OPEN WORKSHOP ON MEASUREMENT CHALLENGES – LABORATORY MEDICINE

METROLOGY FOR INNOVATIVE NANOTHERAPEUTICS

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LABORATOIRE NATIONAL DE MÉTROLOGIE ET D'ESSAIS

MEDICINAL PRODUCTS AND MEDICAL DEVICES CONTAINING NANOMATERIALS: DEFINITIONS IN EUROPE

Medicinal product

Mode of action: Intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

Nanomaterial definition: At least one component at nano-scale size that should not exceed 1000 nm, if definable specific properties are related to the particle size

Active pharmaceutical ingredient (API) encapsulated: small molecules or biological macromolecules (e.g. Nucleic acids)

(Pita, Ehmann, & Papaluca, 2016-EMA)

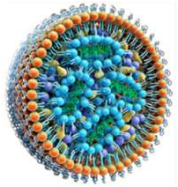
Medical devices

Mode of action: intended to be used for diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, ….., and which does not achieve its principal intended action by pharmacological, immunological or metabolic means… (physical principle).

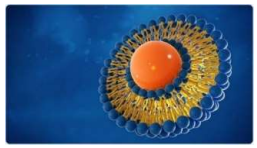
Nanomaterial definition: 2011/696/EU definition: particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm

MDR REGULATION (EU) 2017/745

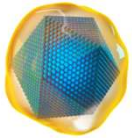
Some examples of NPs used as nanotherapeutics, adjuvants for radiotherapy or imaging devices



Lipid based nanoparticles

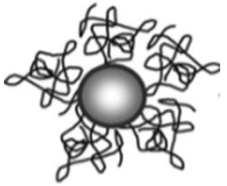


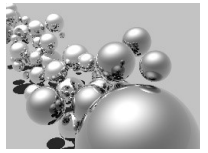
Liposomes



Hafnium oxide nanoparticles

Dextran coated iron oxide

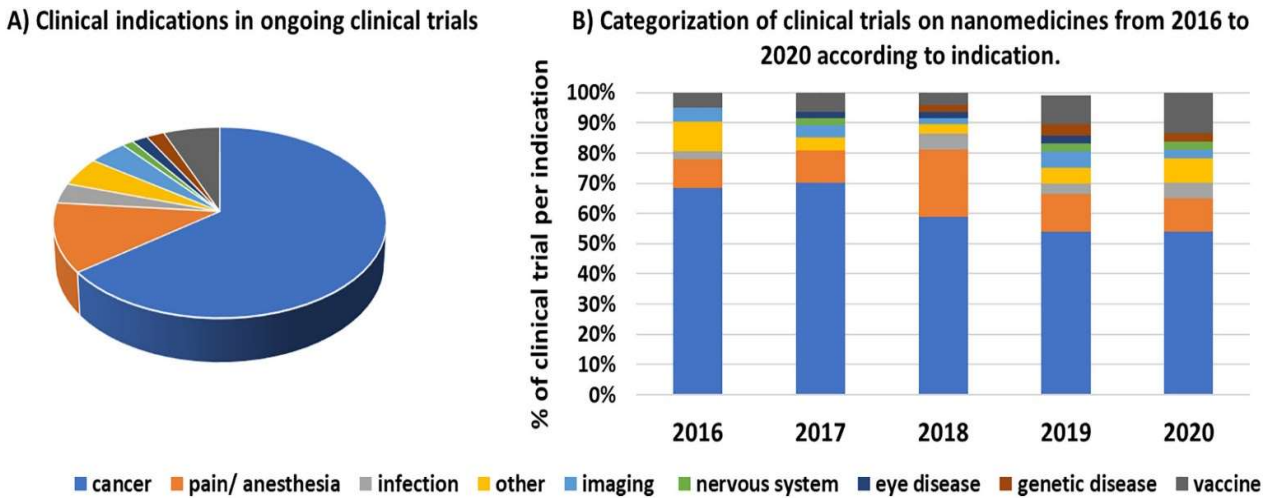




Metallic nanoparticles

KEY SOCIETAL CHALLENGES AND ASSOCIATED PRIORITIES OF THE EUROPEAN COMMISSION (EC)

