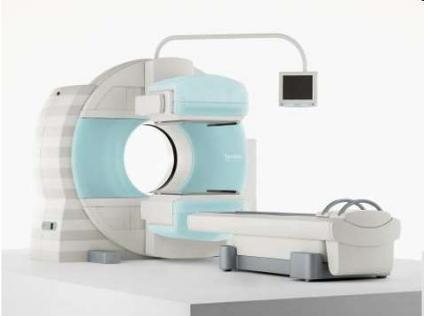


Critical issues of the regulatory pathway for nanostructured medical devices

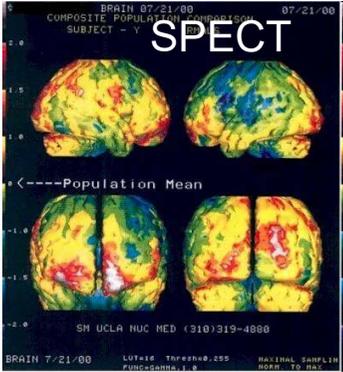
Giuseppe D'Avenio, Carla Daniele, Mauro Grigioni

National Center for Innovative Technologies in Public Health,
Istituto Superiore di Sanità Rome, Italy

Medical devices



SPECT/CT scanner



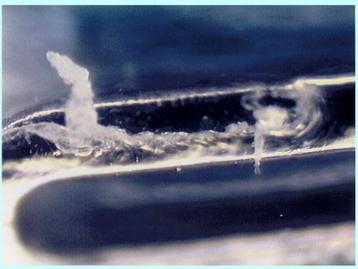
valvuloplasty rings



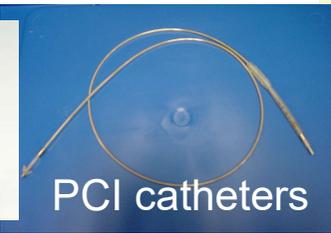
valved conduits



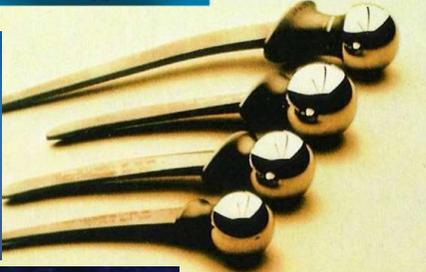
Drug-eluting stents



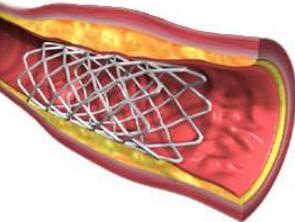
PMK



PCI catheters



hip prostheses



AIMD programmers

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.

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)*

MD: essential requirements

Article 3 (MDD): “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

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.
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.
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), as specified by the manufacturer.

Conformity to essential requirements

Relevant steps for the evaluation of the conformity of a given MD to the essential requirements:

- ✚ Risk management (EN ISO 14971)
- ✚ In-vitro evaluation
- ✚ In-vivo preclinical study
- ✚ Clinical evaluation, Annex X of MDD



Technical dossier of the MD



CE Mark



(after assessment of a Notified Body, except for class I devices)

Developments in the regulatory framework for MDs in Europe

On 5 April 2017, 2 new Regulations on medical devices were adopted. These replace the existing Directives.

[Regulation \(EU\) 2017/745](#) of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

[Regulation \(EU\) 2017/746](#) of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

The new rules will only apply after a transitional period. Namely, 3 years after entry into force for the Regulation on medical devices (spring 2020) and 5 years after entry into force (spring 2022) for the Regulation on in vitro diagnostic medical devices.

<https://www.europarl.europa.eu/news/en/press-room/20200415IPR77113/parliament-decides-to-postpone-new-requirements-for-medical-devices>

17-04-2020

Parliament adopted the Commission proposal on Friday, by urgent procedure with 693 votes to 1 and 2 abstentions, allowing **the application of the Medical Devices Regulation to be postponed by one year until 26 May 2021.**

Given the current pressure on national health authorities and manufacturers of medical devices, there is a fear that there could be shortages or delays in getting the medical devices needed to fight COVID-19, were they to follow the new rules of the Medical Devices Regulation from May this year.

The European Parliament is therefore supporting the proposal to postpone the application of this Regulation by one year to allow authorities and manufacturers alike to prioritise the fight against the coronavirus pandemic by continuing under current procedures.

On April 24, 2020, the proposal, which had been submitted by the European Commission, was published in the Official Journal of the European Union.

Stella Kyriakides, Commissioner for Health and Food Safety, said: “Yesterday’s adoption will allow us all, in this time of crisis, to maintain our focus on the most critical issues and to ensure the continued availability of vitally important medical devices.”

