WHITE PAPER

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EU MDR: How Are You Covered on Nanomaterials New Requirements

If you are manufacturer on record for any of the below, rest of this article is important for you:

"Catheters, Synthetic bone graft, Orthopedic implants, Wound care, IVD, In vivo imaging, AIMD, Dental fillers and composites, Dental crowns, Instruments"

To be on the same page, some definitions to start with:

'NanoMaterial' means 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 1-100 nm; Fullerenes, Graphene flakes and single-wall Carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials; ('particle', means a minute piece of matter with defined physical boundaries; 'agglomerate', 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; 'aggregate', means a particle comprising of strongly bound or fused particles).

For MDD, no explicit requirements in relation to nanomaterials defined. For EU MDR, there are more specific and prescriptive requirements due to scientific uncertainty about the risks and benefits of nanomaterials used for devices'. The definition of a nanomaterial in the MDR is consistent with the definition from 2011/696/EU noted in Section 1 earlier; however, Article 3 allows the definition to be amended based on technical and scientific progress. The MDR (Article 2) also includes definitions of nano-particles, nano-agglomerates and nano-aggregates which is consistent with PAS 71:2011.

Annex I (general safety and performance requirements – GSPRs), Section 10.6, of the MDR contains a specific requirement that manufacturers must address in relation to the chemical, physical and biological properties and reducing the risk (by device design and manufacturing processes) linked to the size of particles that can be released into the patient's or user's body, in-particular nano-materials. Medical devices containing nano-materials will need to address this requirement in the risk management process and risk controls related to this GSPR will need to be verified in the pre-clinical evaluation. There is also a new classification rule in the MDR (Rule 19 in Annex VIII) covering devices incorporating or consisting of nano-materials.

To determine risks and quantitative/qualitative assessments, your underlying best bet is "Guidance on the determination of potential health effects of nanomaterials used in medical devices" by E**U Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)** adopted in 2015.

The alleged use of nano-materials has been identified by Notified Bodies in the following applications:

- Carbon nano-tubes in bone cements
- Nano-paste hydroxylapatite powder for bone void filling
- Polymer setting material with nano-particles in dental cements
- Polycrystalline nano-ceramics in dental restorative materials
- Nano-silver or other nano-materials used as coatings on implants and catheters
- Nano-silver used as an antibacterial agent, for example in wound dressings

For patients, the following exposure routes may be applicable:

- Inhalation exposure, e.g. related to intubation, dental procedures;
- Dermal exposure;
- Mucosal exposure (via various mucosal tissues, e.g. in the mouth, vagina/penis);
- Oral exposure;
- Parenteral exposure (introduced into the body by a means other than through the gastrointestinal tract, e.g., by injection into the bloodstream (intravenous) or a muscle (intramuscular), surgical procedures using medical devices or from implanting devices in any tissue;
- Ocular exposure

An estimation of potential external and internal exposure as a starting point for risk evaluation for medical devices containing nano-materials:

			Type of application of nanomaterails External exposure/internal exposure				
			Free	Fixed (coating)	Fixed (coating)	Embedded	Embedded
Type of device	**Type of contact**	**Duration of contact**		**Weak (physisorb)**	**Weak (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	
	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, na = not applicable

Framework for risk assessment of nanomaterials used in medical devices:

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

F = full assessment L = limited assessment VL = very limited or N = no further assessment *=limited assessment if it can be shown that penetration/distribution is very limited

** Full assessment when absorption is indicated in toxicokinetic studies

10993-22:2017

ISO/TR 10993-22:2017 Biological evaluation of medical devices – Part 22: Guidance on nanomaterials. The scope of this standard covers medical devices composed of or containing nanomaterials and also medical devices that generate nano-objects either intentionally (e.g. iron oxide nanoparticles for injection and heating of tumors) or unintentionally (e.g. wear debris from joint replacement articulating surfaces or dental fillings that are polished in situ).

ISO/TR 10993-22:2017 also has details on characterization methods (similar to the SCENIHR report discussed earlier), information on reference materials, sample preparation, release Toxico-Kinetics (covering absorption, distribution, metabolism and excretion/elimination) and the toxicological evaluation. There are a number of challenges in the evaluation of nanomaterials due to their nature including increased reactivity, partial dissolution, aggregation/agglomeration and transformation via hydration.

ISO/TR 10993-22 advocates asking three fundamental questions when evaluating nano-materials:

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

Summary

A case-by-case approach is necessary for risk evaluation of medical devices containing nanomaterials. A phased approach is proposed to avoid unnecessary testing.

In phase 1, an evaluation is needed of the potential for the device to release nano-particles either directly or due to wear of the device during use. If the nano-material is fully embedded in the device, the consideration of potential wear resulting in the release of particles will probably be necessary. In addition, potential local effects of the device incorporating nano-materials should be considered. For other devices containing nano-particles, both release and wear considerations are necessary. If the release of particles during the use of the medical device is deemed to be realistic, physicochemical tests are likely to be required to establish the nature of the released particles, the rate of release and factors likely to influence this. If as a result of these studies it is concluded that even under realistic worst case use conditions, particle release does not occur or will be negligible, further evaluation may be limited mainly to investigating local reactions... When exposure is expected due to nanoparticle release, further evaluation of the risks is necessary.

In phase 2, the aim is to determine the distribution of the particles released and also their persistence potential. In the case of non-invasive devices, the potential of particles to enter the systemic circulation and thereby be distributed to various tissues is the prime consideration. If it is concluded that it is unlikely that the particles could enter the systemic circulation even under realistic worst-case conditions of use, then only a very limited toxicity testing protocol is needed, which would be generally limited to local effects at the contact site. For invasive devices, a more detailed study of the potential of the particles to access and remain in specific tissues is required by toxicokinetic studies. The findings from these studies will influence the choice of further toxicity testing methods.

In phase 3, the hazard is assessed by selecting toxicity tests that are relevant based on the nature of the observed exposure and potential persistent in specific organs. For some assays, evaluating potential hazards of nanomaterials adaptation of existing assays may be necessary. In the future, as our knowledge of the properties of nanomaterials improves, it may be possible to predict the nature, distribution, tissue levels and potential persistence of the particles but this is unlikely to be possible in the near future.

The information gathered will give input for the final risk characterization (phase 4). The estimated risk should be compared to the risk from the use of comparable devices not incorporating nano-materials in judging the acceptability of the risk. In addition to the estimated potential risk, ultimately the potential benefit for the patient should also be considered in the final risk assessment.

In conclusion, the potential risk due to the use of nanomaterials in medical devices is mainly associated with the possibility for release of free nanoparticles from the device and to the duration of exposure. The potential release is dependent on the method of use of the nanomaterials, as a free nanomaterial, nanomaterials fixed on surfaces or nanomaterials embedded in a matrix. In addition to particle release and potential effects of these particles, possible local effects at the site of application should also be considered. Importantly, wear-and-tear of a medical device may result in the generation 52 of nanosized particles even when the medical device does not contain nanomaterials. In addition, it is also possible to apply this Guidance for the safety evaluation and risk assessment of particles with a size larger than 100 nm.

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