Regulatory Considerations for Nanomedicine

Prof. Dr. Scott E. McNeil

EPFL Nanoparticles Summer School

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Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

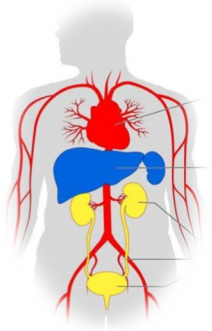
Nanomedicine capabilities

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.

Nanomedicines: preclinical characterisation

Physicochemical Characterization

Size/Size Distribution
- Dynamic Light Scattering
- Electron Microscopy (TE
- Atomic Force Microscopy
- Field Flow Fractionation MALLS

Composition
- TEM with EDS
- Inductively coupled plasr (ICP-MS)
- Spectroscopy (NMR, CD UV-vis)

Purity
- Chromatography
- ICP-MS

Stability
- Stability can be measure of instruments with respe temperature, pH, etc.

Immunological Characterization

Sterility
- Bacterial/Viral/Mycopl
- Endotoxin

In Vitro Hematology
- Hemolysis
- Platelet Aggregation
- Coagulation
- Complement Activati
- Plasma Protein Bindi

In Vitro Immune Cell F
- Cytokine Induction
- Chemotaxis
- Phagocytosis
- Leukocyte Proliferati
- Leukocyte Procoagul

In Vivo Immunotoxicit
- Local lymph node pr
- T-cell dependent anti

PK/Tox Characterization

Initial Disposition Stu
- Tissue distribution
- Clearance
- Half-life

Single and Repeat Do
- Blood Chemistry
- Hematology
- Histopathology (42 t
- Gross Pathology

Pharmacology
- Clinical Tx cycle
- PK Parameters
- AUC, Cmax, CL, t ½

Biology Characterization

In Vitro Toxicity
- Cytotoxicity
- Oxidative Stress
- Autophagy

In Vivo Efficacy Models
- Xenograft
- Orthotopic
- Metastatic
- Chemically-induced
- Genetically engineered mouse models (GEMM)
- Patient-derived xenografts (PDX)

Non-invasive Imaging
- Positron emission tomography (PET)
- Single-photon emission computed tomography (SPECT)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Bioluminescence (BLI)
- Fluorescence

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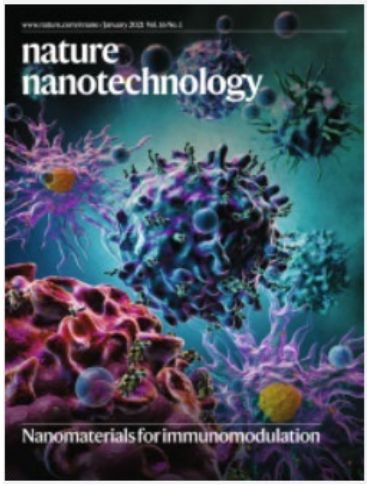
Nanotechnology Characterization Laboratory
http://ncl.cancer.gov

The “critical path”….

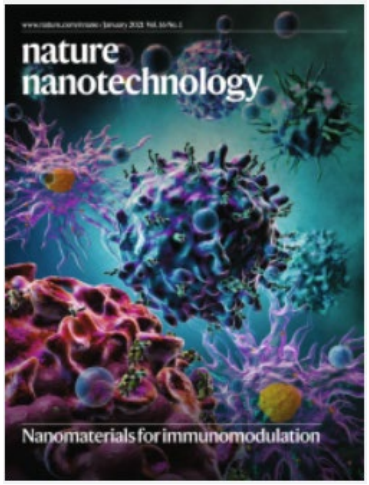
a.k.a “the valley of death”…..



Innovation

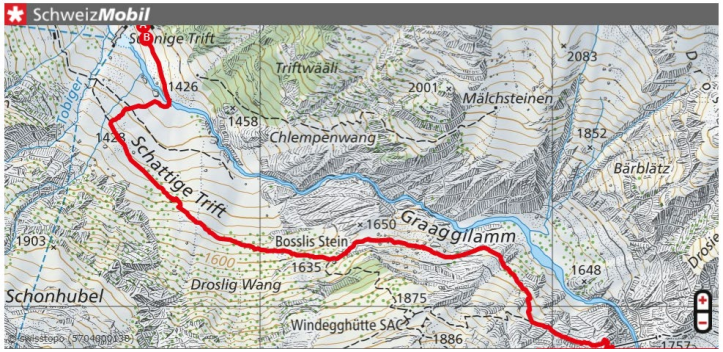
Commercialization

The nanomedicine “critical path”….



Innovation

Commercialization

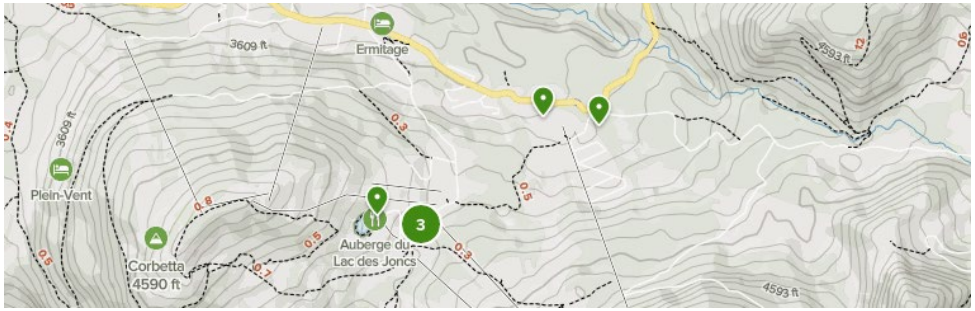


…still scary, but less deadly.

