NIA
Nanotechnology
Industries Association

Nanotechnology Industries Association

Regulatory aspects of Clinical translation of nano-enabled products

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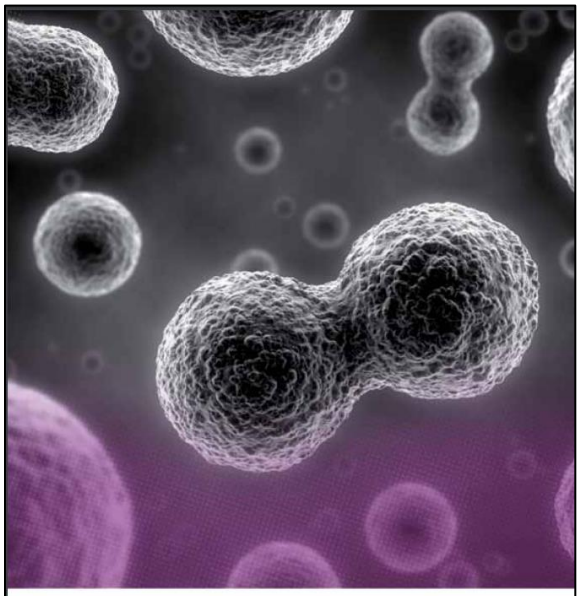
A missile against cancer



nanother

Nanother aims to successfully transform polymer nanomaterials into nanocarriers via biofunctionalisation (the linking of antibodies & ligands for detection), the binding of tumour cells, and the linking, delivery and release of therapeutic agents to treat the targeted tumour cells.

Nanother aims to select the best nanocarriers throughout the project by rigorously testing toxicity, biocompatibility, efficacy and biodistribution as an integral part of the selection process in order to continue developing only the most efficient, biocompatible and least toxic nanoparticles. The nanocarriers selected will be further developed and scaled-up, giving future exploitable nanoproducts.

EL CORREO

Sociedad | Sucesos | Educación | Salud | Premios Fronteras del Conocimiento | Cambio Climático

Un misil contra el cáncer

Un grupo de investigación europeo liderado por una empresa vasca trabajará en el desarrollo de una nueva medicación antitumoral más efectiva y menos agresiva

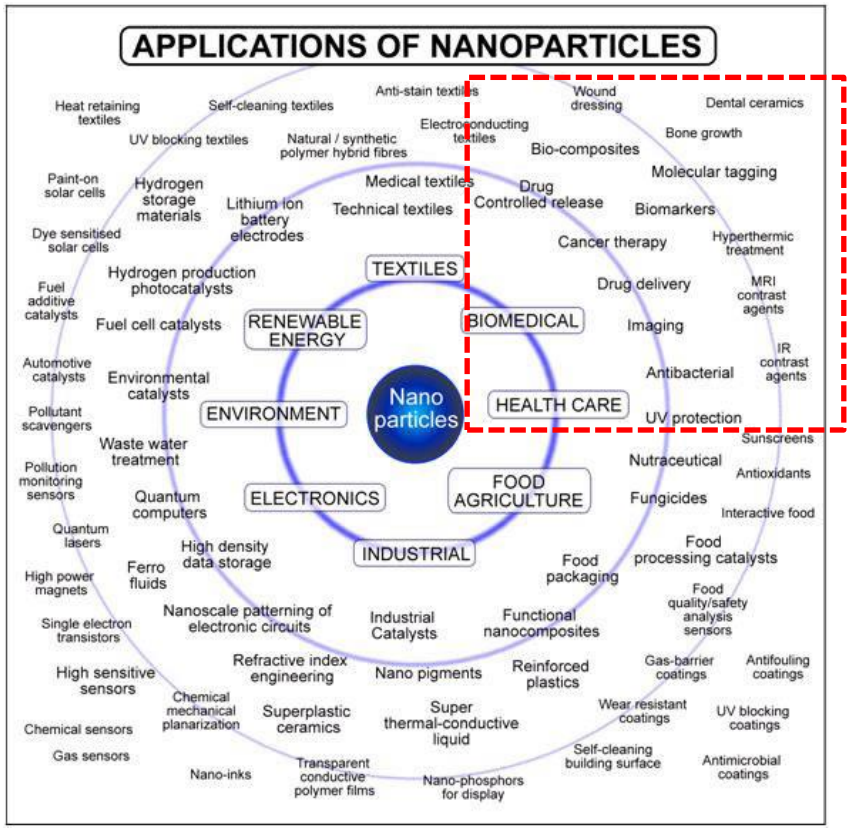
FERMÍN APEZTEGUIA
| BILBAO
Miércoles, 22 octubre 2008, 09:48

Un grupo de 18 empresas europeas liderado por una firma vasca busca una nueva medicación contra el cáncer más efectiva y menos agresiva. El consorcio, apadrinado por la Unión Europea, trabaja en el desarrollo de un fármaco capaz de detectar los tumores y destruirlos sin causar daños colaterales en el organismo. Lo que quieren es algo así como un pequeño misil teledirigido que al estallar fulmine sólo las células cancerosas y deje intactas las sanas. De momento, disponen de un plazo de cuatro años y un presupuesto de once millones de euros para intentar conseguirlo.

El Correo 2008

SIXTH FRAMEWORK PROGRAMME
European Commission

Nanotechnology in contemporary science and industry



Nanoenabled health products (no definition)

- May contain a fraction of engineered nanomaterials
- May completely consist of engineered nanomaterials
- May produced engineered nanomaterials over time
- May contain surface structures in the nanoscale

Adapted from Takuya Tsuzuki, "Commercial scale production of inorganic nanoparticles," International Journal of Nanotechnology, 6 (2009) 567.

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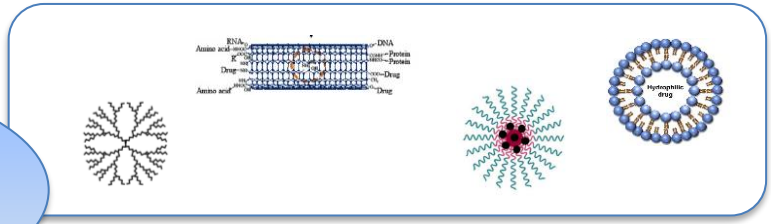
Types of nano-enabled health products

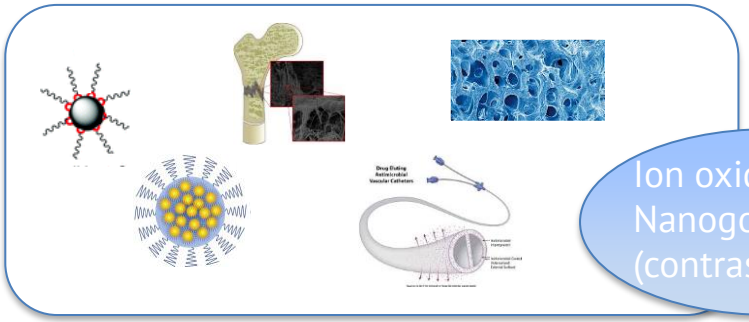
Dendrimer
Miscelle
Liposome
Carbon nanotubes



