Safety and effectiveness of nanostructured medical devices

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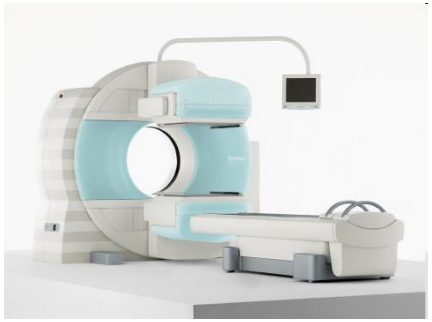
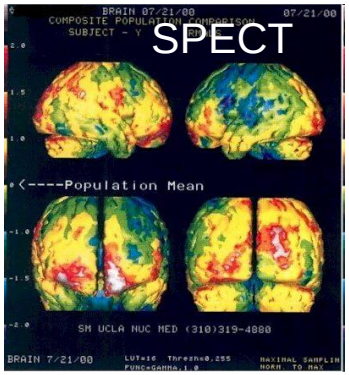
Medical devices

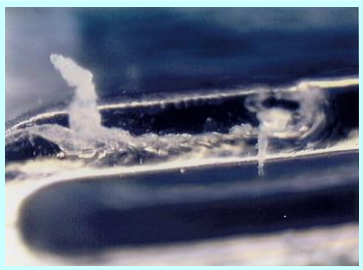


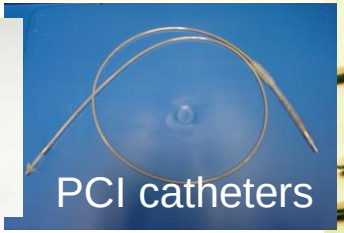
SPECT/CT scanner

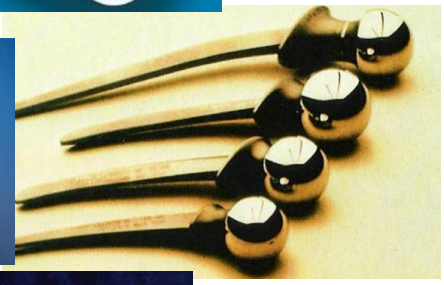


valvuloplasty rings

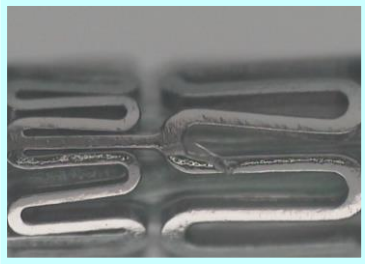
valved conduits

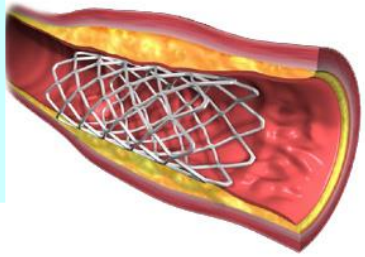


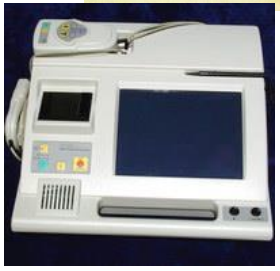




hip prostheses







AIMD programmers

Current framework for medical devices in Europe

- *Directive 90/385/CEE (AIMD, Active Implantable Medical Devices)*
- *Directive 93/42/CEE (Medical Devices)*
- *Directive 98/79/CE (IVD, In Vitro Diagnostic MD)*
- *Directive 2001/83/CE (Medicinal products for human use)*

- *Latest revision of MD (and AIMD) Directive: Directive 2007/47/CE*

(Note: no mention of "nanomaterial" or "nanostructure" in it)

Medical devices: definition according to Directive 93/42/CEE and subsequent amendments

'Medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

— investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medical devices: Essential requirements

Article 3 (MD Directive): "The devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned."

ANNEX I

ESSENTIAL REQUIREMENTS

I. GENERAL REQUIREMENTS

II. REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION

1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not **compromise the clinical condition or the safety of patients**, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

3. The devices must **achieve the performances intended by the manufacturer** and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a) [*MD def.*], as specified by the manufacturer.