Regulatory Considerations

“the destination”

“planning the trip”



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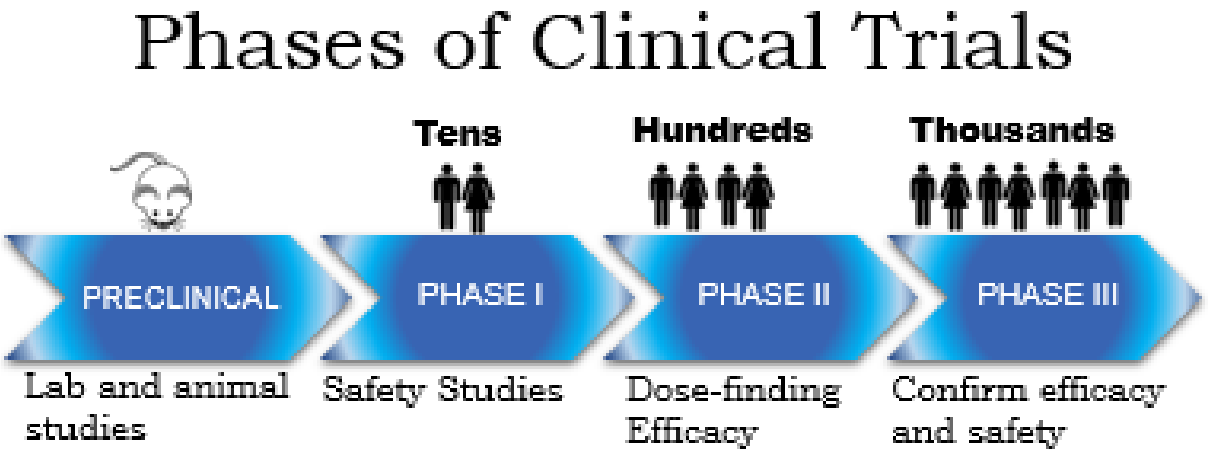
Regulatory: new chemical entity (NCE)



Authority: EMA vs. FDA

FDA: Investigative New Drug (**IND**) Application

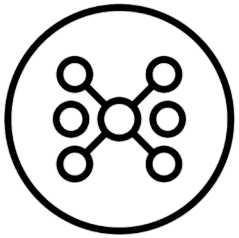
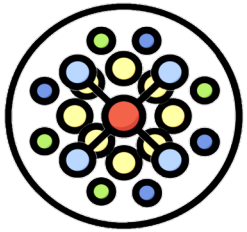
EMA: Clinical Trials Application Form

New Drug Application (**NDA**)

EMA: Marketing authorization application (MAA)

Image credits: https://www.ideas-itn.eu/introduction/

Nanomedicines are “complex drugs”

a. conventional medicinal product drug product = active substance (AS) + excipients	**b. nanomedicine product** drug product = complex assembly
	
characterization • full characterization possible	**characterization** • cannot be fully characterized (heterogenous & complex structure)
biological activity • dependent on AS	**biological activity** • altered PD & PK profile • dependent on AS but components previously considered excipients contribute to product quality & efficacy

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Terminology: Active Pharmaceutical Ingredient (API) ?

Regulatory: which pathway?

	Full dossier	Generic	Abridged application (hybrid)
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Article 8(3)	Article 10(**1**)	Article 10(**3**)
FDA U.S. FOOD & DRUG ADMINISTRATION	505(b)(**1**)	505(j)	505(b)(**2**)

Plus:

- Unmet medical need, rare diseases
  - Regulation (EC) No 847/2000
- Exceptional Use approval
  - Article 14 (8)

Regulatory pathway for New Chemical Entity (NCE)

Full dossier

Important considerations:

- Biomarker or imaging
  - MRI is most costly part of cancer clinical trial
- Endpoints
  - Safety, efficacy, or both?
- Patient enrollment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Article 8(3)

FDA U.S. FOOD & DRUG ADMINISTRATION

505(b)(**1**)

Cost for development: €€€€

Regulatory pathways

Most nanomedicines are reformulations of previously approved drugs

If an investigator develops a nanoformulation of an approved drug, is a full clinical trial required? Is it a generic?

	Full dossier	**Generic**
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Article 8(3)	Article 10(**1**)
FDA U.S. FOOD & DRUG ADMINISTRATION	505(b)(**1**)	505(j)
Cost for development:	€€€€	€

Generics

Let’s start with the yellow trials….

“trials” or “trials” ?

Regulatory pathway for Generic

Generic

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Article 10(1)

U.S. FOOD & DRUG ADMINISTRATION

505(j)

Requirements:

"A generic medicine is developed to be the same as a medicine that has already been authorized, called the reference medicine*."

1. A generic medicine contains the same active substance(s) as the reference medicine
2. It is used at the same dose(s) to treat the same disease(s)."
3. However, a generic medicine's inactive ingredients, name, appearance and packaging can be different

Cost for development: €

*Also known as the Reference Listed Drug (RLD).

Regulatory: considerations for 'generics'

Excipient: "an inactive substance that serves as the vehicle or medium for a drug or other active substance"

- Nanomedicines are certainly delivery *vehicles*
- But...they may influence PK and Tox
- 'Rule of thumb' (Faustregel): change a covalent bond → new chemical entity (NCE)
  - Novel polymers or lipids may require extensive Tox evaluation

Note about 'G.R.A.S' materials

Depends on route of administration

GRAS = generally regarded as safe

Regulatory: “nanosimilar” studies

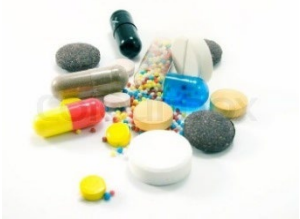
Generic drug products, including nanosimilars, are approved based on therapeutic equivalence to the reference/innovator product