Drug delivery

Nano-enabled medical products

Medical Devices



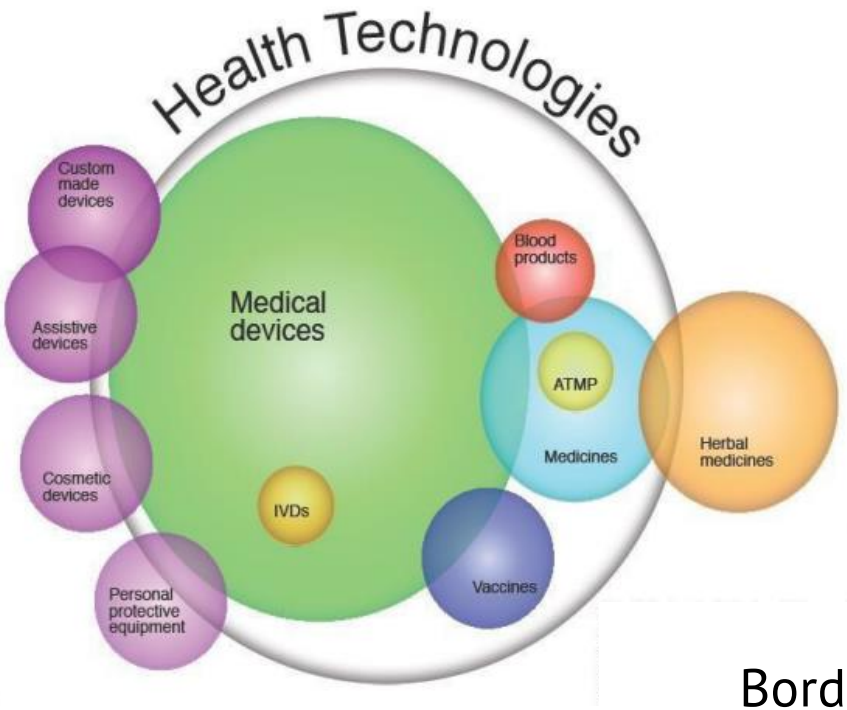
Ion oxide
Nanogold
(contrast agents)

In vitro diagnostics

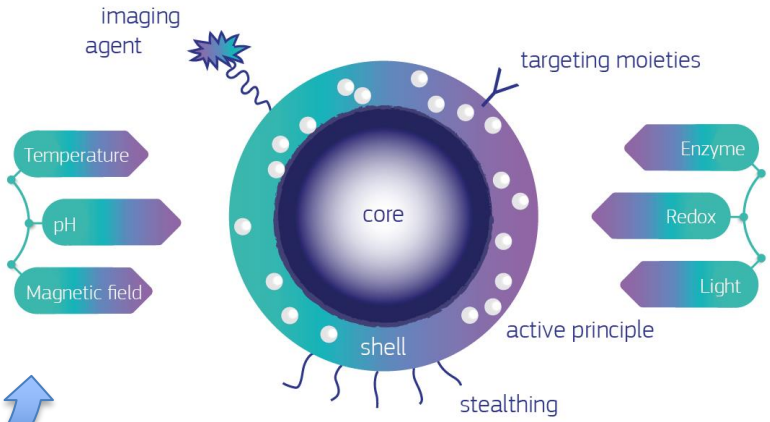
Gold
QDs

Regulatory Barriers

Which regulation are we addressing?



Depends on the mode of action!

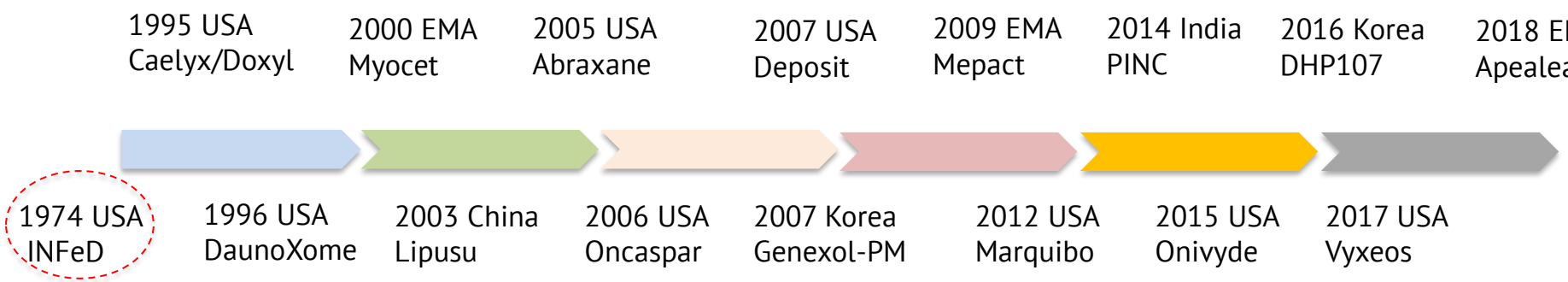


Borderline Products
(Competent authorities of Member states)

Guideline for borderline products 2022

The Refine White Paper 2019

Translation from bench to bed (cancer nanomedicines)



23 scientific publications "nanoparticles for cancer"

>25000 scientific publications

Only 15 drugs approved

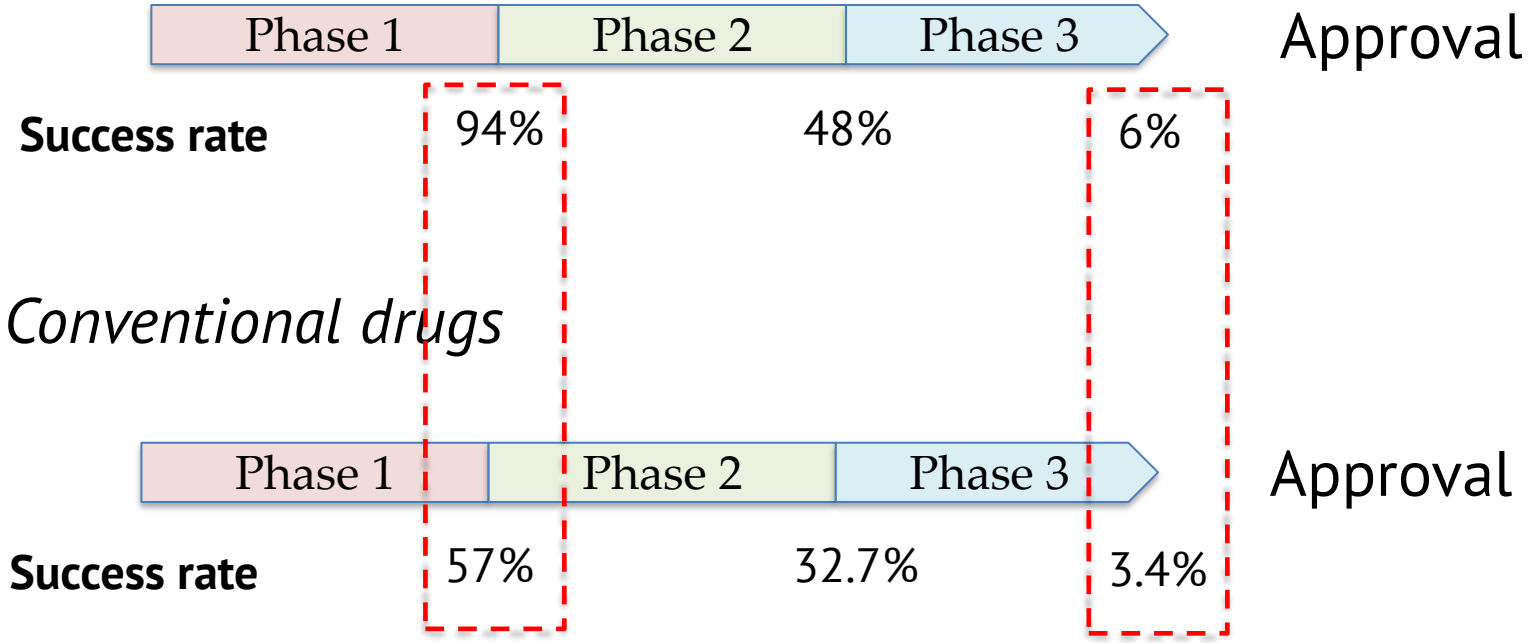
Clinical trials:
Phase 1: 91
Phase 2: 78
Phase 3: 21