Compliance to the Essential requirements

Relevant parts of the assessment of the compliance of a MD to the Essential requirements:

- Risk management (EN ISO 14971)
- In vitro evaluation (e.g., bench testing)
- In vivo preclinical studies
- Clinical evaluation, Annex X of MDD (critical evaluation of the relevant scientific literature and/or clinical investigations)

⇩

Technical file of the MD

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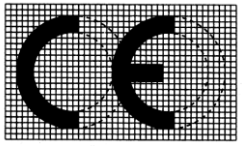


CE conformity marking (after evaluation by the Notified Body)

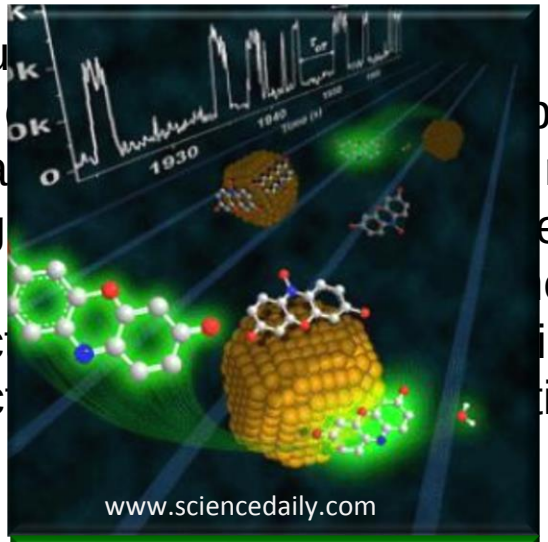
Nanomaterials & Medical devices

Unique properties of materials at the nanoscale (1 nm=10^{-9} m)

$\Rightarrow$ increasing diffusion of medical devices containing nanomaterials

Gold Nanoparticle Catalyst

- ✓ High reactivity
- ✓ High surface/volu
- ✓ High penetration (ocellular compartments
- ✓ Quantum mecha nanometers, the materials' properties chang e at larger scales, and are size-dependent. elting point, fluorescence, electrical conduct ility, and chemical reactivity change as a func ticle.

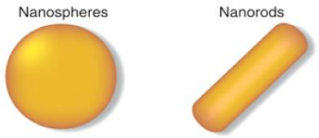


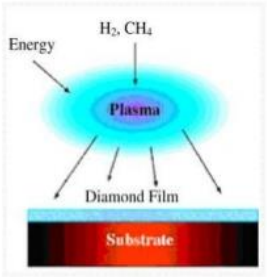
Traditionally known as an inert material, gold turns out to be highly reactive at the nanoscale

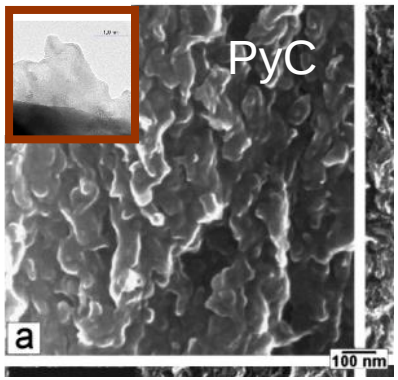
These properties may ot just beneficial, but also harmful!

Necessity to define and iated to nanomaterials in MDs

Nanostructuring of materials







- nanometer-sized particles, thin wires or thin films.

- materials and/or devices in which the nanometer-sized microstructure is limited to a thin (nanometer-sized) surface region of a bulk material (e.g., by PVD, CVD, ion implantation, laser beam treatments..).

- bulk solids with a nanometer-scale microstructure $\Rightarrow$ bulk solids in which the chemical composition, the atomic arrangement and/or the size of the building blocks (e.g. crystallites or atomic/molecular groups) forming the solid vary on a length scale of a few nanometers throughout the bulk (e.g., *pyrolitic carbon*, with crystal domains of diameter 5-30 nm)

