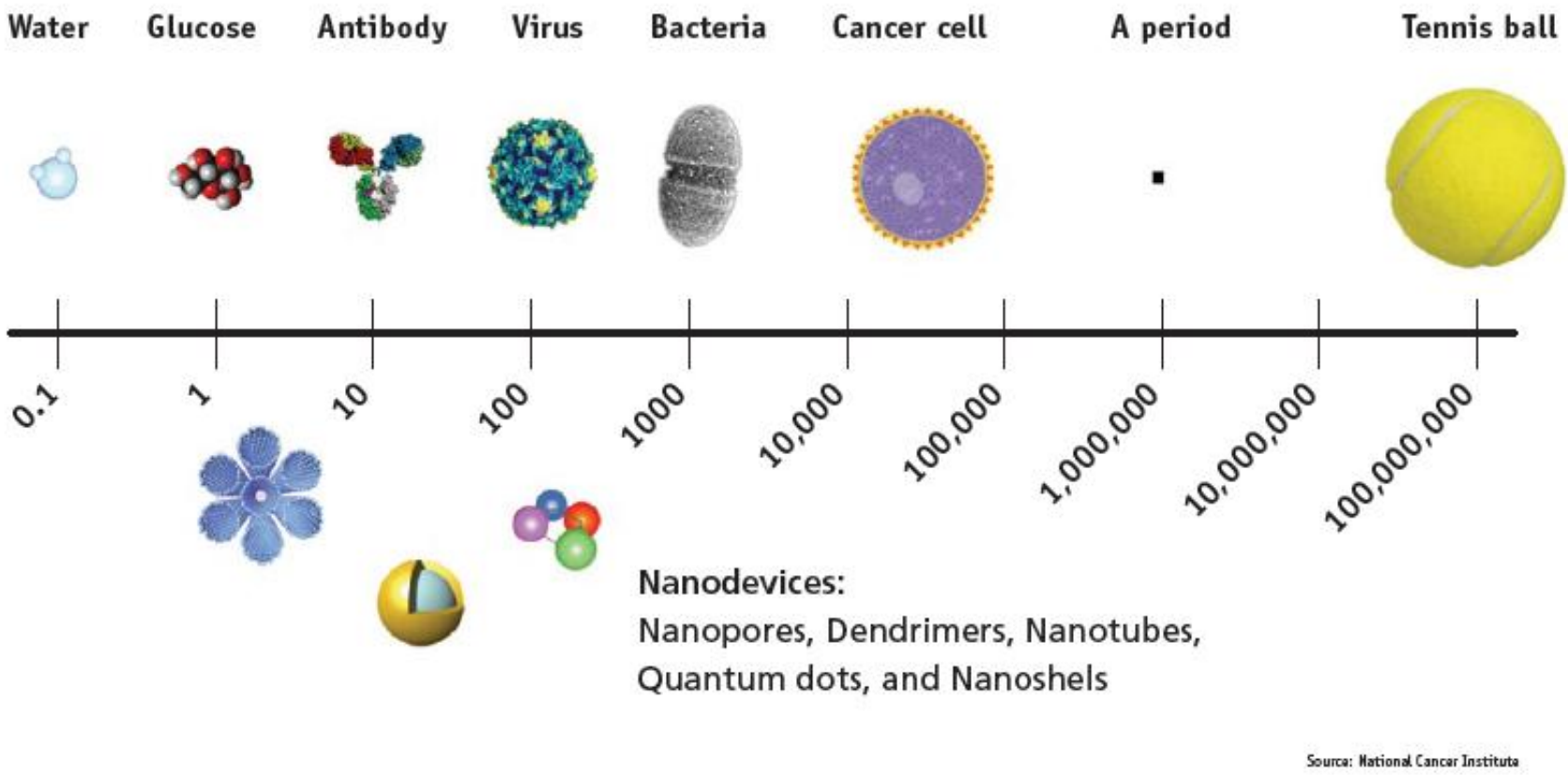
Regulatory considerations for nanomaterial-containing therapeutics