Adapted from He *et al.* 2019

Success rate nanomedicine vs conventional medicines

Cancer drugs

Nanomedicines



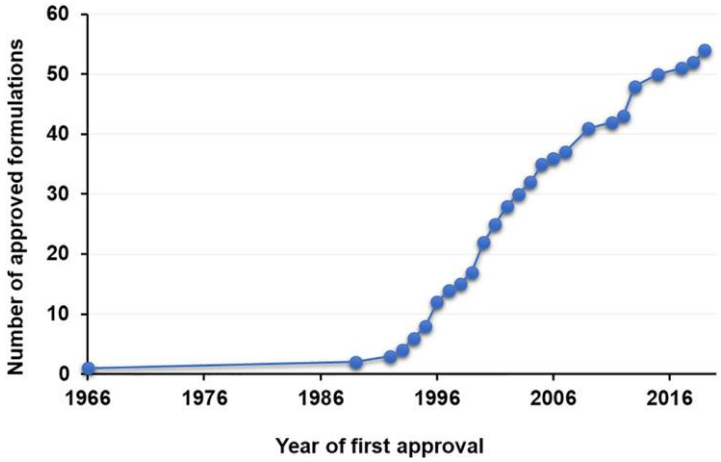
Conventional drugs

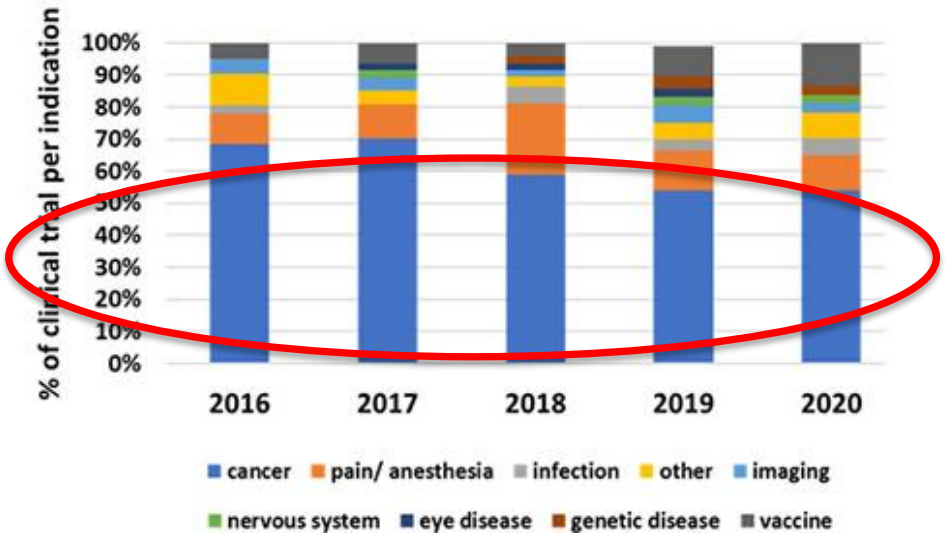
Adapted from He *et al.* 2019

Adapted from Wong *et al.* 2019

Evolution of approved nanomedicine formulations

Overall: 50 nanoformulations (2018)

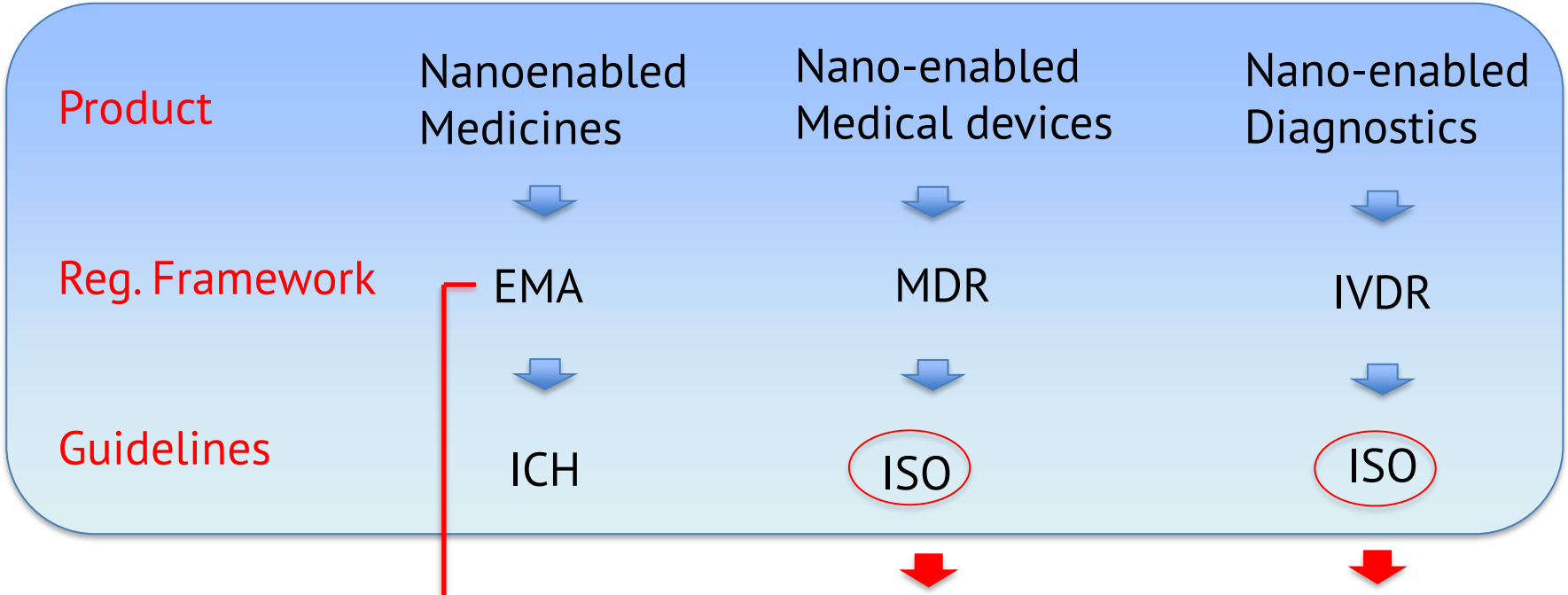




Liposomes
Iron colloids
Protein-based NP
Nanoemulsions
Nanocrystal
Metal oxide NP