Clinical applications in ongoing trials:

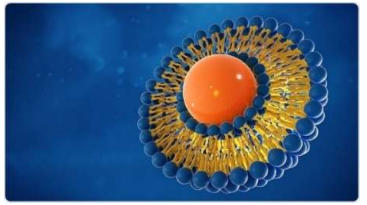


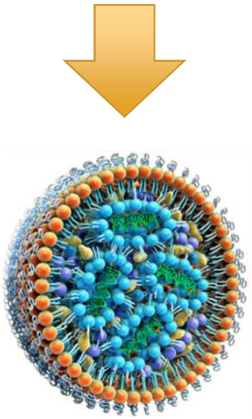
Some key societal priorities from the EC (Horizon Europe):

- Mission Cancer
- Non-communicable and chronic diseases, including rare diseases
- Pandemic preparedness (supporting European Health Emergency preparedness and Response Authority-HERA)
- Antimicrobial resistance (AMR Plan)

https://doi.org/10.1016/j.jconrel.2020.07.007

EVIDENCE-BASED NEEDS AS SET BY INDUSTRY AND REGULATORS

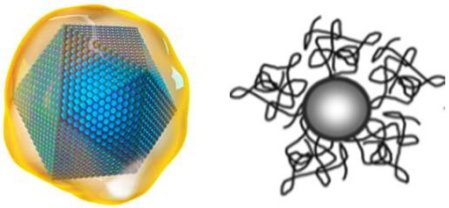




Regulators note a shift from simpler delivery systems to highly complex, multicomponent, multifunctional structures and devices. With this shift, comes a significant analytical challenge and the need for fit-for-purpose measurement methods and standards to support industry and regulatory science.

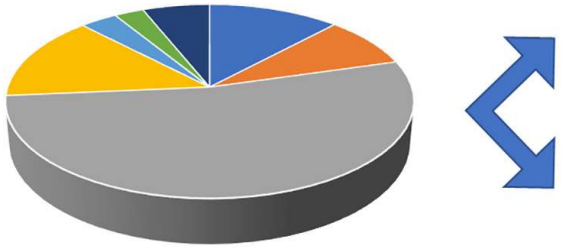
PRIORITISATION IN TERMS OF MATERIALS

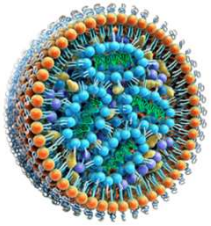
Material classes



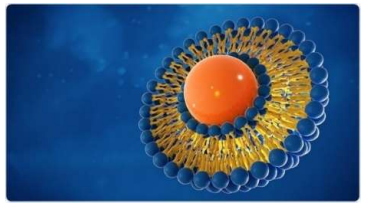
Metal oxide and metal NPs

NP classes in ongoing clinical trails (2008-2020)





