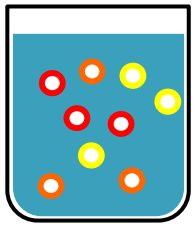
UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE

Nanotechnology-based medicinal products: how to balance innovation and public health?

Paola Minghetti

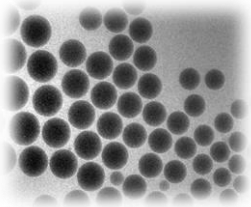
Nanotechnology products… for treating human diseases



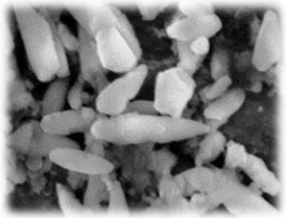
To improve **TECHNOLOGICAL CHARACTERISTICS** of the active ingredient (e.g., high drug solubility and dispersibility of poor soluble drugs)

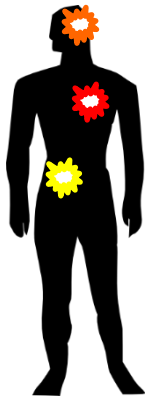
Micelles

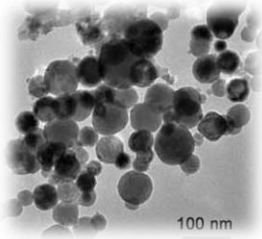
Nanoemulsions



Nanocrystals



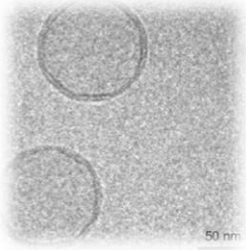




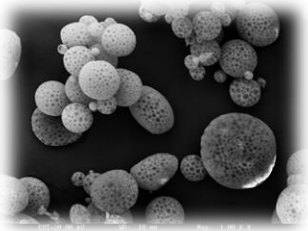
IONs

To modify the drug **PHARMACOKINETICS** and **PHARMACODYNAMICS** in the human body

