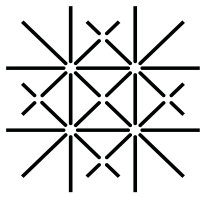
Why do nanomedicines and nanosimilars require a centralised regulatory pathway?

Prof. Dr. Scott E. McNeil



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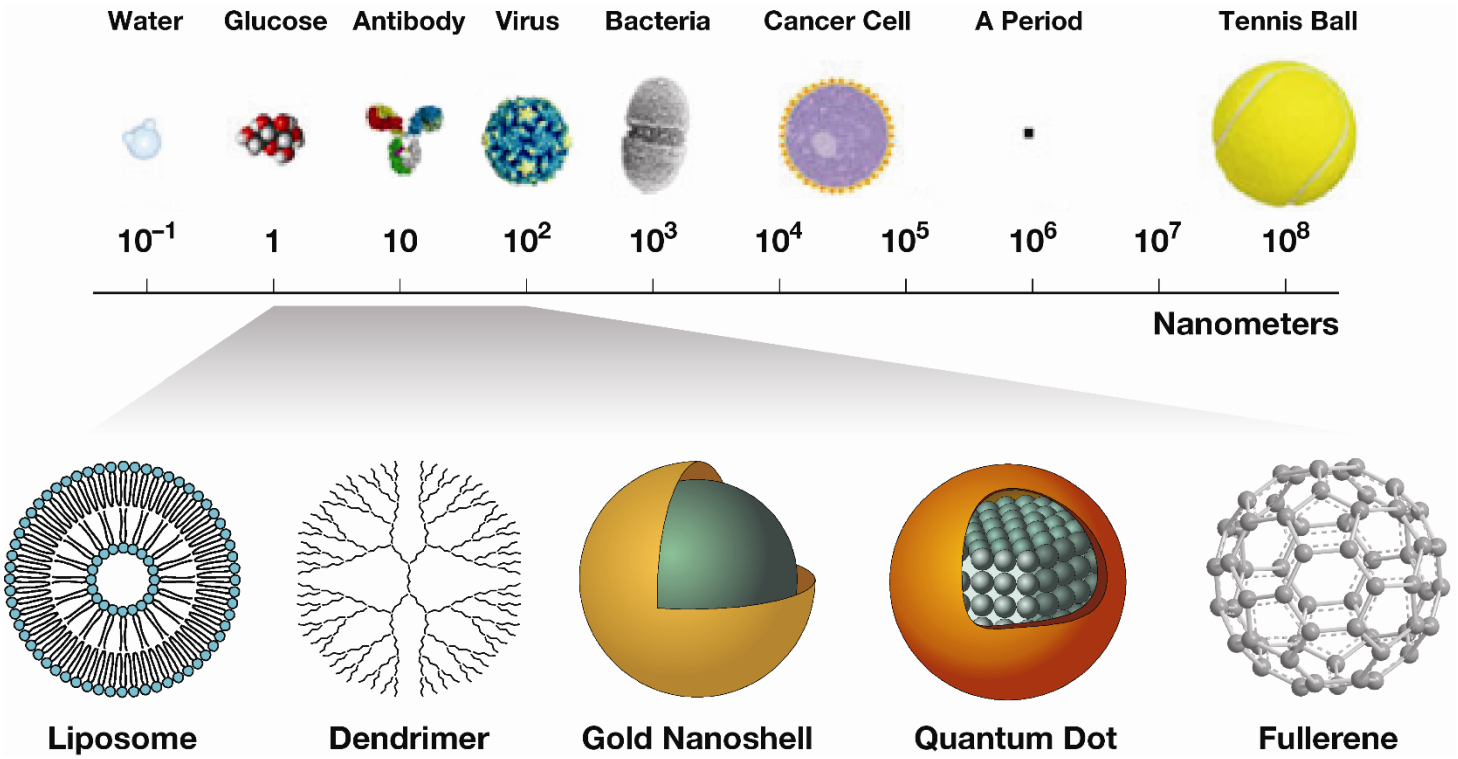
Size scale

