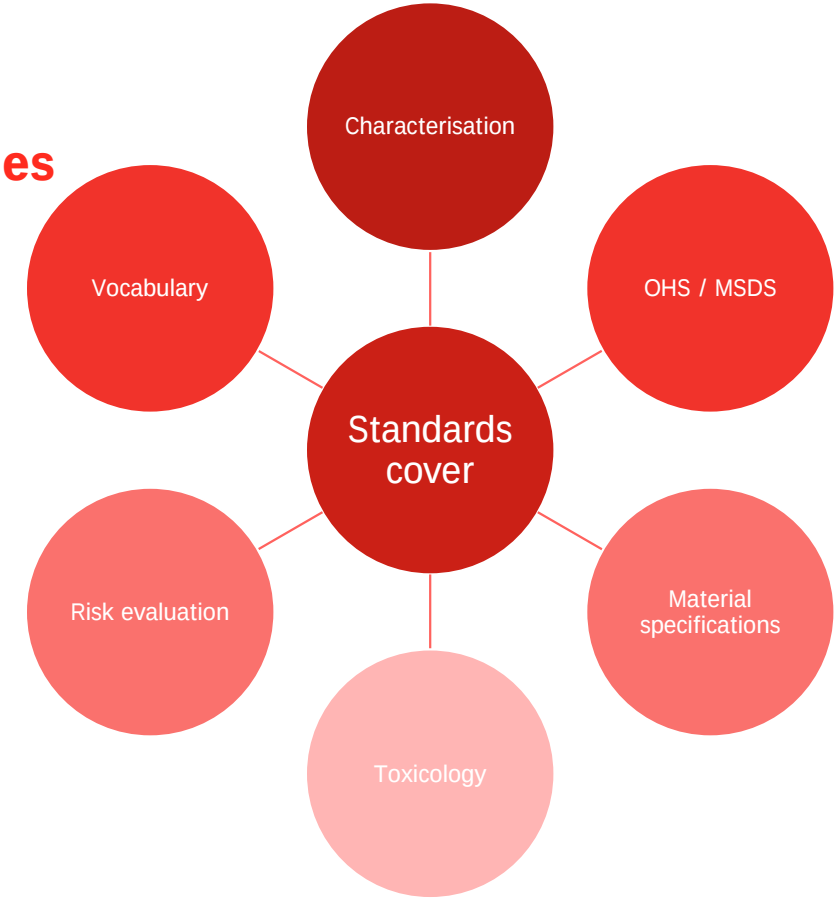
ISO standards

ISO/TC 229 Nanotechnologies

53 published standards

None specifically on medical devices.



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ISO 10993

Series of standards for evaluating biocompatibility of medical devices

Harmonised standards

Evaluation and testing in the risk management process (Part 1)

Animal welfare requirements (Part 2)

Testing

- Genotoxicity, carcinogenicity and reproductive toxicity (3)
- Interactions with blood (4)
- In vitro cytoxtoxity (5)
- Implantation (6)
- Irritation and skin sensitization (10)
- Systemic toxicity (11)
- Immunotoxicology (20)

Ethylene oxide residuals (Part 7)

Chemical / materials characterisation (Parts 9, 13-15, 17-19)

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ISO/DTR 10993-22

Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

Scope

This part of the ISO 10993 series describes considerations for the biological evaluation of medical devices that are composed of or contain nanomaterials. In addition, this guidance may 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.

Definitions (ISO/TS 80004-2:2015)

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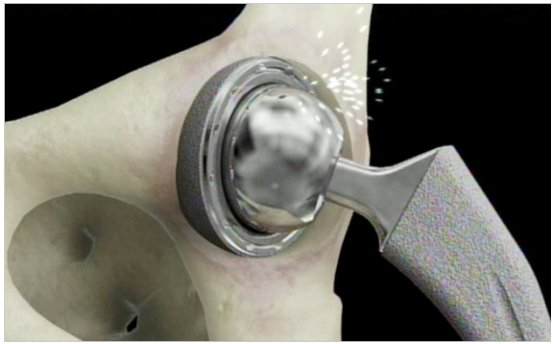
ISO/DTR 10993-22