Germain *et al.* 2020

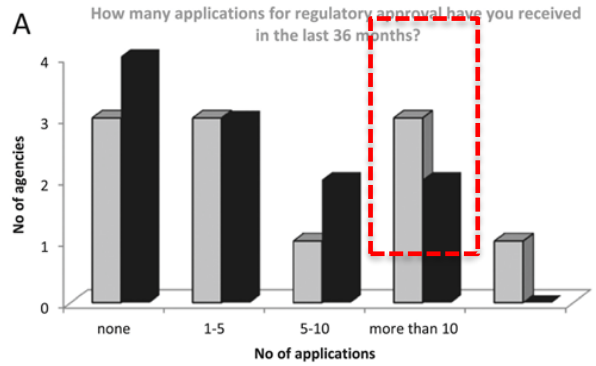
Regulatory Landscape



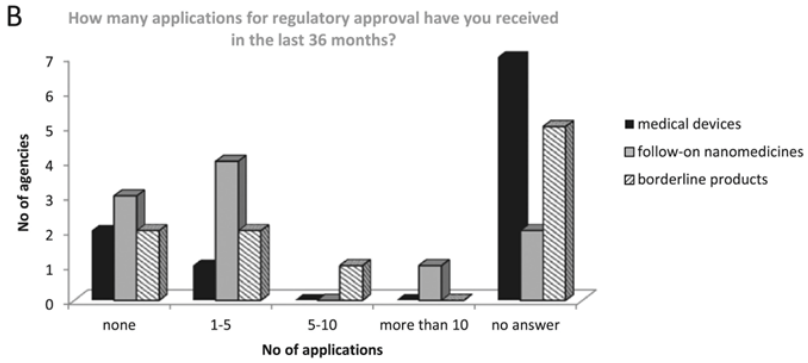
Regulatory experience

From the International Pharmaceutical Regulators Forum (chaired by EMA)

Products challenging the regulatory framework



By type of product



- Health Canada, Canada
- European Medicines Agency, Europe
- Swissmedic, Switzerland
- Food and Drug Administration, US
- National Institute for Public Health and the Environment, The Netherlands
- Centre for Drug Evaluations, Taiwan
- Medicines and Biological Products Office, Brazil
- Pharmaceuticals and Medical Devices Agency, Japan
- Ministry for Food and Drug Administration, Korea

Bremer-Hoffmann *et al*. 2018

Regulators views

- Strong regional differences in the regulation of nanomedicines
- Need for the harmonisation of information requirements on nano-specific properties (across different sectors)
- A number of critical physicochemical properties that have already been proposed in the scientific literature are also supported by regulators to allow regulatory decision making
- Interest of regulatory agencies in an independent nanomedicine characterisation facility that can support them in the evaluation of these systems and at the same time assess the performance of existing and new test methods for their application to the field of nanomedicine.

Bremer-Hoffmann *et al*. 2018

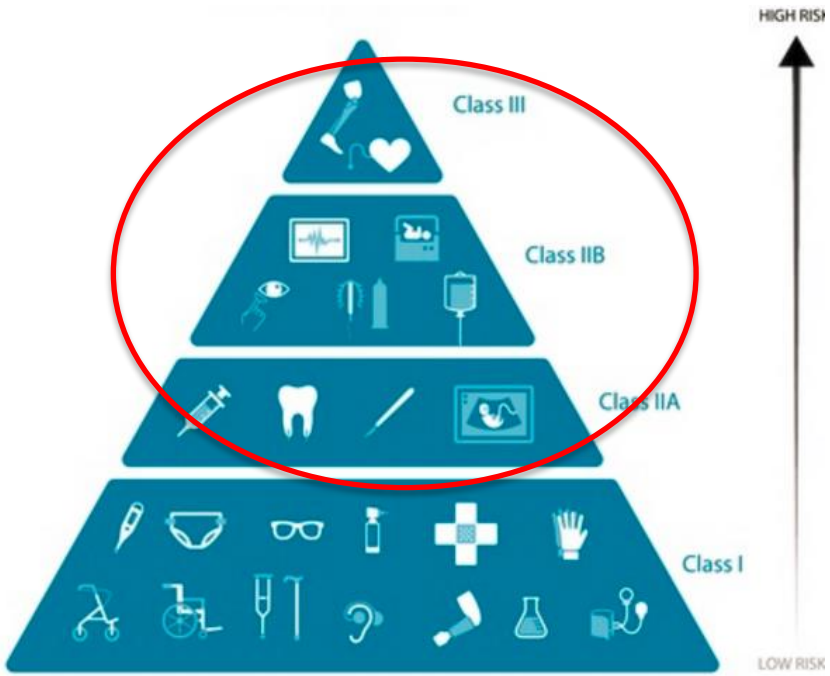
Regulatory Barriers

Consensus Standards Lacking:

-Nanotechnology terminology
-Physicochemical characterisation to quantify nano-bio effects
-Guidelines to evaluate safety of pre-clinical products
-Reference materials
-Issue with *nanosimilars*

- ✓ *There is no nano definition provided by EMA though in most cases nano refers to <1000 nm*
- ✓ *MDR and IVDR follow the Commission's recommendation for a definition of nanomaterial (<100 nm)*

A little inside into MDR. Classification of Medical Devices



All devices incorporating or consisting of nanomaterials 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.

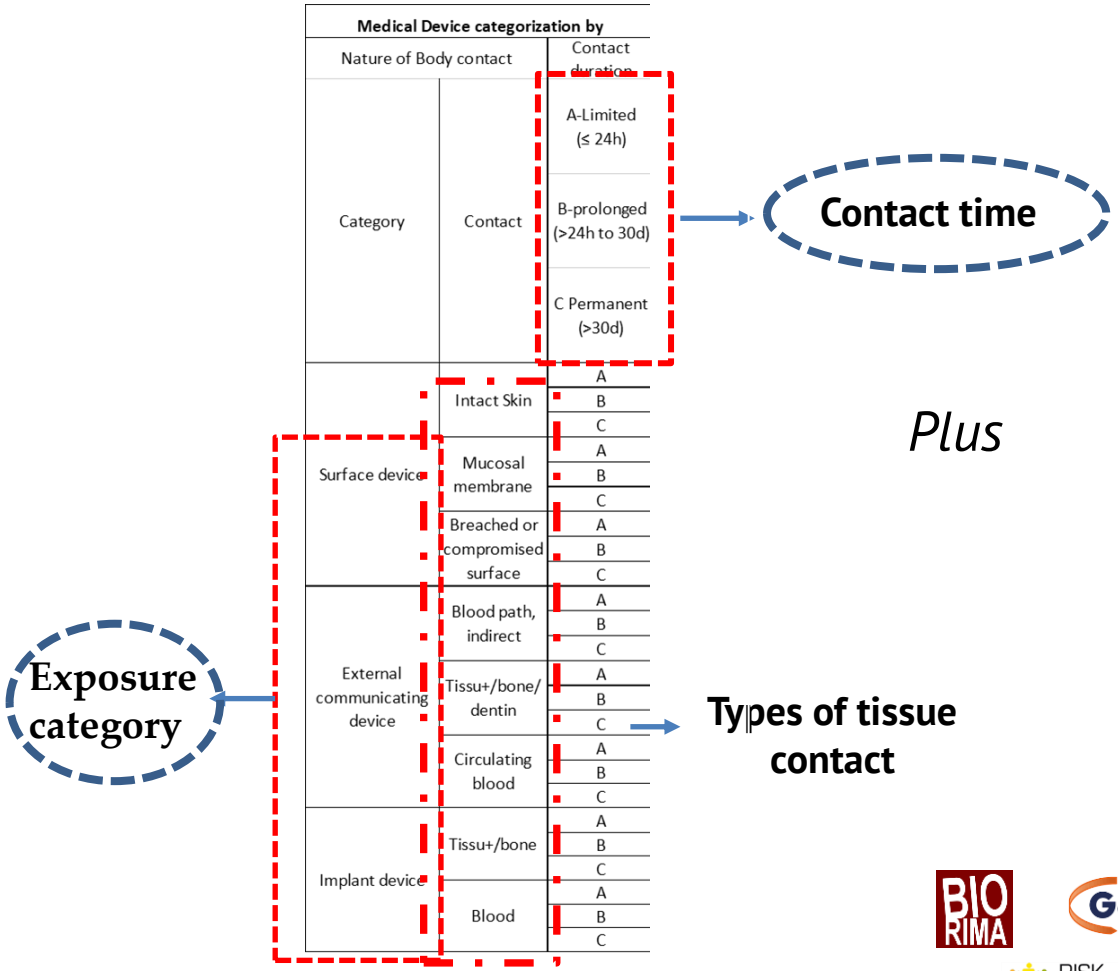
A little inside into MDR. Classification of Medical Devices

