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Medical Devices with Nanomaterials under the EU Regulations

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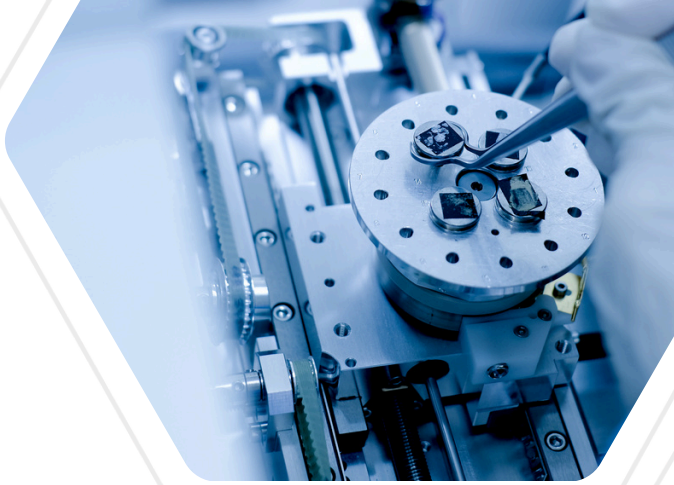
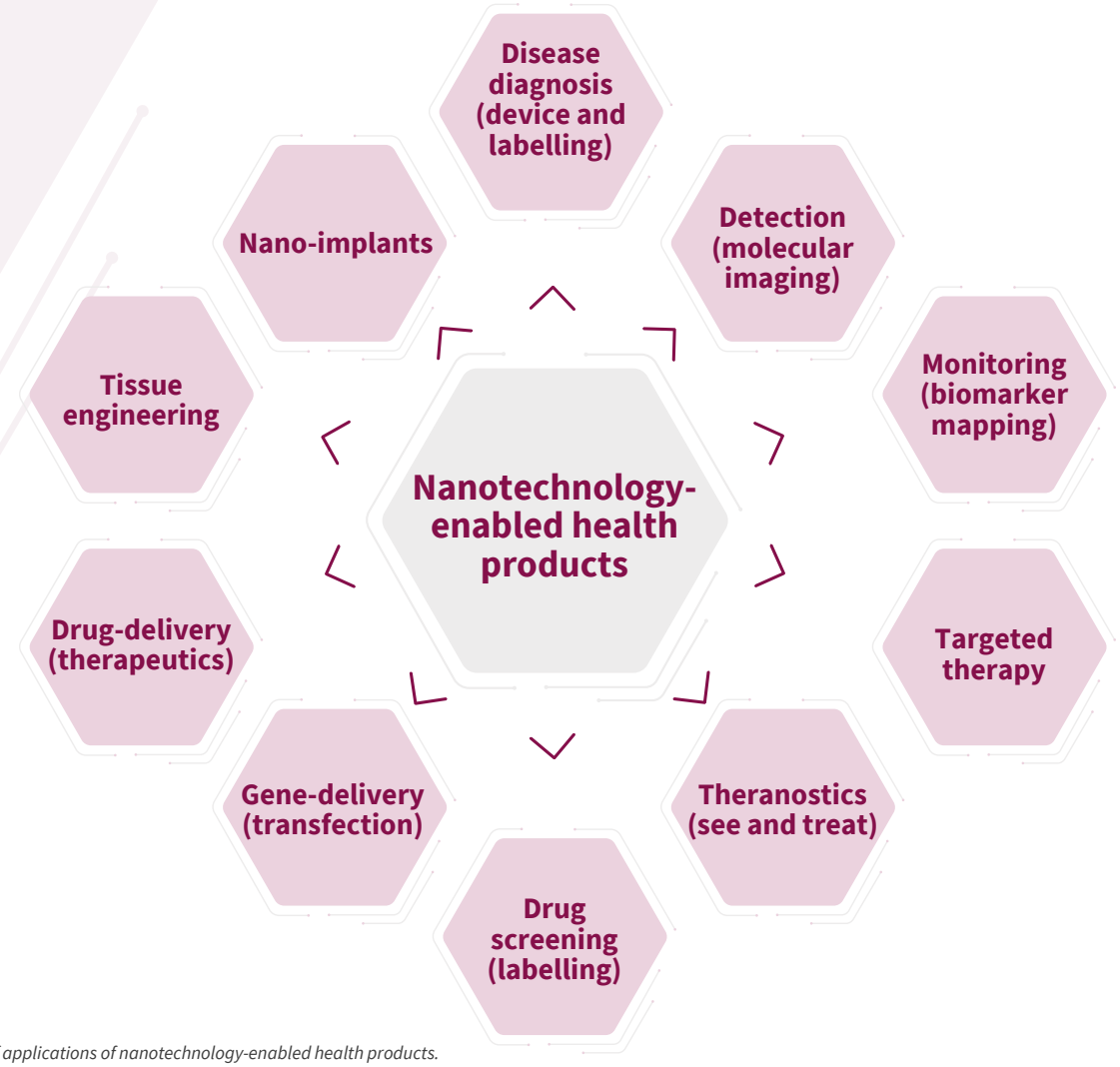