Lipid based nanoparticles



Liposomes

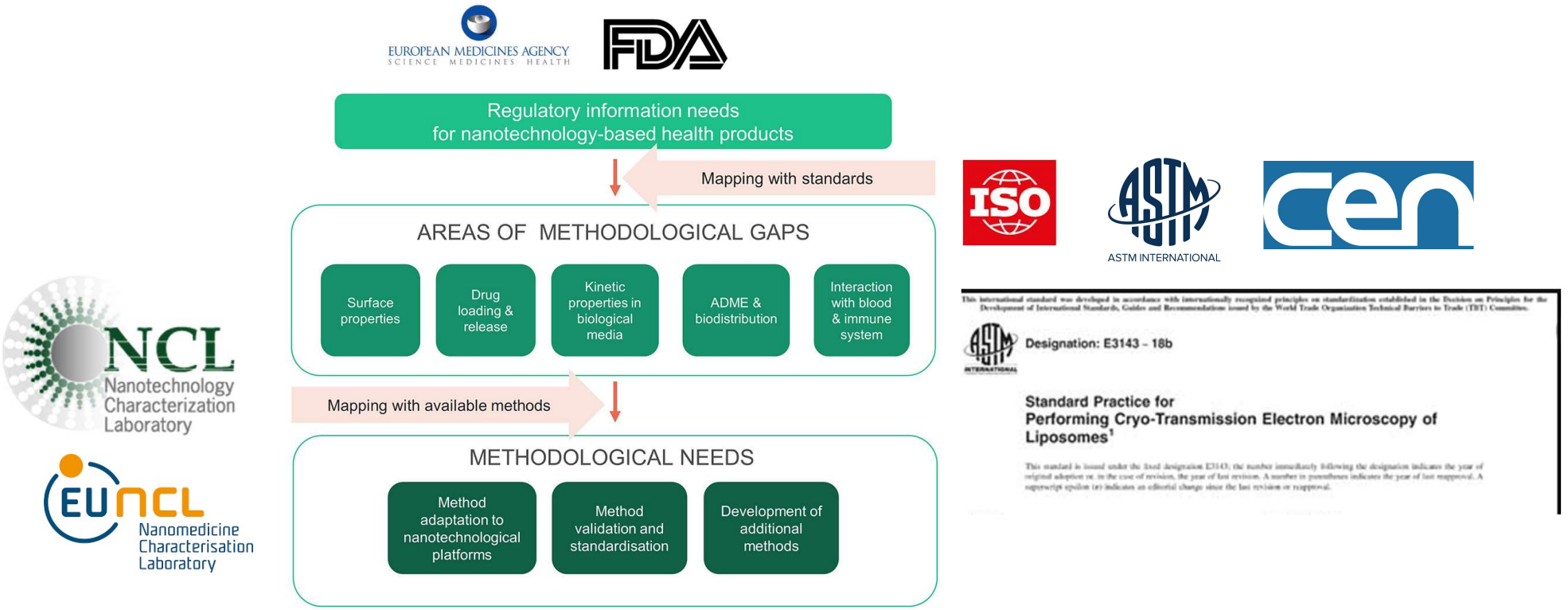
Fit-for-purpose metrologically traceable measurement methods to characterise highly complex, multicomponent, multifunctional structures and devices

■ oxide / metal NPs ■ lipid-based nanoparticles ■ liposomes ■ protein based NPs
■ polymer based NPs ■ micelles ■ others

https://doi.org/10.1016/j.jconrel.2020.07.007

REGULATORY NEEDS ARE GUIDING OUR FUTURE ACTIONS

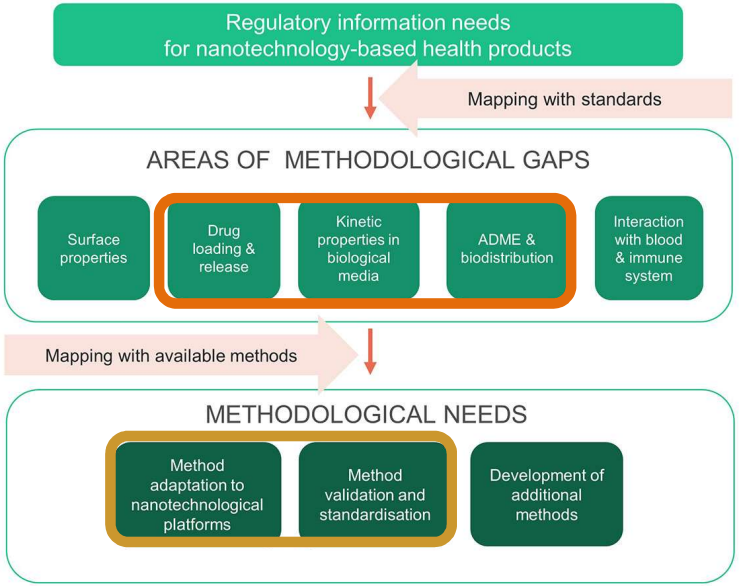
What are the needs for new reference measurement procedures?