Parameters for characterisation and identification of nanomaterials (NM) intended for use in medical devices

Parameter	Description	Methods*
Chemical composition/ identity	Information on the chemical composition of the NM – including purity, nature of any impurities, coatings or surface moieties, encapsulating materials, processing chemicals, dispersing agents and/or other formulants e.g. stabilizers; information on structural formula(e)/ molecular structure(s) of the constituents of nanomaterial must be provided	MS, AAS, ICP-MS, FTIR, NMR UVVis, HPLC, GC/LC-MS, XRD Raman spectroscopy
Particle size (Primary/Secondary)	Information on primary particle size, size range and number size distribution (indicating batch to batch variation – if any). The same information would be needed for secondary particles (e.g. agglomerates and aggregates) if present. At least two methods, one being electron microscopy, should be used	FFF, HDC, HPLC, AUC, CLS disc centrifugation, TEM, SEM, STEM, HRTEM, STM, AFM, DLS, DMA, NTA
Physical form and morphology	Information on the physical form and crystalline phase/shape. The information should indicate whether the NM is present in a particle-, spherical-, flake-, tube-, rod-, or fibre- shape, the aspect ratio, crystal or amorphous form, and whether it is in free particulate form or in an agglomerated/aggregated state as well as whether the preparation is in the form of a powder, solution, suspension or dispersion.	AFM, TEM, HRTEM, SEM, STEM, STM, NMR, XRD
Particle and mass concentration	Information on concentration in terms of particle number and particle mass per volume when in dispersion and per mass when as dry powder.	A wide range of analytical methods, including UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS
Surface charge	Information on zeta potential of the NM.	PALS (for zeta potential)
Redox potential	Information on redox potential, especially for inorganic NMs. Conditions under which redox potential was measured also need to be documented.	Potentiometric methods, X-ray absorption spectroscopy
Solubility and partition properties [a]	Information on solubility of the NM in relevant solvents and their partitioning between aqueous and organic phase (e.g. as log K_{ow} if appropriate).	Solubility/ dissolution rate in water and other solvents
pH	pH of aqueous suspension.	pH in aqueous media
Viscosity	Information on viscosity of liquid dispersions.	OECD 114
Density and pore density	For granular materials, information on density/porosity of unformulated NM and pore density.	DIN ISO 697, EN/ISO 60
Dustiness	Information on dustiness of dry powder products – such as cements and alginates	EN 15051:2006, DIN 33897-2.
Chemical reactivity/ catalytic activity[b]	Information on relevant chemical reactivity or catalytic activity of the NM and of any surface coating of the NM.	Kinetic measurements of chemical, biochemical and/or catalysed reactions
Photocatalytic activity	Information on photocatalytic activity of relevant materials used (e.g. coatings, dental materials)	TEM, UV, X-ray topography
Particle and mass concentration	Information on concentration in terms of particle number and particle mass per volume when in dispersion and per mass when as dry powder.	A wide range of analytical methods, including UV-Vis, HPLC, GC/LC-MS, AAS, ICP-MS
Specific surface area	Information on specific surface area of the NM. At the moment this is only applicable for dry powders	BET
Surface chemistry	Information on NM surface – including any chemical/ biochemical modifications that could modify the surface reactivity,	LDE, SPM, XPS, MS, RS, FTIR, NMR, AUC (for

CROs?
GLP

Testing Guidelines Gaps – Medical Devices



Plus

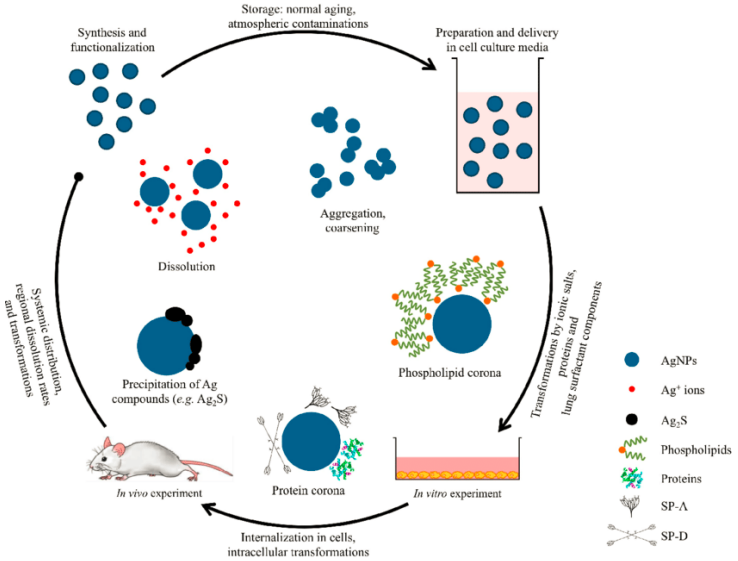
Exposure

- Biodegradable capability
- "Quality" to tear and wear

Analytical techniques may pose a challenge

Testing Guidelines Gaps – Medical Devices

Characterisation of nanomaterials used in medical devices



Adapted from Theodorou and Tetley 2014

ISO 10993-18
ISO 10993-19
ISO/TR 13014

Testing Guidelines Gaps – Medical Devices

Testing proposed	Non-invasive short term use	Non-invasive long term use	Invasive short term use	Invasive long term use
Low exposure	Phys: chem data	Phys: chem data	Phys: chem data	Phys: chem data
	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*	Cytotoxicity *in vitro*
	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*	Irritancy *in vitro*
	Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity
		Genotoxicity *in vitro*		Genotoxicity *in vitro*
				General Immuno toxicity testing
Medium exposure Additional tests		Genotoxicity *in vivo*	Other *in vitro* plus *in silico* testing*	28/90 day *in vivo* toxicity test
		Immuno toxicity at location site	Genotoxicity *in vitro* and *in vivo*	*In vitro* and *in vivo* (repeated dose) genotoxicity testing
		Persistence /accumulation studies at location site only		ADME including persistence /accumulation studies
High exposure Additional tests	Selected *in vivo* acute toxicity tests focussed on location site(s)	Selected *in vivo* chronic toxicity tests focussed on location site(s)	*In vivo* acute toxicity tests	*In vivo* chronic toxicity tests may include reprotox depending on patient group.

