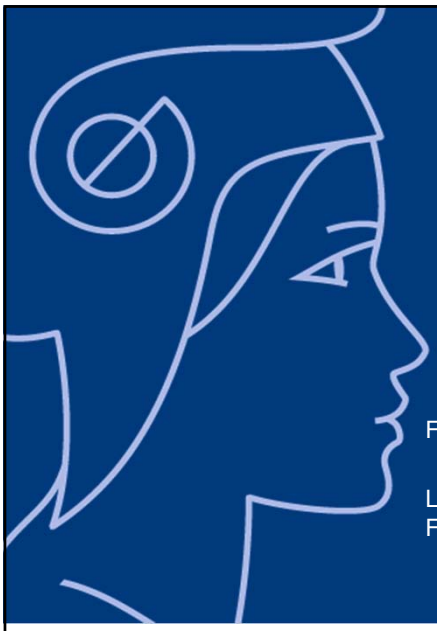


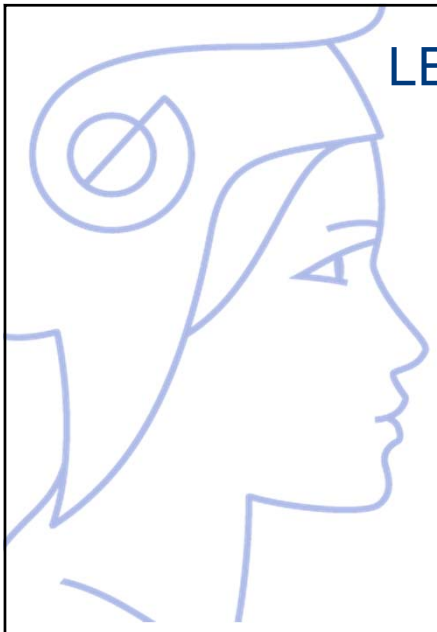
QUALITY REQUIREMENTS FOR NANOMEDICINES:
WHICH ROLE FOR THE EUROPEAN PHARMACOPOEIA?

ANALYTICAL CHALLENGES AND CURRENT STANDARDISATION ACTIVITIES FOR NANOMEDICINES

F. CAPUTO

LNE, LABORATOIRE NATIONAL DE MÉTROLOGIE ET D'ESSAIS, FRANCE

7-8 June 2022

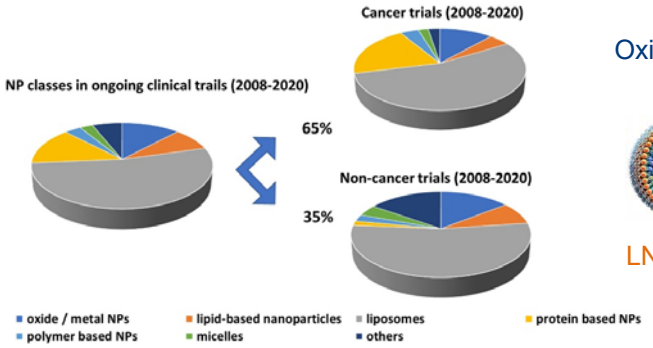


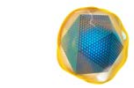
LEARNING OBJECTIVES

- Analytical challenges
- Analysis of the methodological gaps (REFINE H2020 project)
- Validation & standardization frameworks
- Overview of the ongoing international pre-normalization and standardisation activities

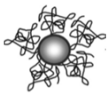
CLINICAL APPLICATION AND ASSOCIATED PRIORITIES

Nanomaterials in ongoing trials:

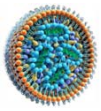




Oxide and metal oxide



Polymeric NPs

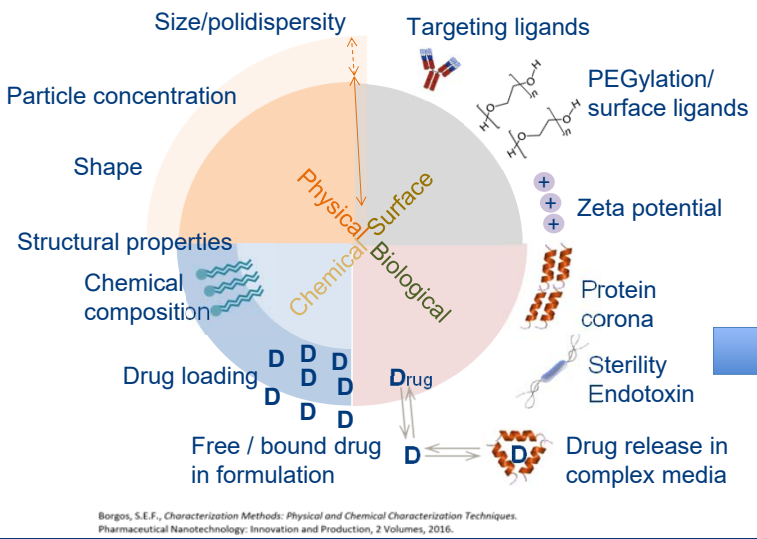


LNPs

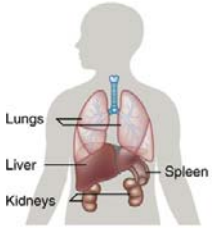
Liposomes

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

WHAT DO WE WANT TO MEASURE?



Borgos, S.E.F., *Characterization Methods: Physical and Chemical Characterization Techniques.* Pharmaceutical Nanotechnology: Innovation and Production, 2 Volumes, 2016.



Safety

Efficacy

Critical quality attributes (CQAs) ???

WHAT DO WE WANT TO MEASURE?

Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 February 2013
EMA/CHMP/806058/2009/Rev. 02
Committee for Human Medicinal Products (CHMP)

Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product

Final

Table 1: Regulatory information needs extracted from the regulatory documents addressing all classes of nanotechnology-based health products [15].

Physicochemical parameters (if applicable)	Biological characterisation (if applicable)
• Chemical composition	**Bioburden control**
▪ Chemical structure ▪ Structural attributes that relate to function ▪ Crystal form ▪ Impurities ▪ Particle size and size distribution ▪ Shape and morphology ▪ Surface properties (e.g., surface area, surface charge, chemical reactivity, ligands, hydrophobicity, and roughness); ▪ Particle concentration ▪ Porosity (if it relates to a function) ▪ Degradation path, kinetics and degradation products ▪ Stability, both physical and chemical under relevant conditions	▪ Sterility and endotoxin levels **Pharmacokinetic parameters** ▪ Stability in blood and serum ▪ Biological fate ▪ Accumulation issues ▪ ADME ▪ Plasma protein binding (formation of protein corona over time) ▪ In vivo degradation/solubilisation rate and pla of degradation **Pharmacodynamic parameters** ▪ Biocompatibility with blood and serum ▪ Additional risks associated with the exposure route: e.g., haemocompatibility for iv administration ▪ In vitro uptake and cytotoxicity of nanomateri to the phagocytes ▪ Interaction with enzymes ▪ Immunogenicity (ICH S8) ▪ Complement activation
Drug delivery systems • Drug loading efficiency • Presence and distribution of any active ingredient associated with the nanomaterial and free in solution • Physical state of the active substance • In vitro drug substance /siRNA release rate in physiologically/clinically relevant media	

https://doi.org/10.1016/j.jconrel.2021.06.016

Regulatory Considerations – FDA

4. Selectivity and Specificity

During method development, the sponsor should verify that the substance being measured is the intended analyte to minimize or avoid interference. Selectivity of the method is routinely

interference. Matrix effects evaluation involves comparing calibration curves in multiple sources of the biological matrix against a calibration curve in the matrix for parallelism (serial dilution of incurred samples) and nonspecific binding. The sponsor should eliminate or minimize any significant interference. If such attempts are unsuccessful, the sponsor could consider the development of an orthogonal method to eliminate or minimize the interference.

FDA - Bioanalytical Method Validation, Guidance for Industry, 2018

C. Nanomaterial Physicochemical Characterization Methods

- Complementary methods: In some cases, several different analytical techniques may be available to characterize a given material attribute, for example particle size or morphology. Due to inherent differences in analytical techniques for measuring a given attribute, different instruments may provide different endpoint measurements. To address technique-related differences, we recommend the use of complementary methods when measuring material attributes that have been established as critical (e.g., use both dynamic light scattering and transmission electron microscopy for size). In addition, a description of what is being measured should also be provided (e.g., hydrodynamic radius versus projected radius, ensemble versus single particle results) in order to account for potential differences. If different techniques are needed -at different stages of processing

FDA – Drug Products, Including Biological Products that Contain Nanomaterials, 2017

Metrology

Regulatory guidances:

Reduce the risk of having unknown systematic errors

Single measurement level, same attribute, different physical principles

Orthogonal

Orthogonal measurements: *measurements that use different physical principles to measure the same property of the same sample with the goal of minimizing method-specific biases and interferences.*

Sizing measurements

Technique	Primary physical principle for sizing measurements	Primary measurand definition
Static light scattering (SLS)	Anisotropic light scattering	Diameter of gyration
X-ray diffraction (XRD)	X ray diffraction from a crystal structure	Crystallite size
Atomic force microscopy (AFM)	**Atomic force between a tip and the particles**	**Geometric diameter-height**
Dynamic light scattering (DLS)	Brownian motion	Hydrodynamic diameter
Nanoparticle tracking analysis (NTA)	Brownian motion	Hydrodynamic diameter
Asymmetric flow field flow fractionation-DLS (AF4-DLS)	Brownian motion	Hydrodynamic diameter
AF4-SLS	Anisotropic light scattering	Diameter of gyration
Centrifugal flow field flow fractionation (CF3)-DLS	Brownian motion	Hydrodynamic diameter
CF3-SLS	Anisotropic light scattering	Diameter of gyration
AF4-NTA	Brownian motion	Hydrodynamic diameter
Size exclusion chromatography-SLS (SEC-SLS)	Anisotropic light scattering	Diameter of gyration
AF4-UV-VIS/RI	Retention time based on AF4 fractionation	Hydrodynamic diameter
SEC-UV-VIS/RI	Retention time based on SEC fractionation	Hydrodynamic diameter
CF3-UV-VIS/RI	Retention time based on CF3 fractionation	Hydrodynamic diameter
Analytical ultracentrifugation (AUC)	Dynamic changes in particle concentration profiles during centrifugation	Hydrodynamic diameter
Centrifugal particle sedimentation (CPS)	Particle sedimentation vs time	Hydrodynamic diameter
Tunable resistive pulse sensing (TRPS)	Transient change of the ionic current in a conductive pore	Hydrodynamic diameter
Transmission electron mictoscopy (TEM)	Particle visualization by electron contrast in transmission mode	Diameter of an equivalent sphere or feret diameter-later dimension
Scanning electron miscroscopy (SEM)	**Particle visualization by electron contrast in scan mode**	**Diameter of an equivalent sphere or ferret diameter-later dimension**

DLS

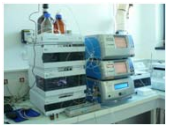
Centrifugal Particle sedimentation (CPS)

Analytical ultra centrifugation(AUC)

Tunable resistive pulse sensing (TRPS)

EM

Asymmetric-flow field-flow fractionation (AF4)

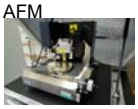


Nanoparticle Tracking Analysis (NTA)

MALS

sp ICP-MS

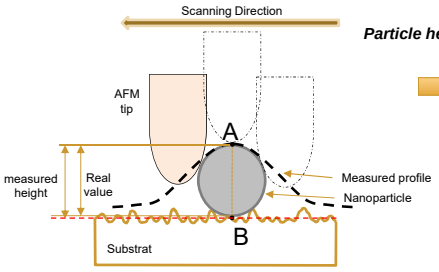
AFM



HYBRID METROLOGY AFM/SEM

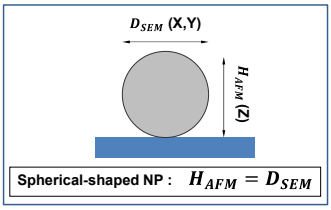
Objective:
Determine the size of a nanoparticle (NP) in all 3 dimensions of space with controlled uncertainty by combining two orthogonal approaches: AFM and SEM

AFM measurement principle



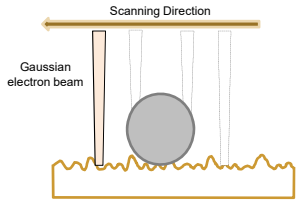
Particle height

Particle Size distribution and morphology



Particle lateral dimension

SEM measurement principle



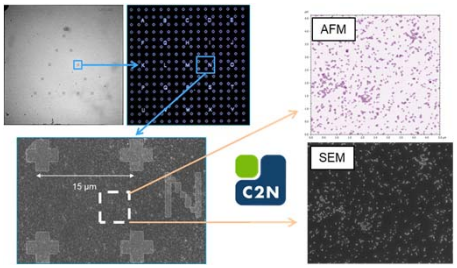
- Tip/sample convolution: Bias in the measurement of lateral dimensions
- No convolution at the top of the particle: Low measurement uncertainty on height (2 nm, k=2)

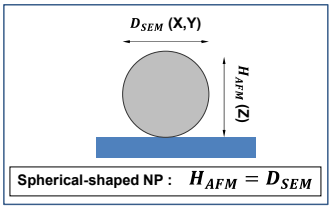
- No quantitative information on z
- 2D projection of the diameter of an equivalent sphere
- Electron beam size close to 1 nm: lower uncertainty in the measurement of the lateral dimension (4.0 nm, k=2)

L. Crouzier and al. Beilstein J. Nanotechnol. **2019,** *10,* 1523–1536.

HYBRID METROLOGY AFM/SEM

Measuring exactly the same population by using a speficic substrate:



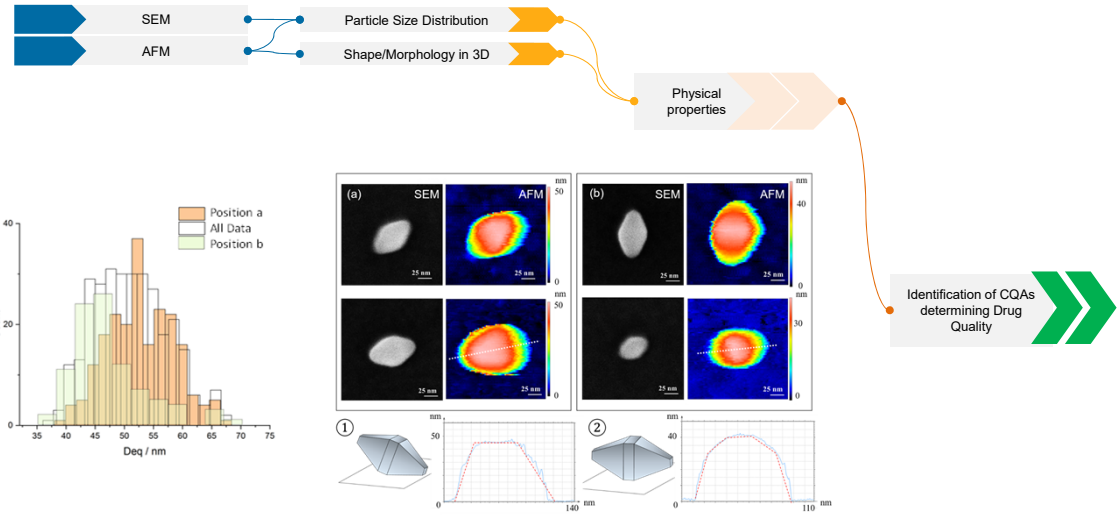


Applicable to small NPs (>10 nm)

Measurements performed with a controlled known uncertainty reducing the bias associated to each specific technique