Definition and Scope

Nanomaterial Definition: A material with at least one external dimension in the 1–100 nm range or an internal structure in that scale. Variation in shape (e.g., rods, tubes, spheres) can influence behaviour and safety.

Broad Applications: Nanostructured coatings, targeted drug delivery systems, and diagnostic platforms are among the growing range of medical device uses.

Characterisation Factors: Key parameters include particle size distribution, shape, surface charge, chemical composition, and reactivity, all of which can significantly impact biocompatibility.



Examples of applications of nanotechnology-enabled health products.

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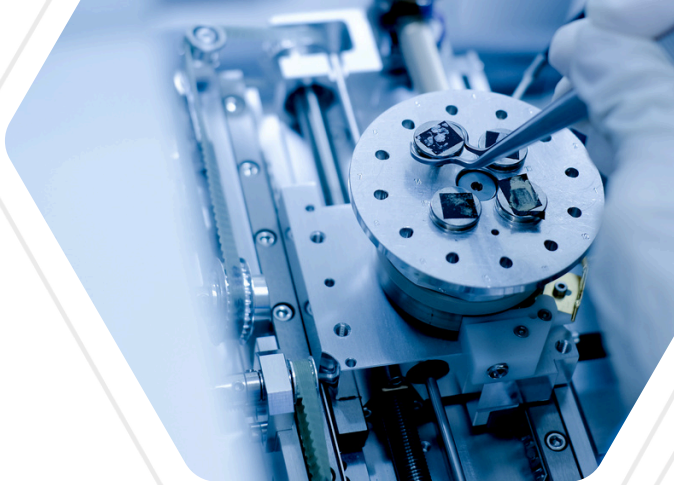
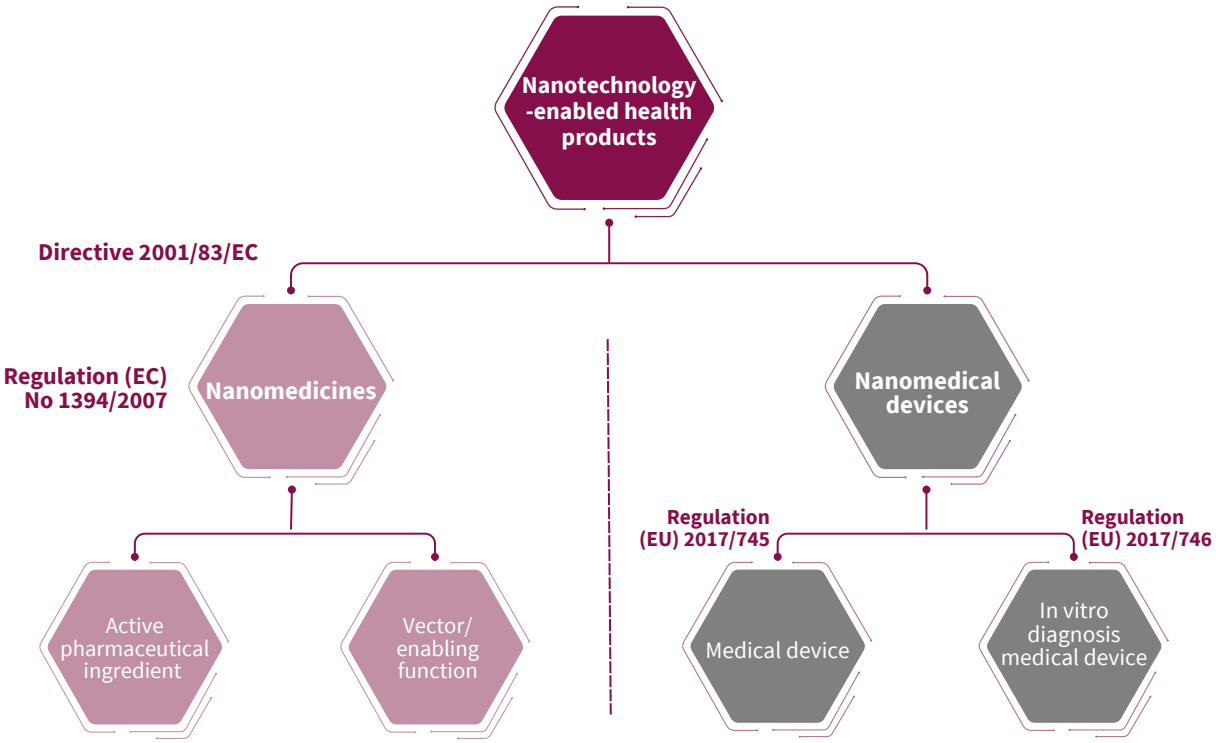


Relevant legal frameworks in the EU

Nanotechnology offers innovative opportunities in medical devices, such as new methods for therapeutic delivery and improved implant durability. In the European Union, nanotechnology-enabled health products (NHPs) can fall under the **legal frameworks** for either **medicines or medical devices**. To determine the applicable regulatory framework, it is crucial to **analyse the intended purpose of the final product and its primary mechanism of action** to achieve that intended purpose.

For those NHPs regulated as Medical Device within the European Union, Regulation (EU) 2017/745 (MDR) requires detailed evaluation of nanomaterial properties, potential toxicity, and long-term effects on patient safety.