Considerations in addition to the biological evaluation according to ISO 10993-1



1 Surface nanostructures

2 Nano-objects bound to or incorporated within a medical device; without intention to be released

3 Nano-objects/nanostructures on the surface of or within a medical device; with intentional/expected release from the device

4 Nano-object medical device

5 Nano-objects released from a medical device as product of degradation, wear, or from mechanical treatment processes (e.g. in situ grinding or polishing)

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ISO/DTR 10993-22

Considerations in addition to the biological evaluation according to ISO 10993-1

- Release kinetics (rate and quantity) of the nano-objects and contact duration of the medical device
- Potential cellular or tissue effects due to direct interaction with nano-objects/nanomaterials (beneficial or adverse).
- Characterization of physicochemical properties of the released nano-objects
- Toxicokinetics and tissue distribution of the nano-objects
- Biological evaluation of the nano-objects
- Potential of nano-objects to be generated by degradation, wear or mechanical treatment processes

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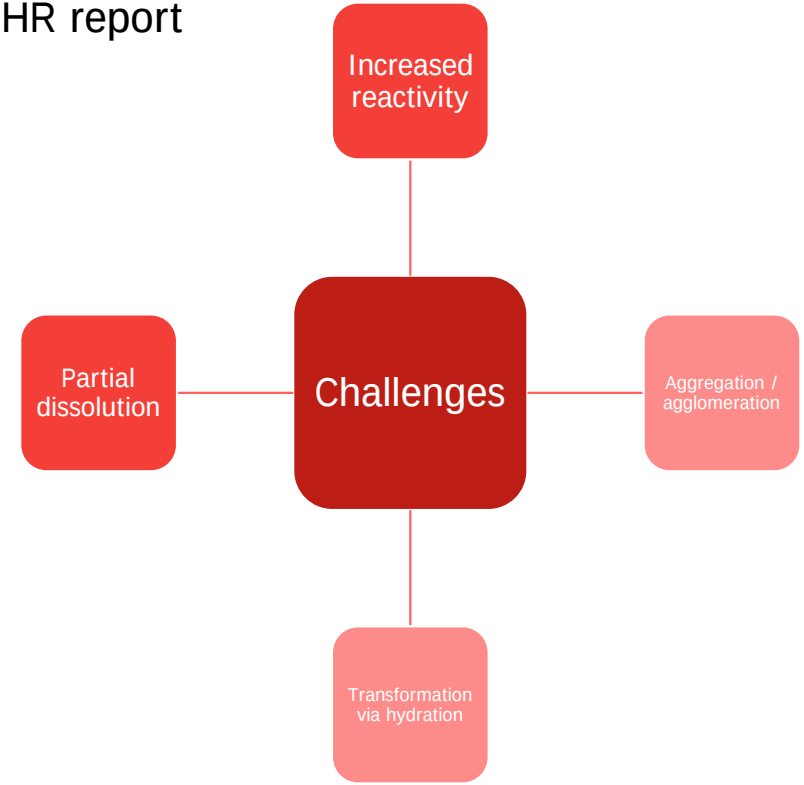
ISO/DTR 10993-22

Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

- Characterisation – similar to SCENIHR report
- Reference materials
- Sample preparation
- Release
- Toxicokinetics
- Toxicological evaluation