Used for batch variability assessment by metal oxide NPs producers

L. Crouzier and al. Beilstein J. Nanotechnol. **2019,** *10,* 1523–1536.



Metrology

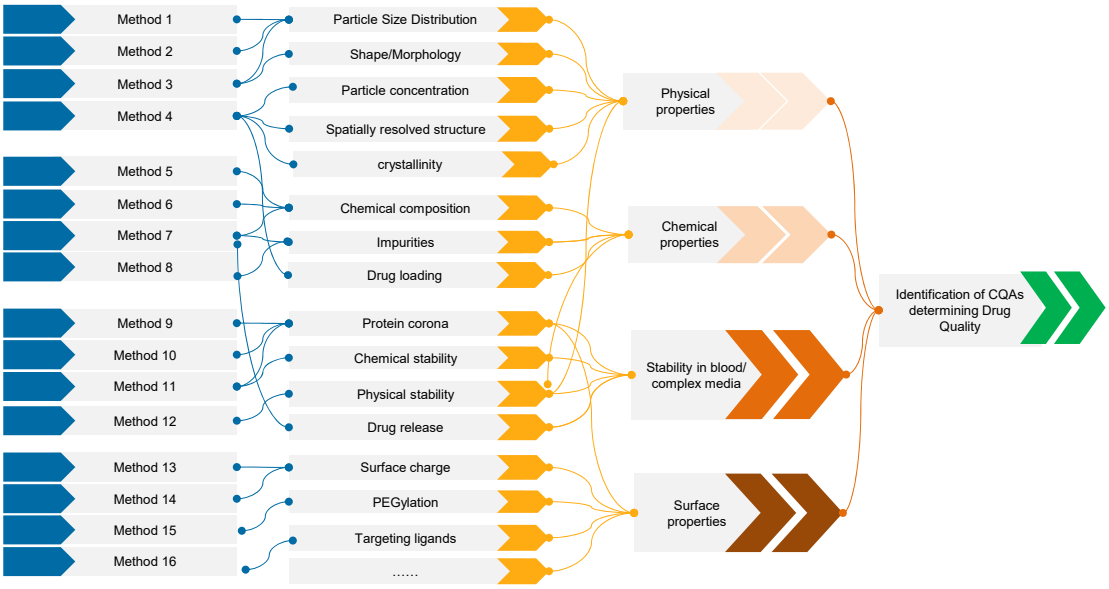
Regulatory guidances:

Combine informations to answer a specific question

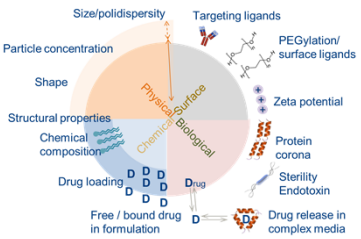
Multiple measurements (on different measurands) corroborating each

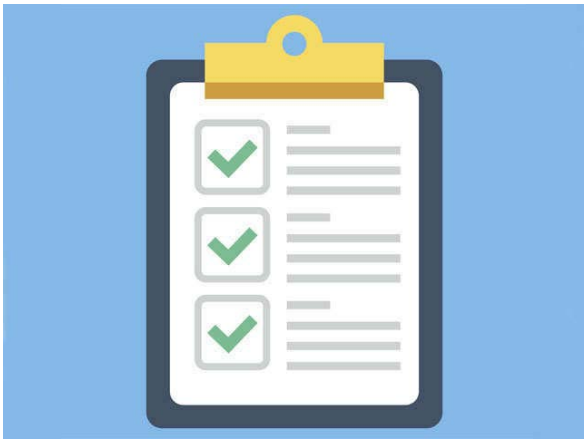
Complementary

***Complementary measurements**: measurements that are used to corroborate each other to support the same decision.*



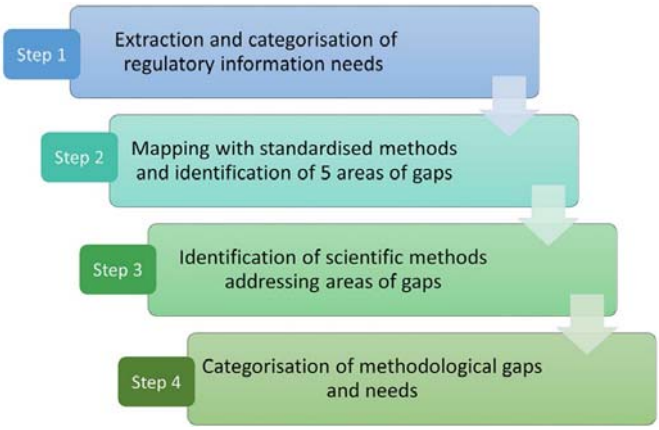
WHAT STANDARDS DO WE HAVE?





THE REFINE GAP ANALYSIS:

The REFINE GAP analysis:

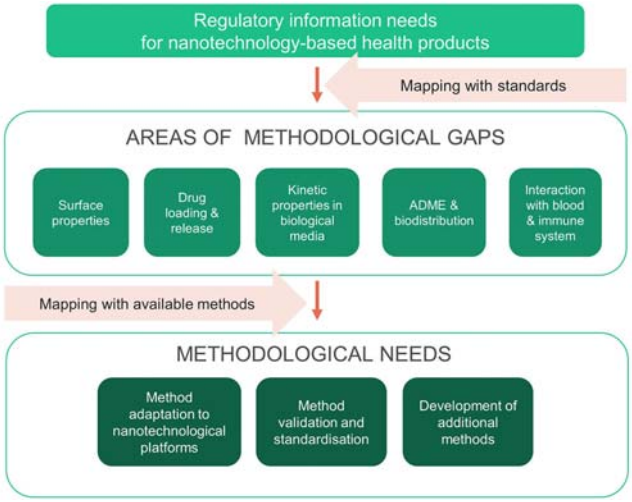


Journal of Controlled Release
Volume 336, 10 August 2021, Pages 192-206

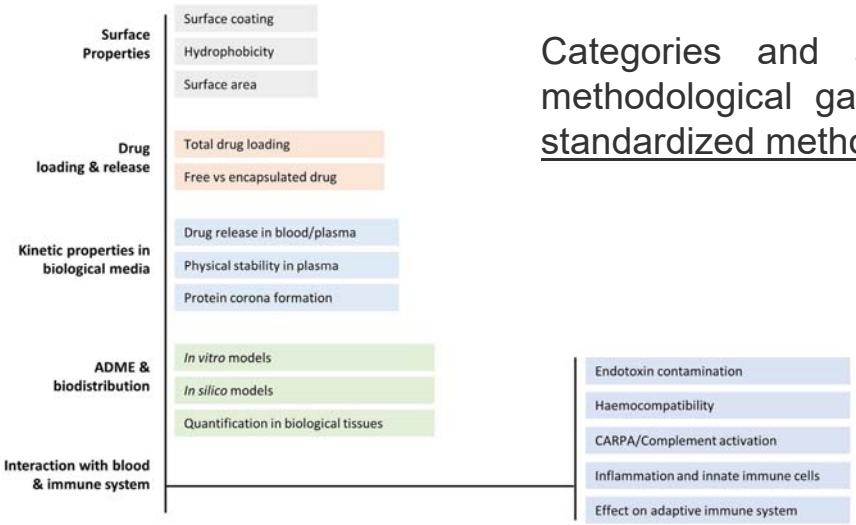
Review article

Methodological needs in the quality and safety characterisation of nanotechnology-based health products: Priorities for method development and standardisation

B. Halamoda-Kenzaoui [a], R.J. Vandebriel [b], A. Howarth [c], M. Siccardi [c], C.A.W. David [c], N.J. Liptrott [c], M. Santin [d], S.E. Borgos [e], S. Bremer-Hoffmann [a], F. Caputo [e]



https://doi.org/10.1016/j.jconrel.2021.06.016



Categories and subcategories of methodological gaps, for which <u>no standardized methods</u> are available

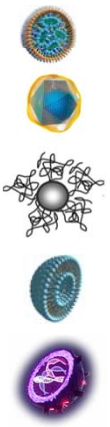
https://doi.org/10.1016/j.jconrel.2021.06.016

METHODOLOGICAL NEEDS

Important: ad hoc optimisation for specific NP/API classes is needed

Table 7
Categorisation of main methodological needs.

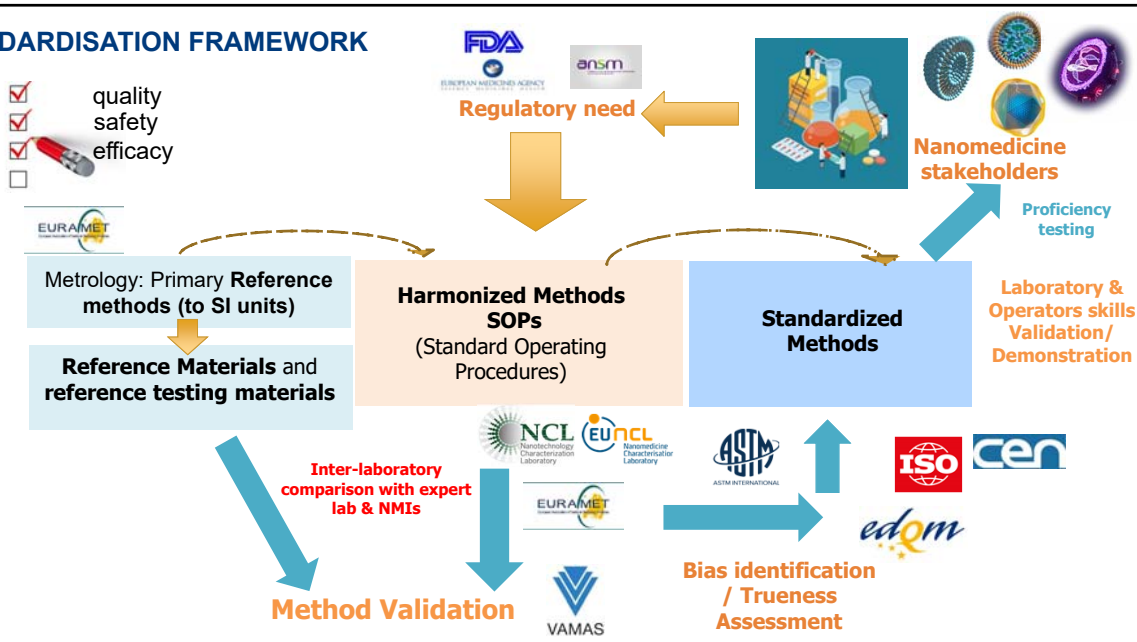
Category 1 Method adaption to specific/new nanomaterial	Category 2 Method validation and standardisation	Category 3 Development of additional methods
PCC: All PCC methods have to be optimized for each specific NP/API class, according to general guidelines. **Biodistribution and ADME:** Adjustments are necessary for each technological platform, for ADME and for *in silico* models **Immune system:** ➢ LAL-based methods for endotoxin	**PCC:** ➢ Drug loading and drug release in complex media ➢ Hydrophobicity ➢ Physical stability in complex media **Biodistribution and ADME:** ➢ Barrier models *in vitro* ➢ Detection/quantitation of whole nanomaterials in simple and complex media including in cells ➢ Existing PBPK models **Immune system:** ➢ Effect on macrophages ➢ Uptake by phagocytes ➢ Inflammation ➢ Activation of complement system ➢ Thrombogenicity ➢ Effect on lymphocytes and antibodies (existing methods)	**PCC:** ➢ Release and quantification of large API such as nucleic acids ➢ Specific surface area evaluation in aqueous media ➢ Quantification of surface coating and analysis of coating heterogeneity ➢ For small organic nanomaterials: Fractionation methods for stability studies in complex media and determination of protein corona composition **Biodistribution and ADME:** ➢ Detection/quantitation of unlabelled organic nanomaterials in cells, tissues and subcellular structures ➢ Sophisticated *in vitro* models for the prediction of human pharmacokinetics **Immune system:** ➢ Endotoxin contamination: alternative methods to LAL ➢ Advanced *in vitro* models to assess effects on adaptive immune system



https://doi.org/10.1016/j.jconrel.2021.06.016

HOW DO WE GET THERE?

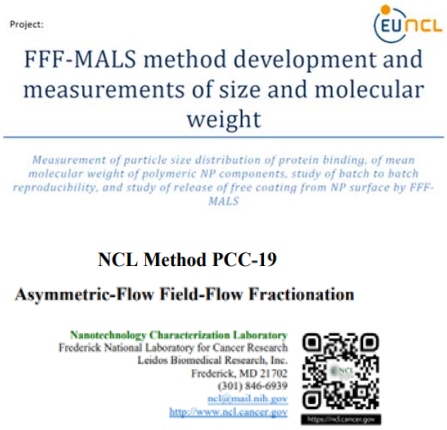
STANDARDISATION FRAMEWORK



EXPERT INFRASTRUCTURES

[Assay Cascade Protocols | Nanotechnology Characterization Lab (NCL) (cancer.gov)]

EUNCL Nanomedicine Characterisation Laboratory



Project:

FFF-MALS method development and measurements of size and molecular weight

Measurement of particle size distribution of protein binding, of mean molecular weight of polymeric NP components, study of batch to batch reproducibility, and study of release of free coating from NP surface by FFF-MALS

NCL Method PCC-19

Asymmetric-Flow Field-Flow Fractionation

Nanotechnology Characterization Laboratory
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
Frederick, MD 21702
(301) 846-6939
ncl@mail.nih.gov
http://www.ncl.cancer.gov

AT THE EUROPEAN LEVEL: EURAMET

EURAMET e.V.
- Association of European NMIs
- Inaugurated in 2007
- Successor of EUROMET (1987-2006)
- Legal Entity: German non profit association

EURAMET - THE EUROPEAN ASSOCIATION OF NATIONAL METROLOGY INSTITUTES (NMIs)
https://www.euramet.org/about-euramet/?L=0 propose some dedicated calls

Objectives of the European Partnership on Metrology under Horizon Europe:

- **Establish European Metrology Networks** in competitive and emerging areas;
- **Fund joint research projects** that increase and accelerate innovation using metrology solutions, capabilities and infrastructure;
- **Increase and coordinate the role of metrology in the design and implementation of regulation and standardisation**
- **Engage with stakeholders** along the metrology value chain to maximise uptake of emerging technologies and contribution to addressing major societal challenges.

HEALTH CALL 2022: JRP ON NANOTHERAPEUTICS

Reference testing materials for Lipid based NPs and Metal oxide NPs

Methodologies for (i) **the particle size and concentration of small (<10 nm) MONPs nanoparticles and of aggregated not spherical objects**, the (ii) **lipid composition of LNPs** and (iii) **the surface properties** of LNPs and MONPs, including the amount, chemical composition and homogeneity of the surface coating.

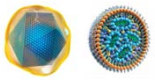
Sample preparation methods prior to the measurements of LNPs and MONPs **stability in biological matrices, to minimise matrix interferences**.

Correlative methods and model tissue phantoms (3D cellular aggregates and 3D printed artificial tissue samples) **to measure nanoparticle uptake and distribution in single cells and tissues**..

International cooperation, advance pre-normative and standard developments

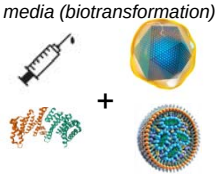
Challenges:

Critical quality attributes



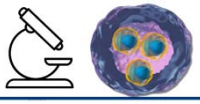
Lack of reference materials
Aggregation/stability
Highly complex structure
Chemical composition
Surface properties

Kinetic properties in biological media (biotransformation)



Particle isolation from biological media prior to the assessment of their biotransformation

Biodistribution



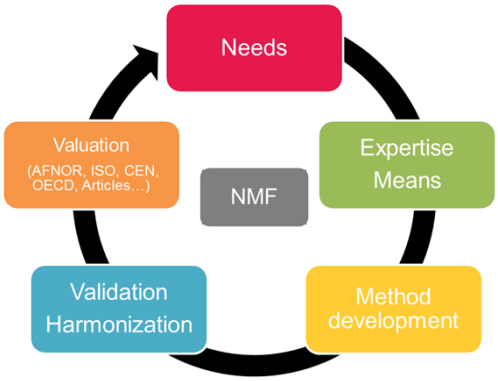
Detection and quantification in cells and tissues

AT THE FRENCH LEVEL: « NANOMESUREFRANCE » (NMF)

What is NMF?

« SESAME Filières PIA » Funding *(2021-2024)*

- Creation of a **unique association, supported by LNE**, **bringing together** all the **actors** *(manufacturer and integrator of nanomaterials, instrument manufacturers)* and **expertise** *(service providers, academic platforms, research institutes)* **necessary to support**, in a serene and sustainable development of nanomaterials / nanotechnologies, their industrialization and resulting innovations
- **Identification** and prioritization of **needs** for **harmonization / validation** of **characterization** and **evaluation methodologies**.
- **Mapping** and **pooling** of **resources / expertise** with € 1.5 million of investment (LNE).