1 nanometer = 10^{-9} meter



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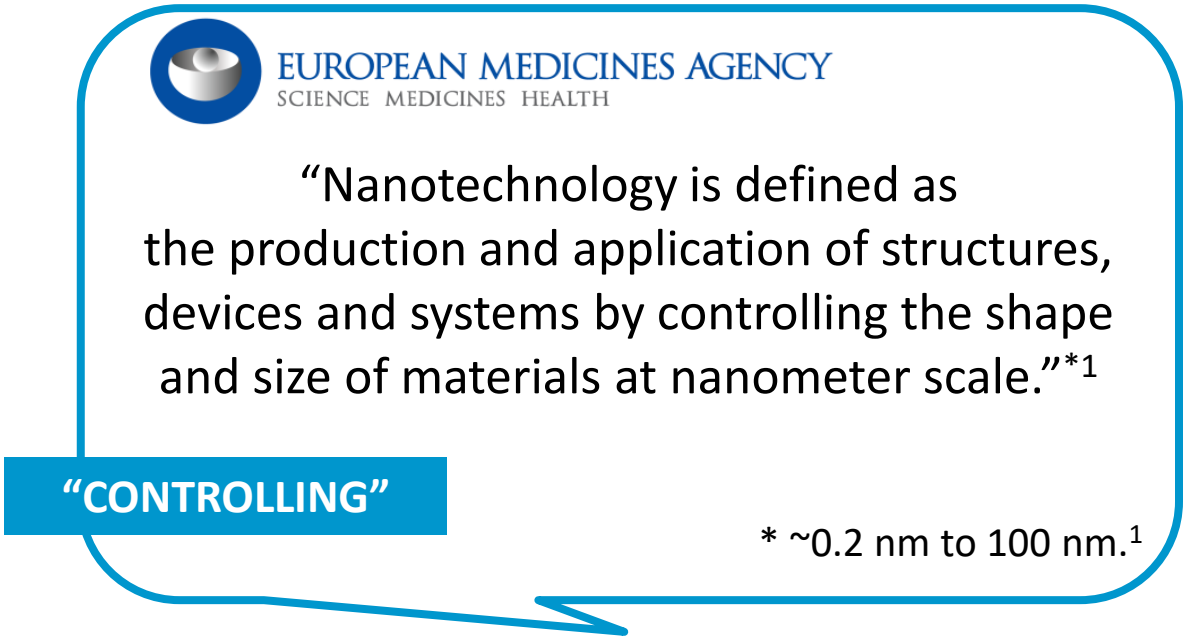
Definition of nanomedicine by regulators



Used interchangably: 'nanotechnology', 'nanomedicine', 'nanoparticle', 'nanoformulation'

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1. EMA. Reflection paper on nanotechnology-based medicinal products for Human Use. 2006..

Nanomedicines in clinical practice[1]

Nano-technology	Active substance	Indication	Approved
Nano-crystals	Olanzapine	Schizophrenia	2008
	Paliperidone palmitate (3-month)	Schizophrenia	2016 (EU) 2015 (US)
	Paliperidone palmitate (1-month)	Schizophrenia	2011 (EU) 2009 (US)
Nano-particles	Ferric carboxymaltose	Iron deficiency	2007
	Ferumoxytol	Iron deficiency	2009
	High molecular weight iron dextran	Iron deficiency	1996
	Iron gluconate	Iron deficiency	1999
	Iron isomaltoside 1000	Iron deficiency	2009
	Iron sucrose	Iron deficiency	1949 (EU) 1992 (US)
	Low molecular wight iron dextran	Iron deficiency	2001
	Paclitaxel	Metastatic breast cancer	2005

1. Flühmann B, et al. Eur J Pharm Sci. 2019;128:73–80.

Nanomedicines in clinical practice[1]

