



# CDER Perspective on Nanotechnology

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# Outline

- Applications of nanotechnology in CDER products
  - Already approved products
  - Anticipated products
- Evaluation of nanotechnology-based drug applications: key aspects of their regulatory review.



# Impact of nanotechnology on already marketed CDER products

- Sunscreens
  - Nanoscale TiO<sub>2</sub> and ZnO
- Reformulations of previously approved products
  - Nanoemulsions
  - Nanocrystal colloid dispersions

# Currently marketed sunscreens formulated with nanoparticles



**(RED) PRODUCTS CONTAIN MANUFACTURED NANOPARTICLES**

PRODUCT	MANUFACTURER	NANO CONTENT CLAIM
Applied Therapeutics™	Applied Therapeutics™	Others claim nano content
Bebe/Enfant High Protection SPF 50	Mustela	Others claim nano content
Blue Lizard® BABY	Crown Laboratories, Inc.	Manufacturers claim nano content
Blue Lizard® Regular	Crown Laboratories, Inc.	Others claim nano content
Blue Lizard® Sensitive	Crown Laboratories, Inc.	Manufacturers claim nano content
Chemical-Free Sunscreen SPF 15	Burt's Bees® Inc.	Manufacturers claim nano content
Cotz SPF 58	Fallene	Others claim nano content

BRAND	MANUFACTURER	NANO CONTENT CLAIM
Daily Sun Defense SPF 20	SkinCeuticals®	Others claim nano content
IS Clinical SPF 20 Moisturizing Treatment Sunscreen	Innovative® Skincare	Others claim nano content
Kids Tear Free SPF 30	Banana Boat®	Others claim nano content
Lips 'n Face Protection Creme and Sunblock Creme	Dermatone® Laboratories	Others claim nano content
Physical UV Defense SPF 30	SkinCeuticals®	Others claim nano content
Rosacea Care Sunscreen "30"	Rosacea Care.	Manufacturers claim nano content
Solar Rx SPF 30+ Nano-Zinc Oxide Sunblock	Keys Soap	Others claim nano content
Soltan® Facial Sun Defence Cream - Optisol®	Boots® and Oxonica® Ltd.	Others claim nano content
Spectra3 SPF 50	Coppertone®	Others claim nano content
SPF 20 Sunscreen Powder	Innovative® Skincare	Others claim nano content
Sport UV Defense SPF 45	SkinCeuticals®	Others claim nano content
Sunscreen Plus Clear Zinc SPF30+	Cancer Council Australia	Manufacturers claim nano content
SunSense™ SPF 30+ Sunscreen	NuCelle® Inc.	Manufacturers claim nano content
TiO2 Automotive Sunscreen*	Nano Chemical Systems Holdings, Inc.	Manufacturers claim nano content
Ultimate UV Defense SPF 30	SkinCeuticals®	Others claim nano content
UV Pearls	Sol-Gel Technologies	Manufacturers claim nano content
ZinClear™ Nano Zinc Oxide	Advanced Nanotechnology Limited	Manufacturers claim nano content



# Currently marketed prescription drugs with nanoscale particles

Product	Type of nanoparticle	Indication	Particle Size
Magenvist	Gadolinium dimeglumine	MRI contrast agent	< 1 nm
Feridex	Superparamagnetic Iron Oxide	MRI contrast agent	120 – 180 nm
Rapamune	Nanocrystal/Sirolimus	Immunosuppressant	100 – 1000 nm
Emend	Nanocrystal / Aprepitant	Antiemetic	100 – 1000 nm
TriCor	Nanocrystal / Fenofibrate	Hypolipidemic	
Megace ES	Nanocrystal / Megestrol Acetate	Appetite enhancer	
Doxil	Liposome / Doxorubicin	Antineoplastic	~ 100 nm
AmBisome	Liposome / Amphotericin	Antifungal	
Diprivan	Liposome / Propofol	Anesthetic	
Abraxane	Albumin-coated nanoparticles	Antineoplastic	~ 130 nm
Definity	Liquid coated gas particles	Echography contrast agent	



# Impact of nanotechnology on future CDER products: DRUG DELIVER SYSTEMS

- Targeted therapy
  - Minimize drug use; lesser frequency of drug use
  - Enhance safety profile
- Novel dosage forms (such as use of electrical currents or high velocity propulsion for transdermal delivery)
  - Enhanced patient compliance
  - Controlled or sustained release
- Multifunctional particles
- Protection of associated drug against enzymatic and chemical degradation
- Small particles, large surface area
  - High drug entrapment efficiency due to large surface area
  - Enhanced bioavailability
  - Access to less accessible sites



# Drug delivery: cost benefits

- Extend lifespan of product by reformulating through novel delivery system
- Enhance effective patent protection
- Drug delivery formulation research is low-cost compared to drug discovery for NME
- Minimizing use of expensive drugs to reduce cost of product



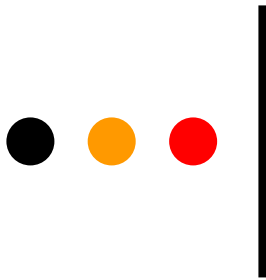
# Proposed functions for nanoparticles in drugs