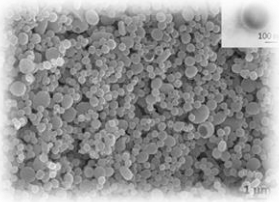
Lipid vesicles



Nanoparticles



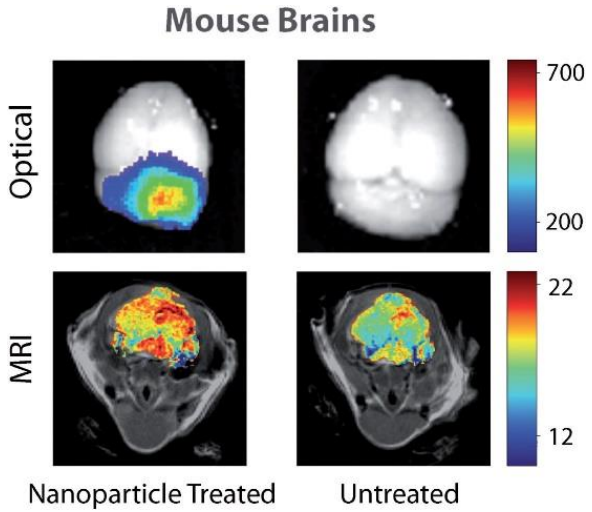
Nanogels



Functionalization of nanosystem surface

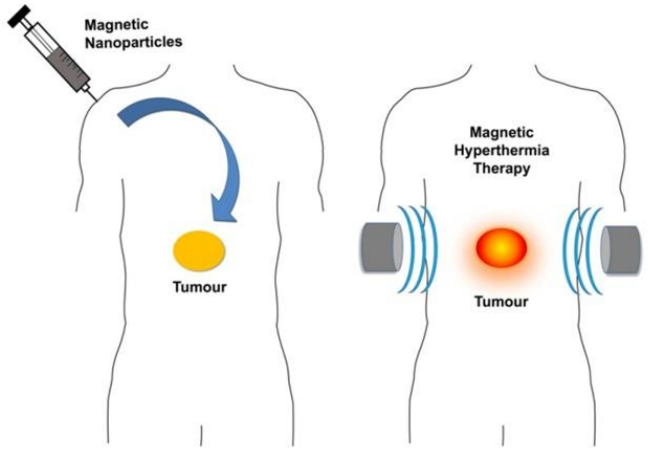
…for treating/diagnose human diseases

DIAGNOSIS



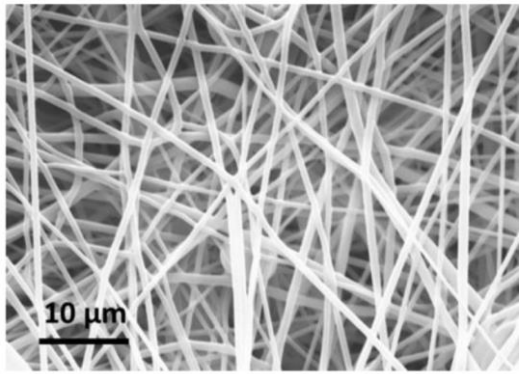
Superparamagnetic nanoparticles for MRI

TREATMENT



Nanoparticle-mediated hyperthermia in cancer therapy

REPLACEMENT OF THE ANATOMY

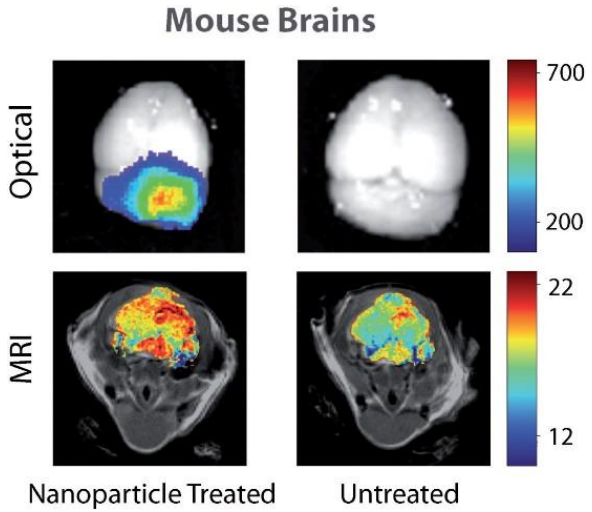


Scaffold made of nanofibers for regenerative therapies

Dorati et al., Carbohydrate polymers 2018, 199:150-160
Stephen et al., Mater Today 2011, 14:330-338

