# Regulatory Research Supporting the Development of Drug Products Containing Nanomaterials
# A US-FDA Perspective

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GSRS19
25 September 2019

# Disclaimer

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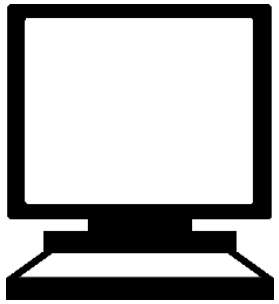
# Pharmaceutical Quality

**A quality product of any kind consistently meets the expectations of the user.**



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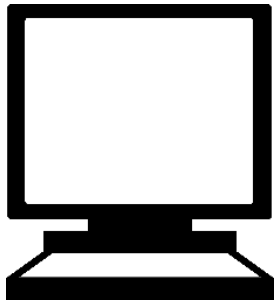



**Drugs are no different.**

# Patients expect safe and effective medicine with every dose they take.

**Pharmaceutical quality is**

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

# Center for Drug Evaluation and Research (CDER)

- Reviews applications for new and generic drugs, new indications for already approved products, and active ingredients and labeling for over-the-counter drugs.

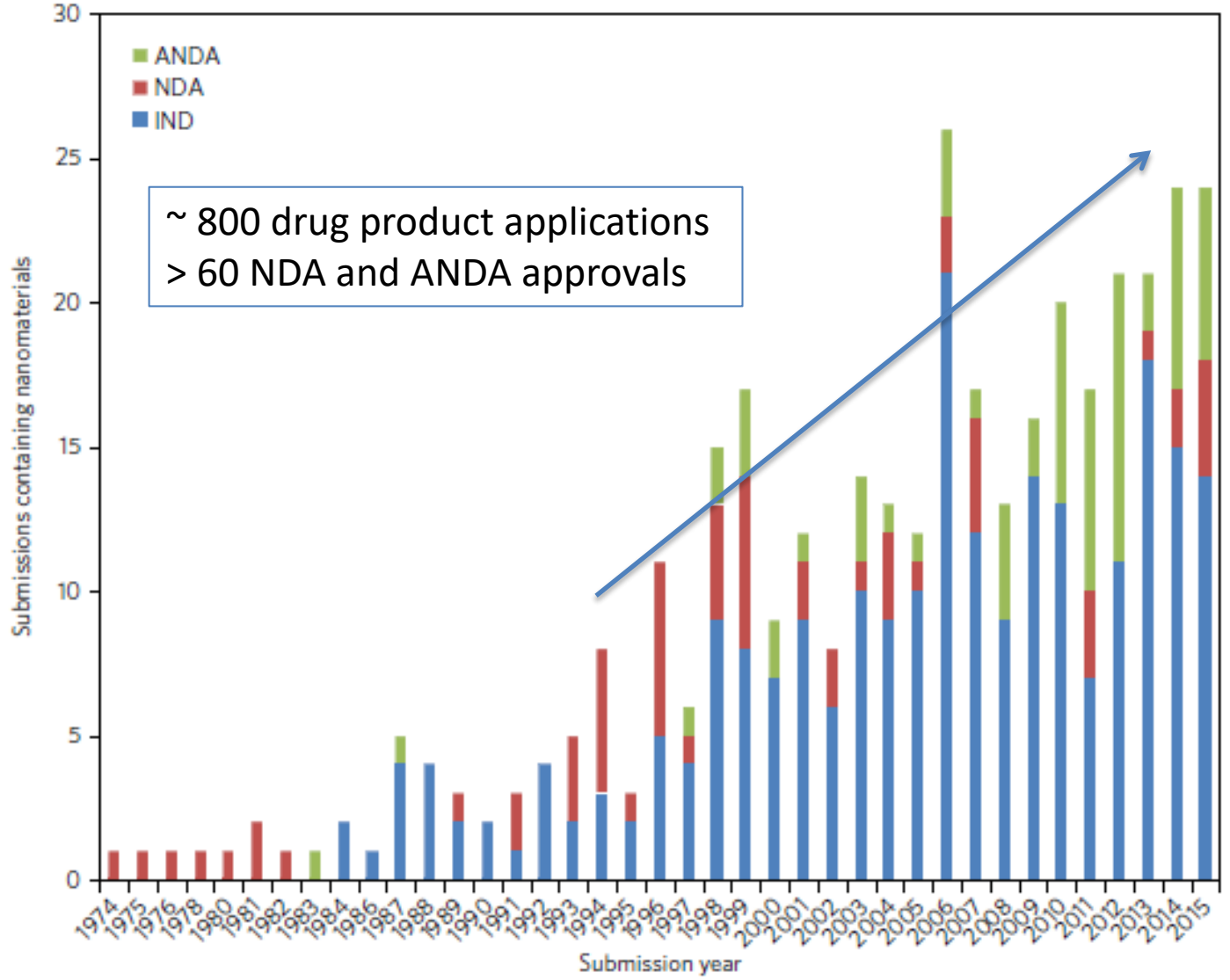
- Drugs are evaluated for safety, efficacy, and quality.