Nanomaterials & Medical devices

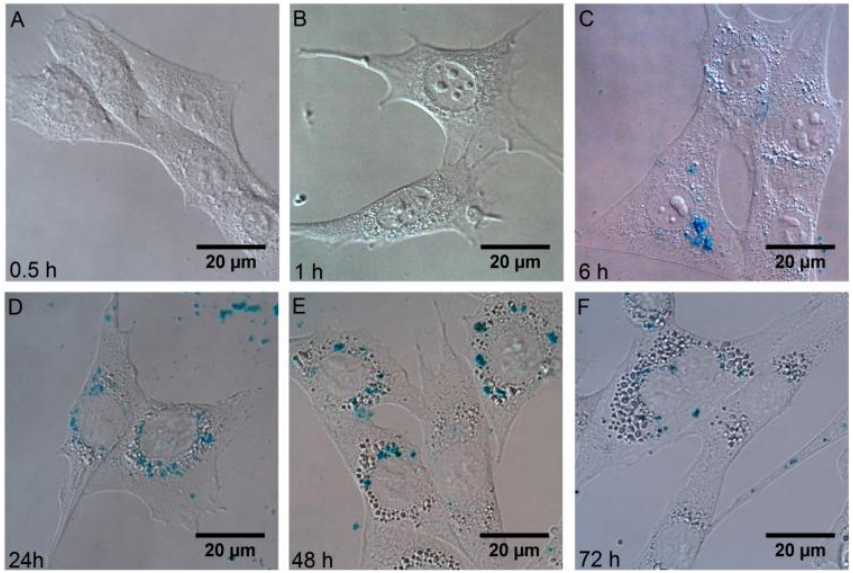
Examples of nanomaterials present in MDs:

- Carbon nanotubes or nanoparticles in bone cements
- Hydroxyapatite nanoparticles in preparations for filling bone cavities
- Nanosilver or other nanomaterials used as surface coating on implants or catheters
- Nanosilver used as antibacterial agent
- Functionalised magnetic nanoparticles (iron oxide) for heat treatment of tumors with e.m. fields

Possible hazards associated to nanomaterials

NP accumulation in cells: nanotoxicity?

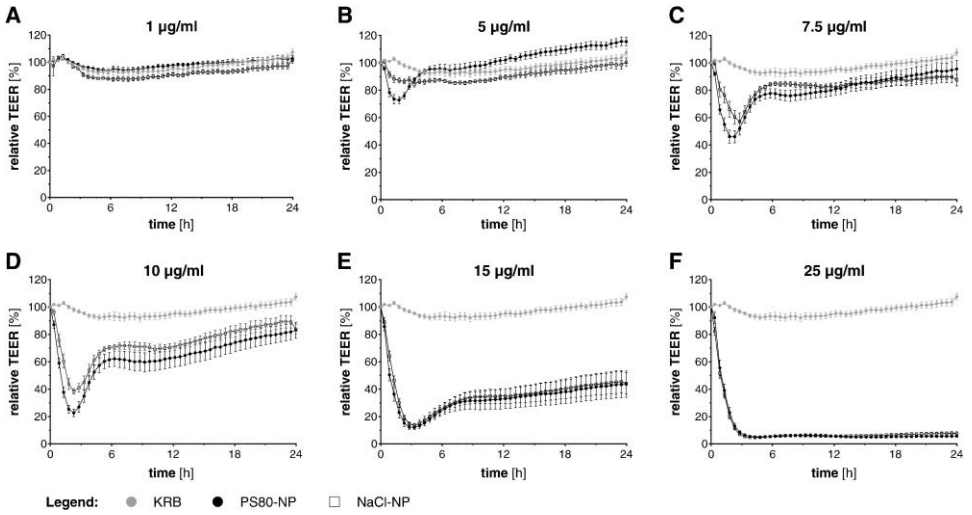
Jarockyte et al, 2016



Fixed NIH3T3 cells (mouse embryonic fibroblasts) after 0.5–72 h of incubation with 65 ng/mL of Fe_3O_4 (stained with Prussian Blue) (A–F).

Effect on the integrity of BBB

(Kolter et al, 2015) The influence of nanoparticles on BBB integrity was studied by measuring the transendothelial electrical resistance (TEER). The TEER correlates with the permeability and the tightness.



BBB integrity after treatment with PBCA-nanoparticles in concentrations between 1 and 25 µg/ml comparing PS80-coated (PS80-NP) and 0.9% NaCl-treated (NaCl-NP) nanoparticles over 24 h in concentrations of (A) 1 µg/ml, (B) 5 µg/ml, (C) 7.5 µg/ml, (D) 10 µg/ml, (E) 15 µg/ml and (F) 25 µg/ml; n = 4.

Standards for MDs

Standardisation has played a leading role in creating the EU Single Market. Standards support market-based competition and help ensure the interoperability of complementary products and services. They reduce costs, improve safety, and enhance competition.