Therapeutic Equivalence =

Pharmaceutical Equivalence + **Biological Equivalence**

Same dosage form and excipients

Equivalent clinical safety and efficacy



E.g., PCC, in vitro drug release

E.g., in vivo ADMET

TE = PE + BE

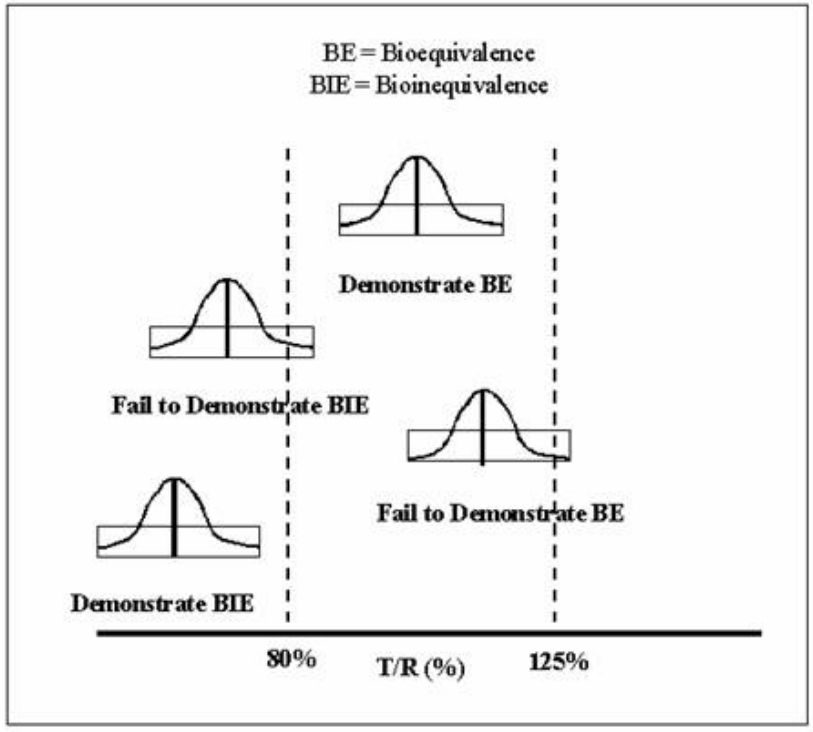
Biological equivalence (BE)

TE = PE + BE

Bioequivalence: 80% - 125% criteria (PK parameters)
Drug: Encapsulated, free, protein bound

Comparability Bridging Study: A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.

Number of patients << a traditional clinical trial (Phase 1-3)



T/R % = test drug / reference listed drug (RLD)

Case study: liposomal doxorubicin*

Evaluates **BE**† for 'Sun' liposomal doxorubicin with Caelyx®

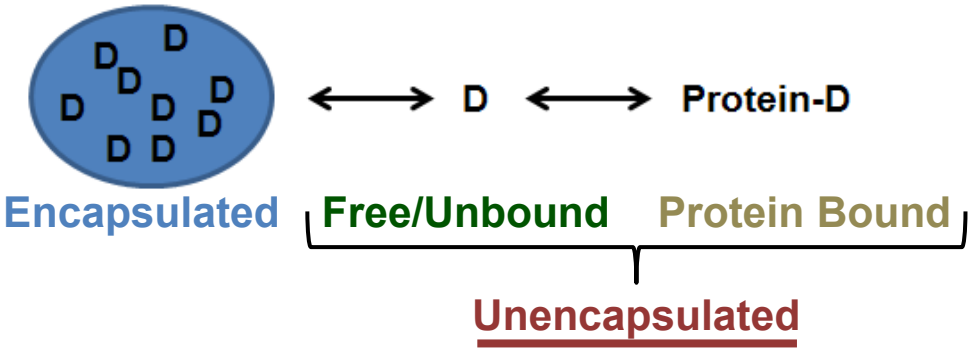
† **PE** studies showed equivalence, and will not be discussed here

*Reference: "European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) (2011a) CHMP Assessment Report: Doxorubicin Sun."

Case study: liposomal doxorubicin*

Evaluates **BE**† for 'Sun' liposomal doxorubicin with Caelyx®

D = drug



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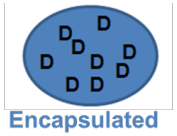
*Reference: "European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) (2011a) CHMP Assessment Report: Doxorubicin Sun."

Case study: liposomal doxorubicin

Encapsulated drug: 

T/R % = test drug / reference listed drug

TABLE-14.2 -1B SUMMARY OF STATISTICAL ANALYSIS TOTAL DOXORUBICIN (N = 23) Ln- Transformed Data								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-t}	8.16	8.20	3513.33	3652.32	96.19	89.83 to 103.01	13.39	0.3396
AUC_{0-inf}	8.22	8.26	3730.07	3870.70	96.37	89.69 to 103.54	14.05	0.3839
C_{max}	3.49	3.51	32.68	33.32	98.08	93.42 to 102.97	9.50	0.4991

?

EMA comments:

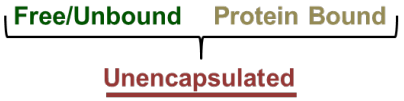
Encapsulated doxorubicin

The concentration-time curve is  y characterised. Bioequivalence is established for encapsulated doxorubicin, withir 5.00% criteria. The Applicant has also provided 90% CIs for log-transformed data of V_d and clearance, which are also within 80.00-125.00%.

Note: bridging study has only 23 patients, even less than a normal Phase 2 trial

Case study: liposomal doxorubicin

Free, un-encapsulated drug:



Ln- Transformed Data (n=23)								
PK Variables	Least Square Means		Geometric Means[3]		Ratio of Least-Square Means[1] %	90% Geometric C.I.[2]	Intra-Subject CV %	P-value[4]
	Test	Reference	Test	Reference				
AUC_{0-48}	8.89	8.85	7246.31	6983.76	103.76	85.76 to 125.53	38.40	0.7413
AUC_{49-337}	9.77	9.68	17424.83	15957.42	109.20	93.21 to 127.93	31.57	0.3488

EMA comments:

The 90% confidence intervals d Cmax are not within 80.00-125.00% standard bioequivalence criteria. Theref lence of free (un-encapsulated) doxorubicin between the test and reference product ha: ablished.

BE not achieved. Likely failed due to statistical power: sample size.

Quality Standards

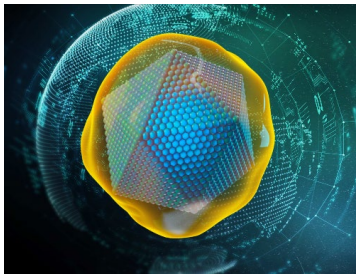
How do I ensure my formulation will be considered as a generic?

Quality standards

Monographs articulate the quality expectations for a medicine including for its identity, strength, purity, and performance. They also describe the tests to validate that a medicine and its ingredients meet these criteria.

General Chapters provide broadly applicable information to industry on accepted processes, tests and methods to support product development and manufacturing for innovative, generic and biosimilar medicines.