Nakissa Sadrieh, Ph.D.
Office of Pharmaceutical Science
CDER/FDA

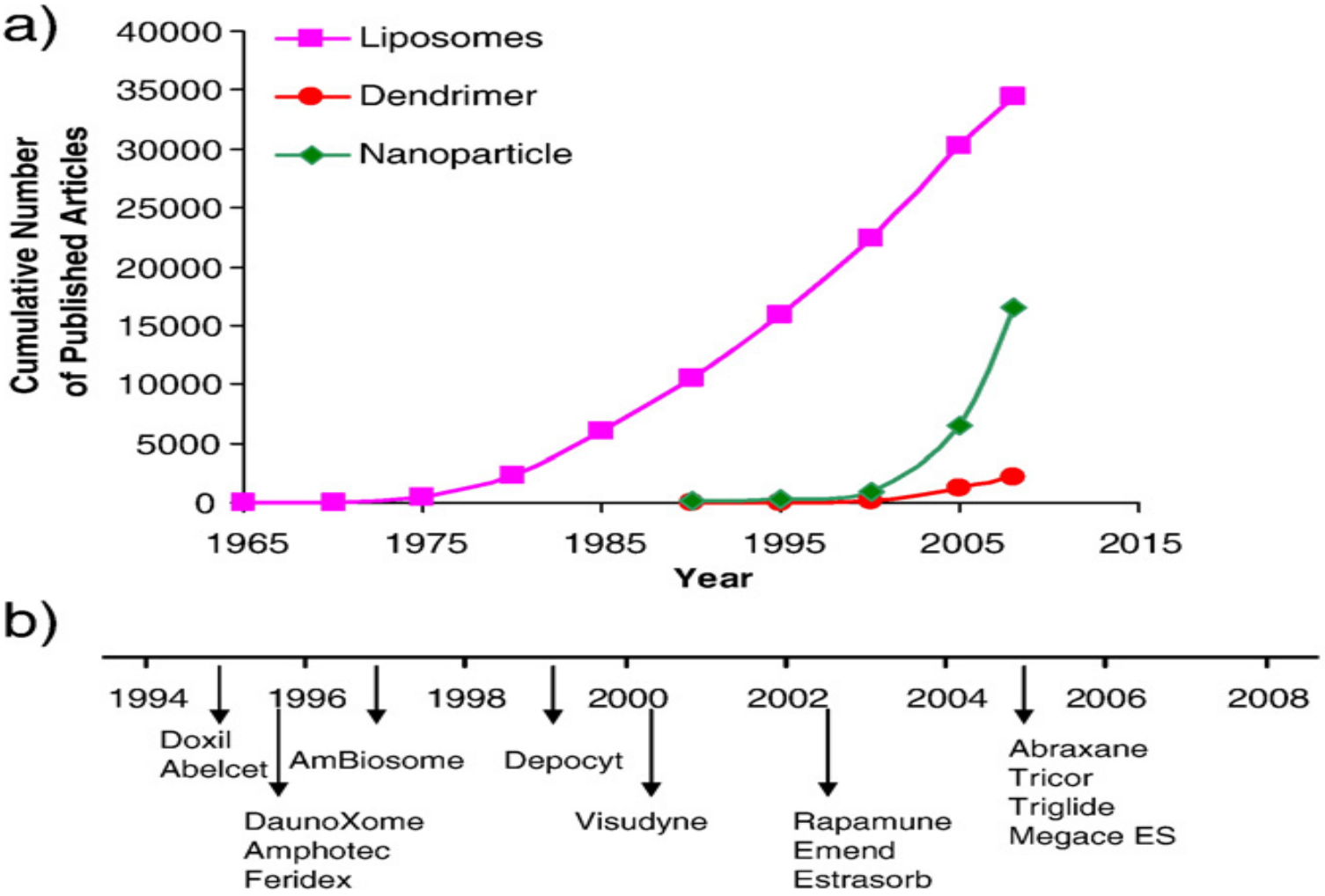
Relative scale of nanotechnology-based products



What is nanotechnology?