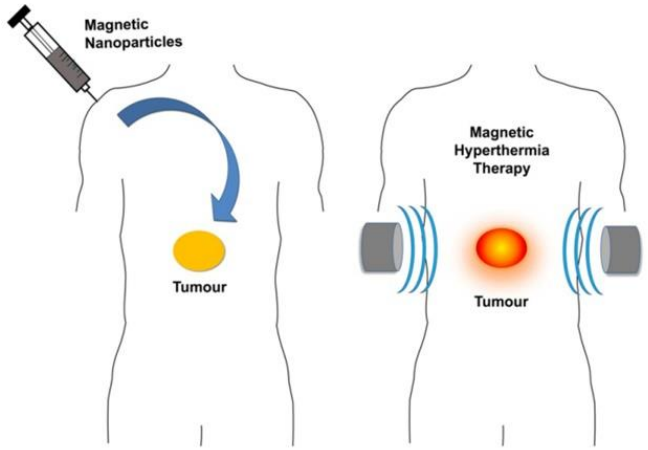
…for treating/diagnose human diseases

DIAGNOSIS



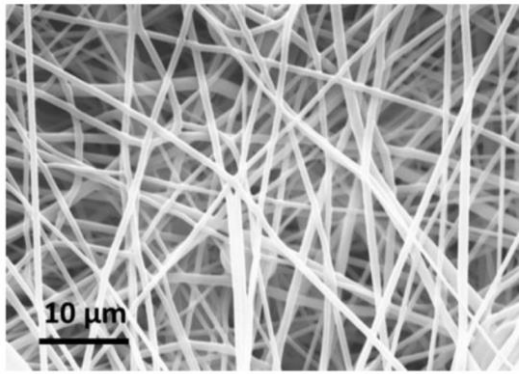
Superparamagnetic nanoparticles for MRI

TREATMENT



Nanoparticle-mediated hyperthermia in cancer therapy

REPLACEMENT OF THE ANATOMY

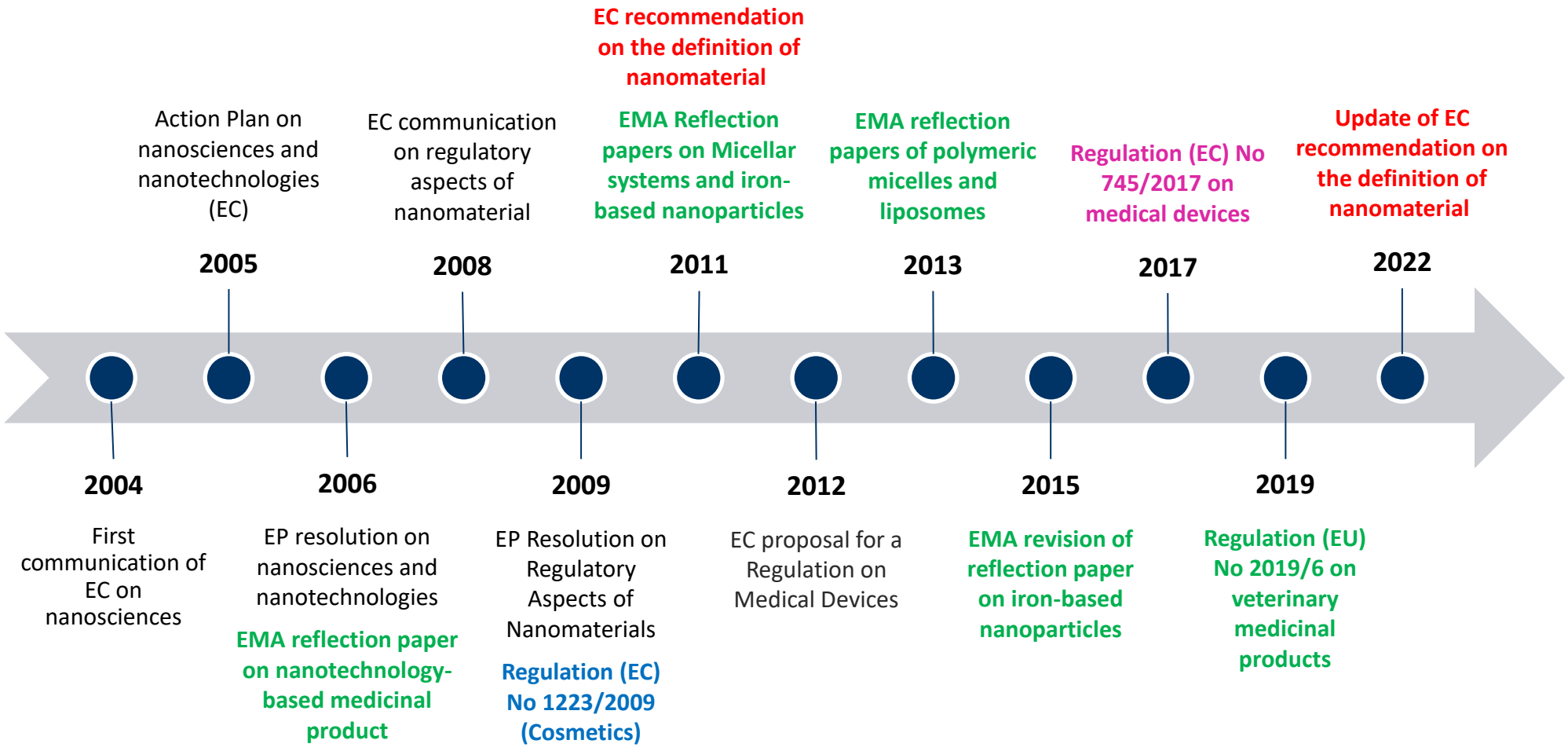


Scaffold made of nanofibers for regenerative therapies

The efficacy/safety balance must be acceptable for human use

Dorati et al., Carbohydrate polymers 2018, 199:150-160
Stephen et al., Mater Today 2011, 14:330-338

