DIE NEUE NANOMEDIZIN – VON DER IDEE ZUM PRODUKT

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Deutsche Plattform NanoBioMedizin

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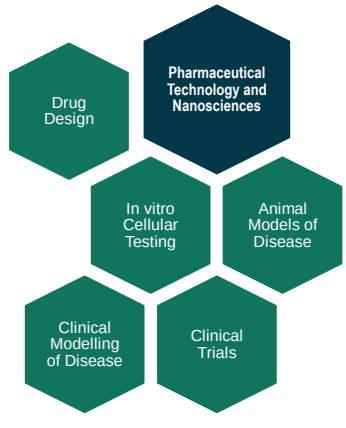
LOEWE GOETHE UNIVERSITÄT FRANKFURT AM MAIN Fraunhofer IME

TRANSLATIONAL MEDICINE AND PHARMACOLOGY

- Between 2012 and 2014 **Goethe University** and the **Fraunhofer-Institute of Molecular Biology and Applied Ecology** joint in the LOEWE cluster for applied pharmaceutical research
- In 2015 the LOEWE center **Translational Medicine and Pharmacology** was founded

LOEWE



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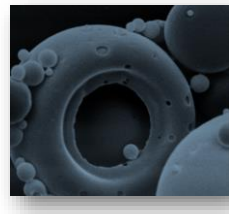
PHARMACEUTICAL TECHNOLOGY AND NANOSCIENCES

- Development of **nanosized drug delivery systems**, predominantly for **parenteral and peroral route of administration**
- Applied pharmaceutical research designing nanoproducts for markets by using **GMP-compliant technologies** (e.g. nanomilling, microfluidics, hot melt extrusion)
- Expertise in analytical technologies, e.g. **physicochemical characterization** and **drug release testing** of nanoformulations and nanomaterials



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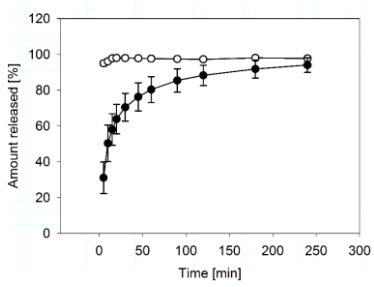
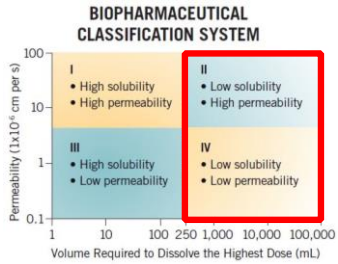
WHY USE NANOTECHNOLOGY?

- Enhancing dissolution rate by a factor of 2 to 200
- Increased bioavailability





Source: Modified from Beyer et al. 2015, Pharm Res;

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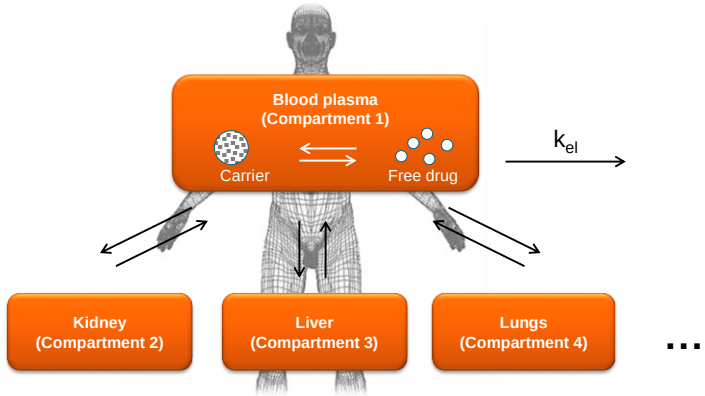
WHY USE NANOTECHNOLOGY?

- Changing body distribution makes therapy more effective and some toxicities in the deeper compartments less threatening



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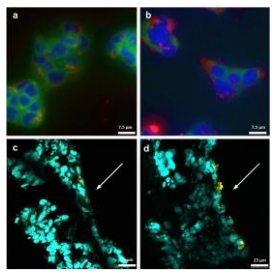
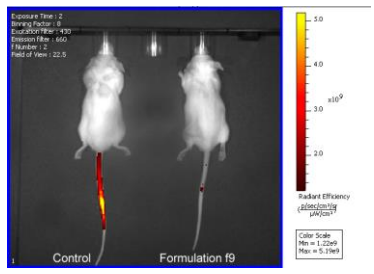
WHY USE NANOTECHNOLOGY?