Hazard Assessment

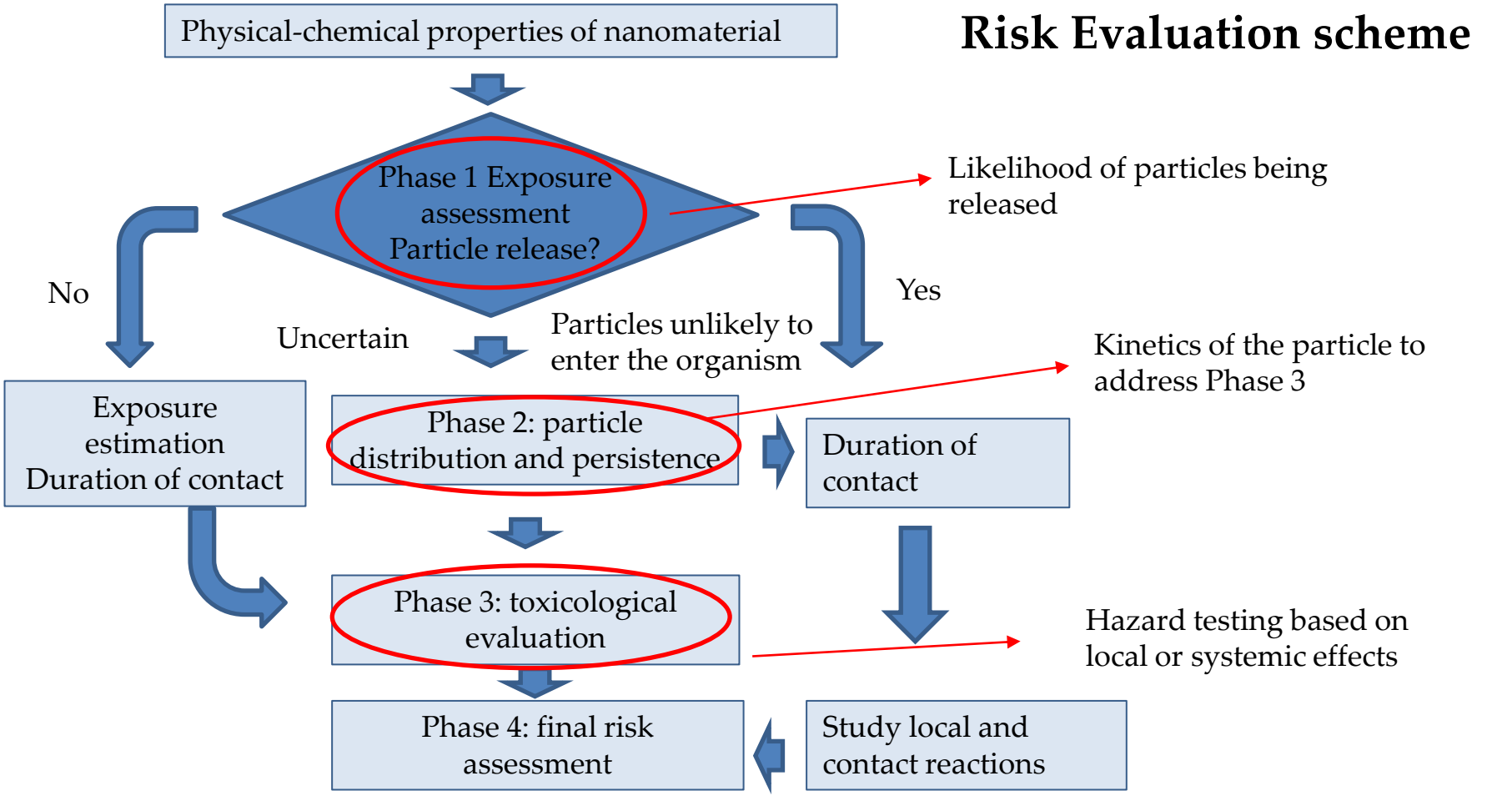
CROs?
GLP

ISO19007:2018-MTS
ISO10993-3 Genotoxicity
ISO10993-4 Haemotoxicity
ISO10993-12 Acute toxicity

Are we doing the right translation?

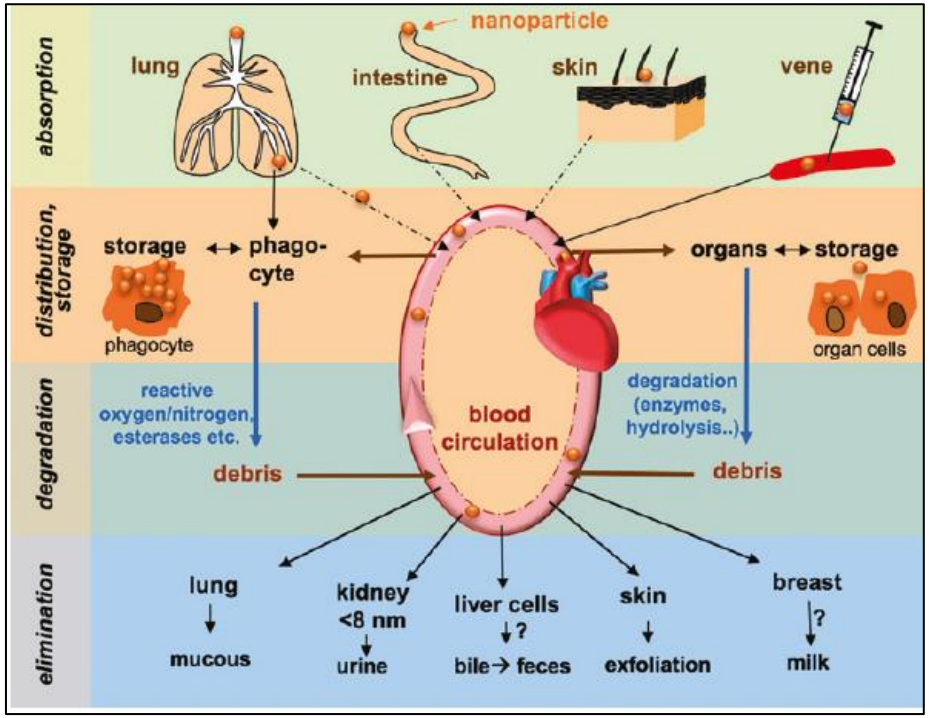
BIO RIMA
Gov4Nano meeting the needs of nanotechnology
PATROLS Advanced Tools for NanoSafety Testing
NanoHarmony
OECD
RISK GONE

A little inside into MDR. Classification of Medical Devices



A little inside into MDR. Classification of Medical Devices

Toxicokinetics of nanomaterials in Medical Devices



Adapted from Gubala et al. IUPAC 2017

ADME: absorption, distribution, metabolism and excretion

Uptake: ocular, inhalation, oral, dermal, transdermal

Blood clearance happens fast so focus on target organs:

Liver, Spleen, Bone Marrow, Kidney

Tissue accumulation/persistence of a nanomaterial should be investigated.
In case of no absorption, no systemic toxicity testing required.