Radiotherapy



https://www.nanobiotix.com/

- ‘NBTXR3’ by Nanobiotix
  - Intratumoral injection
  - 50nm radioenhancer made from crystalline hafnium oxide (HfO2), with a negatively-charged phosphate coating
  - Generates free radicals when radiated with X-rays

Interesting note on its regulatory review:

NBTXR3 is considered a device by EMA, but as a drug by FDA

- Drug vs. Device: mechanism of action
- Radio*therapy*

“Beyond the yellow trails…”

Generics

Abridged applications

Regulatory: nanosimilar vs. novel formulation

- Previous example was liposome compared to liposome, both with the same API
  - EMA refers to this as a ‘nanosimilar’
    - ‘Follow-on’

- But...what about a novel nanoformulation vs. a traditional /non-nano drug?
  - Abridged pathway can apply, **if** the API is already approved

Regulatory: ‘follow-on’

For previously approved drugs, the investigator can submit a hybrid application

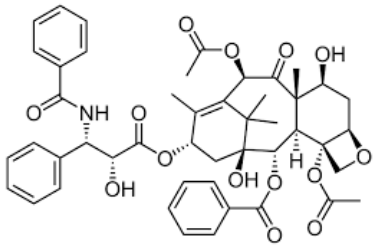
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	**Abridged application (hybrid)**	Article 10(**3**)
FDA U.S. FOOD & DRUG ADMINISTRATION	**New drug application (NDA)**	505(b)(**2**)

Costs: €€ to €€€€

- Hussaarts et al.; Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. Ann N Y Acad Sci. 2017 Nov;1407(1):39-49.
- Klein, K., et. al.; (2021), A pragmatic regulatory approach for complex generics through the U.S. FDA 505(j) or 505(b)(2) approval pathways. Ann. N.Y. Acad. Sci., 1502: 5-13.

Regulatory: precedence

Legacy drug: Taxol (paclitaxel)



In 2006: Abraxane was approved through 505(b)(2). Taxol was the RLD. (EMA approval in 2008, via **10(3)** pathway)

In 2019: Pazenir was approved as a generic, through EMA **10(1)**. Abraxane was the RLD

"...the applicant justified that Pazenir was eligible for a biowaiver based on qualitative and quantitative comparability with the reference product and based on the nature of the product, rapidly dissociating upon in vivo dilution and binding to endogenous albumin." (source: EMA Pazenir EPAR)

Bridging study not required

Regulatory: which pathway? **It depends!**

	Full dossier	**Generic**	**Abridged application (hybrid)**
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Article 8(3)	Article 10(**1**)	Article 10(**3**)
FDA U.S. FOOD & DRUG ADMINISTRATION	505(b)(**1**)	505(j)	505(b)(**2**)

Monograph

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

TE = PE + BE

Same API

Excipient or Active substance?

Definitions

- Active substance / Active ingredient
- Excipient / Inactive ingredient

Term	EU	US
Active substance/ active ingredient (API)	Active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.[a]	Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.
Excipient/ inactive ingredient	Excipient is any constituent of a medicinal product other than the active substance and the packaging material.[b]	Inactive ingredient means any component other than an active ingredient [d]

Term	EU	US
Active substance/ active ingredient (API)	Active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.	Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.
Excipient/ inactive ingredient	Excipient is any constituent of a medicinal product other than the active substance and the packaging material.	Inactive ingredient means any component other than an active ingredient

Nanoformulations: Excipient or API ?

Drug Products, Including Biological Products, that Contain Nanomaterials, Guidance for Industry, April 2022

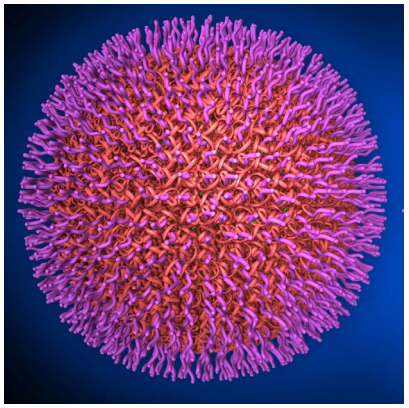
Current FDA guidance on evaluating the safety of new excipients* applies when an excipient is deliberately modified into a nanomaterial. An adequate safety evaluation should be provided when the nanomaterial's safety is not fully demonstrated by existing safety data with respect to level of exposure, duration of exposure, and route of administration.

* See FDA's guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005).

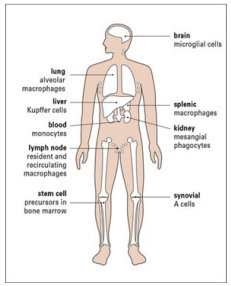
Excipient: Any inactive ingredient that is intentionally included in a drug product, but that is not intended to exert therapeutic, prophylactic, or diagnostic effect(s) at the intended dosage, although it may act to improve product delivery (e.g., enhance absorption or control release of the drug substance).

"improve product delivery" ≈ "furnish pharmacological activity"

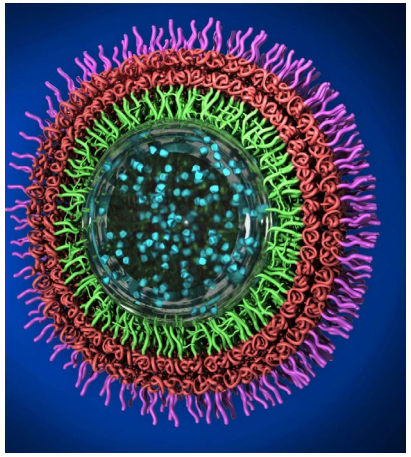
Excipient definition…so what?