The EU regulatory framework of nanotechnology products



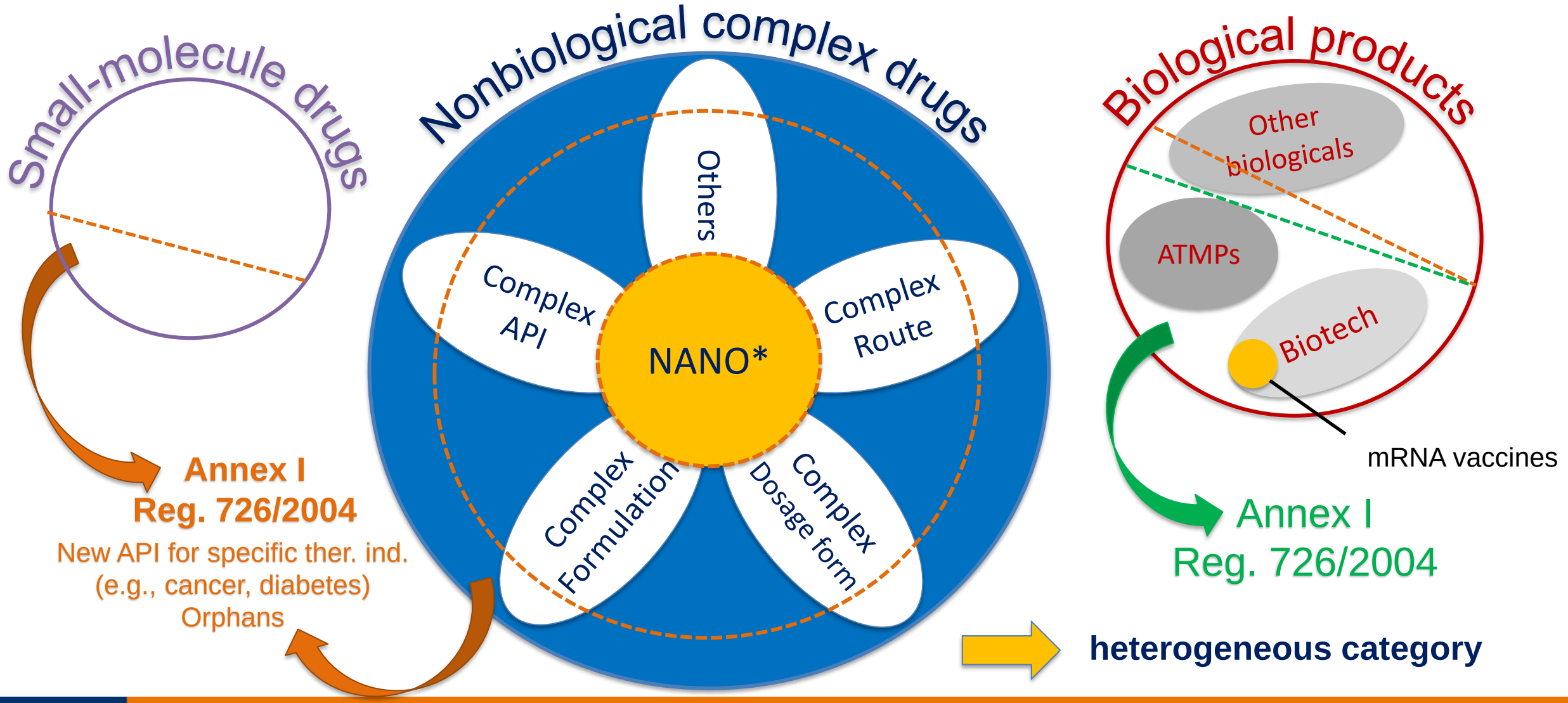
The European legislation is still stratified, and several criticisms remain because of the lack of well-established scientific knowledge on nanomaterials. The assessment of safety/efficacy of nanomaterials in medicinal products and medical devices is still based on case-by-case approach.