AND NANOMEDICINE?

- Health (medicinal products and medical devices) will be one of the first 4 active working groups

Contacts:
georges.favre@lne.fr
francois-xavier.ouf@lne.fr

JOIN US: HTTPS://WWW.LNE.FR/FR/EVENEMENTS/WORKSHOP-NANOMEDECINE

EXAMPLE#1 OF INTERNATIONAL STANDARDISATION EFFORTS

1. Identify a need → 2. Develop a robust SOP → 3. Develop a standard test method

Targeted attributes:

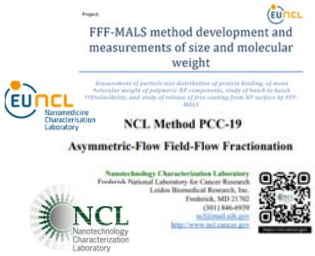
- Physical stability
- Aggregation
- Kinetic properties in complex media

Formulations:

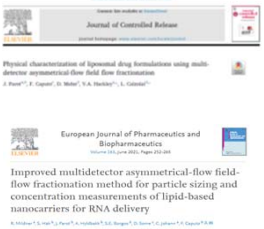
Technique:

Multi detector-asymmetric flow field flow fractionation

Generic SOPs:



Specific development:



EU-US community of Research

Working items within the ASTM E56.02:

Analysis of Liposome Drug Formulations using Multidetector Asymmetrical-Flow Field-Flow Fractionation.

OTHER EXAMPLES…

ASTM E56.08 published:

1. ASTM E3238-20 Standard Test Method for Quantitative Measurement of the **Chemoattractant Capacity** of a Nanoparticulate Material in Vitro
2. ASTM E3275-21 Standard Guide for **Visualization and Identification of Nanomaterials in Biological and Nonbiological Matrices** Using Darkfield Microscopy/Hyperspectral Imaging (DFM/HSI) Analysis
3. ASTM E3297-21 Standard Test Method for **Lipid Quantitation in Liposomal Formulations** Using High Performance Liquid Chromatography (HPLC) with a Charged Aerosol Detector (CAD)
4. ASTM E3324-22 Standard Test Method for **Lipid Quantitation in Liposomal Formulations** Using Ultra-High-Performance Liquid Chromatography (UHPLC) with Triple Quadrupole Mass Spectrometry (TQMS)
5. ASTM E3323-21 Standard Test Method for **Lipid Quantitation in Liposomal Formulations** Using High Performance Liquid Chromatography (HPLC) with an Evaporative Light-Scattering Detector (ELSD)

In Process at ASTM E56.08:

1. WK60553 Standard Guide for Evaluating **Impact of Particles** and Other Materials on **Phagocytic Function** In Vitro
2. WK60554 Standard Test Method for the **Detection of Nitric Oxide Production** in Vitro
3. WK69051 Standard Test Method for **Assessing the Activation of the Complement System in Human Plasma** Through Quantification of iC3b Concentration by ELISA
4. WK67980 Standard Test Method for **Quantifying Poly(ethylene glycol) Coating on the Surface of Gold Nanostructured** Materials Using High Performance Liquid Chromatography with Evaporative Light Scattering Detection (HPLC/ELSD)
5. WK75607 New Standard Guide for **Characterization of Encapsulation, Extraction, and Analysis of RNA in Lipid Nanoparticle Formulations** for Drug Delivery

OTHER EXAMPLES…

In progress at ISO TC229:

– documentary standard on **liposome terminology**;

–**Total and free drug quantitation** in doxorubicin hydrochloride **liposomal formulations**;

–**Nanotechnologies-mRNA-containing nanoemulsions** for medical application: characteristics and measurement methods;

Proposed but not taken up (yet) at the ASTM E56.08:

1. Evaluation of in **vitro drug release of doxorubicin in Liposomal Doxorubicin**
2. Estimation of **fixed aqueous layer thickness of liposomes**.
3. Determination of **free, encapsulated and total ammonium and sulfate ions in doxorubicin-liposomal drug systems**. (Ion chromatography)
4. Quantitation of **lipid degradants in liposomal drug formulations** (Expand it to include all other lipids that are used in liposomes and lipid nanoparticles, and include the degradant component)
5. Determination of **encapsulated and free doxorubicin in liposomal doxorubicin formulations** (To avoid competing interest with the ongoing ISO standard, we can expand it to another drug of interest, e.g.:
6. **PEG coating and CTAB impurity** assessment **on gold nanorods**

STANDARDSATION CHALLENGES:

- Long process

But we are learning..

- No one "fits it all“-> need of specific methods for each nanoparticle type
- Fractionated environment (harmonisation and coordination highly needed)

Diapositive 30

FG4 indiquer la date et le titre dans le pied de page de chaque slide
Favre Georges; 02/12/2021

JOINING FORCES

Continue to collaborate and link with other international initiatives all together to serve the community with reliable characterization methods able to tackle the new challenges in the field.

ACKNOWLEDGEMENTS

LNE:
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J. D. Clogston, NCI-NCL
L. Calzolai, JRC,
D. Mehn, JRC
R. Mildner, Wyatt
M. Chen, Wyatt
F. Meier, Postonva
R. Drexel

Orthogonal complementary :
B. Nelson, NIST
E. Petersen, NIST
C. Simon, NIST
J. Parot, SINTEF
SE Borgos, SINTEF
X Xu, FDA
M. Roesslein, EMPA
L. Calzolai, JRC

..

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N.J.Liptrott, University of Liverpool
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S.E.Borgos, SINTEF
S.Bremer-Hoffmann, JRC
M. Rösslein, EMPA
K. Spring, bioanalytik-muenster

Quality requirements for nanomedicines:
which role for the European Pharmacopoeia?
7-8 June 2022, Strasbourg, France

Regulatory challenges for complex drug products, including nanomedicines

Jon S.B. de Vlieger, PhD

Coordinator NBCD Working Group

Director BD at Foundation Lygature

June 2022

Jon.deVlieger@lygature.org

Non Biological Complex Drugs working group

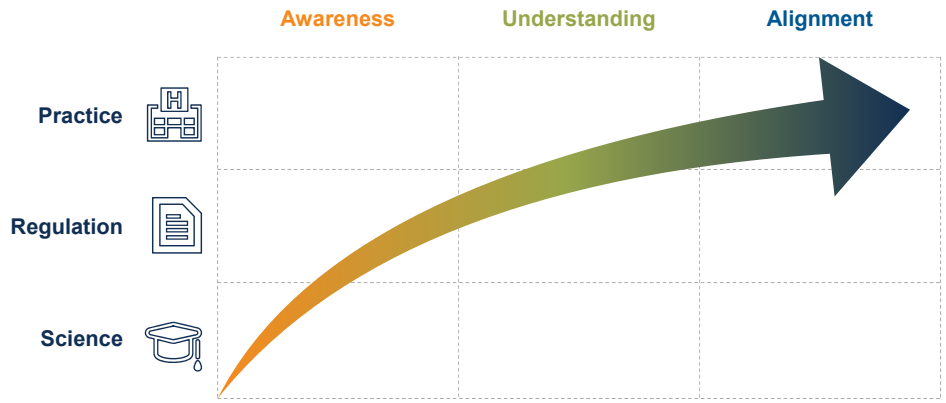
Parts of this presentation were generated within the context of the NBCD Working Group

- The NBCD working group has the mission to ensure that **appropriate *science*-based approval and post-approval standards are created and globally introduced for NBCDs to ensure patient safety and benefit**.
- The Working Group collaborated with many different partners over the years including the Nanotechnology Characterization Lab, Sanofi-Aventis Groupe, Teva Pharmaceutical Industries Ltd., University of Lisboa, Allergan Plc, Abbvie and many more.
- Current partners are the University of Geneva, University of Basel and Vifor International Inc. Hosted by Lygature, a not-for-profit organization based in the Netherlands, the working group consists of experts from industry, academia, and knowledge institutes.
- In addition to in-kind contribution of all partners, funding is provided by our industry partners.

Non Biological Complex Drugs working group

www.NBCDs.info

The Mission & Vision of the NBCD Working Group: From awareness in science towards alignment in practice



Non Biological Complex Drugs working group

We map the issues, engage in discussion and inform policy.

Map the issues

- Patient safety & benefit
- Terminology
- CMC/Manufacturing
- Characterization/CQAs
- PK/PD
- In vivo performance
- Substitution / interchangeability

Engage in discussions

- FDA / EMA / other regulators
- Knowledgeable institutes (e.g. WHO)
- Manufacturers
- Conferences

Inform policy

- Science-based
- Global alignment
- Educational
- Interchangeability?
- Substitution?

Non Biological Complex Drugs working group

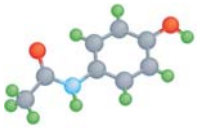
Numerous scientific outputs have been produced by the NBCD Working Group in the last years

- >15 papers
- 3 blogs
- 1 book published

1 Non-biological complex drugs including nanomedicines

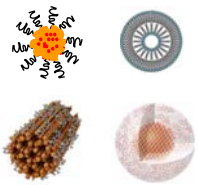
The rise of bio- and nano-technologies has accelerated the development of complex medicines

Conventional drugs



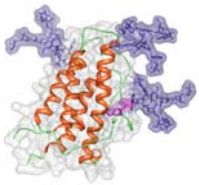
Small molecule drugs
(MW <500d)
e.g. ASA
Fully characterized

(Nano) technology drugs



Complex *(non-biological) drugs*
(MW range 5-900kDa)
e.g. Iron carbohydrates, liposomes
Not fully characterized

Biotechnology drugs



Complex (biological) drugs
(MW range 5-900kDa)
e.g. *mAbs*
Not fully characterized

Non Biological Complex Drugs working group

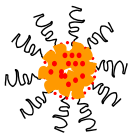
What is an NBCD? (1)

A non-biological complex drug (NBCD)…

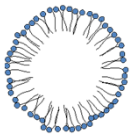
- … is a synthetic medicinal product that is **not a biological medicine**
- … with an active substance that is **not homo-molecular** but contains different (closely related, often nano-particulate) structures
- … that **cannot be fully characterized** by physicochemical analytical means.

A **well-controlled** robust manufacturing process is fundamental to ensure quality, safety and efficacy.

Full definition NBCD:Crommelin et al. Different pharmaceutical products need similar terminology; AAPS J. 2014

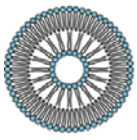


Micelles

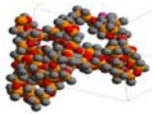


Nanoemulsions

Iron-carbohydrate complexes



Liposomes



Polymers

Non Biological Complex Drugs working group

What is an NBCD? (2)

NBCDs are used to treat a **variety of serious medical conditions** including cancer, auto-immune diseases, infectious diseases, anemia, and more.

Doxorubicin liposomes
- Cancer
- Originator: Doxil® (Janssen)

Glatiramer acetate
- Multiple sclerosis
- Originator: Copaxone® (Teva Pharmaceuticals)

Cyclosporine ophthalmic emulsion
- Chronic dry eye disease
- Originator: Restasis® (Allergan)

Iron sucrose
- Anemia
- Originator: Venofer® (Vifor Pharma)

Sevelamer carbonate
- Control of phosphorus levels (chronic kidney disease)
- Originator: Renvela® (Sanofi)

Patisiran lipid complex injection
- Polyneuropathy caused by hATTR amyloidosis
- Originator: ONPATTRO® (Alnylam)

How do NBCDs compare to other drugs?

	SMALL MOLECULE DRUGS	NBCDs	BIOLOGICS
Molecular weight	Low (<500)	High (range 5-900 kDa)	
Structure	Simple, well-defined	Complex, heterogeneous, defined by manufacturing process	
Modifications	Well-defined	Many options	
Manufacturing	Chemical synthesis	Synthetic technologies *(incl. nanotech)*	Produced in living cells or organisms
Stability	Stable	Generally unstable, sensitive to external conditions	
Immunogenicity	Mostly non-immunogenic	Immunogenicity varies	Mostly immunogenic
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	

Adapted from GaBI Online – Generics and Biosimilars Initiative www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs, based on Declerck and Schellekens.

How do NBCDs compare to other drugs?

	SMALL MOLECULE DRUGS	NBCDs	BIOLOGICS
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	

Adapted from GaBI Online – Generics and Biosimilars Initiative www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs, based on Declerck and Schellekens.

Non Biological Complex Drugs working group

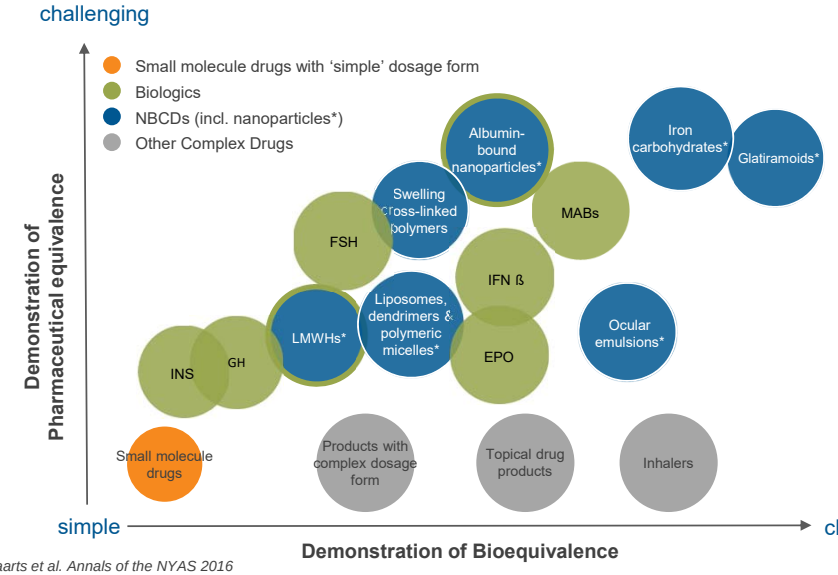
How do NBCDs compare to other drugs?

	SMALL MOLECULE DRUGS	NBCDs	BIOLOGICS
Copy characteristics	Identical copies can be made	Impossible to ensure identical copy versions	
	GENERIC APPROACH *well-established worldwide*	**?**	**BIOSIMILAR APPROACH** *In use and gaining traction*
Authorization of follow-on versions	Pharmaceutical equivalence + Bio-equivalence = Therapeutic equivalence → Interchangeable		Totality of the evidence How similar? Therapeutic alternative? → Interchangeable? Substitutable?

Based on Schellekens et al; Regul Toxicol Pharmacol. 2011 Feb;59(1):176-83.

Non Biological Complex Drugs working group

The complex drug landscape (an impressionist view)

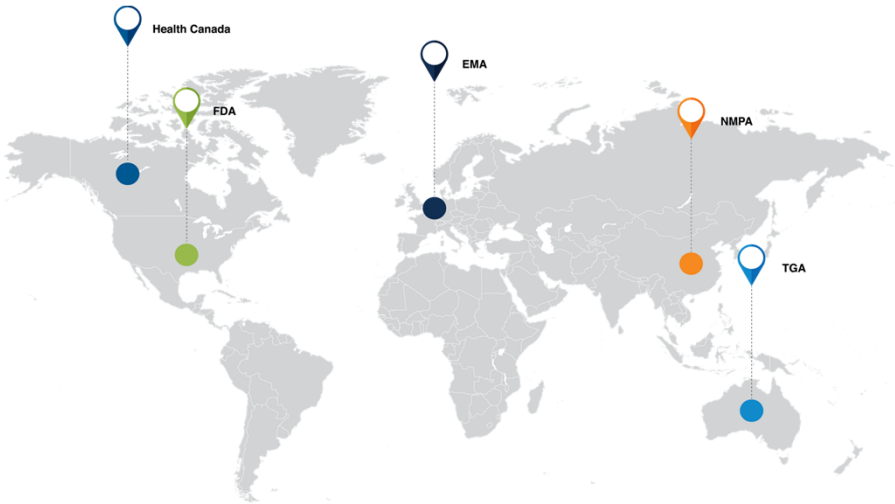


Disclaimer:
This landscape is meant for illustrative purposes only!
The positions are indicative.