- Enable administration of drugs (e.g. during early preclinical development)
- Deliver increased concentrations of a drug to the site of action
- Reduce side effects by optimizing systemic exposure with free drug





Source: Beyer et al. 2015, Pharm Res; Villa Nova et al. 2015, Int J Pharm

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WHY USE NANOTECHNOLOGY?

Formulation name	Technology	Compound	Type
Abraxane®	Nanoparticles	Paclitaxel	Parenteral nanocarrier
Ambisome®	Liposomes	Amphothericin B	Parenteral nanocarrier
DaunoXome®	Liposomes	Daunorubicin	Parenteral nanocarrier
Depocyt®	Liposomes	Cytarabin	Parenteral nanocarrier
DepoDUR®	Liposomes	Morphoine	Parenteral nanocarrier
Doxil® / Caelix®	PEGylated Liposomes	Doxorubicin	Parenteral nanocarrier
Gastromark™	Silica-coated iron oxide nanoparticles	Iron oxide nanoparticles	Peroral nanocarrier (diagnostic)

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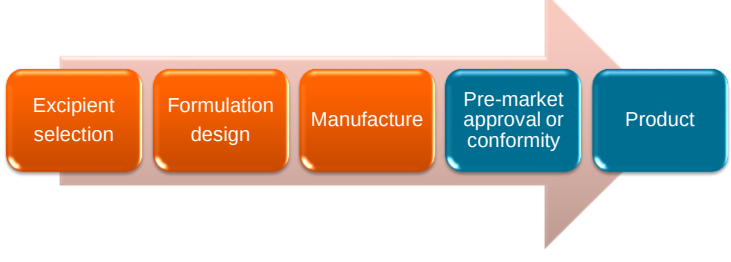
WHAT HURDLES TO DEAL WITH?

- Excipients used in **pharmaceuticals**, **cosmetics**, **medical devices** or **food products** have to undergo specific safety assessment if used in form of nanomaterials
- If nanotechnology is applied there is specific characterization needed for **the final formulation design**



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REGULATIONS ON NANOMATERIALS

- **Recommendation of the European Commission for a definition of nanomaterials (2011/696/EU)**

*"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 nm - 100 nm**."*

- **Guidance for the industry**

*„whether a material […] is engineered to have **at least one external dimension** […] in the nanoscale range (**approximately 1 nm to 100 nm**)"*

*„whether a material […] is **engineered to exhibit properties** […] that are **attributable to its dimensions, even if those fall outside the nanoscale range**, up to one micrometer (1000 nm)"*

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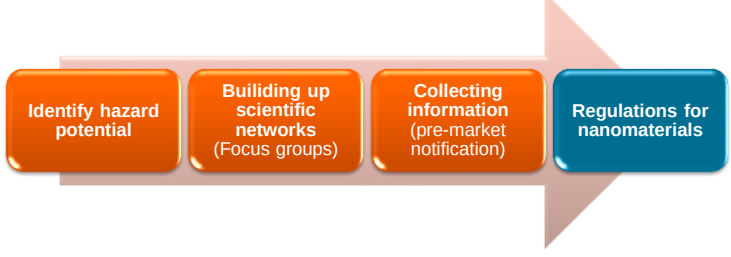
REGULATIONS ON NANOMATERIALS

- Nanomaterials have been identified to be **associated with specific risks**
- Scientific networks **have been built up** by various institutions (EPA, FDA, EFSA, SCCS, EMA, OECD…)
- Currently, information on **chemicals and final products is collected**
- A logical consequence **will be changes in the regulatory framework**



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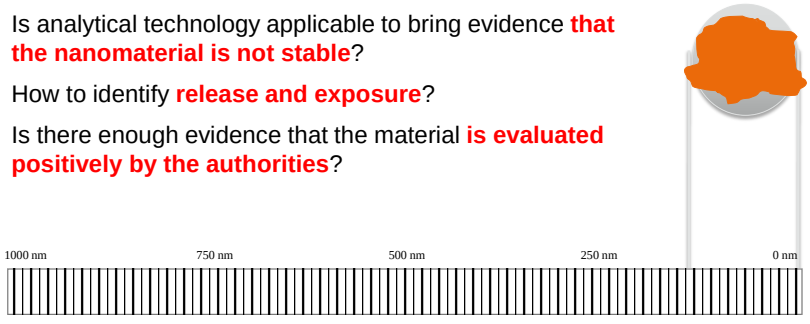
MAKING NANOPRODUCTS FOR THE MARKET

- Does the product **contain nanomaterials**?
- Is analytical technology applicable to bring evidence **that it is not a nanomaterial**?
- Is analytical technology applicable to bring evidence **that the nanomaterial is not stable**?
- How to identify **release and exposure**?
- Is there enough evidence that the material **is evaluated positively by the authorities**?