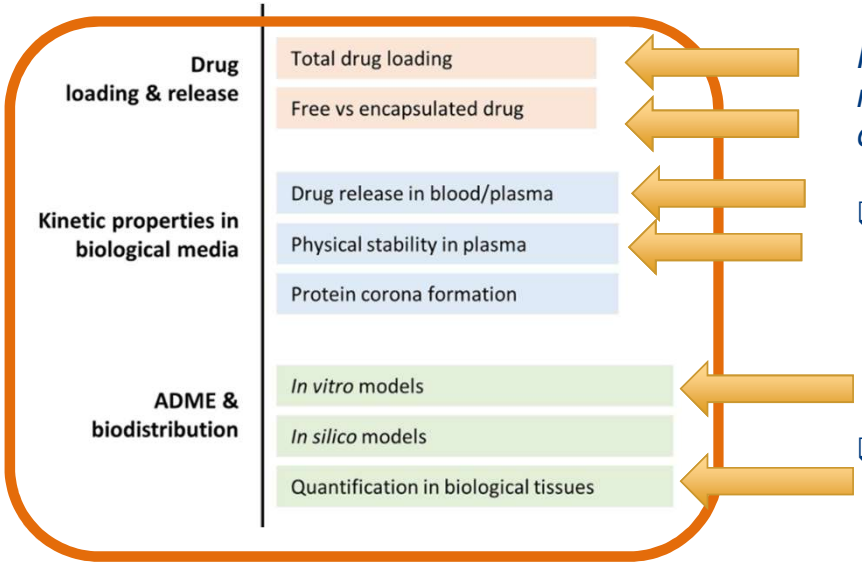


https://www.sciencedirect.com/science/article/pii/S0168365921003035#f0035

FUTURE PRT- METHODOLOGICAL NEEDS

Provide reference methods to measure the physical-chemical properties of medicinal products and devices in biological media (biotransformation) influencing their biodistribution and safety





Focus on pre-existing methods (SOP, guidance documents available) that:

- ❑ *need adaptation to different nanoparticle classes an/or to measurement in biological media*
- ❑ *are ready to be metrologically validated*

https://www.sciencedirect.com/science/article/pii/S0168365921003035#f0035

FUTURE PRT- METHODOLOGICAL NEEDS

Fractionation of nanoparticles from biological matrices:

- Analytical and metrological issues in sample preparation
- Hyphenated separation methods such as AF4 or SEC or ultracentrifugation coupled with off line or online detection (link to ASTM WK68060 Analysis of Liposomal Drug Formulations using Multidetector Asymmetrical-Flow Field-Flow Fractionation (AF4).)

Physical-chemical properties and stability of the nanocarrier in biological media

- Particle concentration, particle release and dissolution propensity, e.g. by (sp)-ICP-MS, MD-AF4, PTA,…
- Physical properties, including size and aggregation propensity by ICP-MS, EM, AFM, light scattering, SAXS,….
- Chemical composition & structure of the carrier and of the single components (LC-MS/MS, Raman, XPS, EM, …)

Physical-chemical stability of the drug in biological media (medicinal products only)

- Drug payload and release (ultracentrifugation combined with LC-MS/MS-> working item on small molecules loaded in liposomes has been proposed in ISO 229)
- Drug stability, integrity/ identity, oxidation and impurities (guide on RNA detection proposed in ASTM E56)

Quantification of the nanoparticles in biological tissues

- Cellular uptake and cellular biodistribution
- Bioaccumulation in tissues, e.g. by mass spectrometry and other imaging techniques

FUTURE PRT-NETWORKING AND INTERNATIONAL COOPERATION

Networking: Support the cooperation across measurement experts and manufacturers with the aim to also transfer reference methods to end users.

Interactions with regulators: involve EMA and national authorities in the discussion

EMA 2025 Strategic Reflections: "*To underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems*"

International cooperation: to promote synergy across multiple standard bodies, including for example CEN, ISO and ASTM, and reduce duplication:

- LINK CEN with standardization work developed at ASTM E56, ISO TC 229, VAMAS (TWA 40, TWA 34)
- Participate to common initiative to develop standard test methods together with NMIs outside Europe, e.g. together with NIST
- Participate to activities aiming at the development of standard reference materials that have been initiated outside Europe

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REFINE GAP analysis

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Thank you for your attention!!!

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