Musazzi et al. Drug. Discov. Today (2017); doi:10.1016/j.drudis.2017.01.016

Nanomedicine products

- **Which marketing authorization (MA) procedure should they have to follow?**

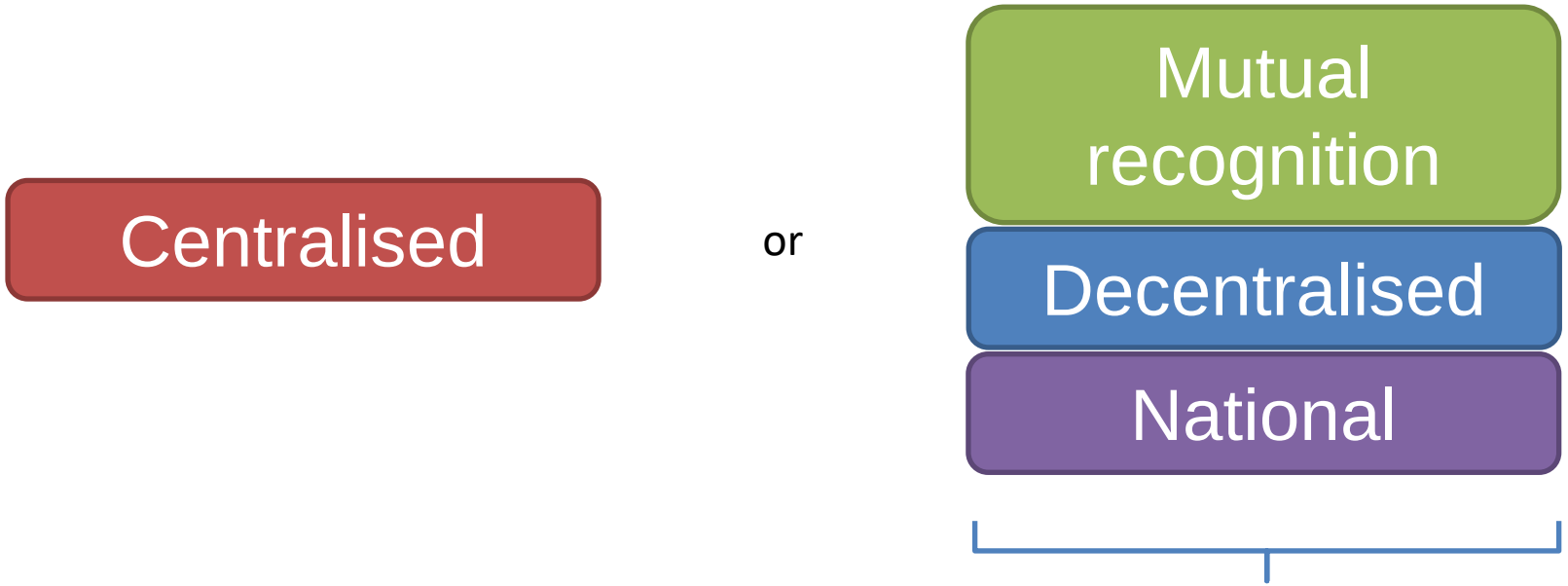
- What data should be submitted to EMA/NCAs? (first-in-human/follow-on products)