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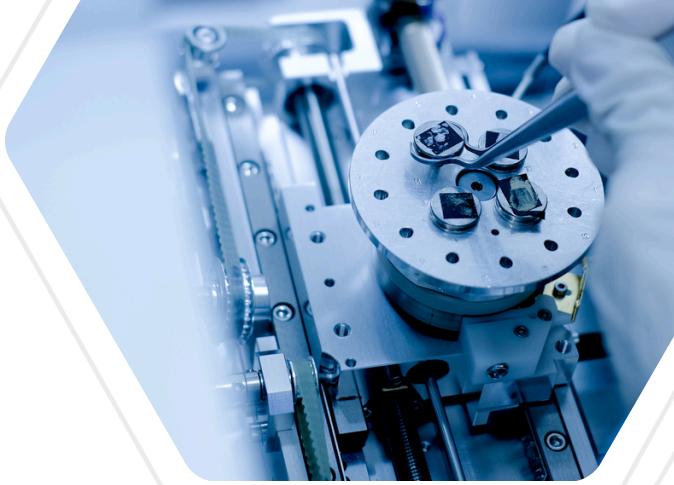
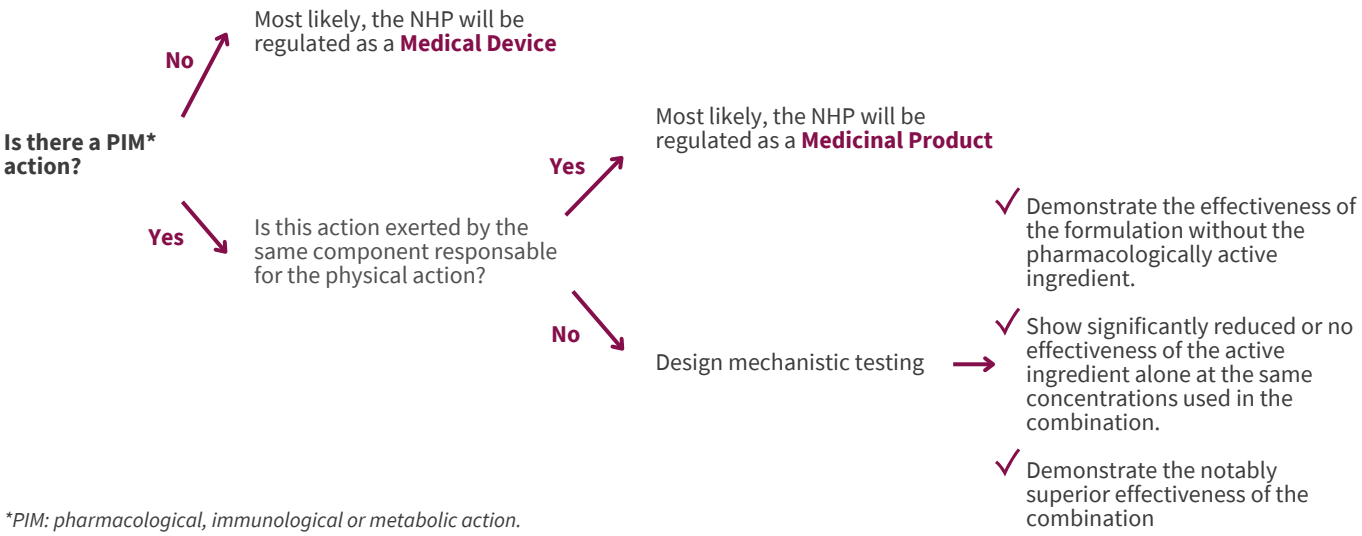


Justification of primary mode of action

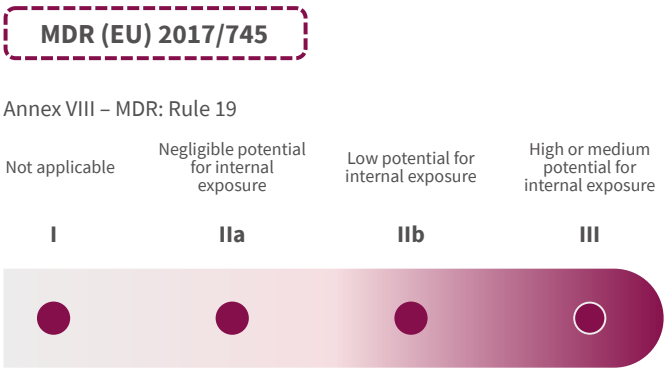


PIM: pharmacological, immunological or metabolic action.

Regulation (UE) 2017/745 (MDR)

Medical devices regulated under the **MDR** are categorized into four risk classes (I, IIa, IIb, and III), based primarily on the intended use of the product. The classification also considers factors, such as the invasiveness of the product, the duration and nature of patient contact, and other special technological characteristics. There are 22 classification rules in total, defined in **Annex VIII** of the MDR. Notably, the MDR introduces a specific classification rule for products that incorporate **nanomaterials** within their composition, **Rule 19**. In the EU, NHPs regulated as medical devices are always classified, at a minimum, as Class IIa as per Rule 19; therefore, the conformity assessment always requires the involvement of a notified body (NB). The technical expertise for which NBs have been designated in accordance with the MDR is identified by the so-called 'MDR codes', as defined in the **MDCG 2019-14 Explanatory** note on MDR Codes. Specifically, in order to certify medical devices incorporating nanomaterials, the NB must be designated with the following code MDS 1007 'Devices incorporating or consisting of nanomaterials.