ADME/Tox profile



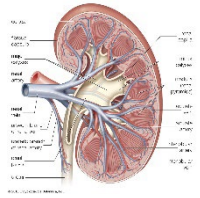
$t_{1/2}$ ~ 6 hrs



Current requirement

Components as excipients

ADME/Tox profile



$t_{1/2}$ ~ 10 mins

(Image source: Prof Robert Prud'homme, Princeton University)

AUC ($t_{1/2}$ ~ 6 hrs) >> AUC ($t_{1/2}$ ~ 10 mins)

Also: Lipid components will form micelles

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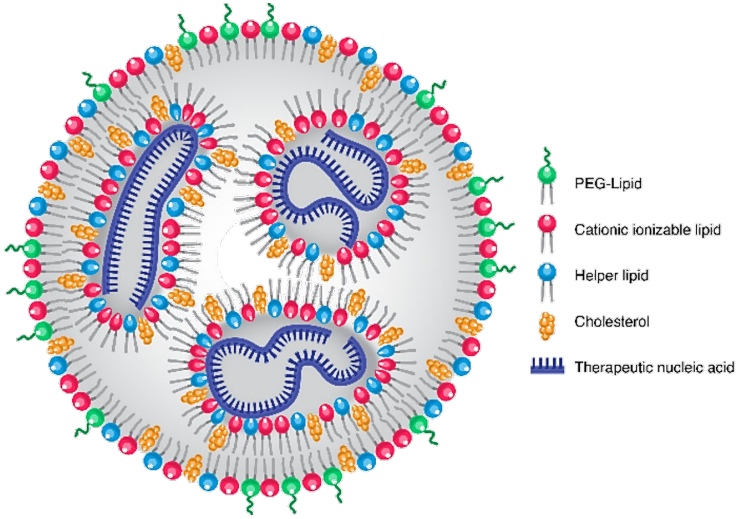
Case study: RNA-based drugs with similar LNP delivery systems

3 drugs use similar lipid nanoparticle (LNP) delivery systems containing 4 lipids: ionizable cationic lipid, PEGylated lipid, cholesterol, structural lipid



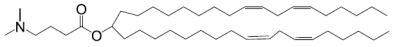
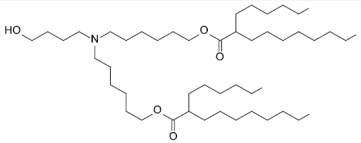
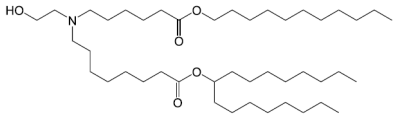
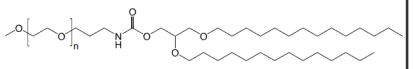
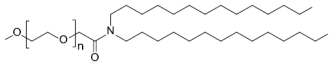
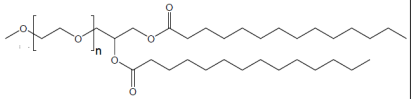
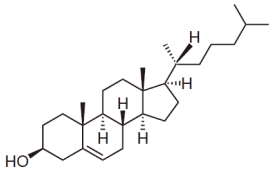
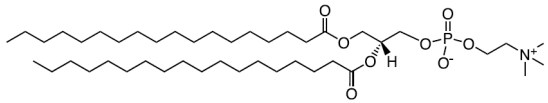
Kularatne et al, Pharmaceuticals **2022**, *15*(7), 897; **https://doi.org/10.3390/ph15070897**

Onpattro®
RNAi-based therapy for hereditary transthyretin amyloidosis

Comirnaty®
mRNA COVID-19 vaccine

Spikevax®
mRNA COVID-19 vaccine

Case study: RNA-based drugs with similar LNP delivery systems

	Onpattro®	Comirnaty®	Spikevax®
Ionizable lipid	 DLin-MC3-DMA	 ALC-0315	 SM-102
PEGylated lipid	 PEG2000-C-DMG	 ALC-0159	 PEG2000-DMG
Cholesterol			
DSPC			

Hemmrich and McNeil, “Active ingredient vs excipient debate for nanomedicines”, *Nature Nanotechnology*, 2023

Case studies

ONPATTRO

- **First RNA drug approved with an LNP delivery system.**
- **siRNA is the active ingredient, thus the lipid nanoparticles are accordingly considered as excipients.**

FDA	EMA
Drug Substance ALN-18328 siRNA **Drug Product** Patisiran (ALN-TTR02; patisiran-LNP) is a ribonucleic acid (RNA) interference (RNAi) therapeutic product comprised of 2 mg/mL patisiran drug substance (ALN-18328) and lipid excipients DLinMC3-DMA, DSPC, cholesterol, and PEG2000-C-DMG as lipid nanoparticles (LNPs) in isotonic phosphate buffered saline.	**Drug Substance ALN-18328** siRNA **Drug Product** siRNA DS + lipids + buffer The finished product manufacturing process consists of five main steps as outlined below: 1. Preparation of active substance and lipid solutions 2. Mixing of solutions to form lipid nanoparticles (LNP) 3. Ultrafiltration, exchange of buffer and initial concentration 4. Dilution to final concentration and bioburden filtration 5. Sterile filtration and filling into vials

Case studies

COMIRNATY

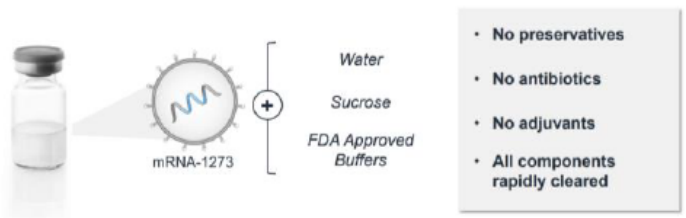
- **Pfizer has gone the usual way as per definitions. mRNA is the active substance in both submissions, to the FDA and the EMA.**
- **Consequently, the lipids are added in the drug product manufacturing and considered as inactive ingredients i.e. excipients.**

FDA	EMA
Drug Substance BNT162b2 BNT162b2 DS= modRNA **Drug Product** modRNA DS + lipids + buffer + and cryoprotectant manufactured by mixing the modRNA DS with lipids during lipid particle (LNP) formulation followed bv by fill/finish	**Drug Substance** BNT162b2 active substance = modRNA **Drug Product** modRNA DS + lipids + buffer + and cryoprotectant active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage

Case studies

SPIKEVAX

- **Moderna considers the mRNA encapsulated with the 4 lipids as a drug substance meaning the mRNA-LNP complex is the active ingredient including the lipids!**
- **In line with this, the 4 lipids are NOT considered excipients.**
- **FDA accepted this approach, EMA did not.**

FDA	EMA
Drug Substance mRNA-1273 LNP CX-024414 mRNA Drug Substance (DS) intermediate + Lipids **Drug Product** Drug product is the m-RNA-1273 LNP + water +sucrose+ buffers **In the Vial** 	**Drug Substance** Active substance (CX-024414) = mRNA **Drug Product** mRNA is encapsulated by 4 lipid excipients leading to a mRNA-loaded LNP intermediate which is further processed to produce the finished product (step consists of dilution of the mRNA-loaded LNP intermediate with a formulation buffer followed by 0.2 µm sterile filtration, filling, stoppering, capping inspection, labelling and packaging).