A harmonised standard is a European standard developed by a recognised European Standards Organisation. Manufacturers, other economic operators, or conformity assessment bodies can use harmonised standards to demonstrate that products, services, or processes comply with relevant EU legislation.

In the framework of the MDD, there is yet no available harmonised standard for nanostructured MDs
https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices_en

⇒ Increased burden for manufacturers in order to demonstrate compliance of nanostructured MDs to the Essential requirements of the Directive

Other identified knowledge gaps

- Standards of the ISO 10993 series cover biocompatibility and toxicity issues of traditional biomaterials, but the extension to nanostructured materials is not granted
- ISO/DTR 10993-22 «Biological evaluation of medical devices -- Part 22: Guidance on nanomaterials» Status: *Under development*
- Lack of commonly agreed biological testing protocols for nanomaterials
- Variability of biological response for the same nanomaterial in different labs, probably due to differences in material preparation, chemical contaminants or protocols

Available literature about safety/effectiveness of nanostructured MDs

(("safety"[MeSH Terms] OR "safety"[All Fields]) AND ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields] OR "nanoparticle"[All Fields])) AND "medical device"[All Fields] ⇒ 5 papers

(effectiveness[All Fields] AND ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields] OR "nanoparticle"[All Fields])) AND "medical device"[All Fields] ⇒ 4 papers

(("safety"[MeSH Terms] OR "safety"[All Fields]) AND nanostructured[All Fields]) AND "medical device"[All Fields] ⇒ 2 papers

(effectiveness[All Fields] AND nanostructured[All Fields]) AND "medical device"[All Fields] ⇒ 1 paper

Nanomaterials & Medical devices

afssaps Agence française de sécurité sanitaire des produits de santé DEDIM / DSM / New devices unit	**NanoDM Report:** **Biological assessment of medical devices containing nanomaterials**	Date: 18/08/2011 Final version 5-Ang Ref.: DTVLVL110802651

(2010-2011)

The first part of this report gives an overview of the advances brought about by nanomaterials and their use in medical devices already on the market and those under development. The second part outlines current knowledge of the biological effects of nanomaterials. The third part focuses on the current regulatory and standardisation framework to examine its suitability for medical devices containing nanomaterials. Finally, based on these analyses, the report gives recommendations for the manufacturers of medical devices containing nanomaterials to improve the biological risk assessment during the life cycle of the medical device: from design via application all through to recycling after use.

In conclusion, current guidance documents are appropriate for the biological assessment of medical devices containing nanomaterials. However, case-by-case adaptations are required in order to take into account the specific features of the nanomaterials. Firstly, as in any medical device evaluation, the favourable benefit/risk ratio must be highlighted. More specifically, the benefits of adding nanomaterials to the medical device must be discussed (benefits should clearly outweigh potential risks).
Secondly, the recommendations proposed by the French Health Products Safety Agency provide support for the manufacturers of medical devices containing nanomaterials. These recommendations mainly concern information disclosure and transparency, the identification and characterization of the materials used and the precautions to be taken when evaluating biological risks.

Nanomaterials & Medical devices

2016
Viewpoint of the ANSM (formerly AFSSAPS), Agence nationale de sécurité du médicament et des produits de santé (France):

"Scientific monitoring implementation within the ANSM can track the use of nanotechnology in medical devices: it still limited mainly to devices under development, so not yet marketed.
As for drugs, the objectives are:
increase performance (e,g, a bone cement containing hydroxyapatite nanoparticles to speed osseointegration); reduce the occurrence of adverse events (e.g., dressings containing silver nanoparticles to prevent the occurrence of infections).
In the current state of knowledge and tools available however, it is difficult to evaluate new potential risks. The ANSM considers that the use of nanoparticulate properties in medical devices is only justified if it brings a significant benefit compared with a more conventional approach. It publishes recommendations for the evaluation of medical devices containing nanomaterials."

http://ansm.sante.fr/L-ANSM2/Nanotechnologies/Dispositifs-medicaux/(offset)/2

Nanomaterials & Medical devices

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Nanotechnologies in medical devices

RIVM Report 2015-0149

Nanotechnologies in medical devices

The application of nanotechnologies in medical devices is a growing area and numerous medical disciplines benefit from innovative features enabled by nanotechnologies. Knowledge about the safety evaluation of nanotechnology is also evolving. Recently, scientific guidance has become available, specifying considerations to be taken into account when nanotechnology is used for the manufacture of a medical device. The combination of knowledge and guidance forms a suitable basis for the risk assessment of nanomedical devices. These are the main conclusions of an overview performed by RIVM on applications of nanotechnology in medical devices.