- National Nanotechnology Initiative (NNI) Multi-agency participation
  - Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range.
  - Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
  - Ability to control or manipulate on the atomic scale.
- Multiple definitions for nanotechnology exist
- Most definitions focus on size/function between 1- 100 nm
- Some definitions go as high as hundreds of nanometers
- No “official” FDA definition currently available

Increased interest in medical applications of nanotechnology



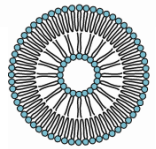
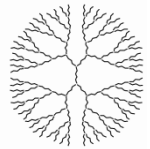
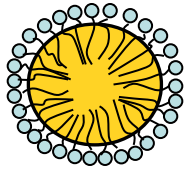
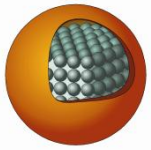
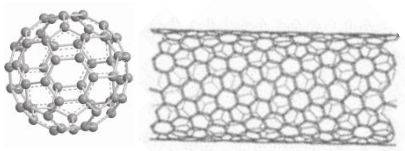
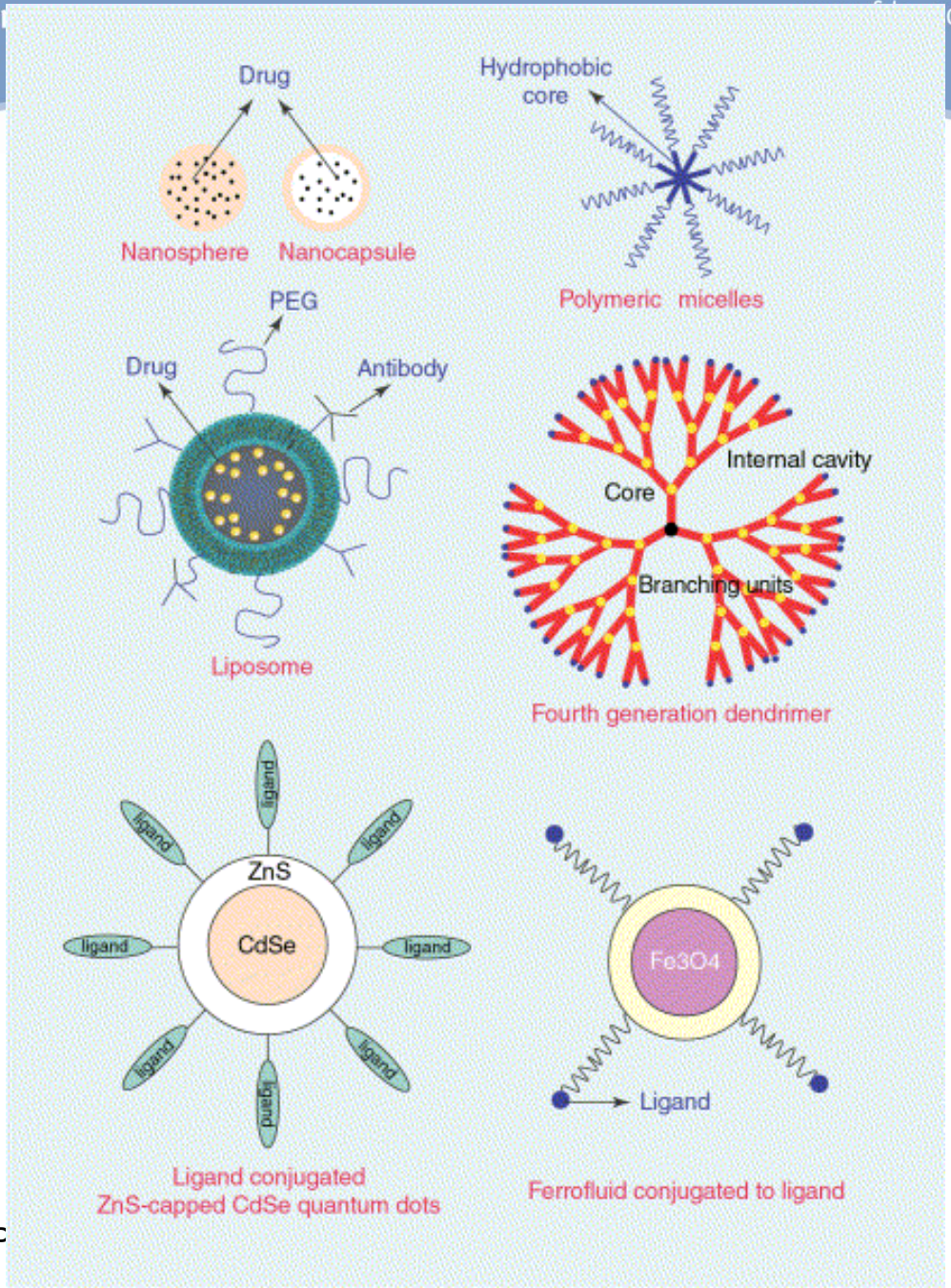
Type	Definition	Schematic
Liposomes	Liposomes are vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments (24).	
Micelles	Micelles are self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell currently used for the solubilization of various poorly soluble pharmaceuticals (25).	
Dendrimers	Dendrimer is a polymer in which the atoms are arranged in many branches and sub-branches along a central backbone of carbon atoms (26).	
Metal colloids	Metal colloids refers to a state of subdivision, that the molecules or polymolecular particles dispersed in a medium have at least in one direction a dimension between 1 nm and 1µm, i.e. silver, gold,and iron oxide (27).	
Nanoemulsion	Nanoemulsions are emulsions with droplet size in the nanometer scale. Emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules, in the other liquid phase, stabilized by the presence of an emulsifying agent (28).	
Quantum dots	Nanoparticle that exhibits size-dependent electronic and optical properties due to quantum confinement (29).	
Fullerenes, Carbon nanotubes	Fullerene: Closed cage structure having more than 20 carbon atoms consisting of three-coordinate carbon atoms. Carbon nanotube refer to a seamless tube constructed from graphene than can be either a single-wall or multi-wall carbon nanotube compromising multiple concentric tubes (30).	