Interesting precedent!

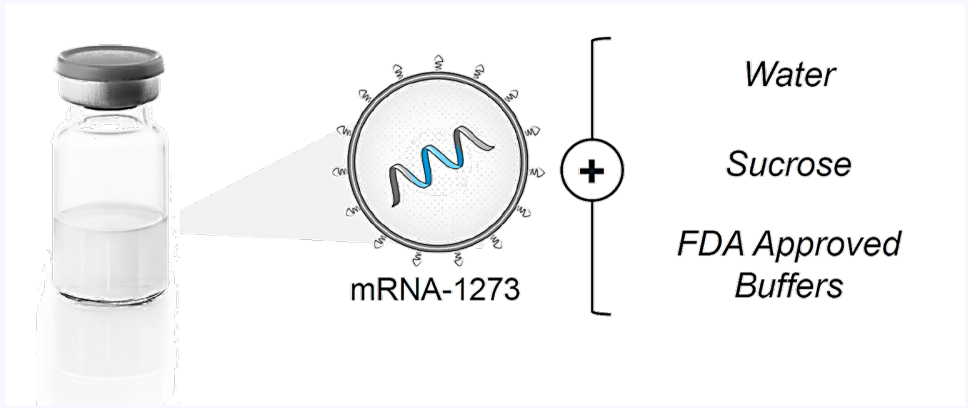
Universität Basel
Departement Pharmazeutische Wissenschaften

Hemmrich and McNeil, *Nature Nanotechnology*, 18:692–695 (2023)

Case study: RNA-based drugs with similar LNP delivery systems

Drug	EMA	FDA
Onpattro® RNAi-based therapy for hereditary transthyretin amyloidosis	lipids = excipients	lipids = excipients
Comirnaty® mRNA COVID-19 vaccine	lipids = excipients	lipids = excipients
Spikevax® mRNA COVID-19 vaccine	lipids = excipients	lipids = part of drug substance

FDA accepted the classification of lipids in Spikevax as part of drug substance, whereas similar lipids in Onpattro and Comirnaty were ruled as excipients.



Composite vs. Component-wise

Hemmrich and McNeil, *Nature Nanotechnology*, 2023

Regulatory Sciences

Precedent & baseline?

- FDA's Spikevax case ruling is a precedent for composite NPs as active ingredients
- It sets a baseline for companies to prepare regulatory dossiers & for regulators to evaluate these products

What next?

- Each nanomedicine is unique regulators cannot just make a general statement on the classification of composite NPs as active ingredients
- **Regulatory Science shall allow for a transparent dialogue among all stakeholders!**

Our position*:

The <u>composite</u> nanoparticle should be reviewed as the active substance, for *stable* NPs.

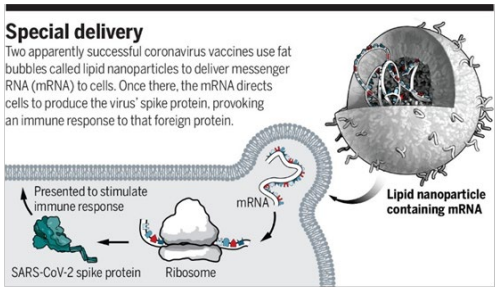
*Hemmrich and McNeil, *Nature Nanotechnology*, 18:692–695 (2023)

Clinical Translation of Nucleic Acid APIs

Route of Administration

Success with mRNA vaccines!

- intramuscular injection (*i.m.*)



Source: Meredith Wadman (2020), Science, 370:6520, pp. 1022

ONPATTRO® (patisiran)

- i.v. administration of siRNA
- 19% infusion reaction

i.m. ≠ i.v.

2.2 Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) *[see Warnings and Precautions (5.1)]*. Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf

Strategies for translation of *i.v.* nucleic acid APIs

- Base modification (e.g., pseudouridine) overcomes the TLR-3/7/8 innate response, but not *all* cytoplasmic NA sensors*.
- Choose an orphan disease or unmet medical need
  - ONPATTRO® is for hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
  - 50K patients worldwide
- Regulatory risk is << less for orphan diseases
  - FDA: defined as affecting < 200K patients in U.S.
  - Fast Track, Priority Review , etc.
- Screen formulations using IVIVC assays
  - Innate immunity
  - Improvise, adapt, overcome!

NCL, https://ncl.cancer.gov

Immunological Characterization

Sterility
- Bacterial/Viral/Mycoplasma
- Endotoxin

In Vitro Hematology
- Hemolysis
- Platelet Aggregation
- Coagulation
- Complement Activation
- Plasma Protein Binding

In Vitro Immune Cell Function
- Cytokine Induction
- Chemotaxis
- Phagocytosis
- Leukocyte Proliferation
- Leukocyte Procoagulant Activity

In Vivo Immunotoxicity
- Local lymph node proliferation assay
- T-cell dependent antibody response

*Miyake, et. al., Journal of Leukocyte Biology, 101:135–142, 2017, https://doi.org/10.1189/jlb.4MR0316-108R

Nanomed Regulatory: things to remember

- Abbreviated / abridged studies allow nanoformulations to bypass full clinical trials
  - Compare against RLD
  - But not for NCE or a change in covalent bonds
    - May not be suitable for novel ‘first in man’ polymers
- TE = PE + BE
  - the 80% - 125% criteria
- Evaluate both encapsulated and free (un-encapsulated)
- Excipient vs. Active substance

Additional considerations for commercialization

What comes after Marketing Authorization (MAA) ?