Nano-technology	Active substance	Indication	Approved
Polymeric drugs	Glatiramer acetate	Multiple sclerosis	1996
	Pegaptanib	Wet muscular degeneration	2004
Liposomes	Amphotericin B	Fungal Infections	1990 (EU) 1997 (US)
	Bupivacaine	Anaesthetic	2011
	Daunorubicin	Cancer advanced HIV-associated Kaposi's sarcoma	1996
	Doxorubicin hydrochloride	Breast neoplasms	2000
	Doxorubicin hydrochloride (pegylated)	Breast neoplasms, multiple myeloma, ovarian neoplasms, Kaposi's sarcoma	1995
	Mifamurtide	Osteosarcoma	2009
	Morphine	Pain relief	2004
	Verteporfin	Macular degeneration, myopia, degenerative	2000
	Vincristine	Philadelphia chromosome-negative acute lymphoblastic leukaemia	2012

Nano-based vaccines COVID-19 2020

1. Flühmann B, et al. Eur J Pharm Sci. 2019;128:73–80.

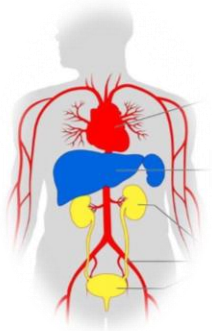
Nanoformulations can….

Formulate Insoluble/Unstable Therapeutic Agents

- Nanoformulation can serve as a solubilizing or stabilizing platform for therapeutic agents.
- APIs that were once considered incompatible for systemic delivery can be formulated using nanotechnology, allowing for in vivo investigations.

Alter Pharmacokinetics

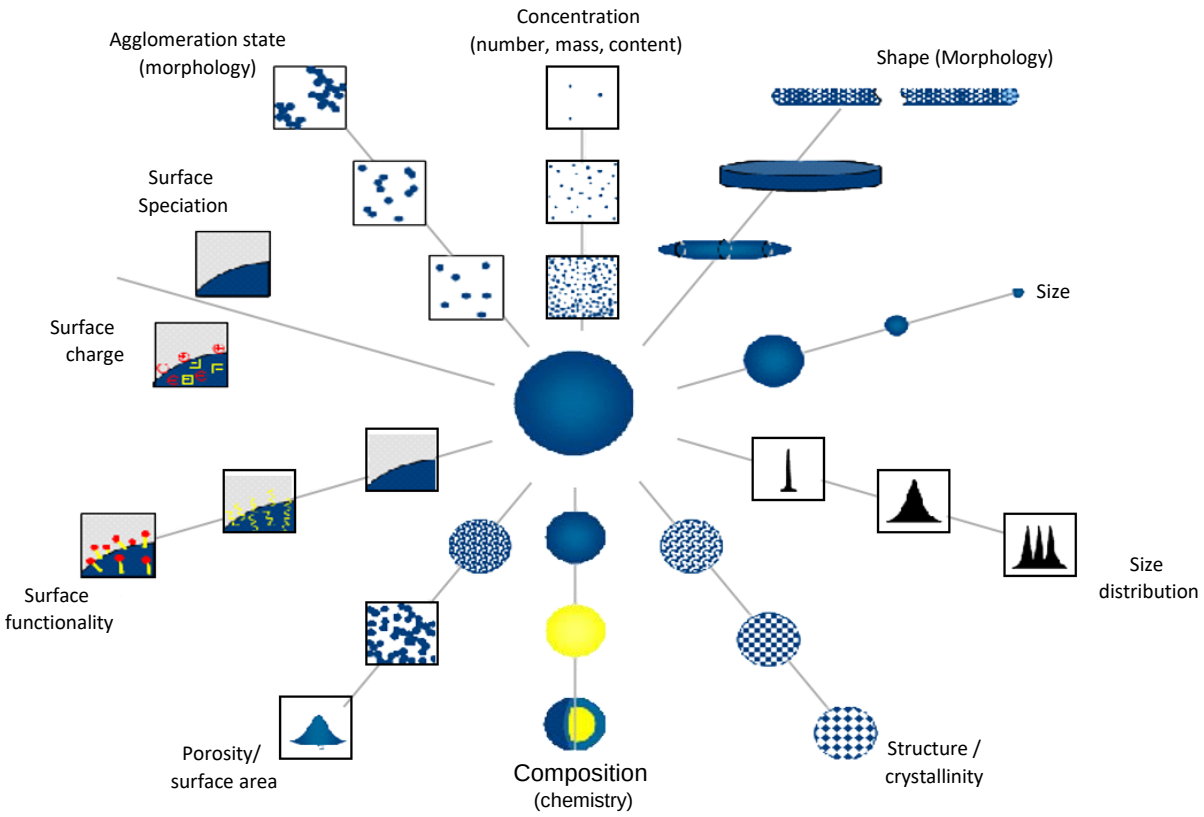
- Nanoformulations can modify the biodistribution and extend the half-life of an API.
- PK of multiple therapeutic agents can be coordinated to induce synergistic therapeutic effects.