OECD guidelines adapted to nanomaterials ISO 10993-22

A little inside into MDR. Classification of Medical Devices

Main Questions:

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

ISO10993-22 Guidance on nanomaterials

Cytotoxicity: Uptake, Cell type, ox. tress, dose metrics, aggregation, electric charge/optical properties

Genotoxicity, carcinogenicity, reprotoxicity: *in vitro* -demonstrate exposure to the cell nucleus (DNA damage*), in vivo* –ensure NM reaches target organ

Immutoxicity, skin irriation, sensitisation: NMs enter MPS cells which play a central role in immune system, nano-protein complex can result in sensitization, skin penetration dependent on size and shape

Haemocompatibility: translocation to systemic circulation, can induce prothrombotic effects and platelet activation, surface area, complement system activation – inflammatory and hypersensitivity reactions

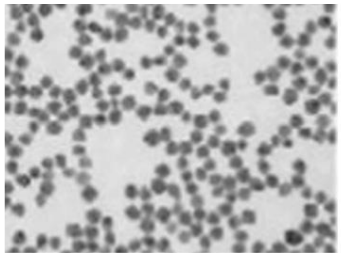
Systemic toxicity: cannot be predicted by bulk material toxicity, potentially crossing all protective barriers including the nuclear membrane, blood-brain and foeto-placental barriers, special emphasis on the MPS (liver, spleen), kidneys, brain, bone marrow

Pyrogenicity: various implantation sites, direct injection into appropriate tissue, controls

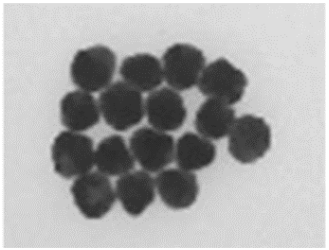
Testing Guidelines Gaps – Medical Devices

MDR. Risk Assessment should be performed on a case by case basis

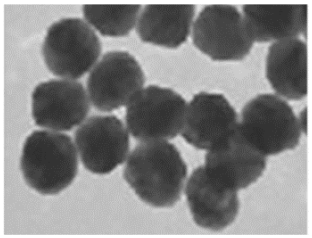
Transmission electron micrographs of Ag particles



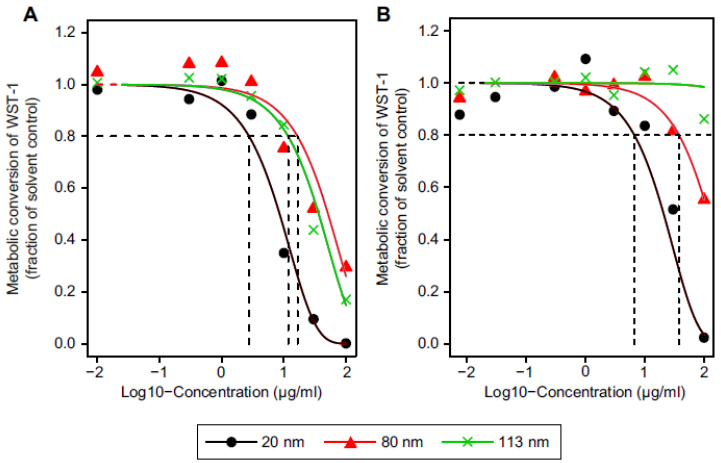
20 nm



80 nm



113 nm



Metabolic conversion of WST-1 in L929 fibroblasts (A) and RAW 264.7 macrophages (B) as a function of concentration of silver nanoparticles. Dashed lines represent EC20 values.

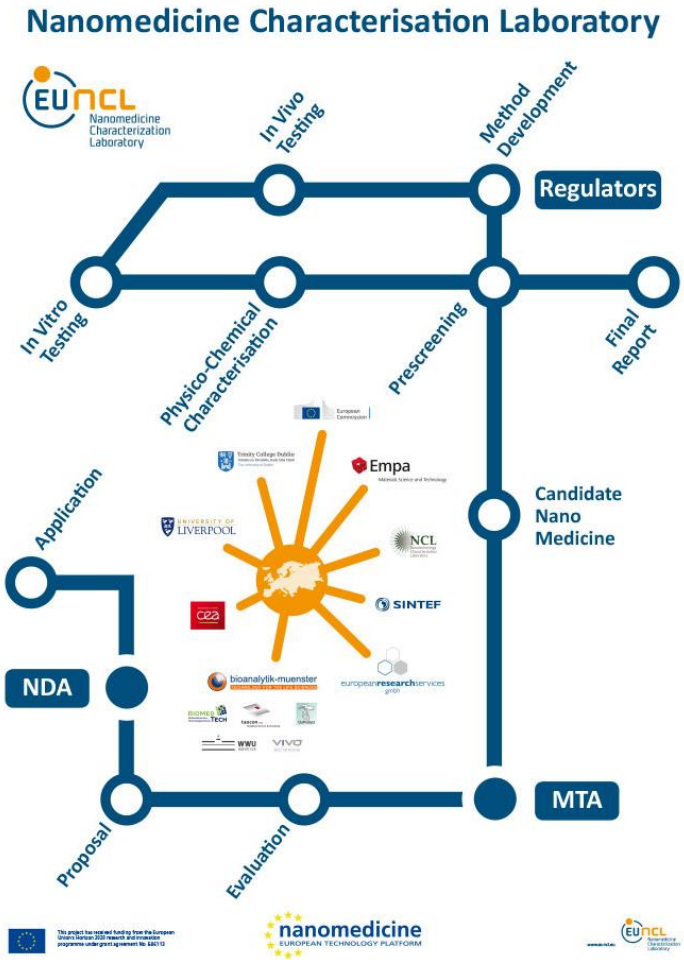
Park et. 2011

European Medicines Agency

Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals	Raise awareness of new nanomedicines via the EU-Innovation Network, and foster collaboration with JRC and other international partners
	Share knowledge and harmonize regulatory practices: Generate guidance addressing PK/PD (including modelling) requirements and long-term efficacy and safety;
	Develop and standardise new testing methods related to quality/safety assessment of nanomedicines
	Understand the critical quality attributes (CQA) of a given product and the relationship between those and the biological activity and in-vivo behaviour of the product;

EMA Regulatory Science to 2025 – Strategic reflection

Nanomedicine Characterisation Laboratory



Fosters the use and deployment of:

- Standard operating procedures (SOPs),
- Benchmark materials,
- Quality management for the preclinical characterisation of Med-NPs