Adapted from Hussaarts et al. Annals of the NYAS 2016

Non Biological Complex Drugs working group

Regulatory guidance for complex drugs are being prepared around the globe



Canada
Public consultation of draft guidance by Health Canada

United States
Published guidance for complex medicine developers by FDA

European Union
Published guidance for complex medicine developers by EMA

China
Public consultation of draft guidance by NMPA

Australia
Public consultation of draft guidance by TGA

Disclaimer: This overview is not exhaustive

Non Biological Complex Drugs working group

Product complexity leads to different regulatory approaches worldwide

Doxil® (USA) marketed as **Caelyx**® (EU) by Janssen

Lipodox (Sun Pharma)

FDA (2012): temporarily imported without approval due to shortage of Doxil

DOXOrubicin Sun (Sun Pharma)

- FDA (2013): approved as a generic for Doxil
- EMA (2016): rejected as a generic for Caelyx

Copaxone®
Teva Pharmaceuticals

Glatopa (Momenta)

FDA: approved in 2015 through Generics application based on sameness defined by FDA, without clinical studies

Glatiramer Acetate (Synthon)

EMA: Approved in 2016 through hybrid application, including one Phase III study

Non Biological Complex Drugs working group

Two failed attempts to approve follow-on version of liposomal doxorubicin in the EU are an example of the regulatory challenges

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2016

Withdrawal of the marketing authorisation application

"the CHMP was of the opinion that the studies did not provide enough evidence to show that **Doxorubicin SUN** was similar to the reference medicine [Caelyx]"

31 January 2019

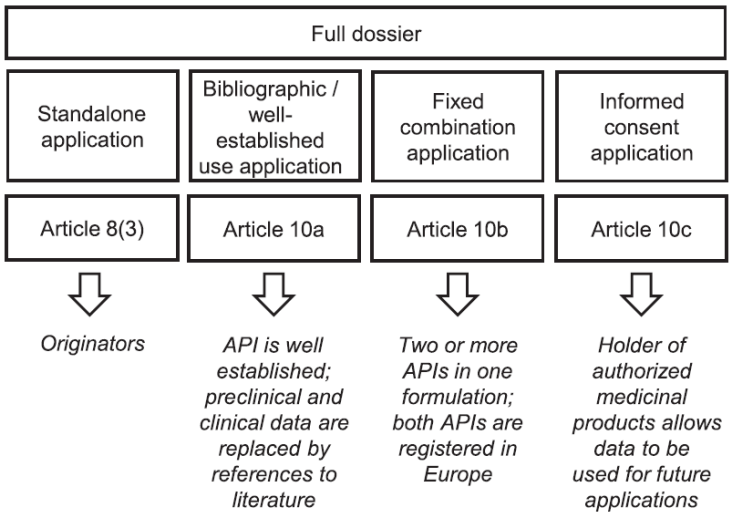
Medicine was refused authorization for use in the EU

"the CHMP was of the opinion that there was insufficient evidence to show that **Doxolipad** was bioequivalent to Caelyx"

Non Biological Complex Drugs working group

2 Framework for approval of (nano) medicines

The framework for approval of (nano) medicines in Europe



From: 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.

Non Biological Complex Drugs working group

National, decentralised or centralised procedures?

Each EU Member State has its own national authorisation procedures

If a company wishes to request marketing authorisation in several EU Member States for a medicine that is outside the scope of the centralised procedure, it may use one of the following routes:

- mutual-recognition procedure, whereby a marketing authorisation granted in one Member State can be recognised in other EU countries;
- decentralised procedure, whereby a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU Member States.

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

Biotech products and ATMPs have to follow the centralised procedure to obtain marketing authorization (EMA)

The centralised procedure is **compulsory** for:

- human medicines containing a new active substance to treat:
  - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
  - cancer;
  - diabetes;
  - neurodegenerative diseases;
  - auto-immune and other immune dysfunctions;
  - viral diseases.
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- orphan medicines (medicines for rare diseases);
- veterinary medicines for use as growth or yield enhancers.

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

Biotech products and ATMPs have to follow the centralized procedure to obtain marketing authorization (EMA)

It is **optional** for other medicines:

- containing new active substances for indications other than those stated above;
- that are a significant therapeutic, scientific or technical innovation;
- whose authorisation would be in the interest of public or animal health at EU level.

What is the benefit of the centralised procedure for EU citizens?

Medicines are authorised in all EU countries at the same time

Centralised safety monitoring

Product information available in all EU languages at the same time

10-6-2022
https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines
Non Biological Complex Drugs working group

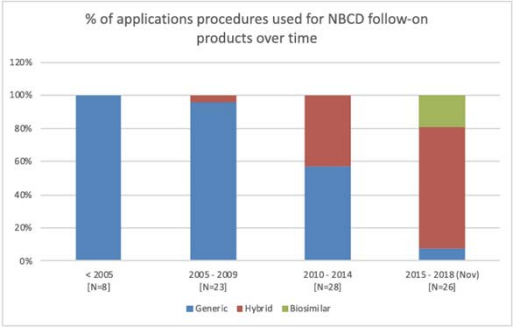
Today, the European regulatory landscape for approval of NBCD follow-on products is heterogenous

European Journal of Pharmaceutical Sciences
Volume 133, 15 May 2019, Pages 228-235

The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations

K. Klein [a, b, c], P. Stolk [a, b, c], M.L. De Bruin [a, d], H.G.M. Leufkens [a, b], D.J.A. Crommelin [e], J.S.B. De Vlieger [b]

Show more



- Time trend analysis in the EU shows an increase of the use of the hybrid application procedure via Article 10(3) for approvals of NBCD follow-on products
- Recent approval of Sucrofer® (a follow-on product for Venofer®) through the hybrid application procedure via Article 10(3), in contrast to previous use of the generic application procedure via Article 10(1), shows a change in the regulatory approach for certain NBCDs in the EU

More consistency in the EU regulatory approach is proposed

European Journal of Pharmaceutical Sciences
Volume 133, 15 May 2019, Pages 228-235

….. NBCDs are currently not recognised as a separate product class, and no distinct regulatory pathway exists for the approval of NBCD follow-on products. This study shows the **variation in the regulatory approaches** for NBCDs and their follow-on products in the EU**, predominantly relying on non-centralised procedures.**

…….. A more consistent approach for regulating NBCDs in the EU could already be achieved by **building on the EMA guidance documents on nanomedicines** and provide an outline on appropriate regulatory pathways for specific NBCD product classes (e.g. generic or hybrid application).

…… Furthermore, like biotechnology-derived products or advanced therapy medicinal products (ATMPs), **NBCDs could also benefit from a mandatory centralised procedure**, as this will **guarantee consistency in the scientific evaluation of follow-on products.**

EMA research priorities include nanomedicines

Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals	▸ Raise awareness of new nanomedicines and materials via the EU-Innovation Network, and foster collaboration with DG JRC and other international partners (e.g. IPRP), to 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 the quality and 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;

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

EMA "nanomedicine" guidance available:

Multidisciplinary: nanomedicines

Share

The European Medicines Agency's scientific guidelines on nanomedicines help medicine developers prepare marketing authorisation applications for human medicines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

- Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product
- Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product
- Development of block-copolymer-micelle medicinal products
- Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

FDA Draft Guidance, issued December 2017

Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

DRAFT GUIDANCE

U.S. FOOD & DRUG ADMINISTRATION

NBCD WG main comments:

- It reads as a white paper
- Deals with NDAs and ANDAs
- Premise renders the document invalid for many products
- Product specific guidance more useful
- CQAs key topic

FDA Draft Guidance, issued December 2017

Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

DRAFT GUIDANCE

U.S. FOOD & DRUG ADMINISTRATION

Line 184-185: Critical point in the text: *'This guidance is based on the premise……'*

(1) *adequate characterization* of the nanomaterial, and

(2) understanding of a nanomaterial's intended use and application, and how the *nanomaterial attributes relate to product quality, safety, and efficacy*, is a suitable framework for evaluating potential risk(s) associated with drug products containing nanomaterials.'

Eleven bullet points then follow ('Factors for Assessment of the Nanomaterial').

Multi-stakeholder discussions lead to clarity and understanding:

The AAPS Journal (2019) 21: 56
DOI: 10.1208/s12248-019-0329-7

Check for updates

Meeting Report

Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: "Drug Products, Including Biological Products, that Contain Nanomaterials"

Jon S. B. de Vlieger,[1,9] Daan J. A. Crommelin,[2] Katherine Tyner,[3] Daryl C. Drummond,[4] Wenlei Jiang,[5] Scott E. McNeil,[6] Sesha Neervannan,[7] Rachael M. Crist,[6] and Vinod P. Shah[8]

Biological Complex Drugs working group

Multi-stakeholder discussions lead to clarity and understanding:

GUIDANCE DOCUMENT

Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry

APRIL 2022

Download the Final Guidance Document | Read the Federal Register Notice

Final

Non Biological Complex Drugs working group

What is next?
How can we prevent divergence of our regulatory approaches worldwide?

What do we need to advance the field?

→ Alignment of science-based regulatory views worldwide

- Better analytical tools for in vitro and in vivo analysis
- Engage all stakeholders in discussions
- Better ways to measure efficacy and safety in the clinic
- Scientific findings published by manufacturers (innovator and follow-on)
- Identification of clinically relevant parameters (the critical quality attributes)

?

NBCD Working Group c/o Foundation Lygature

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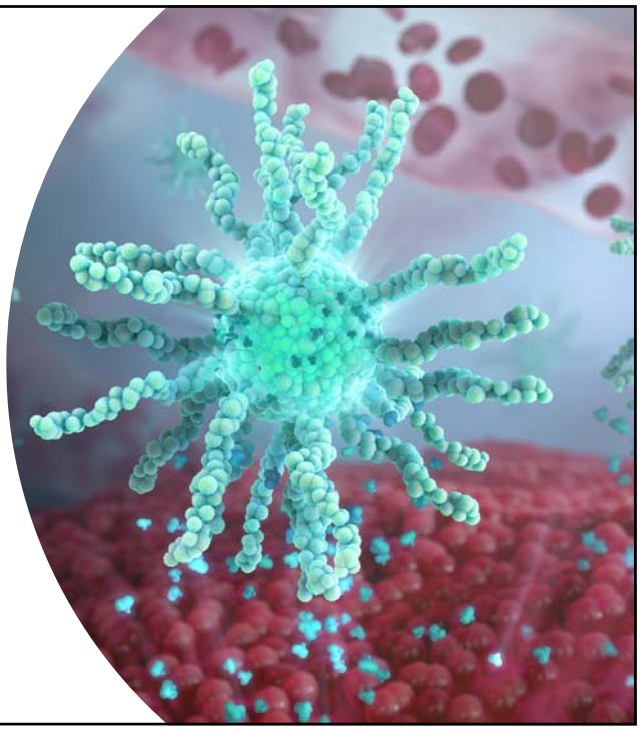
AstraZeneca

Development of nanomedicines through the clinic: a dendrimer conjugate case study



Dr. Silvia Sonzini

Advanced Drug Delivery, Pharmaceutical Sciences, R&D, AstraZeneca, Cambridge, UK

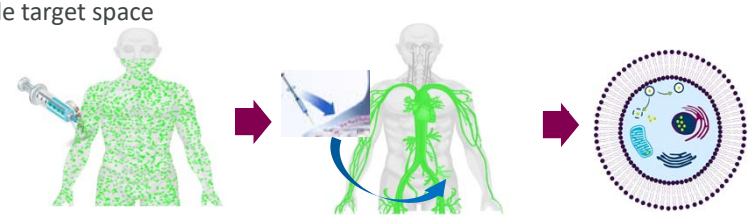
Quality requirements for nanomedicines:
which role for the European Pharmacopoeia?
EDQM – Strasburg - 7th -8th June 2022

Outline

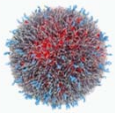
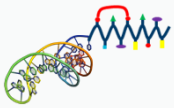
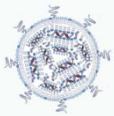
1. Drivers to Nanomeds Development in Oncology
2. Drug-Dendrimer Conjugates and Their CQAs
3. Challenges in Drug-Dendrimer Conjugates Product Characterisation
4. Drug-Dendrimer Conjugates Biocompatibility
5. Overview and Closing Remarks

Advancing Targeted Drug Delivery

- To improve therapeutic index
- To expand druggable target space

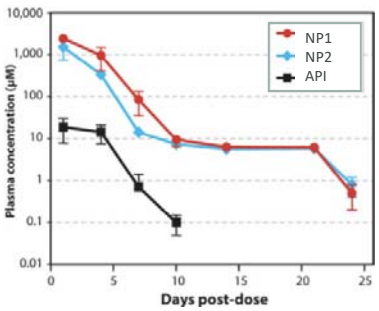


DELIVERY TECHNOLOGIES

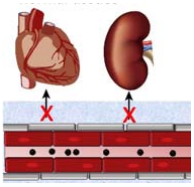
Polymeric Nanoparticles	Poly-L-Lysine Dendrimers	Antibody-Drug Conjugates	Peptide-Drug Conjugates	Lipid Nanoparticles (LNP)	Exosomes
					

Designing Nanomedicines to Improve the Therapeutic Index (TI) of Small Molecule Oncology Agents

Prolonging plasma circulation

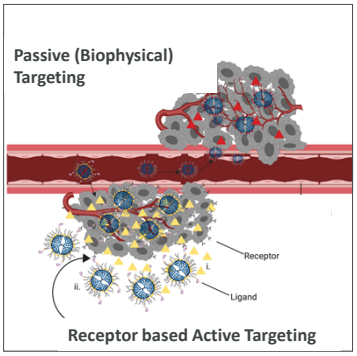


Minimise exposure to normal tissues

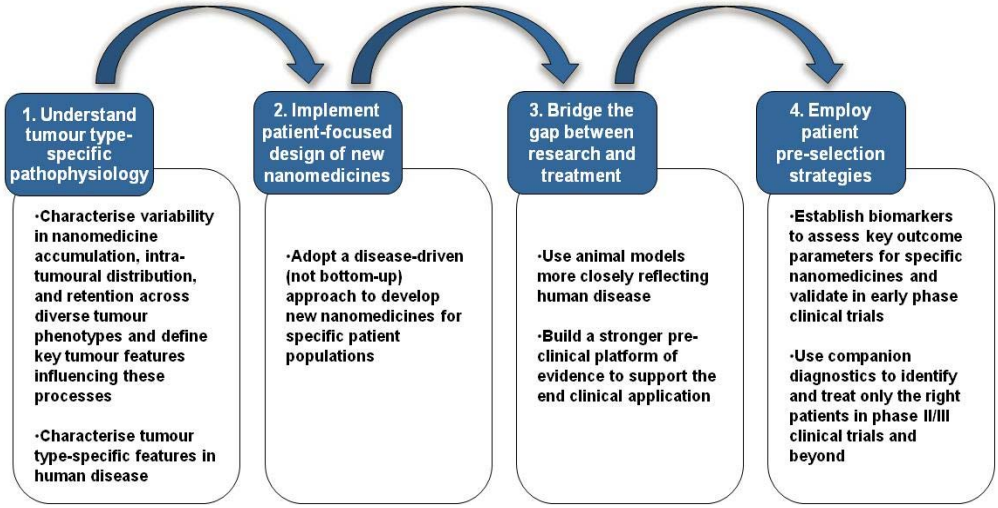


Decrease exposure in healthy tissues/organs

Improve accumulation in tumours via passive or active tissue targeting



Improving the Translation of Nanomedicines



Hare J. et al.
Challenges and Strategies for anticancer nanomedicine development – An Industry Perspective
Advanced Drug Delivery Reviews, May 2016

AZ 5R framework has guided scientific rigor to ask the 'killer' questions

Identifying the **right target**

Making sure our molecule gets to the **right tissue** where it is needed

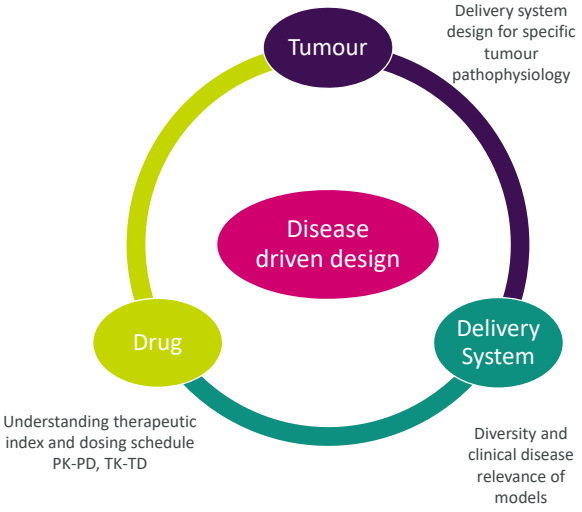
Ensuring **right safety** with minimal side effects