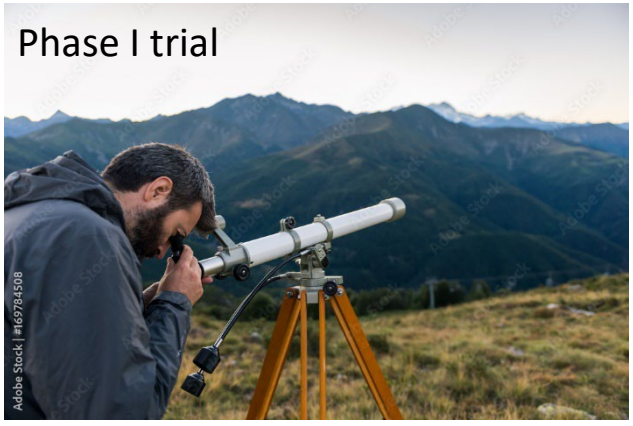
“Beyond here be dragons…”

Regulatory considerations: the Payer

What role do the health technology assessment (HTA) bodies and payers play in clinical trials?

Notional example: I develop a nanomedicine that demonstrates AUC (Phase I trial) that is 5X that of the current standard of care.

- Does the expected ROI support the <u>expensive</u> development of my product?
  - Reimbursement of generics is < 75% of RLD



<u>The destination: **£ $ €**</u>

<u>Reimbursement</u>

Regulatory considerations: the Payer and Reimbursement

HTA perspective: “How does this product decrease the financial burden on the public health system?”

cost and reimbursement ∝ patient benefit

My possible responses:

1. “5X AUC !!”
2. My business model: I will license the technology after Phase 2

3. Plan my Phase 2-3 clinical trials to exploit the **innovation**.
   - in collaboration with regulatory agencies

The destination:
plan your route!

Commercialization by design

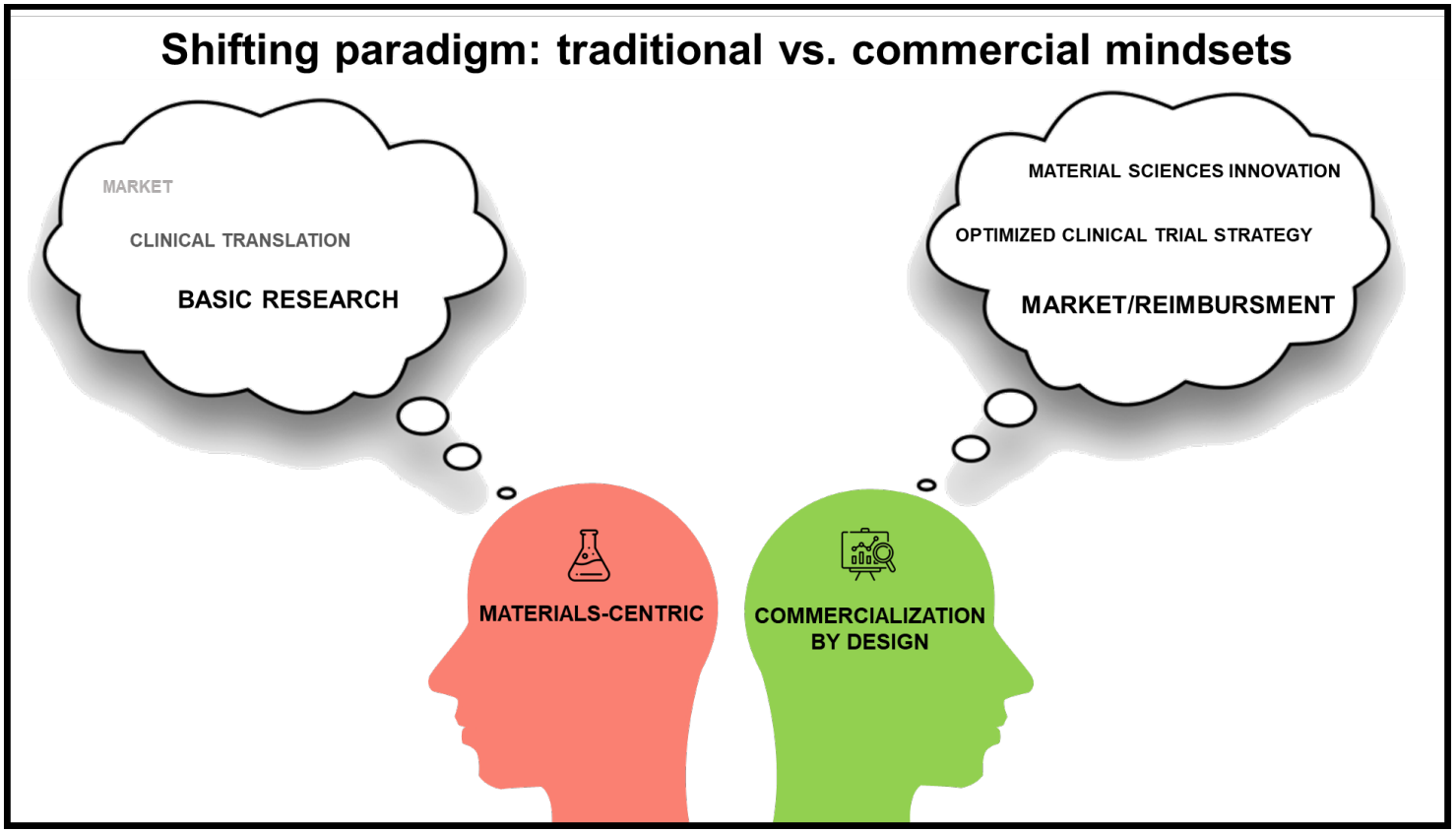
There are recurring concerns regarding the low translation of nanodrugs and their failure to deliver on promises to patients[1].

As several key opinion leaders recently pointed out, the research emphasis has been on the development of innovative materials -- at the expense of translational requirements[2].

[1] D. Sun, et. al., What went wrong with anticancer nanomedicine design and how to make it right, ACS Nano 14 (2020) 12281–12290.

[2] L.M. Liz-Marzán, et. al., What Do We Mean When We Say Nanomedicine?, ACS Nano 16 (2022) 13257–13259.