Figure I - Medical Devices incorporating nanomaterials risk classification



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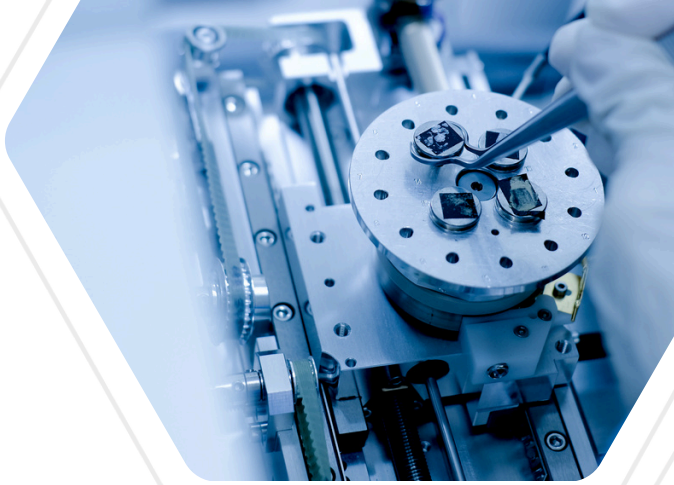

To facilitate the correct application of **Rule 19**, the **Scientific Committee on Emerging and Newly Identified Health Risks** (SCENIHR) **published specific guidance for determining the potential for internal exposure based on the type of nanomaterial application** (free, fixed in a coating, or embedded), the type of contact with the body, and the nature of this contact (refer to table I).

Table I- Estimation of potential external and internal exposure for medical devices containing nanomaterials

			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 (physisor b)	Strong (chemisor b)	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/L	L/L	N/N
		>24 h to 30 d	na	H/H	H/L	M/M	N/N
		>30 d	na	H/H	H/L	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, na= not applicable

H/L means high potential contact and/or external exposure to the nanomaterial / low potential for internal systemic exposure of all organ systems

* the exposure will depend on the degradation time of the medical device

** contacting the blood path at one point. Examples of these types of devices are solution administration sets, transfer sets and blood administration sets (ISO 10993-4:2002)

*** Examples of these types of devices are: intravascular catheters, extracorporeal oxygenating tubing and dialysers (ISO 10993-4:2002).

Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices

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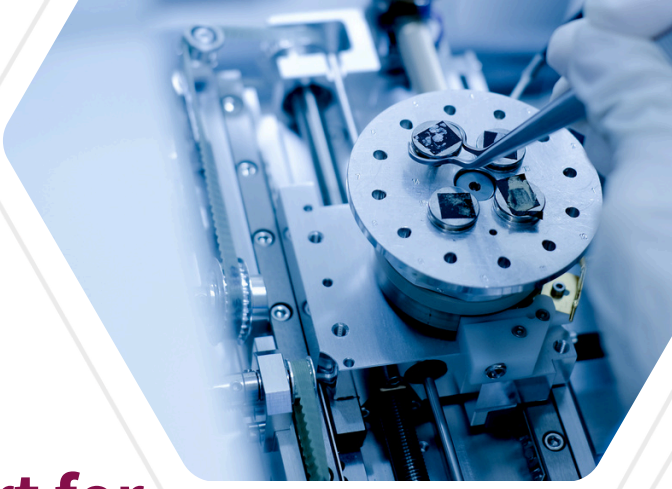

Regulatory state of the art for NHPs regulated as medical devices

To demonstrate conformity with regulatory frameworks for medical devices, including NHPs, in the EU, the manufacturer shall demostrate compliance with relevant general safety and performance requierements (GSPRs). In order to do this, it is essential to **follow guidelines issued by competent authorities, international standards**, and literature references, or apply proprietary methodologies and validate them. Organisations such as **ISO and ASTM are instrumental in forming and updating the standards related to medical devices**. They provide standards for quality assurance, risk management, and both preclinical and clinical evaluations.