Selecting the **right patients** that will benefit

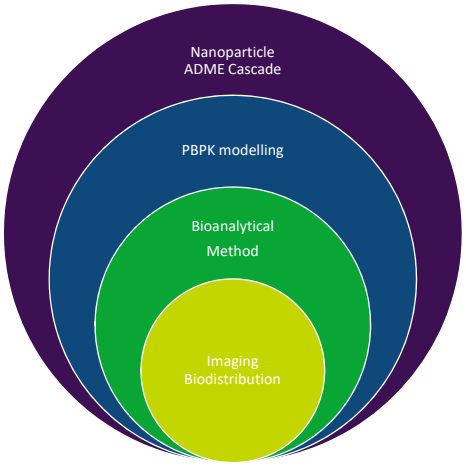
Defining the **right commercial** value and future viability

Underpinned by the **right culture** of truth-seeking behaviours and scientific rigor

Designing Nanomedicines in Oncology



Improving translation of nanomedicines testing cascades

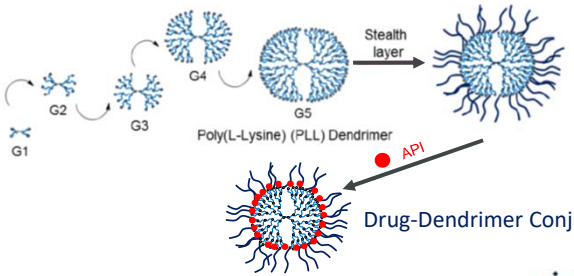


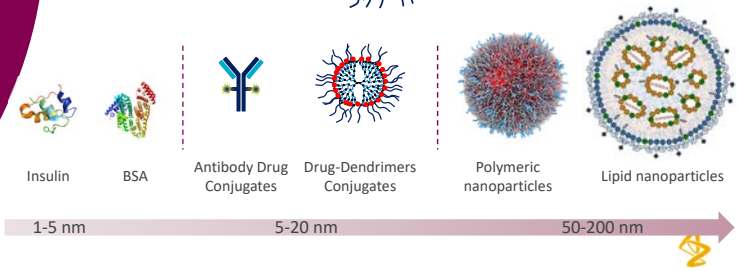
2

Introduction to Drug-Dendrimer Conjugates and Their CQAs

What are dendrimers?

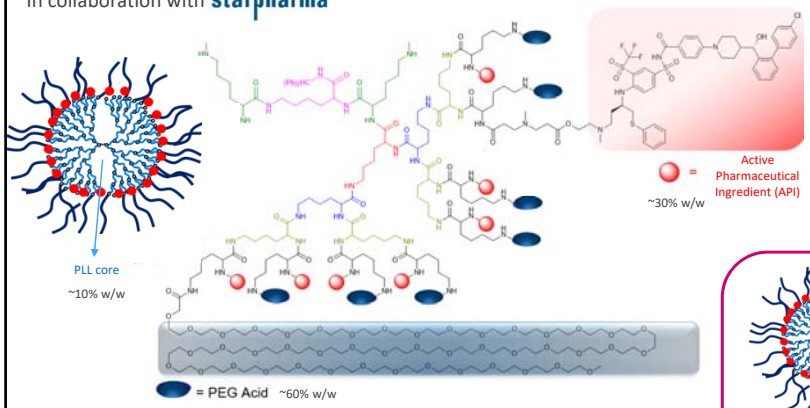
Branched polymers, usually monodispersed, highly symmetric



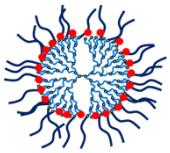


Overview of AZD0466 Drug-Dendrimer Conjugate

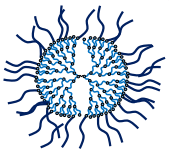
In collaboration with starpharma



Particle description	• Poly-L-Lysine (PLL) G5 core • PEGylated stealth layer
Key platform attributes	• Size : 15-20 nm • Drug loading: covalent conjugation • Release: linker chemistry



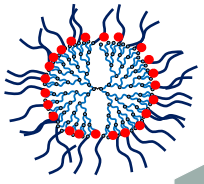
3 AZD0466 batches: B1,B2 and B3



Blank Dendrimer: Same dendrimer but no API

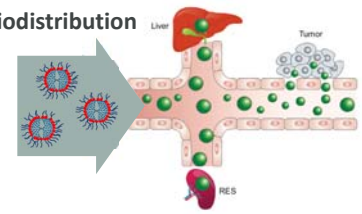
Patterson, C.M., Balachander, S.B., Grant, I. et al. Design and optimisation of dendrimer-conjugated Bcl-2/xL inhibitor, AZD0466, with improved therapeutic index for cancer therapy. Commun Biol 4, 112 (2021). https://doi.org/10.1038/s42003-020-01631-8

Dendrimers Physico-Chemical CQAs and Their Impact



Shelf Life

Biodistribution



Safety and Efficacy

How to address CQA through the development cycle?

Quality Control (QC) Testing

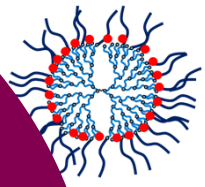
- Tests must be performed in each preclinical and clinical batch
- Desire for quick and cheap characterisation techniques, often batch techniques
- Might not detect small differences and/or identify root cause

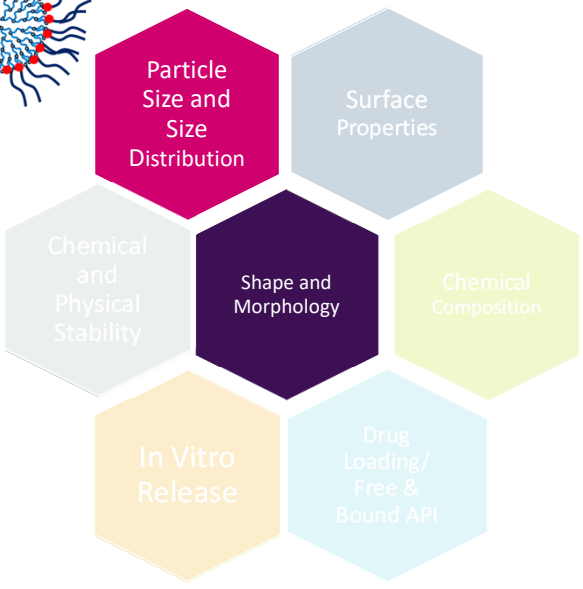
Orthogonal and Advanced Characterisations

- In-depth analysis, usually involving separation techniques
- Requiring method development for each product
- Can measure variations amongst batches and identify root cause
- Used ‘early’ to understand product and ‘late’ for bridging studies (e.g. bioequivalence)

3

Challenges in Drug-Dendrimer Conjugates Product Characterisation

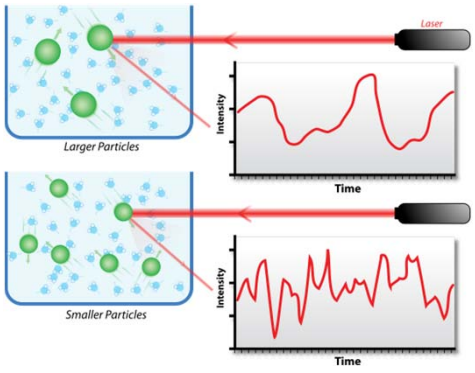




Batch Orthogonal Techniques for Size and Size Distribution: Basics of and Comparison between DLS and TDA

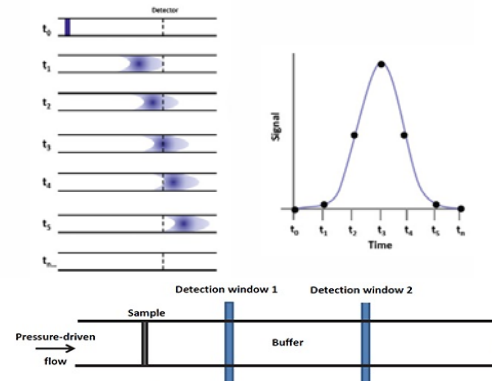
Dynamic Light Scattering (DLS)

Size-based detection based on scattering intensity



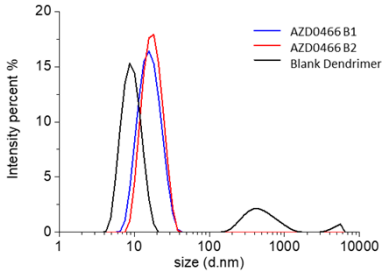
Taylor Dispersion Analysis (TDA)

Mass-based detection *via* UV absorption



Drug-Dendrimers Conjugates Show Similar Properties by Orthogonal Batch Techniques

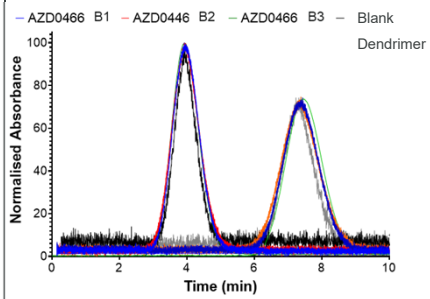
DLS of AZD0466 batches and Blank Dendrimer



Dendrimer without API is smaller and minor differences detected among batches

Sample		AZD0466 B1	AZD0466 B2	Blank Dendrimer
Particle size (nm)	DLS (D_h)	15 (1)	17 (1)	11 (1)
	TDA (D_h)	15 (0.4)	17 (0.4)	11 (0.3)

TDA of AZD0466 batches and Blank Dendrimer

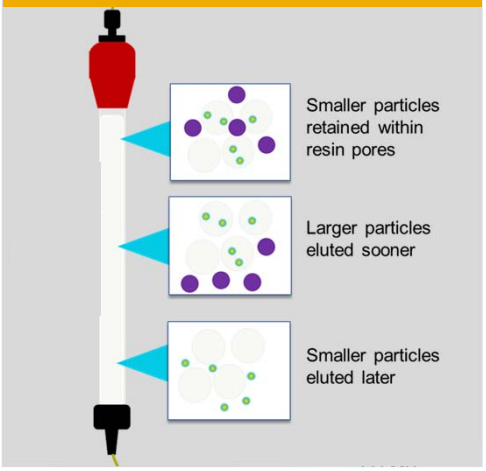


DLS and TDA are equivalent techniques even at this size range

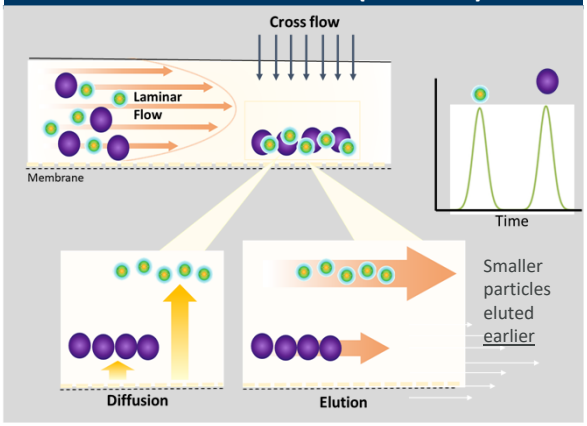
In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

Advanced Characterisation: Orthogonal Separations Techniques

Multi-detector Size Exclusion Chromatography (MD-SEC)



Multi-Detector Asymmetric-Flow Field Flow Fractionation (MD-AF4)

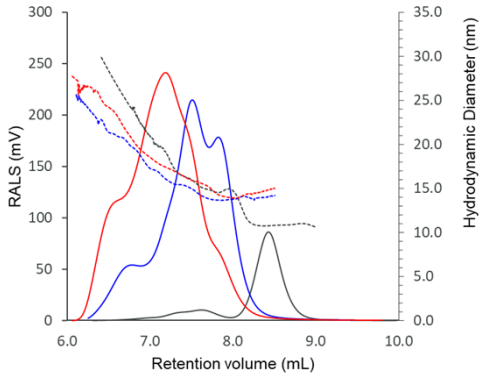


Orthogonal Separation Techniques, Conforming and Confirming

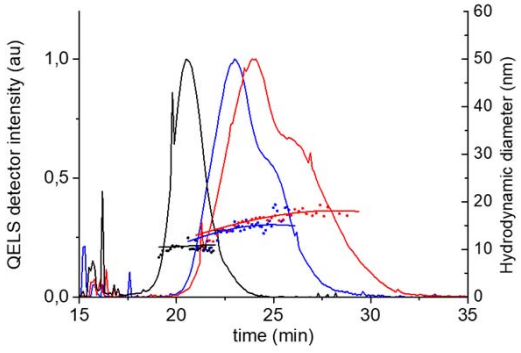
- *The two techniques are equivalent for Drug Product (DP)*
- *Agreement with batch techniques*
- *Batches differences are now more visible*

AZD0466 B1
AZD0466 B2
Blank Dendrimer

MD-SEC

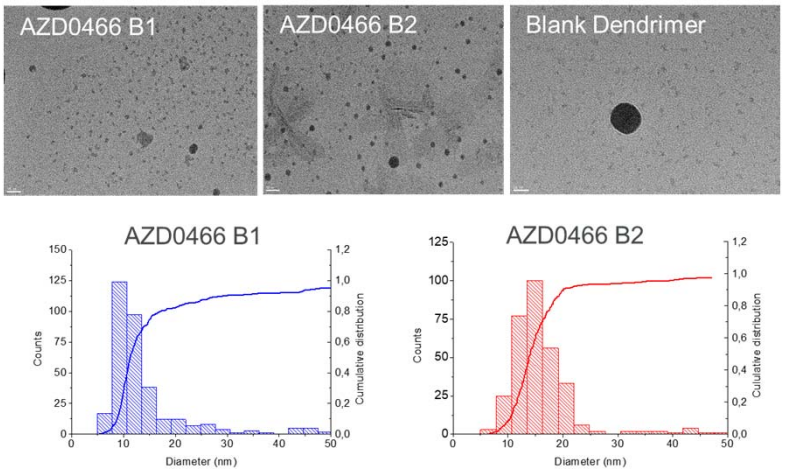


MD-AF4



In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

Morphology and Single Molecule Size Distribution - A Challenging Task for Drug-Dendrimer Conjugates



Using Transmission Electron Microscopy (TEM) for further in-depth characterisation

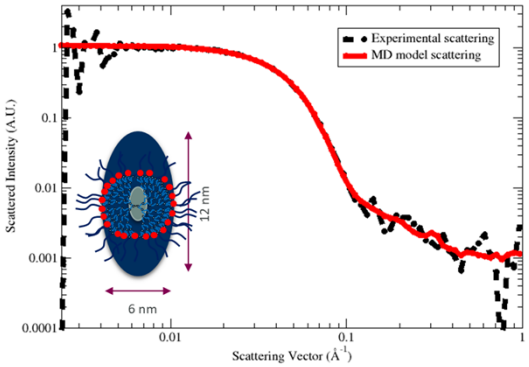
Full agreement with MD-SEC and AF4

No morphology information extracted

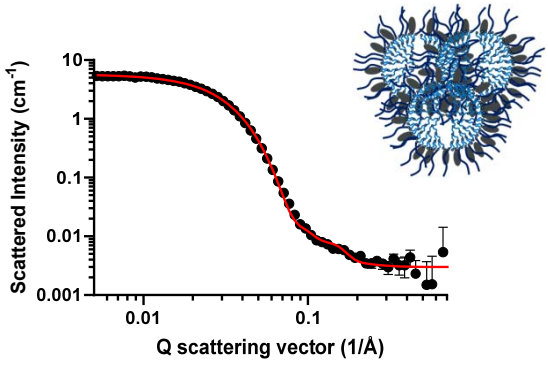
In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

Small-Angle Neutron Scattering Can Resolve Shape on Drug-Dendrimer Conjugates

Measurements in MeOH, informing on size and shape of monomeric AZD0466



Measurements in PBS, Informing on size and shape of oligomers (physical aggregates)