*nanomedicine products, nanodrugs, drug products that contain nanomaterials

Marketing authorization

Centralised procedure: <u>not mandatory</u> for nanomedicine products



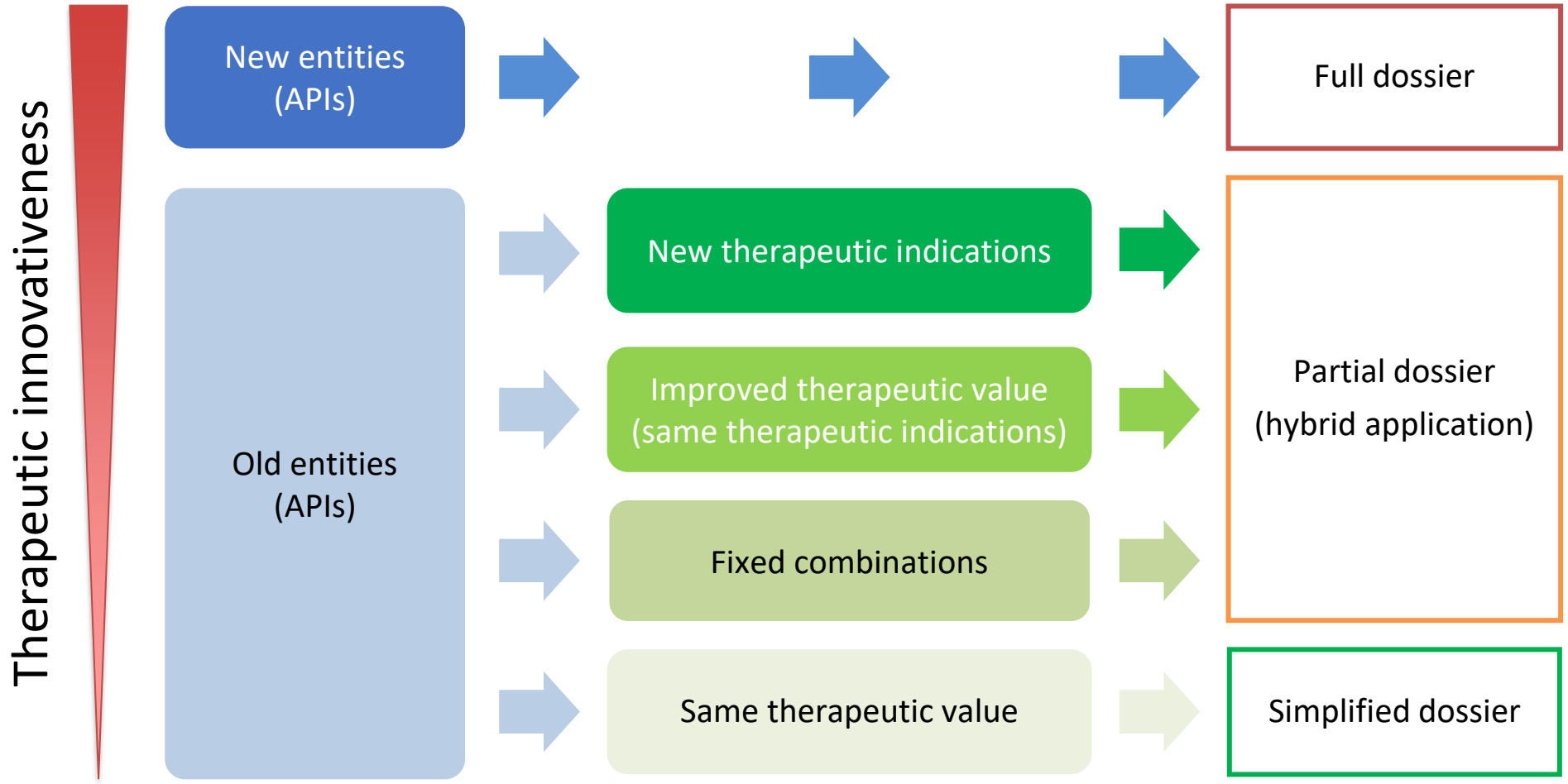
..without harmonized guidelines, risk of different data requirements; different time-to-market in EU Member States

Nanomedicine products

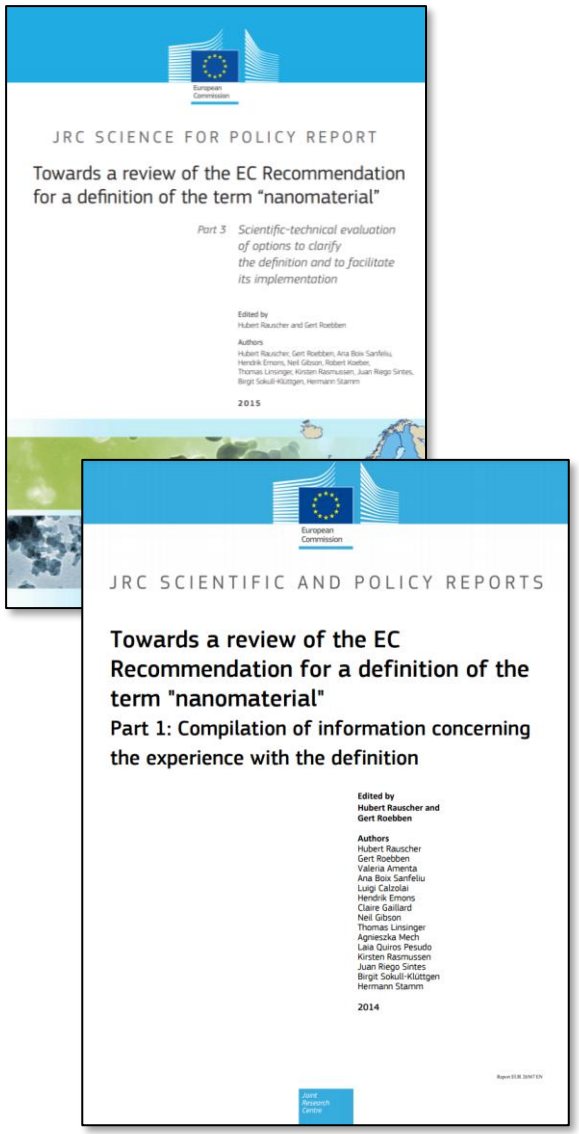
- Which marketing authorization (MA) procedure should they have to follow?