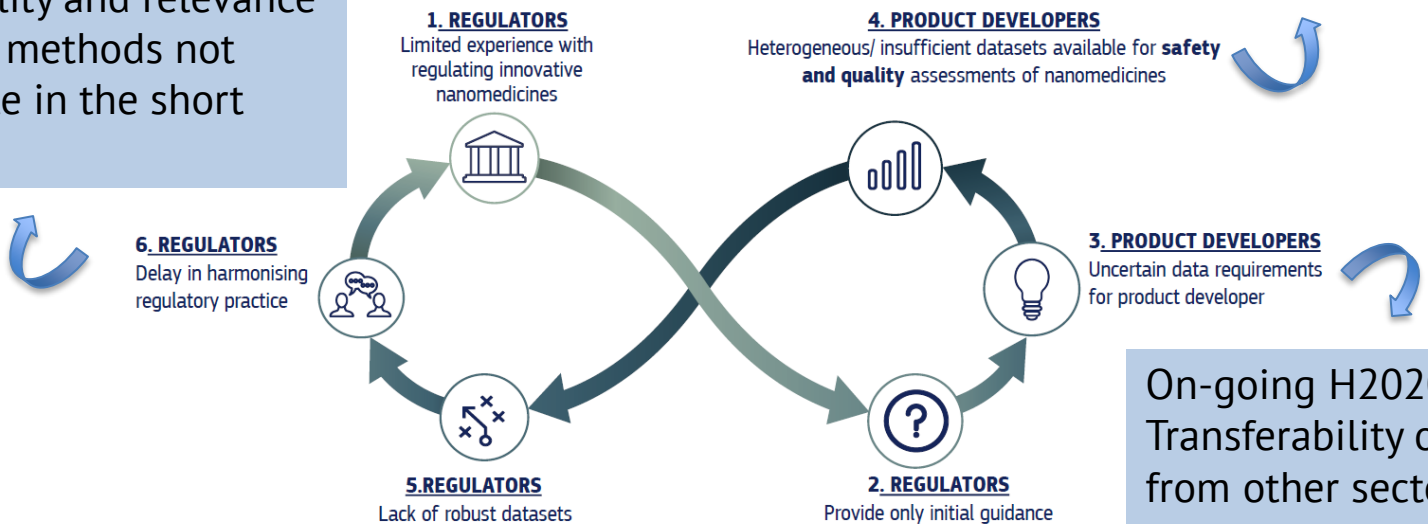
It is a key objective for EUNCL to constantly refine and adapt its assay portfolio and processes in order maintain the provision of state-of-the-art

From 2020

Regulatory Barriers

Close monitoring of scientific literature
In-depth analysis from databases
Proactive Pharmacovigilance

Reliability and relevance of new methods not possible in the short term



On-going H2020 projects
Transferability of methods from other sectors

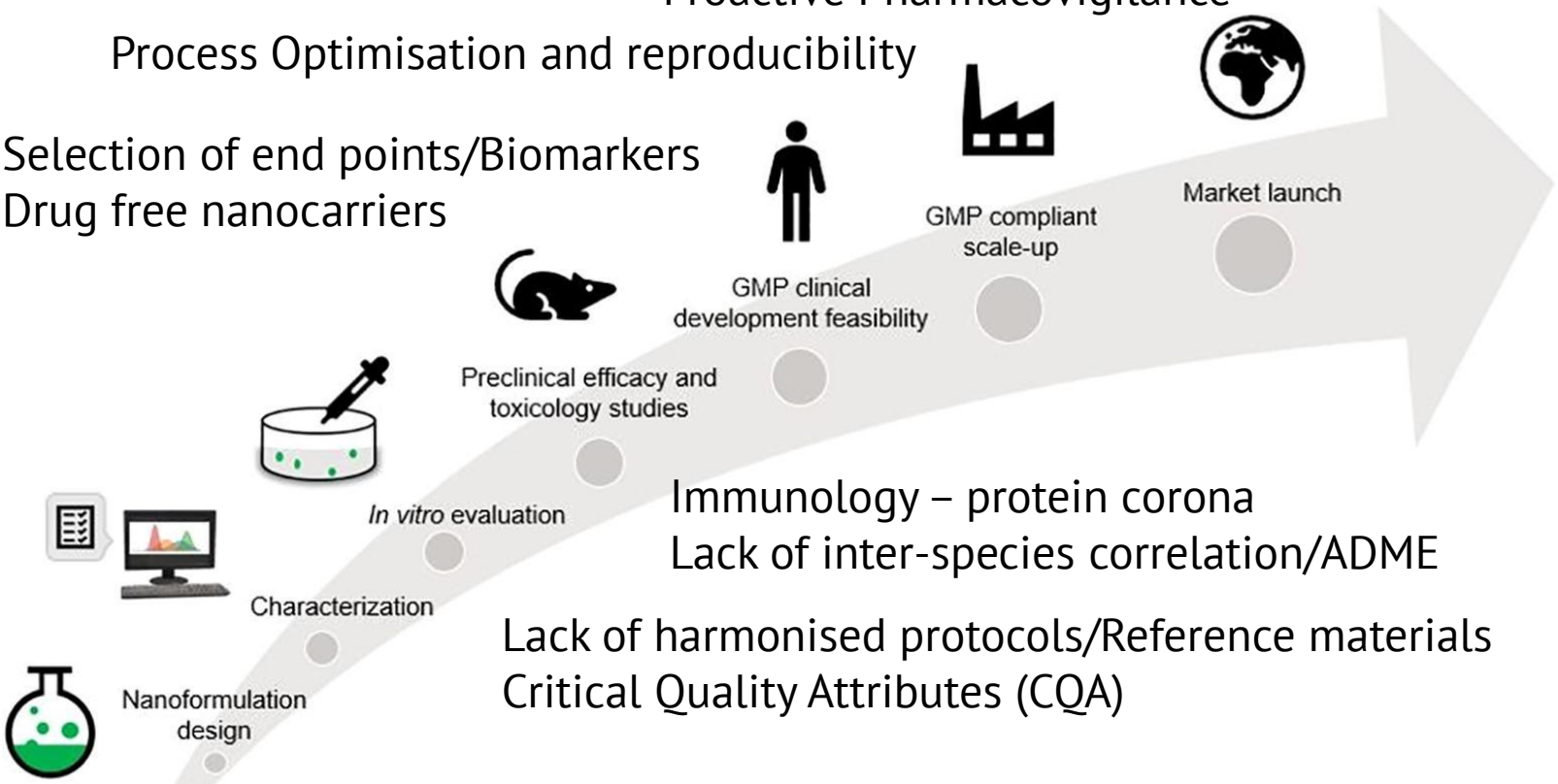
The Refine White Paper 2019

Conclusions

Proactive Pharmacovigilance

Process Optimisation and reproducibility

Selection of end points/Biomarkers
Drug free nanocarriers



Immunology – protein corona
Lack of inter-species correlation/ADME

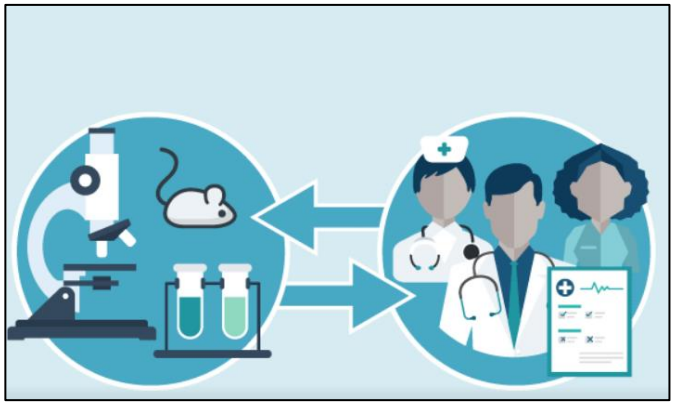
Lack of harmonised protocols/Reference materials
Critical Quality Attributes (CQA)

Identification of regulatory framework
Anticipate issues such as sterility and Impurities

Operti et al 2021

Way forward

"To bridge the gap of nanomedicine lab research to industrial manufacturing, collaboration and integration among academics, scientists, industries, and regulatory agencies is required to develop comprehensive approaches to ensure safe, effective, and translatable nanomedicine products."



Adapted from Agrahari and Hiremath 2017

DowWire News Feature reading

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THANK YOU!

blanca.suarez@nanotechia.org
Director of Regulatory Affairs