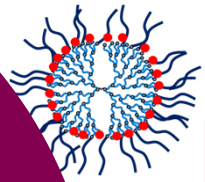
	Diameter (nm)	Aspect ratio
MeOH (monomer)	7	1.5
PBS (oligomers)	12	1.4

In collaboration with Najet Mahmoudi (ISIS) and Jayne Lawrence (Uni of Manchester)

Science & Technology Facilities Council ISIS Neutron and Muon Source

4

Drug-Dendrimer Conjugates Biocompatibility

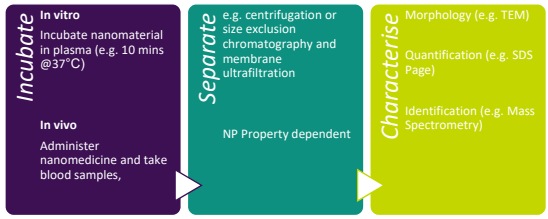


Nanomaterials Stability and Biocompatibility is Pivotal but Lacking in Standardisation

Parenteral nanomaterials interacts with plasma components potentially forming a protein corona

- The protein corona can affect targeting and recognition by the mononuclear phagocyte system, affecting nanomedicines biodistribution
- Protein adsorption can affect size and zeta potential, and is a dynamic process
- Researchers have found differences in the investigation of the protein corona in vitro/in vivo (fibrillation, targeting, richer corona in vivo).
- *How relevant is protein corona to all nanoparticles? And how should it be assessed?*

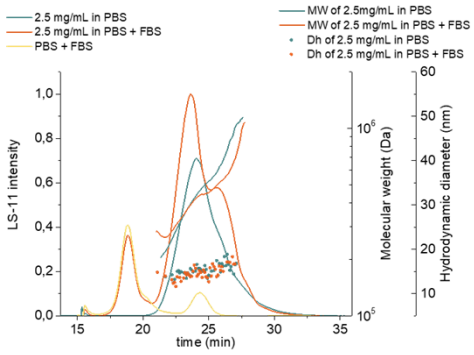
Protein Corona characterisation is highly nanoparticle dependent and not standardised



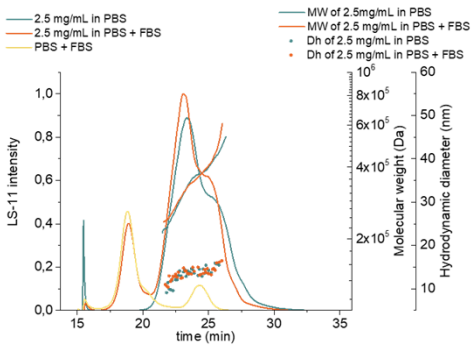
Challenges of Measuring Physical Stability in Complex Media

Due to similar size it is not possible to completely separate AZD0466 from proteins with standard techniques

AZD0466 B1



AZD0466 B2

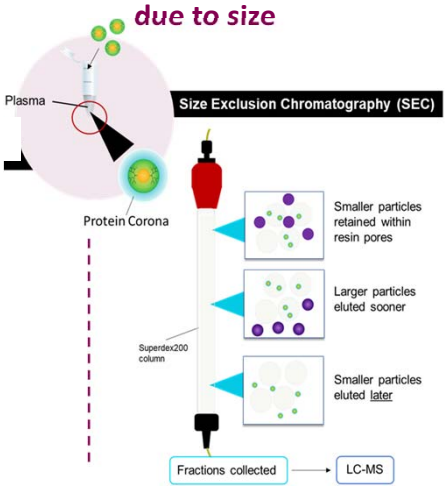


Data in complex media do overall suggest AZD0466 is physically stable in complex media

In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

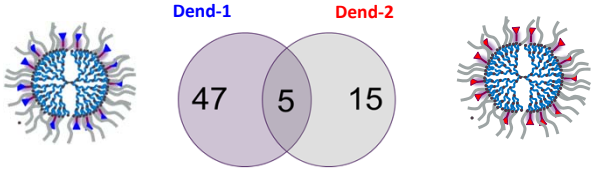
In Vitro Evaluation of Dendrimer Platform Protein Corona

Challenging purification method *due to size*



Mass-Spec analysis shows low protein abundance but API based differences

Dend-1 and Dend-2 have same platform composition but conjugated to different APIs



In Vitro Release and How to Make it Biorelevant

- **Important to understand release mechanism**

  e.g. bond cleavage vs. diffusion, pH and temperature dependence, concentration and surfactant effects

- **Identify cross species translation and sources of variability**

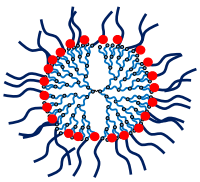
  Important for input to mechanistic in silico models to predict PK

- **Media selection to be biorelevant**

  "In sink" considerations and use of plasma

- **Analytical method is highly dependent on nanoparticle properties**

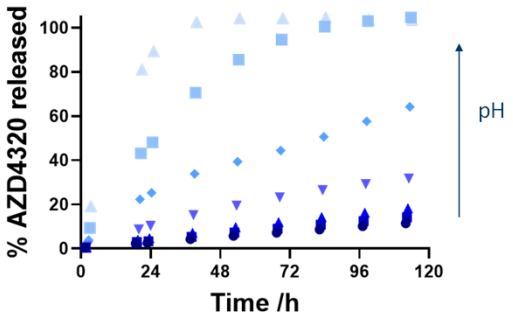
  Is a prep method required ahead on API analysis?



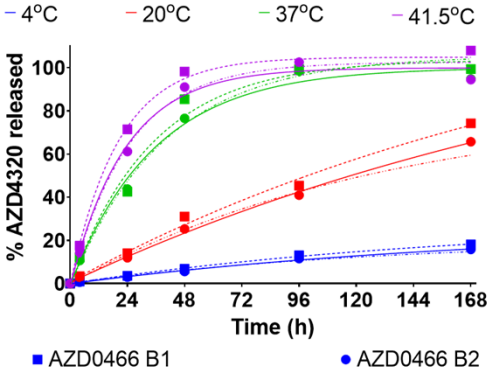
Specification vs. CQA – highly dependent on nanoparticle release mechanism

AZD0466 Release Rate is Dependent on pH and Temperature

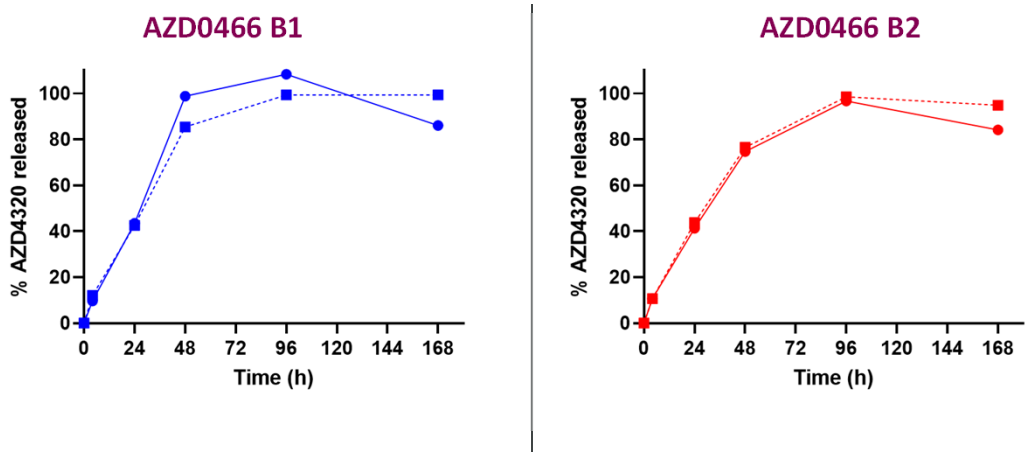
Increasing pH , faster release



Temperature has large effect on kinetic



In Vitro Release (IVR) as Assay to Confirm Chemical Equivalence and Stability of Different Drug-Dendrimer Conjugates Batches

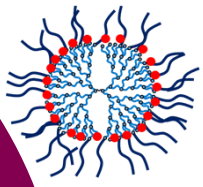


Solid lines PBS pH 7.4 and dashed lines human plasma.

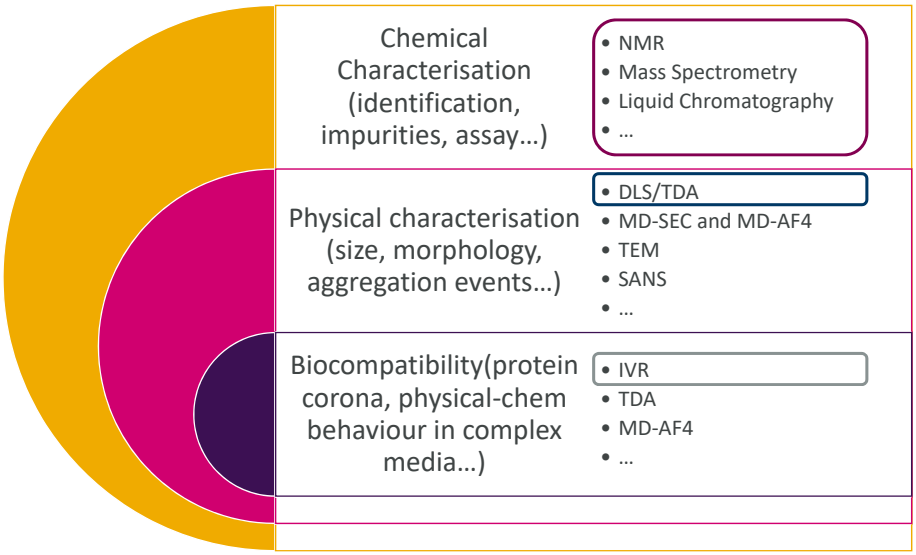
In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

4

Overview and Closing Remarks



Cascade for CQAs of Drug-Dendrimer Conjugates



- *Repeated on each batch preclinically and clinically*
- *Some required for each batch*
- *In depth techniques as chain management*
- *Biopharmaceutics assay*
- *Support for bridging studies*

Acknowledgements

AstraZeneca

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Paul Devine
Hannah Williamson
Maria Stavrou

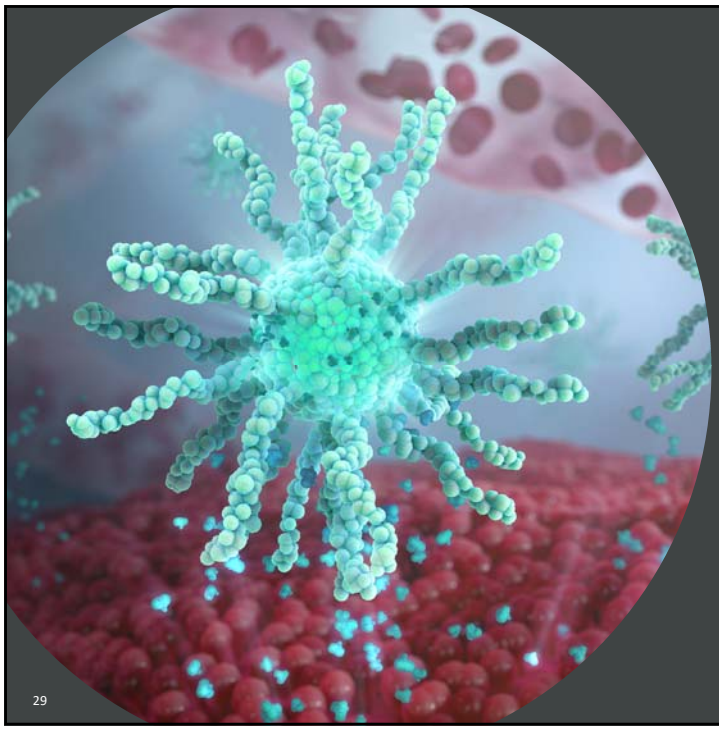
…and the all AZD0466 CMC Team

European Nanomedicine Characterisation Lab (EUNCL)

EUNCL Nanomedicine Characterisation Laboratory

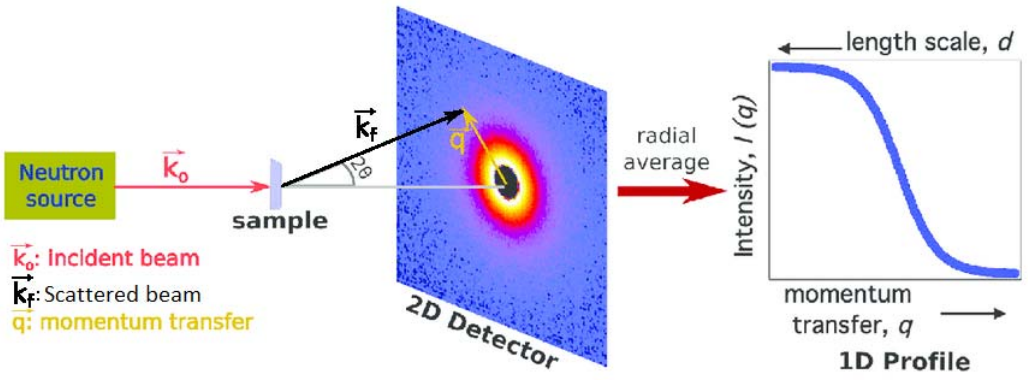
Fanny Caputo
Dora Mehn
Luigi Calzolai
Sven Even Borgos
Astrid Hyldbakk

starpharma



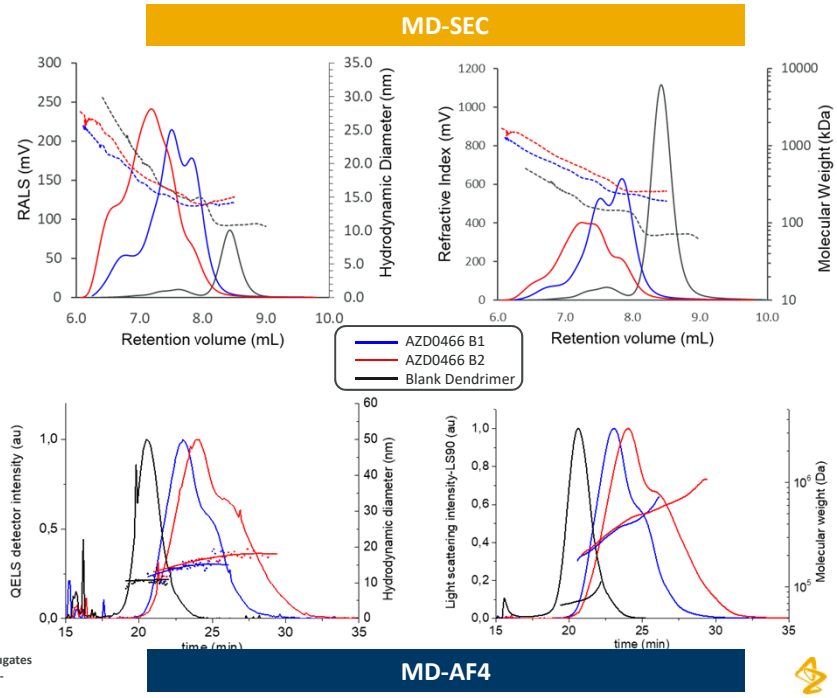
Thank you.

Neutron Scattering – Internal Structure



Orthogonal Separation Techniques, Conforming and Confirming

- *The two techniques are equivalent for Drug Product (DP)*
- *Agreement with batch techniques*
- *Batches differences are now visible*



In-depth physical-chemical characterisation of dendrimer conjugates via orthogonal techniques of Critical Quality Attributes (CQAs) - Manuscript submitted

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
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Quality requirements for nanomedicines: which role for the European Pharmacopoeia?

Liposomal formulations and nanosimilars

Prof. Dr. Scott E. McNeil

8 June 2022

Universität Basel

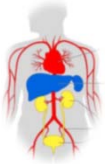
DEPARTMENT OF PHARMACEUTICAL SCIENCES

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.