Table 1

Nanotechnology-based drug delivery systems

Sahoo and Labhasetwar, DDT, 2003

- polymeric biodegradable nanoparticles
- ceramic (inorganic) nanoparticles
- polymeric micelles (amphililic block copolymers)
- liposomes
- dendrimers
- nanocrystals (Quantum dots) for diagnostics applications and imaging
- magnetic nanoparticles (iron oxide for MRI)



Reported advantages of nanoparticles in drug products

- Targeting
  - Passive (leaky vasculature)
  - Active (receptor ligands)
  - Improve PK profile
    - Increase drug concentration at site of action
    - Decrease systemic exposure to drug
  - Lower toxicity profile
- Serve as scaffolding to attach chemical moieties
  - Multifunctional molecules
  - Alteration of surface properties (PEG) to increase solubility or decrease clearance.

Advantages of nanotechnology in drug delivery

- Cost benefits:
  - Extend lifespan of product by reformulating through novel delivery system
  - Enhance effective patent protection
- Personalized medicine:
  - Allows treatment of only those tissues and organs that are diseased, and spares healthy organs and tissues (targeting).
  - Allows tailoring of treatment such that it is optimized with respect to risk-benefit.

In 2007- Development of a FDA Nanotechnology Task Force

- Enable development of safe and effective products
- Address knowledge or policy gaps
- Guide science and technology
- Assess current state of science
- Strengthen collaboration with federal agencies

Nanotechnology Task Force addressed

- **2 Scientific Issues:**
  - Understanding the interaction of nanoscale materials with biological systems
  - Adequacy of testing approaches
- **4 Regulatory Policy Issues:**
  - Ability of FDA to identify FDA-regulated products that contain nanoscale materials
  - Scope of FDA's authority regarding evaluation of safety and effectiveness
  - Labeling
  - National Environmental Policy Act (NEPA)

Science Recommendation1: Understanding biological interactions

- More knowledge needed about
  - biological interactions
  - detection and measurement
- In-house expertise and infrastructure should be strengthened
- Agency-wide regulatory-science coordination for nanoscale materials needed.

Science Recommendation 2: Adequacy of testing approaches

- Current testing approaches to assess safety, effectiveness, and quality of products with nanoscale materials should be evaluated.
- Promote/participate in
  - Development of characterization methods and standards for nanoscale materials
  - Development of models for the behavior of nanoscale particles in-vitro and in-vivo.

Regulatory Policy issue 1: Identification of Products Containing Nanomaterials

Recommendations

- Issue guidance recommending that sponsors identify particle size of small particle materials.
- When warranted, issue a call for data on particle size for over-the-counter drugs and food and color additives.

Regulatory Policy issue 2: Scope of FDA's authority on product Safety and effectiveness

- Issue FR notice to call for safety and effectiveness data
- Issue guidance for products
  - Subject to premarket approval
  - Not subject to premarket approval

Regulatory Policy issue 3: Labeling
Regulatory Policy issue 4: NEPA

- **Labeling**: Address on a product-by-product basis whether labeling must or may contain information on the use of nanomaterials.
- **National Environmental Policy Act (NEPA):** Consider on a product-by-product basis, whether an FDA-regulated product containing nanomaterials qualifies for an existing categorical exclusion or whether extraordinary circumstances exist

Nanotechnology in CDER products

- Marketed products
- Future applications

Some currently marketed CDER products containing nanoscale materials

- Sunscreens
  - Nanoscale TiO2 and ZnO
- Reformulations of previously approved products
  - Nanoemulsions
  - Nanocrystal colloid dispersions
- Liposomes
- Iron oxides

	Drug name	Indication	Particle size range
Liposomal platforms	Doxil	Antineoplastic	75-150 nm
	Albecet	Antifungal	1.2-8.3 μm
	Daunoxome	Antineoplastic	NA
	Amphotec	Antifungal	85-145 nm
	Ambisome	Antifungal	NA
	Depocyt	Lymphomatous meningitis	7.5-20 μm
	Visudyne	Macular degeneration	18-104 nm
Nanocrystal platforms	Rapamune	Immunosuppressant	<440 nm
	Emend	Antiemitic	<250 nm
	Tricor	Hypercholesterolemia and hypertryglyceridemia	~200 nm
	Triglide	Hypercholesterolemia and hypertryglyceridemia	NA
	Megace ES	Anorexia, cachexia or weight loss in AIDS patients	140-150 nm
Other platforms	Feridex	MRI contrast	NA
	Estrasorb	Vasomotor symptoms of menopause	~1 μm
	Abraxane	Metastatic breast cancer	120-150 nm

Primary considerations for regulating nanomaterial-containing products

- Product quality assessment
  - Characterization
  - Quality control
  - Manufacturing
- Product safety assessment
  - Biodistribution
  - Clearance
  - Metabolism
  - Toxicology

Characterization needs

- Development of appropriate tools and methodologies to:
  - Adequately assess product chemistry and unique characteristics of product (complete formulation)
  - Enhance quality control measures
  - Produce consistent formulations with low batch-to-batch variability
  - Link product quality to performance