Committees including ISO/TC 229 and ASTM's E56.08 focus on NHPs. In the EU, **CEN and CENELEC ensure that ISO standards align with the MDR**, and once endorsed, these are published as‘harmonised’ standards, with Annex Z detailing their correlation with MDR’s legal requirements. Adherence to these standards is optional, butcompliance presumes conformity with MDR's GSPRs.

ISO/TR 13014:2012 “Nanotechnologies — Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment” and **ISO/TR 10993-22:2017** “Biological evaluation of medical devices Part 22: Guidance on nanomaterials” are standards that **guide the physico-chemical characterisation** of nanoscale materials for toxicological evaluation. Table II includes a non-exhaustive list of the physico-chemical parameters that are typically evaluated for NHPs under the MDR.

For medical devices incorporating nanomaterials, it is essential to assess the methodology for physicochemical characterisation and the tasks of verification and validation on a case-by-case basis. Standardised methodologies in regulatory guidelines often apply to bulk materials and may not directly suit nanoscale materials.

Additionally, existing models often ignore factors such as the device's ageing process, the specific body site for implantation, and the duration of implantation. As validated test methods for nanomaterials are not yet available, customised risk assessment approaches and individualised tests adapted to the unique properties of nanomaterials are necessary.

Nevertheless, regulatory guidelines by the MDCG in the EU and globally by IMDRF, WHO, and OECD have been increasingly issued for nanomaterial-based health products (NHPs).

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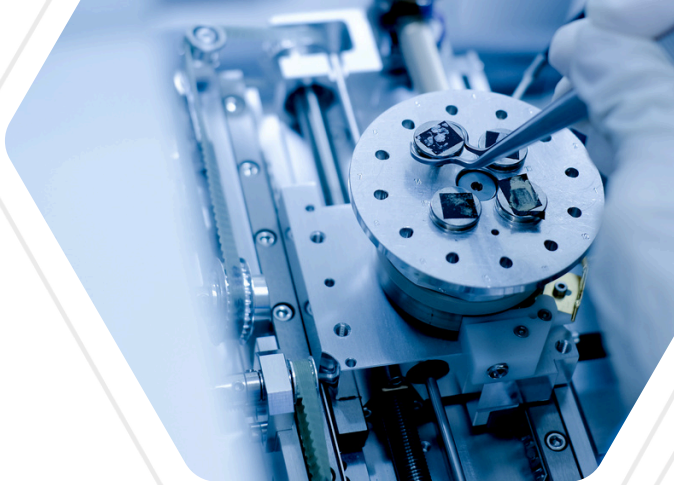

Table II- Non-exhaustive list of physico-chemical parameters that should be considered for NHPs under the MDR.