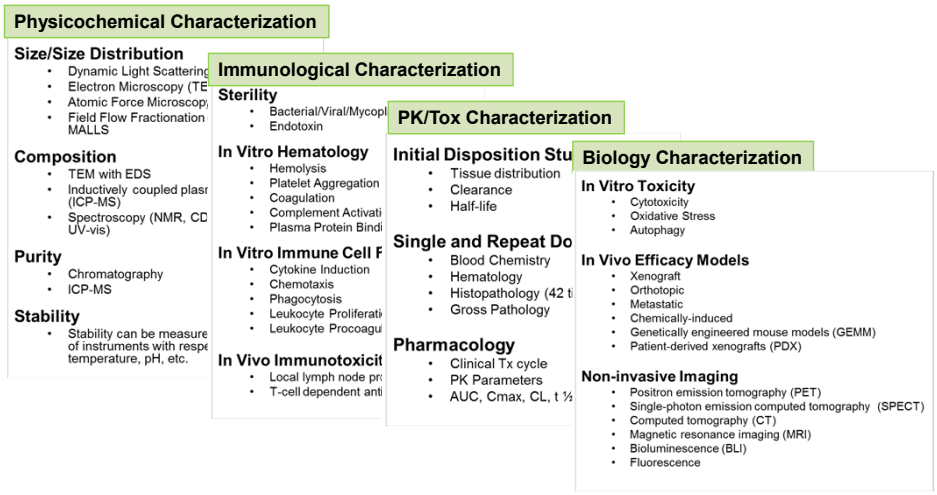
2

Characterisation

Universität Basel
Departement
Pharmazeutische Wissenschaften

3

Nanomedicines: preclinical characterisation



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

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Physicochemical characterisation (PCC)

- PCC for nanoparticles differs from traditional formulations

  Non Biological Complex Drugs: NBCDs are fully synthetic materials that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means.

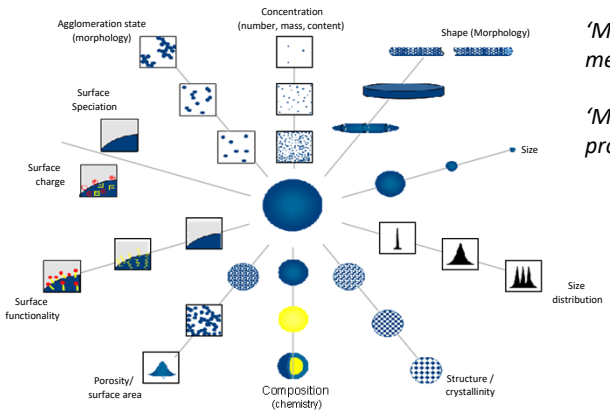
- Nanoparticle surface properties directly influence biocompatibility / PK


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2013
EMA/325027/2013
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

Challenges in physicochemical characterization (PCC)



'Metrology': the science of measurement

'Measurand': physical property that is measured

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

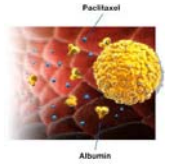
Nanomedicines: they're complex...

Physicochemical properties of the nanoparticle influence the drug's pharmacokinetics and biocompatibility

For nanomedicines, the **Active Pharmaceutical Ingredient** (API) may include components that were previously considered as excipients

Package insert for TAXOL

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.



Package insert for ABRAXANE

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is a white to yellow, sterile lyophilized powder supplied as:

NDC : 68817-134-50 100 mg of paclitaxel in a single-dose vial, individually packaged in a carton.

For ABRAXANE, all components are considered as the API

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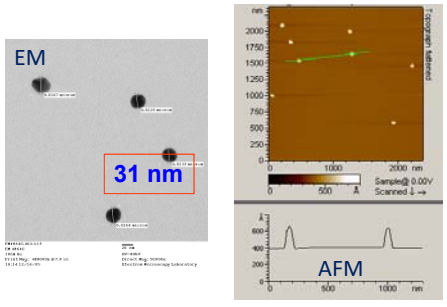
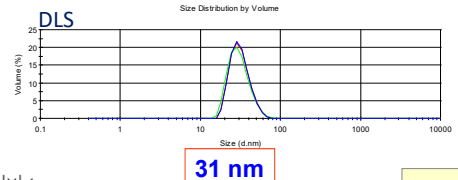
Size in a biological context: 'measurand'

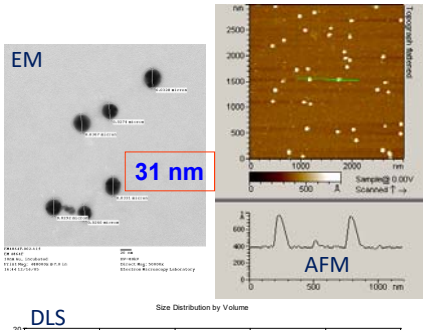
30 nm Gold colloids

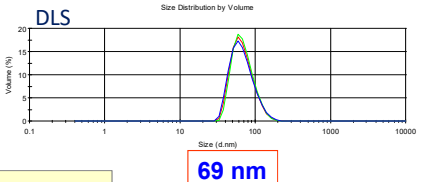




31 nm

30 nm Gold colloids incubated in plasma





69 nm

DLS size ≠ EM size

Dobrovolskaia et al., "Nanomedicine: Nanotechnology, Biology, and Medicine 5, no. 2 (June 2009): 106-117.

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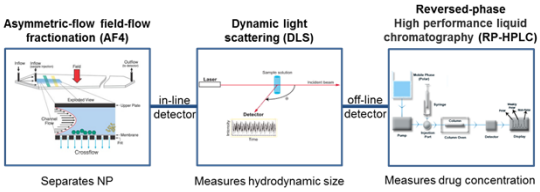
Physicochemical analytics, liposomes

Nanomaterials are inherently heterogenous
- in contrast to small molecules

'Hyphenated' methods

- AF4 separates size populations, defines polydispersity
- Various in-line/off-line detectors can define drug/ligand distribution

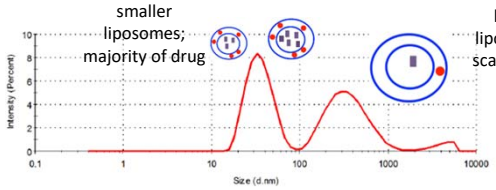


Dual drug loaded liposomes

Batch-mode DLS reveals heterogenous size population... so where are the drugs?

smaller liposomes; majority of drug

larger liposomes; scarce drug



AF4 – DLS – HPLC – UV/Vis

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In-line / hyphenated methods allow the investigator to correlate NP size with the API

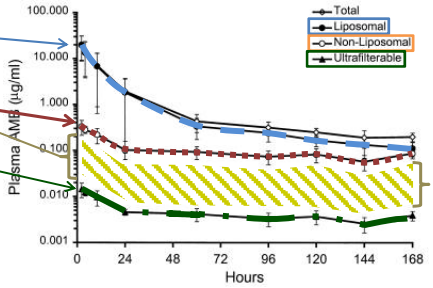
Source: Jeff Clogston, NCL

Bioanalytics (pharmacokinetics)

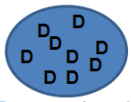
Nanomedicine drug fractions in circulation[1]:

I. NM encapsulated fraction

II. Unencapsulated fraction
- protein bound fraction
- unbound fraction



D = drug



D ⟷ Protein-D

Encapsulated | Free/Unbound | Protein Bound

Unencapsulated

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1. Ambardekar, Vishakha & Stern, Stephan. (2015). NBCD Pharmacokinetics and Bioanalytical Methods to Measure Drug Release. 10.1007/978-3-319-16241-6_8.

More definitions...

Q: how does the 'innovator' nanomedicine compare with its generic version?

Non Biological Complex Drugs

NBCDs are fully synthetic materials that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. This class includes nanomedicines.

Non Biological Complex Drugs working group

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Equivalence of complex drug products: advances in and challenges for current regulatory frameworks

Leonie Hussaarts,[1] Stefan Mühlebach,[2] Vinod P. Shah,[3] Scott McNeil,[4] Gerrit Borchard,[5] Beat Flühmann,[6] Vera Weinstein,[6] Sesha Neervannan,[7] Elwyn Griffiths,[8] Wenlei Jiang,[9] Elena Wolff-Holz,[10] Daan J.A. Crommelin,[11] and Jon S.B. de Vlieger[1]

Critical Quality Attributes

"A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."

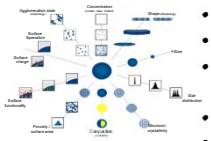
FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry

Q8(R2) Pharmaceutical Development

The importance of defining CQAs

Nanomaterial physicochemical properties greatly influence biocompatibility, but are often challenging to measure, identify.



- Size
- Composition
- Surface coating attachment/density/orientation
- Surface charge
- Shape/architecture
- Stability
- Purity

CQAs

- Pharmacokinetics
- Biodistribution
- Clearance
- Toxicity
- Efficacy
- Bioaccumulation

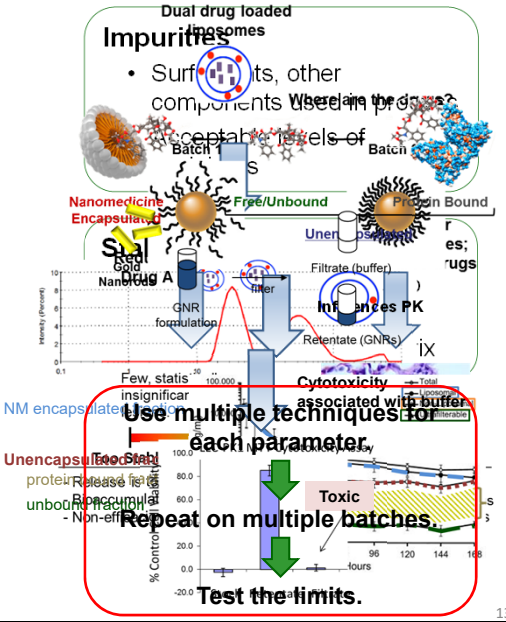
Liposomal CQAs

Image source: NCL

Polydispersity
- Upper and lower limitations on size, shape populations
- Drug/ligand distribution across fractions

Surface Coating
- Total, bound and unbound ligands
- Density, orientation, activity

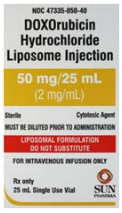
Drug Release
- Free vs. NP-bound vs. protein-bound drug
- Biologically relevant matrix



The importance of CQAs: "nanosimilars"

- Doxorubicin HCl Liposome Injection, a generic version of Doxil, was approved by the FDA (2013).

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.



More generics / follow-on's are coming!

- Merrimack/Actavis(Teva subsidiary)'s generic doxorubicin hydrochloride liposome injection is currently under FDA review.
  - Rights to "generic Doxil" sold to Ipsen in 2017.
- Sorrento Therapeutics completed a bioequivalence study of Cynviloq against nab-paclitaxel (Abraxane).
  - NantWorks acquired rights to Cynviloq in 2015.

MERRIMACK PHARMACEUTICALS

SORRENTO THERAPEUTICS

Regulatory: which pathway?

If an investigator develops a LNP formulation 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(j)	505(b)(**1**)
Cost for development:	€€€€	€

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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 → NCE

Novel polymers or lipids may require extensive Tox evaluation

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Regulatory: 'follow-ons' and nanosimilars

For previously approved drugs, the 'sponsor' can submit a generic / 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.

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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

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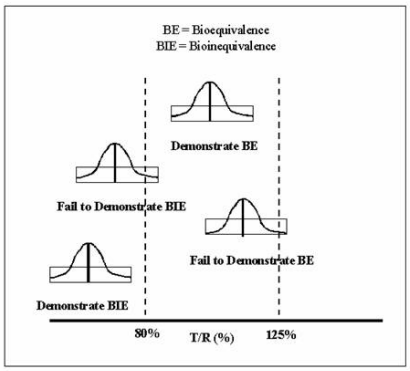
Biological equivalence (BE)

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*

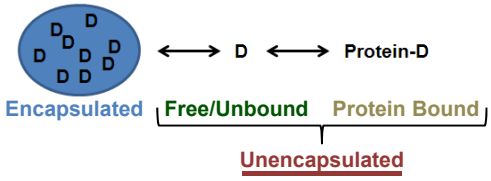
Evaluates **BE** for 'Sun' liposomal doxorubicin with Caelyx®

Sun drug

Reference listed drug (**RLD**)

PE studies showed equivalence, and will not be discussed here

D = drug



*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 / 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%.

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

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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 bioequivalence criteria. Therel test and reference product ha

d Cmax are not within 80.00-125.00% standard lence of free (un-encapsulated) doxorubicin between the ablished.

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BE not achieved. Likely failed due to statistical power / sample size (n=23).

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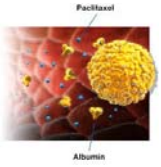
Regulatory: nanosimilar vs. novel formulation

- Previous example was liposome compared to liposome, both with the same API
  - EMA refers to this as a 'nanosimilar'
- But...what about a novel nanoformulation vs. a traditional /non-nano drug?
  - Abridged pathway can still apply, **if** the API is already approved
  - E.g. Abraxane was approved through 505B(2). Taxol was the RLD

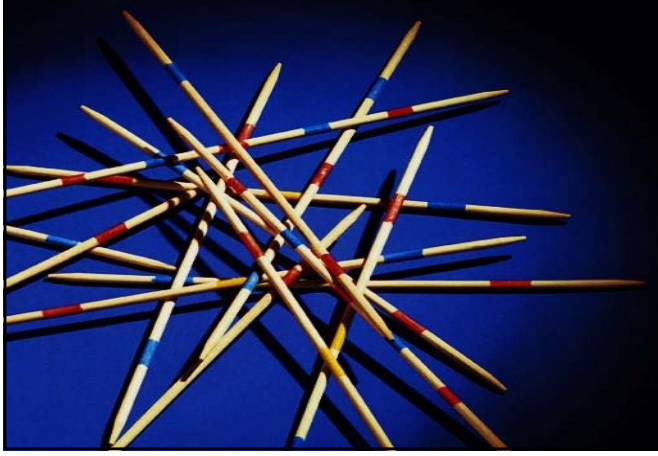


Conclusions

- Nanomedicine is no longer the 'new kid'
  - Dozens approved for clinical practice, hundreds in clinical trials
- Generic versions / nanosimilars are now approved
  - Now we are parents with kids...
- Nanomedicines are NBCDs, and cannot be fully defined by P/C methods
- Identifying CQAs allows for QA, and to compare nanosimilars
- Regulatory: Full dossier, Generic and Abridged applications
- May need to revise the definition of excipient

Prof. Dr. Scott McNeil
Tel: +41 61 207 6404
Email: scott.mcneil@unibas.ch

The challenge of manufacturing complex nanomedicines: learnings from two decades of physicochemical iron carbohydrate characterization



Dr Beat Flühmann

Global Lead Nanomedicine
Vifor Pharma Ltd CH

Steering Committe Member
NBCD Consortium Lygature NL

Comparative efficacy and safety of IV iron preparations

Published head-to-head studies – same dosing regimen

● Efficacy
△ Safety, overall
▲ Safety, specifics
■ Laboratory parameters

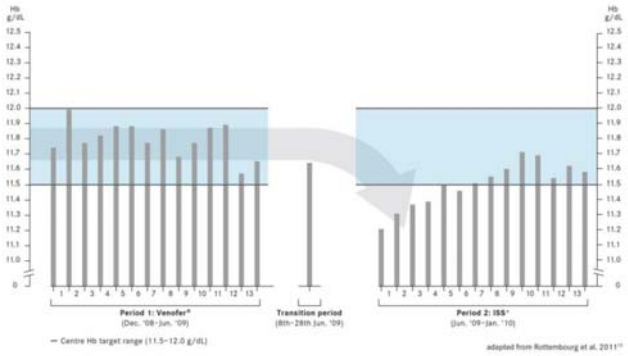
	Agarwal 2007	Pai 2007	Pai 2011	Stefansson 2011	Malindretos 2007	Wolf 2013	Roberts 2016	Sav 2007	Argawal 2011	Louzada 2016	Bhandari 2015
Equivalent results					■	● △		△			
Differing results	■	■	■	■		■	■		■	△ ▲	● △
Comparators											
FCM						❍	❍				
IS	❍	❍	❍	❍	❍		❍	❍	❍	❍	❍
SFG	❍	❍							❍		
FMX											
IIM											❍
LMW-ID		❍	❍	❍				❍			
HMW-ID					❍	❍				❍	
ID (other)											

N~10 — Number of subjects in study — N~60 — N~350

FCM, ferric carboxymaltose; IS, iron sucrose; SFG, sodium ferric gluconate; FMX, ferumoxytol; IIM, iron isomaltoside 1000; LMW-ID, low-molecular weight iron dextran; HMW-ID, high-molecular weight iron dextran; ID (other), other iron dextran

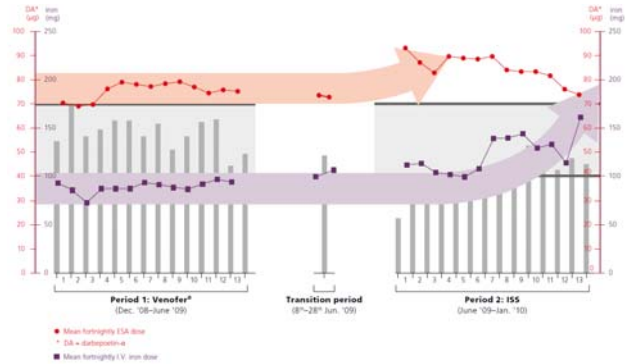
Same Composition Different Manufacturer Therapeutically Equivalent?