- **What data should be submitted to EMA/NCAs? (first-in-human/follow-on products)**

Nanomedicine products…



Quality of nanomedicine products: characterisation



Particle size
- Field flow fractionation (FFF)
- Dynamic light scattering (DLS)
- Atomic force microscopy (AFM)
- Nanoparticle tracking analysis (PTA)
- Size Exclusion Chromatography
- Electron microscopy (EM)
- Centrifugal liquid sedimentation (CLS)

Z-potential
- Electrophoretic light scattering
- Dynamic light scattering (DLS)

Particle Concentrations
- Nanoparticle tracking analysis (PTA)
- Evaporative light scattering detectors

Thermal properties
- Differential Scanning Calorimetry

Morphology
- Electron microscopy (EM)
- Field flow fractionation (FFF)
- Atomic force microscopy (AFM)

Surface structure
- X-ray photoelectron spectroscopy (XPD)
- X-ray diffraction (XRD)

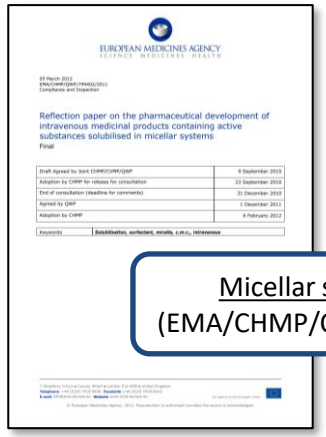
Motion and structure-based feature
- Electron Spin Resonance

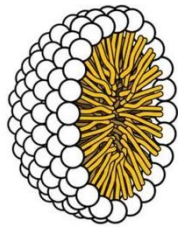
Quality of nanomedicine products: manufacturing process

Small **differences relating to raw materials or differences in manufacturing processes** of the nanomedicine product may have a strong impact on its quality profile*;*

Enforced quality assessment and management (quality by design approach)

EMA guidelines on nanomedicine products

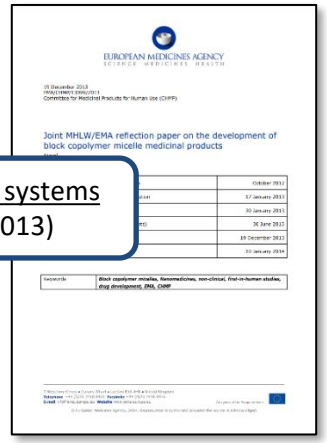




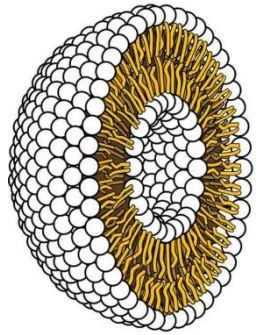
Micellar systems

Micellar systems for i.v.
(EMA/CHMP/QWP/799402/2011)

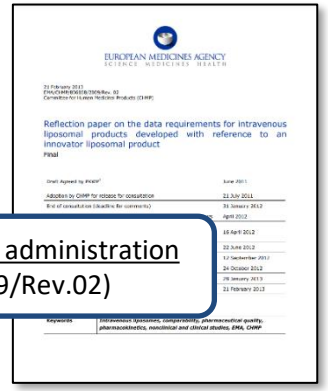
Block co-polymer micellar systems
(EMA/CHMP/13099/2013)



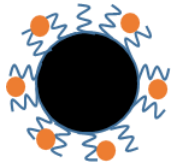
Lipid vesicles

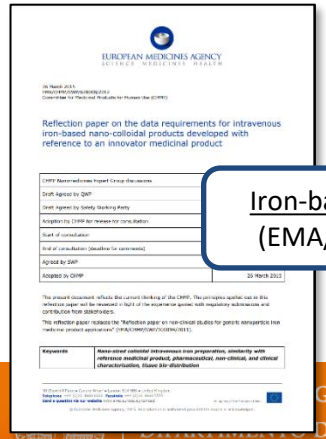


Liposomal products for i.v. administration
(CHMP/806058/2009/Rev.02)