Characteristic	Measurand	Relevant ISO guidance on methodology
Chemical composition and purity	The number and identity of elements alone or in molecules (can be expressed as a chemical formula) Level or concentration of unintended constituents (impurities)	ISO 22309; ISO 22489; ISO 24173; ISO 13084; ISO 18144
Particle size and particle size distribution	**Particle size:** Equivalent spherical diameter for particles displaying a regular geometry Length of one or several specific aspects of the particle geometry **Particle size distribution**: Graphical representation, e.g. histogram, and/or values for statistical parameters such as mean, median, and/or mode	ISO 9276 series; ISO 9277; ISO 13318 series; ISO 13320; ISO 22412; ISO 13322 series; ISO 14488; ISO 14887; ISO 15900; ISO 16700; ISO/TS 19590; ISO 20998-1; ISO 21501 series; ISO 22412
Aggregation/ agglomeration state	Particle size Number of aggregate/ agglomerate particles in comparison to the total number of primary particles Number of primary particles in the aggregate/ agglomerate Distribution of number of primary particles per aggregate/agglomerate	See guidance for particle size; ISO/TR 13097; ISO/TS 12025; ISO 13322-1
Shape	Size-independent descriptors of shape Distribution of values of the size-independent shape descriptors	ISO 16700; ISO 13322-1
Surface area	Volume- and/or mass-specific surface area	ISO 15901-1; ISO 15901-2; ISO 15901-3; ISO 18757; ISO 13322-1; ISO 9277
Surface nanostructures	Size and geometry	ISO 25178
Surface chemistry	Elemental and molecular abundance Reactivity (chemical reaction rate)	ISO/TR 14187; ISO 18115; ISO 24236; ISO 15471; ISO 18118; ISO/TR 19319; ISO 17973
Surface charge	Net number of positive and negative charges per unit particle surface area Zeta potential	ISO 20998; ISO 13099
Solubility/ dispersibility	Solubility: Maximum mass or concentration of the solute that can be dissolved in a unit mass or volume of a solvent at specified (or standard) temperature or pressure Dispersibility: Maximum mass or concentration of the dispersed phase present in a unit mass of the dispersing medium (solvent) or unit volume of the dispersion (solvent plus dispersed phase) at specified (or standard) temperature and pressure	ISO 20998; ISO 13099

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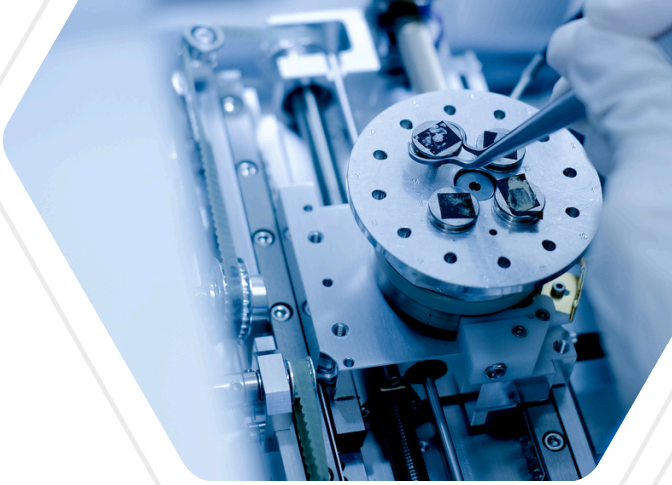

Regulatory documentation

- **Core Requirements:** The technical documentation must justify the device's design, including detailed analysis of nanomaterial properties, potential risks, and specific mitigation measures.
- **Aligning with Standards:** Tests and methodologies should follow validated protocols wherever applicable.
- **Robust Evidence:** Clear demonstration that benefits outweigh risks, supported by clinical and preclinical data, is crucial for regulatory compliance.
- **Clarity of Information:** The device label should note the presence of nanomaterials, ensuring users and healthcare professionals are aware of any precautions. Refer to EN ISO 15223-1:2021 "Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements" symbol 5.4.11.

Reference number and graphic	Title	*Description*
5.4.11 	Contains nano materials	Indicates a *medical device* that contains nano materials

Conclusion

- **Numerous devices on the market incorporate nanomaterials**, covering a wide range of classifications and technologies.
- **Regulators worldwide are actively considering these devices**, assessing their risks, and creating relevant regulations.
- **Evaluating and addressing the risks posed by devices that contain or produce nanomaterials is crucial**.
- **Current characterisation techniques designed for macro materials may not suffice for nanomaterials**, indicating a need for adaptation.

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