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(18) ‘**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;

(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;

Developments in the regulatory framework for MDs in Europe

MD Regulation 2017/745

MDs incorporating or consisting of nanomaterial must now be grouped in class III, if there is at least a medium potential for internal exposure (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.

Rule 19 - All devices incorporating or consisting of nanomaterial are classified as:

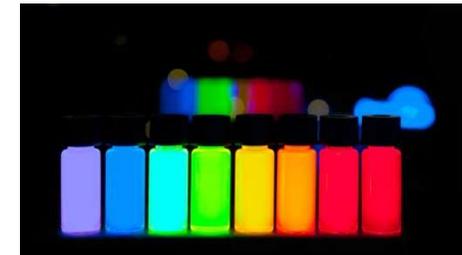
- **class III** if they present a high or medium potential for internal exposure;
- **class IIb** if they present a low potential for internal exposure; and
- **class IIa** if they present a negligible potential for internal exposure.

Nanomaterials & Medical devices

Unique properties of materials at the nanoscale (1 nm=10⁻⁹ m)

⇒ increasing diffusion of medical devices containing nanomaterials

- ✓ High reactivity
- ✓ High surface/volume ratio
- ✓ High penetration capability into cellular/subcellular compartments
- ✓ Quantum mechanical effects: at 1–100 nanometers, the materials' properties change significantly from those at larger scales, and are size-dependent.
- ✓ Properties such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity change as a function of the size of the particle.



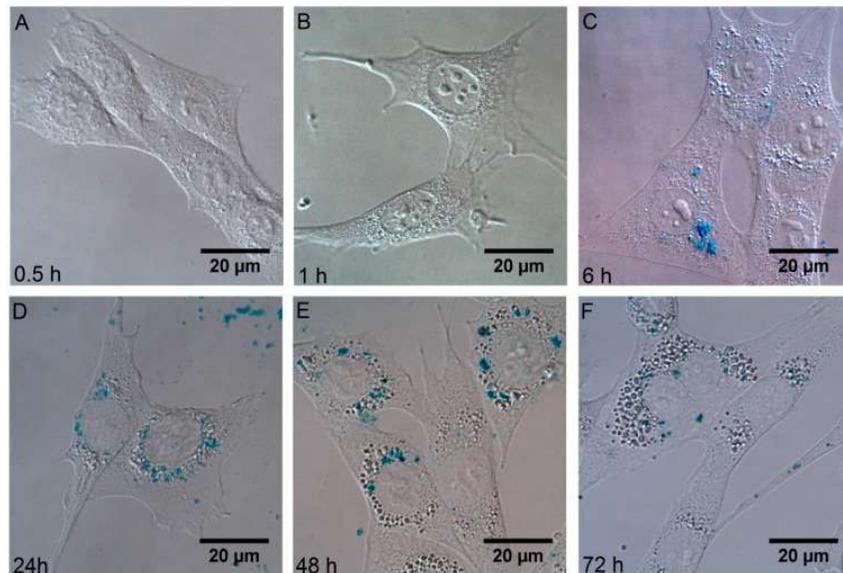
Quantum dots

Necessity to define and monitor the risks associated to nanomaterials in MDs

Possible hazards associated to nanomaterials

NP accumulation in cells:
nanotoxicity

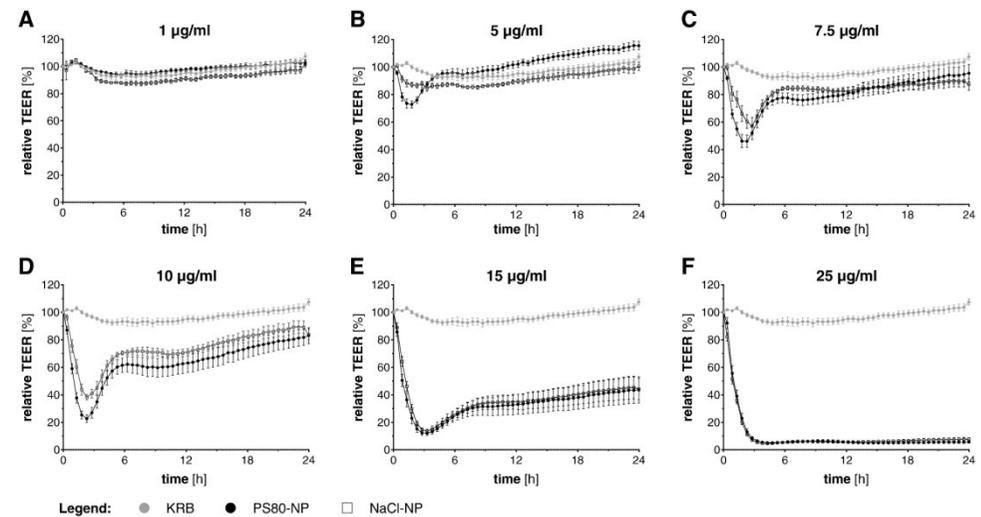
Jarockyte et al, 2016



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.