Plan your route…

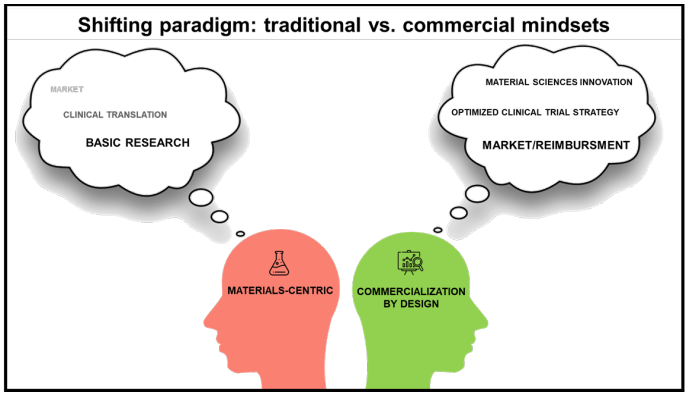


Key to reimbursement: solve a clinical problem!

Universität Basel
Departement Pharmazeutische Wissenschaften

Hemmrich and McNeil. (2024). Strategic aspects for the commercialization of nanomedicines, J. Controlled Release 369, 617-621.

Commercialization by design



Clinical need

- Gap in current standard of care?
- Efficacy and safety

Reimbursement (HTA)

- Improvement in efficacy
- Decreased side effects

Regulatory pathway

- Unmet medical need
- Endpoints (MRI, biomarkers)

Nanomedicine solution?

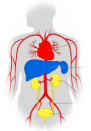
Nanomedicine capabilities

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.

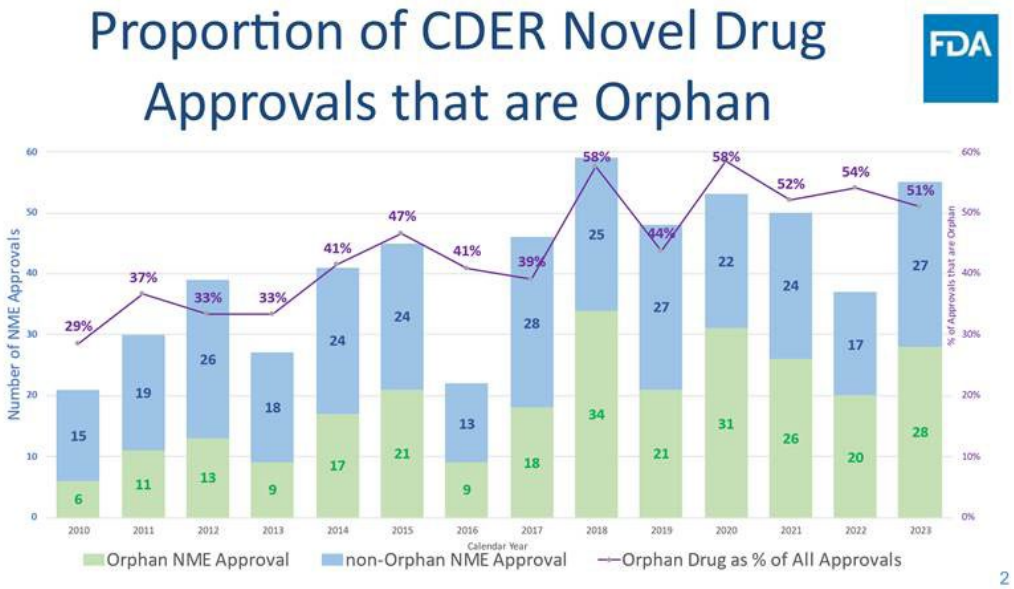
Solve a clinical problem….

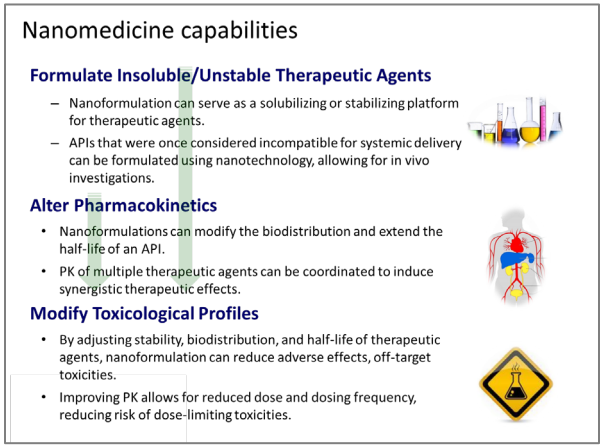
	Full dossier	Generic	Abridged application (hybrid)
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	Article 8(3)	Article 10(**1**)	Article 10(**3**)
FDA U.S. FOOD & DRUG ADMINISTRATION	505(b)(**1**)	505(j)	505(b)(**2**)

Plus:

- Orphan drug, rare diseases
  - Regulation (EC) No 847/2000
- Exceptional Use approval
  - Article 14 (8)

Regulatory assistance for Orphan Diseases/UMNs





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRIME: priority medicines

FDA U.S. FOOD & DRUG ADMINISTRATION

Accelerating Rare disease Cures (ARC) Program

Case study: lysosomal storage diseases (LSDs)

- Defects in lysosomal enzymes
  - 50 different types
- Enzyme replacement therapy
  - 20 vials i.v. infusion, twice a month
  - Cost: CHF 120K per year
  - ERT: € 12B annual market
- Adverse events
  - 95% of patients will develop anti-drug antibodies (ADA)
  - For infantile Pompe disease, there is no alternative

Clinical need(s):
- Decreased ADA response
- Improve efficacy: $T_{1/2}$, distribution

Regulatory Considerations

Thanks!

Contact info:

Prof. Scott McNeil

scott.mcneil@unibas.ch

Dr. Eva Hemmrich

Boris Ševarika

Assistant / PhD candidate
(Nanopharmaceutical & Regulatory Science)

Adèle Couvidou

Assistant / Postdoc
(Nanopharmaceutical & Regulatory Science)

Universität Basel
Departement
Pharmazeutische Wissenschaften