There are many properties of nanomaterials that can be characterized

PROPERTIES[a]	COMMON TECHNIQUES[b]
MORPHOLOGY	
Size (primary particle)	TEM, SEM, AFM, XRD
Size (primary/aggregate/agglomerate)[c]	TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)
Size distribution	TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA
Molecular weight	SLS, AUC, GPC
Structure/Shape	TEM, SEM, AFM, NMR
Stability (3D structure)	DLS, AUC, FFF, SEM, TEM
SURFACE	
Surface area	BET
Surface charge	SPM, GE, Titration methods
Zeta potential	LDE, ESA, PALS
Surface coating composition	SPM, XPS, MS, RS, FTIR, NMR
Surface coating coverage	AFM, AUC, TGA
Surface reactivity	Varies with nanomaterial
Surface-core interaction	SPM, RS, ITC, AUC, GE
Topology	SEM, SPM, MS
CHEMICAL	
Chemical composition (core, surface)	XPS, MS, AAS, ICP-MS, RS, FTIR, NMR
Purity	ICP-MS, AAS, AUC, HPLC, DSC
Stability (chemical)	MS, HPLC, RS, FTIR
Solubility (chemical)	Varies with nanomaterial
Structure (chemical)	NMR, XRD
Crystallinity	XRD, DSC
Catalytic activity	Varies with nanomaterial
OTHER	
Drug loading	MS, HPLC, UV-Vis, varies with nanomaterial
Drug potency/functionality	Varies with nanomaterial
In vitro release (detection)	UV-Vis, MS, HPLC, varies with nanomaterial
Deformability	AFM, DMA(2)

[a] *The property list is not definitive. Other properties may be reported.*
[b] *Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.*
[c] *These techniques will measure the average particle size, but can not necessarily distinguish between primary particles, aggregates, and agglomerates.*

Multiple methods to assess properties of nanomaterials

ABBREVIATIONS

AAS	Atomic absorption spectroscopy	ITC	Isothermal titration calorimetry
AFM	Atomic force microscopy	LDE	Laser doppler electrophoresis
AUC	Analytical ultracentrifugation	MS	Mass spectrometry (GCMS, TOFMS, SIMS, etc.)
BET	Brunauer, Emmett, and Teller method	NMR	Nuclear magnetic resonance
CHDF	Capillary hydrodynamic fractionation	PALS	Phase analysis light scattering
DLS	Dynamic light scattering	RS	Raman spectroscopy
DMA(1)	Differential mobility analyzer	SEM	Scanning electron microscopy
DMA(2)	Dynamic mechanical analyzer	SLS	Static light scattering
DSC	Differential scanning calorimetry	SMA	Scanning mobility particle sizer
ESA	Electroacoustic spectroscopy	SPM	Surface probe microscopy (AFM, STM, NSOM, etc)
FFF	Field flow fractionation	TEM	Transmission electron microscopy
FTIR	Fourier transform infrared spectroscopy	TGA	Thermal gravimetric analysis
GE	Gel electrophoresis	UV-Vis	Ultraviolet-visible spectrometry
GPC	Gel permeation chromatography	XDC	X-ray disk centrifuge
HPLC	High performance liquid chromatography	XPS	X-ray photoelectron spectroscopy
ICP-MS	Inductively coupled plasma mass spectrometry	XRD	X-ray diffraction

References

Tyner, K.M. “Nano-methods” in *Handbook of Analysis and Pharmaceutical Quality* , Shayne Gad, Ed. John Wiley and Sons, NJ. *In publication.*

Dair, B.J., Tyner, K.M., Sapsford, K.E. “Techniques for the characterization of nanoparticle-bioconjugates” in *Nanoparticles in Bioengineering* , Raushal Rege and Igor Medintz, Ed. Artech House, MA. *In publication*

Safety considerations

- **What is safety?**
  - Dose that does not result in toxicity
  - Relative safety: risk-benefit ratio?
  - Depends on:
    - Disease
    - Target population
- **How do we measure safety?**
  - Clinically
  - Preclinically

Preclinical safety assessment

- **Traditionally to answer questions that cannot be answered with clinical studies:**
  - Can women of child-bearing age take the drug?
  - Might there be harm to the fetus?
  - Will prolonged exposure result in cancer?