Legend: ● KRB ● PS80-NP □ NaCl-NP

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

Nanomaterials & Medical devices

Examples of nanomaterials present in MDs:

- Carbon nanotubes or nanoparticles (e.g., hydroxyapatite NP) in bone cements
- Nanosilver or other nanomaterials used as surface coating on implants or catheters
- Functionalised magnetic nanoparticles (iron oxide) for heat treatment of tumors with e.m. fields
- Nanoparticles used in dental nanocomposites

Nanomaterials & Medical devices: 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
- ✚ 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
- ✚ Nanostructured MDs: absence of *harmonized standards* relative to this class of MDs

NP-related issues in cytotoxicity testing

Nanoparticles can interact with soluble indicators used in traditional assays (as per EN ISO 10993-5):

- Data from A549 cells incubated with carbon nanotubes fake a strong cytotoxic effect within the MTT assay after 24 h that reaches roughly 50%, whereas the same treatment with SWCNTs, but detection with WST-1, reveals no cytotoxicity. SWCNTs appear to interact with some tetrazolium salts such as MTT but not with others (such as WST-1, INT, XTT). [Wörle-Knirsch et al, 2006]
- Reports of the occurrence of photocatalytic interactions between titanium dioxide (TiO₂, titania) nanoparticles and the MTT cytotoxicity indicator. These interactions induce the reduction of MTT and formation of purple formazan under biologically relevant conditions. The formazan precipitation was found to be proportional to the TiO₂ concentration, being enhanced under laboratory daylight exposure. The results show false viability increases with up to 14% (for TiO₂ concentrations generally higher than 50 ug/ml), induced by the TiO₂-MTT reaction. This type of artifacts may lead to underestimated toxicity or false proliferation results. [Lupu et al, 2013]

Recommendations of ISO/TR 10993-22:2017 Biological evaluation of medical devices — Part 22: Guidance on nanomaterials: “Corroboration of several test results from different methodologies might be required for a scientifically sound interpretation”

Drug delivery and regulatory issues

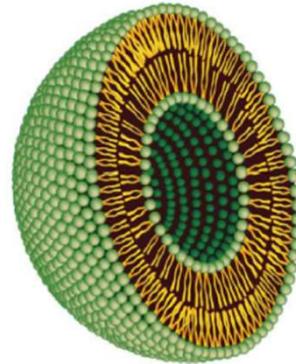
(MDD, Article 1) 3. Where a device is intended to administer a medicinal product within the meaning of Article 1 of **Directive 2001/83/EC**, that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product.

If, however, such a device is placed on the market in such a way that **the device and the medicinal product form a single integral product** which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. The relevant essential requirements of Annex I to this Directive shall apply as far as safety and performance-related device features are concerned.

4. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body **with action ancillary to that of the device**, that device shall be assessed and authorized in accordance with this Directive.

Lipid-based nanocarriers as nanomedical devices

Bozzuto and Molinari, 2015



Medical Device Directive
(from May 26th, 2021: MDR)

Directive 2001/83/EC

EMA/635791/2019

Why is Caelyx pegylated liposomal (active substance: Doxorubicin) authorised in the EU?

The European Medicines Agency decided that Caelyx pegylated liposomal's benefits are greater than its risks and it can be authorised for use in the EU.

Testing of polymeric nanobiomaterials (NBM): assessment of the literature

Most studies are performed with drug-loaded formulations, without a simultaneous evaluation of the unloaded polymeric NBMs. In these situations, it is difficult to know whether effects are due to the drug, the NBM or both. Furthermore, testing for contaminants – particularly endotoxins such as LPS that may not be eliminated using common sterilising techniques – is almost always missing from reports. *In vitro* testing of LPS-contaminated polymeric NBMs could thus generate misleading results and false assumptions about bioactivity or toxicity, ultimately affecting a robust evaluation of the possible effects on human health.

Som, C. et al: Guidelines for implementing a Safe-by-Design approach for medicinal polymeric nanocarriers, Empa St.Gallen, June 2019

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. Moreover, harmonised standards for this type of MDs are not yet available.
- ✚ In general terms, the safety profile of nanostructured MDs is related to nanoparticle release and time of exposure.
- ✚ It is generally accepted that the ISO 10993 series should be revised to consider the biocompatibility and toxicity of nanomaterials.
- ✚ For nanostructured MDs, different regulatory obligations may apply, with a consequent burden for the manufacturers to demonstrate compliance to them.