- Mean Hb value 11.78±0.99 g/dL vs 11.48±0.98 g/dL (P1 vs P2; p=0.01)



Same Composition Different Manufacturer Therapeutically Equivalent?

- 34.6% increase in I.V. iron during P2 vs. P1 (p=0.001)
- 12.6% increase in mean ESA dose P2 vs. P1



Same Composition Different Manufacturer Therapeutically Equivalent?

VIFOR PHARMA

Table 3. Stability, efficacy and cost criteria results.

Clinical criteria	Period 1	Period 2	p-value
Stability criteria	mean ± SD	mean ± SD	
Red blood cells (T/L)	3.60 (0.45)	3.63 (0.40)	0.89
Leucocytes (G/L)	6.97 (2.19)	6.80 (2.02)	0.61
Platelets (G/L)	206.34 (64.71)	202.91 (59.91)	0.22
Albumin (g/L)	35.87 (3.57)	36.36 (4.99)	<0.001*
Kt/V	1.655 (0.214)	1.665 (0.207)	0.48
Number of hemodialysis sessions per patient	67.6 (12.81)	67.1 (13.75)	0.73
Efficacy criteria	mean ± SD	mean ± SD	
Hb (g/dL)	10.93 (1.01)	10.94 (0.95)	0.92
Serum iron (µmol/L)	10.87 (3.44)	10.14 (2.77)	0.07
Serum ferritin (µg/L)	433.17 (206.57)	312.53 (183.32)	<0.001*
Transferrin (g/L)	1.86 (0.37)	1.93 (0.44)	<0.001*
TSAT (%)	24.25 (8.43)	21.44 (7.19)	<0.001*
CRP (mg/L)	13.76 (18.35)	10.68 (11.40)	<0.001*
Dose of IV iron (mg/week)	56.90 (20.83)	59.52 (2.08)	0.41
Dose of ESA (µg/week)	40.73 (27.49)	52.42 (38.55)	0.002*
Number of off-target Hb values	6.98 (5.32)	7.25 (6.28)	0.89
Number of Hb below target values	4.81 (5.80)	4.85 (6.49)	0.84
Number of Hb above target values	2.17 (3.02)	2.40 (3.56)	0.75

NBCD

Arnaud Pagès et all. (2019) Expert Review of Pharmacoeconomics & Outcomes Research, DOI: 10.1080/14737167.2019.1632193

Manufacturing defines the product

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

Nanomaterials are engineered and manufactured to elicit novel product properties and clinical outcomes. The quality, safety, or efficacy of drug products containing nanomaterials can, however, be very sensitive to process conditions and production scales. Moreover, environmental controls should be established early in the development stage to prevent cross-contamination. This type of process and scale dependency, coupled with inherent polydispersity of some nanomaterials, makes it a priority to assess the risk to quality associated with the nanomaterial attributes, and develop adequate detectability of both nanomaterial and process failures at the development stage. As such, the earlier that CQAs can be identified during development, the more quickly in-process controls can be designed and implemented in the manufacturing process. A well-disciplined design control approach can generate key process knowledge, especially for those areas where, in the absence of comprehensive understanding, variability is not predictable, scale effects are unknown, and where results cannot be extrapolated or interpolated to demonstrate safety and efficacy.

NBCD

Draft Guidance, issued December 2017; 1–25.

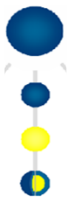
BUSINESS USE

FDA's factors for assessment of nanomaterials

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

1. Adequacy of characterization of the material structure and its function
2. Complexity of the material structure
3. Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects (eg effect of particle size on PK parameters)
4. Understanding the in vivo release mechanism based on the material physicochemical properties
5. Predictability of in vivo release based upon established in vitro release methods
6. Physical and chemical stability
7. Maturity of the nanotechnology (including manufacturing and analytical methods)
8. Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product
9. Physical state of the material upon administration
10. Route of administration
11. Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies

Physicochemical characterization of nanomedicines is a challenge



Composition
(chemistry)

As the originator manufacturer we have to keep the science, technology and knowledge lead

VIFOR PHARMA

Clinical issue identified

Clinical Issues[1]

- In several studies clinical outcome of iron sucrose preparations from various manufacturers were compared
- The studies concluded that the switch from the original IS to the similar led to differences in clinical outcome

Why?

Definition NBCD[2]

- Synthetic, complex, non-homomolecular macromolecules
- Cannot be fully characterized by physiochemical means

The Process Defines the Product[2]

- Subtle differences in the manufacturing conditions may influence various crucial properties of the final product
- Tightly controlled manufacturing process is required

Perspective of authorities

Regulatory Situation[3]

- Currently, FDA/EMA are aware of the complexity of nanomedicines and associated challenges for analytical characterization
- However, regulatory requirements and legislation not clear and require further development

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FDA's factors for assessment of nanomaterials

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

1. Adequacy of characterization of the material structure and its function
2. Complexity of the material structure
3. Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects (eg effect of particle size on PK parameters)
4. Understanding the in vivo release mechanism based on the material physicochemical properties
5. Predictability of in vivo release based upon established in vitro release methods
6. Physical and chemical stability
7. Maturity of the nanotechnology (including manufacturing and analytical methods)
8. Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product
9. Physical state of the material upon administration
10. Route of administration
11. Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies

Critical quality attributes need to be clinically meaningful

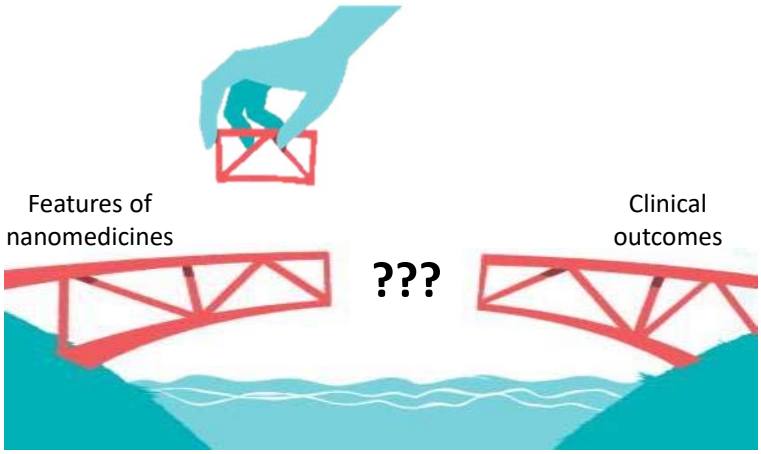
Commentary The AAPS Journal (© 2016)
Theme: Nanotechnology in Complex Drug Products: Learning from the Past, Preparing for the Future DOI: 10.1208/s12248-016-9969-z
Guest Editors: Katherine Tyner, Sau (Larry) Lee, and Marc Wolfgang

A Quality by Design Approach to Developing and Manufacturing Polymeric Nanoparticle Drug Products

Greg Troiano,[1,2] Jim Nolan,[1] Donald Parsons,[1] Christina Van Geen Hoven,[1] and Stephen Z

Severity	Score	Description for Safety	Description for Efficacy	Uncertainty	
Negligible	2	No patient impact	No loss in efficacy	0	Impact established with clinical or *in vivo* data
Minor	4	Minor, reversible patient impact not requiring medical intervention	Minor loss in efficacy		
Moderate	6	Some impact on patient requiring medical intervention, reversible	Major loss in efficacy	2	Impact established *in vitro*
Major	8	Major, possibly irreversible impact on patient, not life threatening	Complete loss in efficacy	4	Hypothetical impact based on literature
Catastrophic	10	Life threatening illness or irreversible injury to patient	Negative efficacy (accelerates disease)	6	Unknown

Nanomedicines what's missing?



FDA's factors for assessment of nanomaterials

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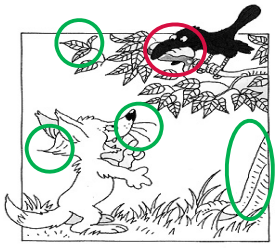
The chalenge with complex products

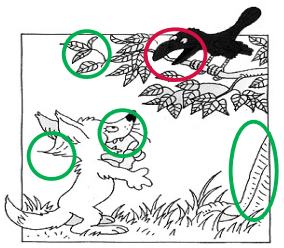
Safety and efficacy demonstrated
- preclinical
- clinical data

Manufacturing Change

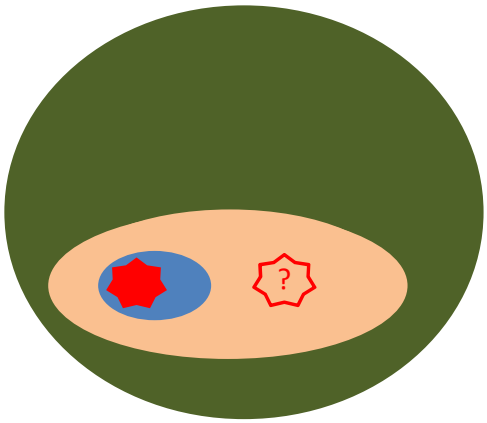
Safety and efficacy demonstrated
- CQA



Complex nanomedicines Can not be fully characterized by physicochemical means



Avoid product drift from manufacturing changes



Entire univers of potential Iron carbohydrate products

Product profile from our manufacturing process or potential new process

Potential iron carbohydrate products as defined by QC testing and release specs

Potential carbohydrate products defined by additional product characteristics

Continuous improvement of product understanding required in an environment of fast science progress

Knowledge Space
Exploratory analytical methods
- Scientific publications
- Internal reports

Product Characteristics
Analytical methodes for comparability
Validated or qualified methods
- Dossier (3.2.S.3 CHARACTERISATION)

Release Specifications
Validated methods
Defined release parameters for batch releas
- Release parameters in dossier (3.2.P.5.1 SPECIFICATIONS)
- Release parameters internal

In total 16 new product characteristics were developed and registered, and the journey goes on

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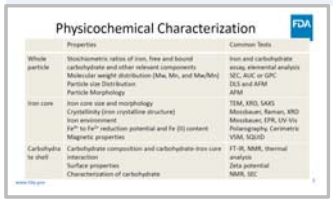
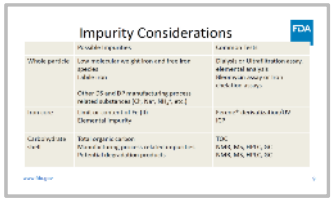
FDA Suggestion

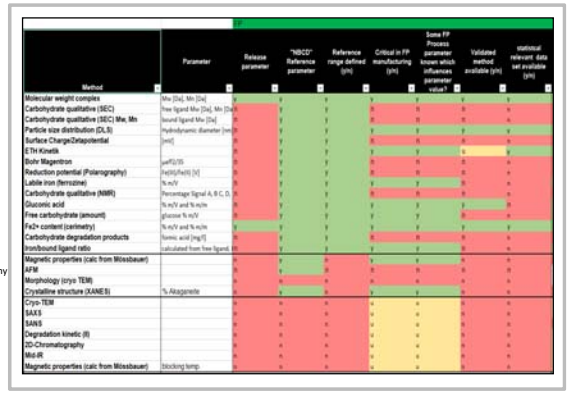




DLS = Dynamic Light Scattering
NMR = Nuclear Magnetic Resonance
AFM = Atomic Force Microscopy
TEM = Transmission Electron Microscopy
SAXS = Small Angle X-ray Scattering
SANS = Small Angle Neutron Scattering
IR = Infrared

UV = Ultraviolet
ICP = Inductively coupled plasma
TOC = Total organic carbon
MS = Mass spectrometry
HPLC = High performance liquid chromatography
GC = Gas chromatography

Thorough evaluation (example)



Mösbauer spectra reveals differences in cristallinity

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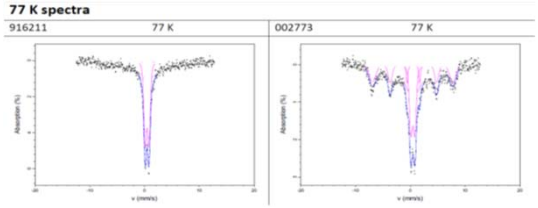
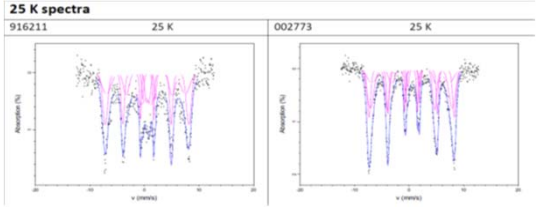
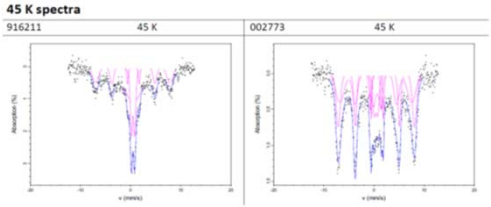
77 K spectra



25 K spectra



45 K spectra

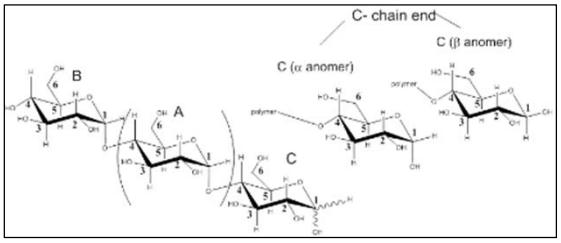


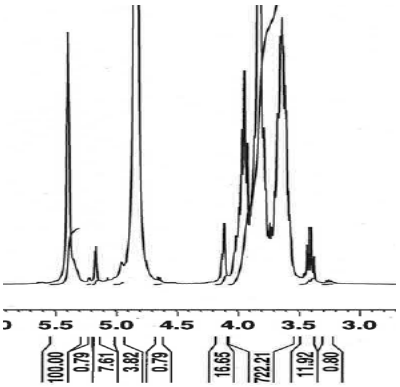
Sample	Average T_B [K]
916211	29.0
002773	59.0

Blocking temperature (T_B) calculated for each sample. T_B is defined as the temperature where the area of the magnetically ordered component is equal to the area of the paramagnetic component

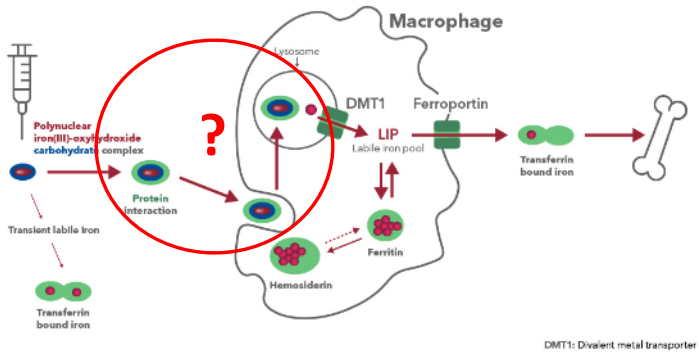
Carbohydrate structure by proton NMR

- Nuclear magnetic resonance (NMR) using proton (^{1}H @ 799.96 MHz) spectra can be used to determine the conformation and identity of the complex sugar moieties





Development of assays monitoring the interaction with the body



In-situ SAXS microfluidics: investigations of nanoparticle interaction with a biological environment