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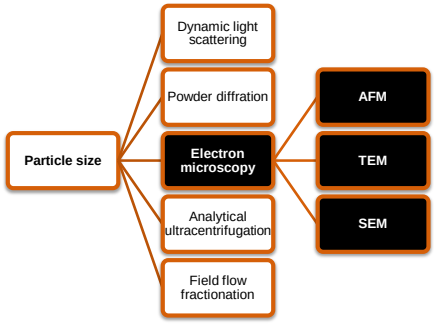
PHYSICOCHEMICAL CHARACTERIZATION

- Analytical technologies based on „two different principles“ are recommended
- No analytical technology fits every case



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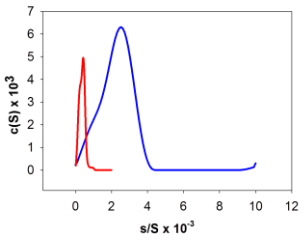
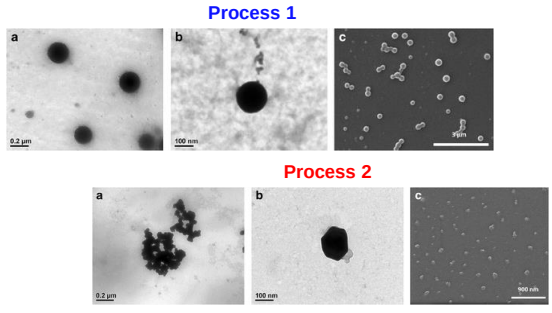
PHYSICOCHEMICAL CHARACTERIZATION

- Confirming quantitative measurements (e.g. DLS) by using qualitative measurements (as recommended by ECHA)
- Combinations of different techniques are mandatory for determining particle size distributions





Source: Beyer et al. 2015a, Pharm Res

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STABILITY AND PERSISTENCE

- Characterizing persistance of nanomaterials for the **intended route of administration**
- Simulating physiological environment to obtain **information on particle stability**
- If particles do not persist in physiological media customers **are not exposed them**

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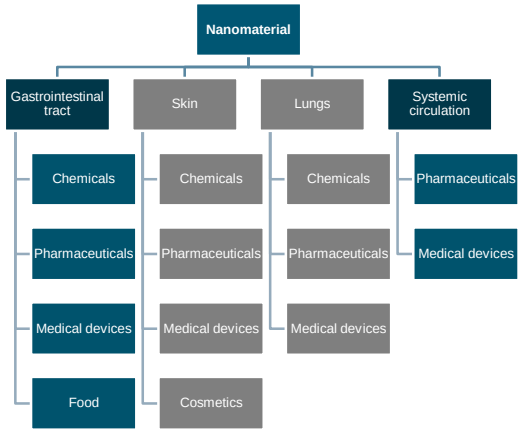
STABILITY AND PERSISTANCE



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STABILITY AND PERSISTANCE

- Simulation of physiological conditions **has been used for drug formulations**
- Biorelevant dissolution testing investigates **impact of degradation processes on solubility**
- Nanospecific biorelevant release testing can be used **to test nanomaterial stability *in vitro***
- Unfortunately the existing procedures (e.g. USP4, TIM) are **not applicable to nanomaterials**

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STABILITY AND PERSISTANCE

- Optimized setup for nanoparticles and liposomes **has been developed at Goethe University**
- Patent covering the „dispersion releaser“ was filed in 2013 (licensing contract in preparation)

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STABILITY AND PERSISTANCE

- Stability measurement requires understanding of **degradation mechanisms and known composition of physiologcal environment**
- Biorelevant media are in place but **no technology for using them with nanoforms**
- We have been interested in formulation changes during drug release when optimizing dispersion releaser technology

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RELEASE AND EXPOSURE

- Release of nanomaterials **from medical devices**
  - Simulating the in vivo situation after implantation
  - Simulating contact time
- Release from **contact materials**
  - Simulating storage situations

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HAZARD IDENTIFICATION AND RISK ASSESSMENT

- Characterization
- Release and exposure scenario
- Hazard identification
- Risk assessment

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