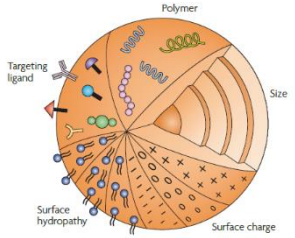
Iron-core nanoparticles



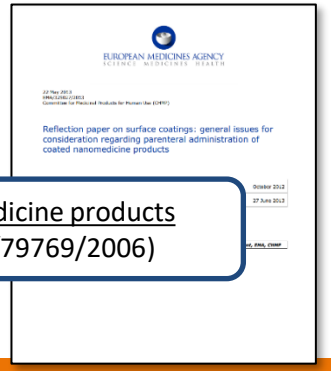


Iron-based nano-colloidal products
(EMA/CHMP/SWP/620008/2012)

Coating of nanosystem surface



Coated nanomedicine products
(EMEA/CHMP/79769/2006)



Copies/Follow-on: type of application

Full Dossier

- New active substances [art. 8].

Partial Dossier

- **Hybrid [art. 10(3)]:**
  - medicinal product (MP) does not fall within the definition of a generic or
  - bioequivalence cannot be demonstrated through bioavailability studies or
  - in case of changes in the active substance, therapeutic indications, strength, pharmaceutical form or route of administration;

- Biosimilar [art. 10(4)]:
  - biological MP similar to a reference biological MP does not meet the conditions in the definition of generic, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product;

- Fixed combination medicinal products [art. 10b].

Simplified Dossier

- **Generic medicinal products [art. 10(1)];**
- Co-marketing [art. 10c];
- Well-established medicinal use (ten years) [art. 10a];
- Traditional herbal medicinal products [art. 13a];
- Homeopathic medicinal products [art. 13].

Copies/Follow-on: type of application

Full Dossier

- New active substances [art. 8].

Partial Dossier

- **Hybrid [art. 10(3)]:**
  - medicinal product (MP) does not fall within the definition of a generic or
  - **bioequivalence cannot be demonstrated through bioavailability studies** or
  - in case of changes in the active substance, therapeutic indications, strength, pharmaceutical form or route of administration;

- Biosimilar [art. 10(4)]:
  - biological MP similar to a reference biological MP does not meet the conditions in the definition of generic, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product;

- Fixed combination medicinal products [art. 10b].

Simplified Dossier

- **Generic medicinal products [art. 10(1)];**
- Co-marketing [art. 10c];
- Well-established medicinal use (ten years) [art. 10a];
- Traditional herbal medicinal products [art. 13a];
- Homeopathic medicinal products [art. 13].

In EU, several copies of nanomedicine products have been authorized as generics

Open issues?

Pharmaceutical development of new nanomedicine products

Post-marketing variations

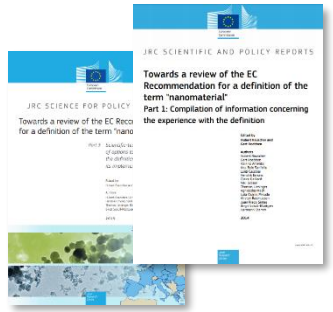
Development of a therapeutically equivalent copy of a nanomedicine products

MARKETING AUTHORISATION

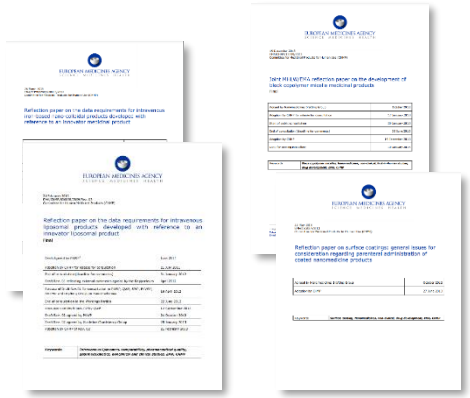
Is a specific regulatory pathways for nanomedicine products needed?

CHARACTERIZATION

Physicochemical characterization of nanomaterials



Class-specific guidelines



PERFORMANCE

Development and validation of in vitro biorelevant methods (/establish IVIVCs) that can be used as surrogate of clinical studies for assessing the similarity between nanosystems.

Musazzi et al., Drug Discov. Today (2017) 22: 870-882
Selmin et al., Drug Discov. Today (2020) 25:321-329


Thank you for your kind attention!