One of the most important types of nanotechnological applications is **nanocoatings**, which increase biocompatibility and thus improve integration with the surrounding tissues of a variety of medical implants used, for example, in cardiology (stent coating), orthopaedics (coating on joint replacement implants) and dentistry (dental implants). In addition, antimicrobial properties of nanomaterials are used in coatings,and also in wound care and medical textiles.

Another clear trend is the use of nanomaterials to **mimic naturally occurring structures**. This leads to optimal biological, physical, and mechanical characteristics of implants.

A third trend of applications is related to the **electrical and magnetic properties of materials on the nanoscale**. This is especially relevant to medical devices used in neurology and cardiology, for instance to improve the treatment of cardiac arrhythmia. Furthermore, nanotechnologies enable the development of batteries with greatly increased lifetime for use in active implantable medical devices.

A number of nanotechnology applications are specific to oncology. Examples include diagnostic tests used in the early detection of cancer, and devices for the identification of the boundaries of a tumour or metastases during surgical interventions. Nanomaterials can also enhance the effect of therapies like chemotherapy or radiation therapy through locally increased temperature, or they can kill tumour cells directly at high temperature.

Like all medical products, the risk assessment of nanomedical devices needs to be performed on a case-by-case basis. The potential for release, leading to a higher or lower exposure to nanomaterials, is considered the most important feature driving the extent of the “nano” risk assessment.

SCENIHR: proposal to overcome the uncertainty

On March 27, 2012, the European Commission (EC) posted a request to the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) for a scientific opinion on the health effects of nanomaterials used in medical devices.

On January 6, 2015, the European Commission (EC) and its Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published the final opinion "Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices." The Guidance provides information on how to evaluate the risk when a nanomaterial is used in a medical device. The EC states that the Guidance addresses the use of nanomaterials in medical devices regarding specific aspects that need to be considered in the safety evaluation of nanomaterials.

SCENIHR: proposal to overcome the uncertainty

SCENIHR - Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices (6 January 2015)

Guidance is provided on physico-chemical characterisation of nanomaterials, the determination of hazards associated with the use of nanomaterials, and risk assessment for the use of nanomaterials in medical devices. The safety evaluation of the nanomaterials used in medical devices is discussed in the context of the general framework for biological evaluation of medical devices as described in the ISO 10993-1:2009 standard. Therefore, the risk assessment should be performed taking into consideration the type of device, the type of tissue contact, and the contact duration, thus identifying the specific exposure scenario.

This Guidance provides information to assist with safety evaluation and risk assessment on the use of nanomaterials in medical devices that should be considered in conjunction with the ISO 10993-1:2009 standard. The Guidance highlights the need for special considerations in relation to the safety evaluation of nanomaterials, in view of the possible distinct properties, interactions, and/or effects that may differ from conventional forms of the same materials. For some assays evaluating potential hazards of nanomaterials adaptation of existing assays may be necessary.

SCENIHR: proposal to overcome the uncertainty

SCENIHR - Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices (6 January 2015)

A *phased approach* is recommended for evaluating the risk of the use of nanomaterials in medical devices based on potential release and characteristics of the nanomaterials to avoid unnecessary testing. The phases cover particle release (phase 1), particle distribution and persistence (phase 2), hazard assessment (toxicological evaluations) (phase 3), risk characterisation/risk assessment (phase 4). In phase 1 an evaluation of the potential for the device to release nanoparticles either directly or due to wear of the device during use should be carried out. In phase 2 the aim is to determine the distribution of the particles released and also their persistence potential. In phase 3 the hazard is assessed using appropriate toxicity tests taking account of the exposure characteristics and potential for persistence in specific organs. This will provide input for the final risk characterisation (phase 4). The estimated risk needs to be compared to the risk from the use of comparable devices not incorporating nanomaterials in judging the acceptability of the risk.

In conclusion, the potential risk from the use of nanomaterials in medical devices is mainly associated with the possibility for release of free nanoparticles from the device and the duration of exposure.