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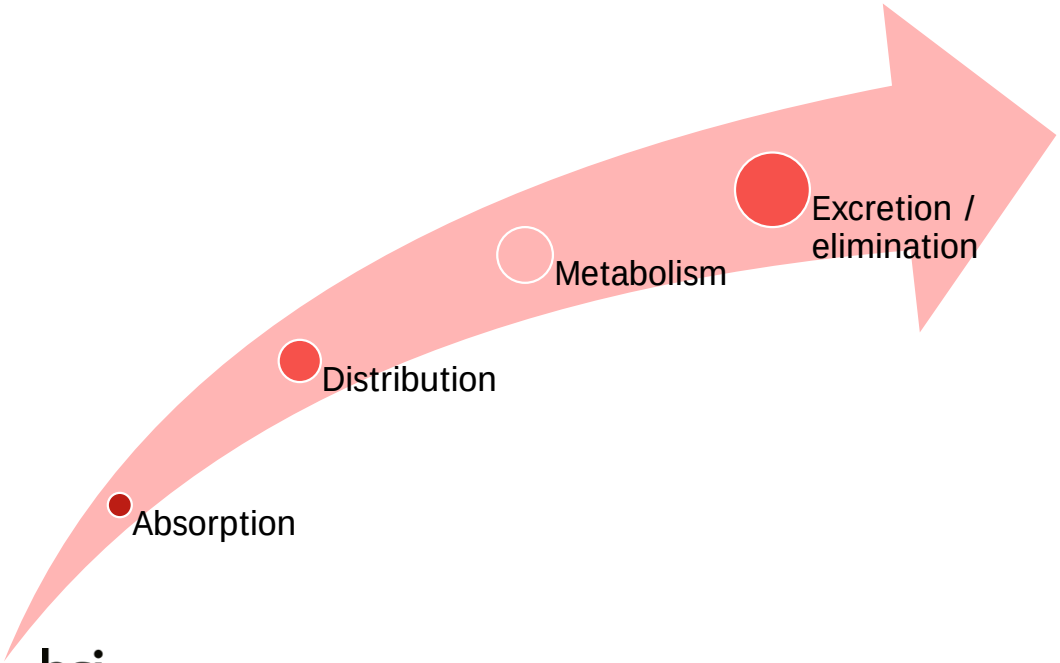
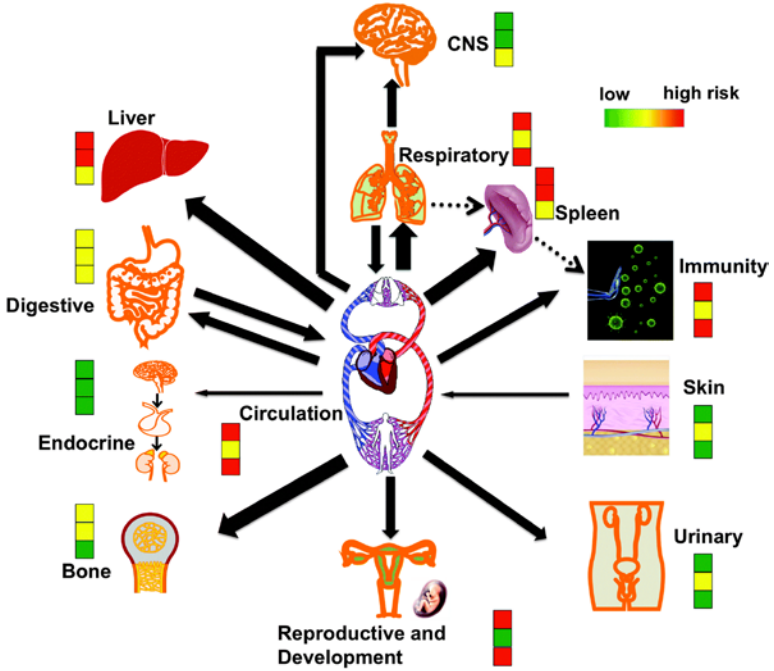
ISO/DTR 10993-22

Toxicokinetics





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ISO/DTR 10993-22

Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

Three fundamental questions:

- Physical description: What does it look like?
- Chemical composition: What is it made of?
- Extrinsic properties: How does it interact with the surrounding environment?