- Platforms or carriers for insoluble or poorly soluble drugs
  - Improve PK properties
- Targeting
- Multifunctionality
  - Serve as scaffolding to attach chemical moieties



# Reported advantages of nanoparticles in drug products

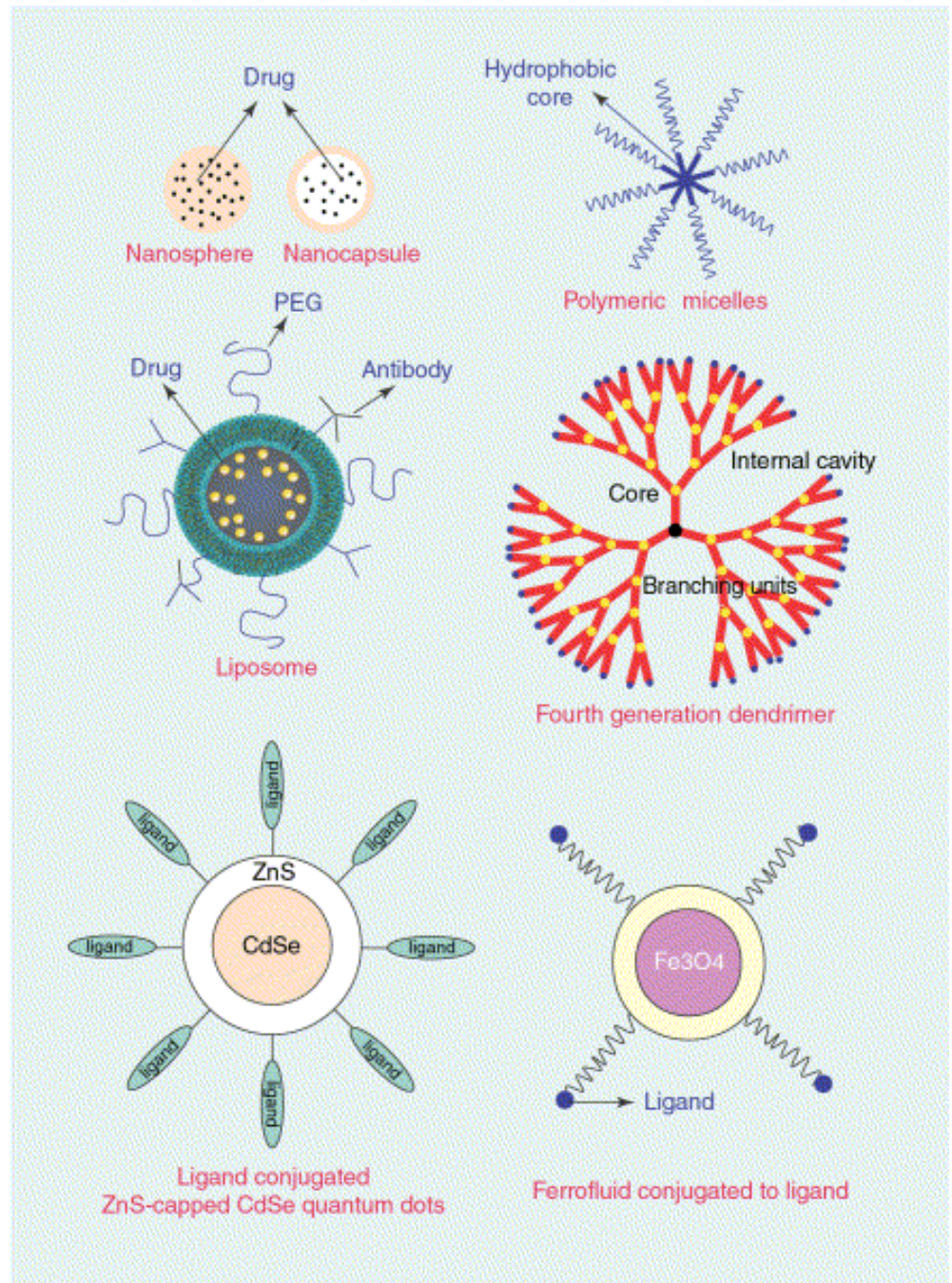
- Targeting
  - Passive (leaky vasculature)
  - Active (receptor ligands)
  - Increase drug concentration at site of action
  - Decrease systemic exposure to drug
  - Lower toxicity profile
- Serve as scaffolding to attach chemical moieties
  - Multifunctional molecules
  - Alteration of surface properties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



## Nanotechnology-based drug delivery systems

Sahoo and Labhasetwar, DDT, 2003

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





# Polymeric biodegradable nanoparticles

- Nanoparticles are solid or colloidal particles 10-1000 nm in size.
- Drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated in nanoparticle matrix.
- Nanoparticles are obtained and include:
  - nanospheres (matrix system with drug dispersed), or
  - nanocapsules (vesicular systems with drug confined to a cavity).
- Advantages:
  - Small size; enhanced penetration
  - Sustained release through biodegradable materials