Elements for the risk analysis of nanostructured MDs

A given product's risk is defined as the combined effect of product toxicity and exposure level (quantity, type and duration of the contact).

Generally the risk analysis for nanostructured MDs will follow these steps:

- *Detailed description of DM*
- *Detailed description of physical-chemical properties of NMs involved in the life cycle of the DM*
- *Physical-chemical characterization of NMs (incidental and intentional), with regard to production and use, involved in the life cycle of the MD.*

The toxicity of the same NM may vary in different locations and forms (airborne, surface bound, suspended…), and also in different points of the product's life cycle. A full assessment of the effects of exposure to NMs would thus require a huge amount of knowledge, not always available.

The future of regulatory framework for DMs in Europe

A draft European Parliament Regulation (not a Directive!), under preparation, should replace soon (scheduled deadline: 2017) the Directives 93/42/EEC (Medical Devices) and 90/385/EEC (Active Implantable Medical Devices).
Contrary to a Directive, a European Regulation does not require transposing to national law.

Definitions introduced by the new Regulation:
'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 be considered as nanomaterials.
For the purposes of the definition of nanomaterial, 'particle', 'agglomerate' and 'aggregate' are defined as follows:
– '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

The future of regulatory framework for DMs in Europe

draft European Parliament Regulation
http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52012PC0542

MDs containing or comprised of a nanomaterial must now be grouped in class III (Rule 19). Exclusion cases concern situations in which the nanomaterial is encapsulated, or bound in such a manner that it cannot be released into the patient's or user's body when the device is used as intended.
Moreover, in the case of class III MDs, the equivalence with other MDs present on the market does not exempt from the requirement to conduct clinical investigations and that the manufacturer must report "any statistically significant progressing in the frequency and severity of non-serious incidents" through a status report. This requires an in-depth and reliable characterisation of the nanoparticles and end products in the context of the mandatory evaluation of biological risks.

Conclusions

- The presence of nanostructures in medical devices can provide tools with unprecedented performance, due to the unique properties of matter at the nanoscale

- Nevertheless, knowledge about safety and effectiveness of nanostructured MDs is still lacking

- Relevant standards for nanostructured MDs are also not yet available in a consolidated version

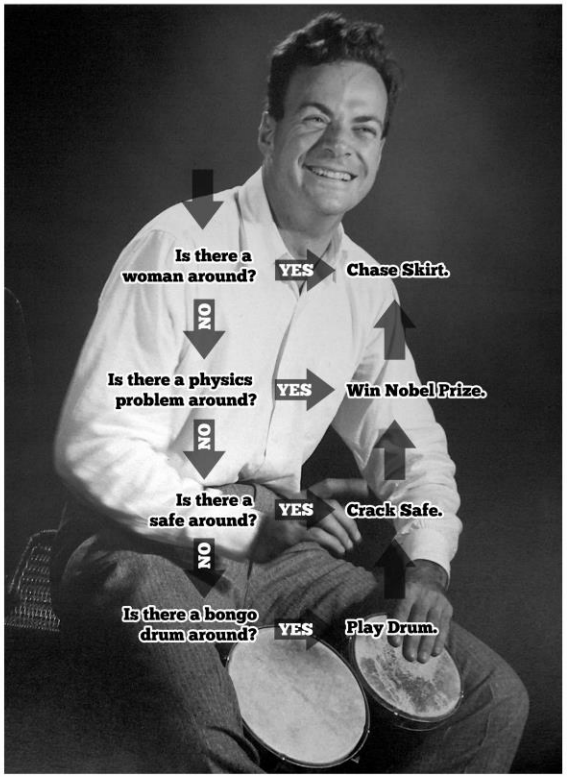
- In general terms, the safety profile of nanostructured MDs is related to nanoparticle release and time of exposure

- The new Regulation of MDs will explicitly consider MDs containing nanomaterials, and assign them to the highest risk class (III), unless NP release can be ruled out.

- This will entail a considerable burden on the manufacturers, who will have to demonstrate the compliance of their product to the Essential requirements under the most exacting conditions. This conservative approach is nevertheless necessary, given the insufficient knowledge about the behaviour of nanostructured MDs, especially at long term.

WWRFD?

(What Would Richard Feynman Do?)



Richard Feynman, 1959:
“There's plenty of room at the bottom”