Modify Toxicological Profiles

- By adjusting stability, biodistribution, and half-life of therapeutic agents, nanoformulation can reduce adverse effects, off-target toxicities.
- Improving PK allows for reduced dose and dosing frequency, reducing risk of dose-limiting toxicities.

Challenges in physicochemical characterisation (PCC)



Physicochemical properties directly influence biocompatibility and product quality

Comprehensive characterisation of <u>all</u> parameters is cost prohibitive

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Hassellöv M, et al. Ecotoxicology. 2008;17(5):344-361.

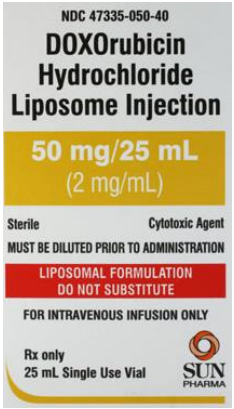
Nanosimilars.....follow-ons, generics

Nanomedicines are complex formulations, and there will always be some degree of polydispersity and batch-to-batch variation.

The challenge is to identify meaningful differences between the follow-on and the reference/innovator product.

Nanosimilars:

- Doxorubicin HCl Liposome Injection, a generic version of Doxil, was approved by the FDA (2013).
- Sorrento Therapeutics completed a bioequivalence study of Cynviloq against nab-paclitaxel (Abraxane).
- Pharmascience has an iron sucrose generic approved by Health Canada (July 2020).
- Sandoz has a ferumoxytol generic approved by the FDA (January 2021)



Characterisation: informing “nanosimilar” studies

Generic drug products, including nanosimilars, are approved based on therapeutic equivalence to the reference/innovator product

Therapeutic Equivalence =

Pharmaceutical Equivalence
Same dosage form and excipients

+

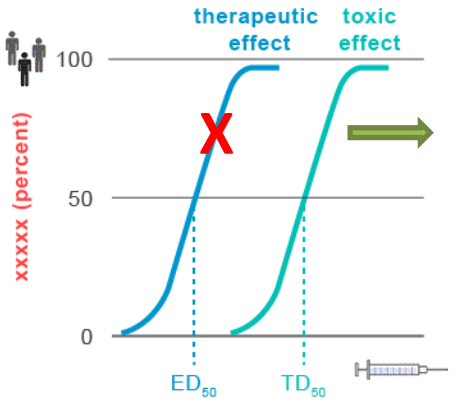
Biological Equivalence
Equivalent clinical safety and efficacy

The centralised regulatory approach is compulsory for many clinical indications, but optional for “significant therapeutic, scientific or technical innovation”

Source: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

Nanomedicine: where are we headed?

- Increased therapeutic index
- **Nanosimilars** are now here
- Novel molecules: will be incorporated into NPs
- siRNAs, vaccines, proteins/enzyme replacement therapy
- Decreased immunogenicity and immunotoxicity



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