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ISO/DTR 10993-22

Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

Multidisciplinary collaborations are necessary in developing a relevant and reliable characterization program for a specific device

- toxicologists
- physical chemists
- engineers
- others

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ISO/DTR 10993-22

General considerations

- References ISO 10993-1

Additional considerations

- Different properties to bulk form (dose)
- NPs can translocate downstream of site of administration
- Cross cellular / intracellular membrane
- Interrupt DNA synthesis and other cellular functions
- Interact with proteins

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ISO/DTR 10993-22

Cytotoxicity

- References ISO 10993-5

Additional considerations

- Cellular uptake
- Cell type
- Oxidative stress
- Dose metrics
- Aggregation
- Electric charge / optical properties

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ISO/DTR 10993-22

Cytotoxicity

- References ISO 10993-5

Dose metrics

- Mass conc.
- Surface area
- Number conc.

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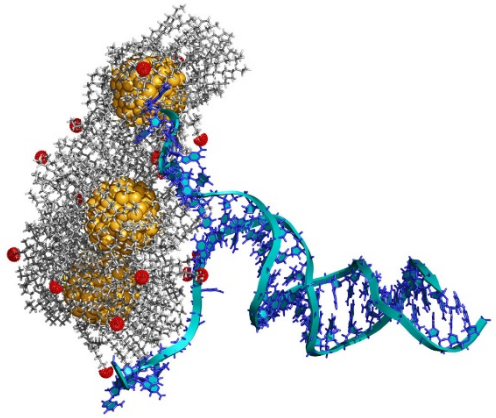
ISO/DTR 10993-22

Genotoxicity, carcinogenicity and reproductive toxicity

- References ISO 10993-3



Additional considerations

In vitro - demonstrate exposure to the cell nucleus (DNA damage)

In vivo – ensure NM reaches target organ

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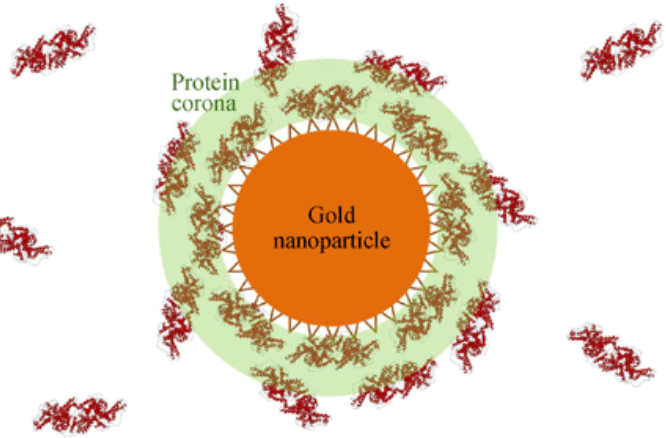
ISO/DTR 10993-22

Immunotoxicity, irritation and sensitization

- References ISO 10993-10 and -20



Additional considerations

NMs enter MPS cells which play a central role in immune system

Nano-object protein complex can result in sensitization

Skin penetration dependent on size and shape

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Haemocompatibility

- References ISO 10993-4

Additional considerations

- NPs can translocate from device to systemic circulation in blood
- Can induce prothrombotic effects and platelet activation
- Surface area
- Complement system activation – inflammatory and hypersensitivity reations

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Systemic toxicity

- References ISO 10993-11

Additional considerations

Cannot be predicted by bulk material toxicity

Potentially crossing all protective barriers including the nuclear membrane, blood-brain and foeto-placental barriers

Special emphasis on the MPS (liver, spleen), kidneys, brain, bone marrow

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Pyrogenicity and implantation

- References ISO 10993-11 and -6

Additional considerations

- Various implantation sites
- Direct injection into appropriate tissue
- Controls