- **To guide clinical studies; will depend on:**
  - Formulation
  - Route of administration
  - Clinical population

Preclinical safety assessment (Cont'd)

- **Evaluate toxicities that cannot be measured in clinical studies**
  - Genotoxicity
  - Carcinogenicity
  - Histopathology
  - Developmental toxicity
- **To help establish a starting dose for the first-in-man clinical studies**

Safety Considerations raised by nanomaterials

- Do nanoparticles gain access to tissues and cells normally bypassed by larger particles?
- What effects do they have on cellular and tissue functions (transient and/or permanent)?
- How long do they remain in the sites where they accumulate?
- How are they cleared from tissues and blood?

Absorption Distribution Metabolism and Excretion (ADME) Considerations

- Can nanoparticles be appropriately labeled for ADME studies?
- Is the biodistribution of nanoparticles different than that of larger sized particles?
- Are there adequate methods for measuring levels of nanoparticles in blood and tissues?
  - Limit of detection, distinction between nanoparticles and aggregates or between intact nanoparticles and metabolized nanoparticles
  - Accuracy of mass balance studies (drugs administered at very low levels or targeted products)?
- Can clearance of targeted nanoparticles be accurately assessed?

Current Preclinical Tests for Safety Evaluation of Drugs Include

- Pharmacology (mechanism of action)
- Safety pharmacology (EKG etc...)
- Toxicology (including clinical pathology and histopathologic analysis)
- ADME
- Genotoxicity
- Developmental toxicity
- Immunotoxicity
- Carcinogenicity
- Other

Adequacy of Current Preclinical Safety Assessment of Drugs

- Existing battery of preclinical tests is very rigorous, because:
  - High dose multiples used
  - At least 2 animal species used
  - Extensive histopathology on most organs
  - Functional tests (cardiac, neurologic, respiratory, reproductive, immune system, etc/…)
  - Extended treatment periods (up to 2 years for carcinogenicity studies)

Additional tests to screen for safety

- Clinical studies
  - Healthy volunteers
  - Patients
  - Organ impaired and at risk populations

Are additional screening tests needed to assess the safety of nanoparticles?

- Only **IF**:
  - There are things that our current tests miss.
  - There are endpoints that additional tests would measure.
- Otherwise, **Not at this time**.

Important considerations towards the development of a regulatory framework for nanotechnology-containing drugs

- Can we identify products containing nanomaterials in already submitted applications?
- Can we identify nanomaterial-containing products in future applications?
- How do we define nanotechnology for the purposes of drug review and evaluation?
- Is there a need to develop specific policies to address nanomaterial-containing product applications?

Guidance for industry

- Many of the already existing guidances will apply to nanomaterial-containing products.
- Agency-wide guidance specifically to cover the use of nanoscale materials in FDA-regulated products is being drafted.
- Some Centers are considering Center-specific MaPPs and Guidance documents.

CDER initiatives in progress

- Development of a database of drug products containing nanoparticles:
  - Identifying classes of nanoparticles
    - Nanocrystals, liposomes, micelles, nanoemulsions, iron oxides, polymers, PEG conjugates, metal based complexes, dendrimers
  - Identifying particle sizes
  - Identifying unique features and functions
- Development of procedures (MaPP) to adequately capture specific information on nanomaterial-containing product submissions.

CDER Research aimed at:

- Understanding the properties of nanoparticles in CDER-regulated products, that require adequate characterization.
- Understanding the instrumentation that best characterize nanoparticles in CDER-regulated products.
- Evaluation of the dermal penetration of TiO2 from sunscreens in appropriate models (completed).
- Using the nanotechnology database under construction, to identify gaps requiring additional research and policy development.

Thank you

- Contact information:

Nakissa.Sadrieh@FDA.HHS.GOV