# Ceramic nanoparticles

- Inorganic (silica, alumina, titania) molecules with entrapped biomolecules
  - Very low size (less than 50 nm) help bypass RES
  - Biologically compatible
  - Surfaces can be modified for targeting in vivo
  - Drug-doped nanoparticles are relatively stable



# Polymeric micelles

- Amphiphilic block copolymers which can self associate to form micelles in aqueous solution
  - Thermodynamically stable in physiological solutions-prolonged systemic circulation and minimal RES uptake (due to small size and hydrophilic shell).
  - Narrow size distribution (less than 100 nm)
  - Useful for the systemic delivery of water-insoluble drugs which are partitioned in the hydrophobic core of the micelles and the outer hydrophilic layers-forms stable dispersion in aqueous media and can be administered intravenously.
  - Can be enhanced by conjugation of targeting ligands.



# Liposomes

- Small unilamellar vesicles
  - Single lipid layer, 25-50 nm
- Large unilamellar vesicles
  - Single lipid layer
- Multilamellar vesicles
  - Several lipid layers
- Can be surface modified
  - with PEG to enhance circulation time
  - With antibodies or ligands for targeting



# Dendrimers

- Macromolecular compounds around inner core
- Nanometer size range and monodisperse
- Can be functionalized with drug molecules or loaded in the interior



# Nanocrystals

- Quantum dots
  - Crystalline core with insulating outer shell.
  - Absorb light at wide range of wavelengths.
  - Emit light of a wavelength depending on size of crystals.
  - Can be functionalized
  - Used for diagnostic purposes.



# Applications of nanoparticles in drug development

- Cancer therapy
- Imaging
- Delivery of vaccines
- Delivery of targeted antibiotics



# Areas that can significantly impact the evaluation of nanomaterial-containing products

- Product quality assessment studies
  - Characterization
  - Quality control
  - Manufacturing
- Product safety assessment studies
  - 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



# What is safety?

- **Dose that does not result in toxicity**
  - Relative safety: risk-benefit ratio?
  - Depends on:
    - Disease (cancer vs. obesity)
    - Target population (pediatric, pregnant women, some form of impairment)
- How do we measure safety?
  - Clinically
  - Preclinically



# Features of nanoparticles that could be analyzed in drug products

- Size
  - Primary particle size
  - Aggregation/agglomeration state
  - 2D and 3 D distribution
  - Particle size distribution
- Chemical composition
  - Element identification and distribution
  - Crystal form
  - Surface composition; surface charge
  - Reactivity



# Purpose of 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



# Purpose of preclinical studies

- 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.



# What tools are used to screen for safety?

- Animal toxicology studies
  - Multiple species
  - 3 doses
  - Multiple endpoints measured
- Clinical studies
  - Healthy volunteers
  - Patients
  - Organ impaired and at risk populations



# Are there other tools needed to measure safety?

- Input is needed from the scientific community to address this question.
  - What do our current tests miss?
  - What would additional tests measure?
  - Would additional tests only improve our evaluation of nanotechnology-based therapeutics or would they add value to all drug product applications?



# Collaborative research with NCTR

Substance	Description	Initiated	Study Leader	FDA collaborators	Other collaborators
TiO <sub>2</sub>	Dermal penetration and toxicity in mice (also Qdots)	2004	P. Howard, NCTR	B. Bronaugh, CFSAN	NTP / NIEHS
TiO <sub>2</sub>	Dermal penetration in minipigs	2006	N. Sadrieh, CDER	L. Buhse, CDER; P. Howard, NCTR; N. Gropee, NCTR	
TiO <sub>2</sub>	Dermal penetration in humans	2006	S. Miller, CDRH	N. Sadrieh, L. Buhse, CDER; P. Howard, NCTR; J. Beer, CDRH	NIH, NCI/NCL
Nano silver	Distribution and toxicity in mice	2008	M. Boudreau, NCTR	Nominated to NTP by FDA	NTP/NIEHS, NIST
Nano gold	Distribution and toxicity in mice	2008	N. Gropee, NCTR	Nominated to NTP by FDA	NTP/NIEHS, NIST, NCI/NCL



# Additional research projects in CDER

- Characterization of nanoparticles in marketed sunscreens (to address Citizen Petition).
- Toxicity of select nanoparticles; correlation of in vitro findings with in vivo results.
- Collaborators: NIST, NCL/NCI, CDRH.



# Challenges ahead

- Define the existing scientific gaps:
  - Identify the critical parameters for various types of nanoparticles that may be used in drug products.
  - Identify and develop appropriate methods to characterize these specific nanoparticle parameters.



# Challenges ahead (continued)

- Conclude on the appropriateness of existing methods to assess safety.
- Identify if additional safety assessment tools need to be developed and what should these new assays measure.



# Conclusions

- Identify the scientific gaps in nanoparticle-based drug development.
- Define the steps to help overcome these gaps.
- Identify the appropriate groups that can help to address the issues.
- Establish collaborations.