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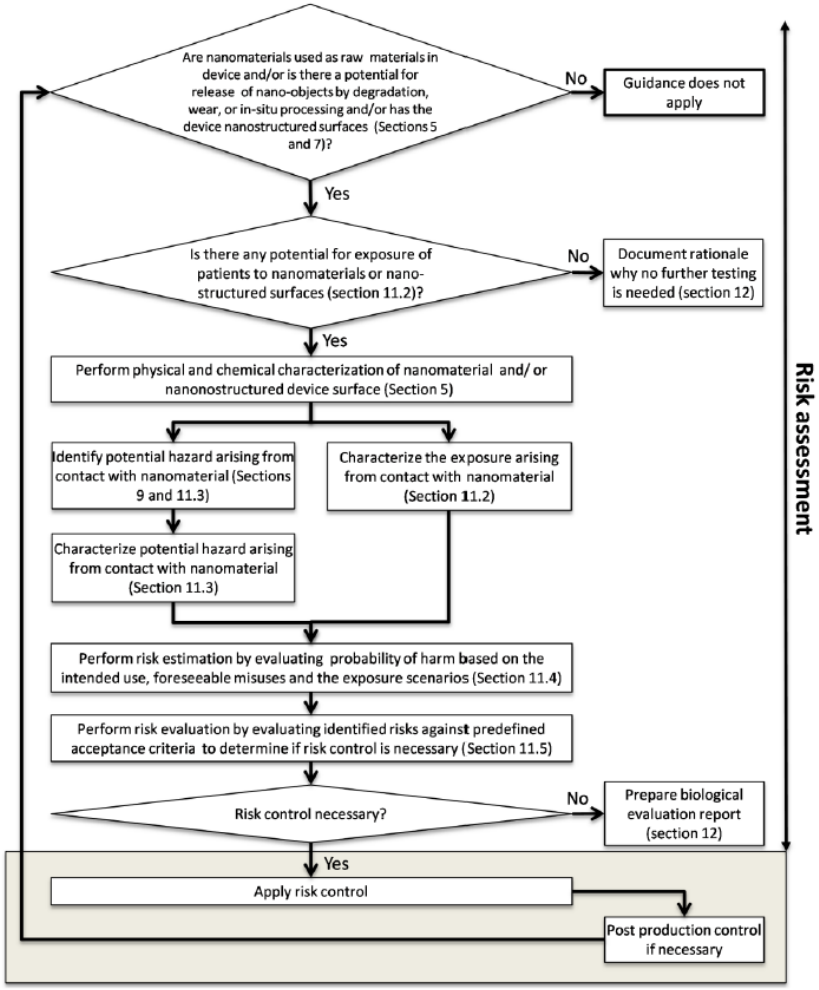
ISO/DTR 10993-22

Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials

- Presentation of characterisation and test results
- Risk assessment
- Biological evaluation report
- Bibliography



FDA

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FDA

FDA's Approach to Regulation of Nanotechnology Products

Where premarket review authority exists, attention to nanomaterials is being incorporated into standing procedures.

For example, new drugs, new animal drugs, biologics, food additives,[3] color additives, certain human devices, and certain new dietary ingredients in dietary supplements are subject to premarket review requirements.

Premarket review processes for these products require applicants to submit data to answer questions related to the safety, effectiveness (where applicable), or regulatory status of the product.

Individual premarket review procedures include attention to whether the use of nanomaterials suggests the need for additional data on safety or effectiveness, as applicable[4].

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FDA

ISO 10993-1 guidance

Limitations may apply when using chemical leachates-based ISO 10993-12 test conditions for the analysis of submicron component biocompatibility assessments.

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FDA

ISO 10993-1 guidance

Assessment

- Careful characterization of the test article.
- Selection of extract conditions (e.g., solvent type) that avoid testing artifacts.
- Assurance that the test article used is representative of the device that is intended to be used clinically.

Test selection

- Consideration of standard biocompatibility tests regarding validity.
- Assurance that the submicron components will not interfere with the conduct of a chosen test.
- Consideration of any additional toxicity issues that might be relevant to submicron particles (absorption, distribution, accumulation, potential metabolism, and elimination).

Conclusions

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Conclusions

Nanomaterials

- A number of nanomaterial–containing devices on the market (covering all classifications and technologies)
- Global regulators are aware, evaluating risks and developing regulations
- Risks need to be considered and evaluated for devices which contain / generate NMs
- Existing ‘state of the art’ characterisation techniques (chemical, physical, biological) used for macro materials may not be appropriate for NMs

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Questions?

Thank you

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