- Information on drug review procedures are provided in CDER guidance documents.
  - Guidance documents represent FDA's current thinking on a topic.
  - https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

# Drug Products: Types of Submissions

- Investigational New Drug Application (IND)
  - Request to administer an investigational drug or biologic to humans
- New Drug Application (NDA)
  - Approval for a new pharmaceutical for sale and marketing
- Biologic License Application (BLA)
  - Comparable to NDA, but for biologics (e.g. monoclonal antibodies, proteins)
- Abbreviated New Drug Application (ANDA)
  - Usually refers to generics

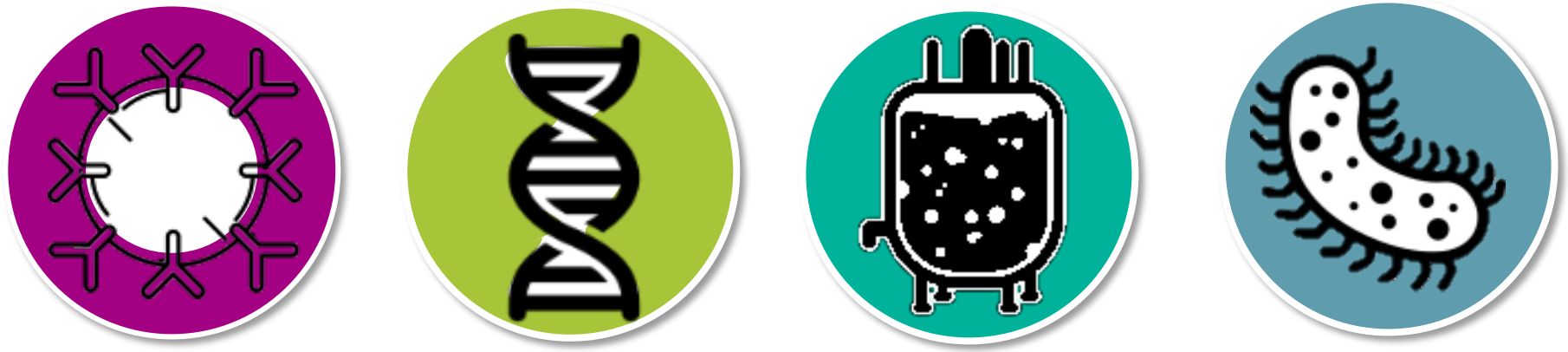
# Submissions to the US FDA of Drug Products Containing Nanomaterials




D'Mello S. et al. Nature Nanotechnology DOI: 10.1038/NNANO.2017.67

# Regulatory Science

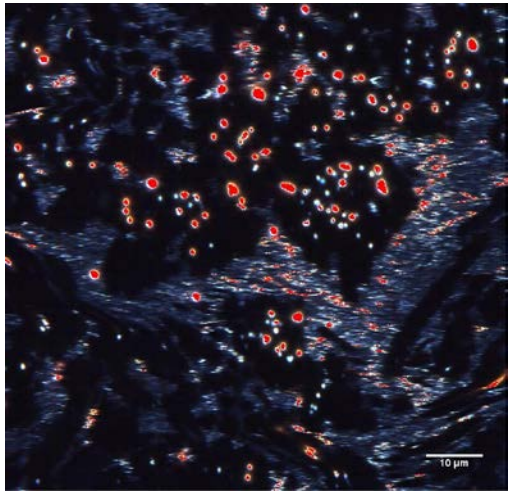
FDA has defined regulatory science as “the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.”



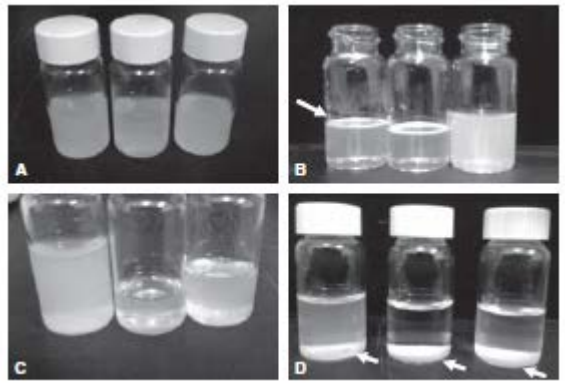
http://www.fda.gov/scienceResearch/specialtopics/RegulatoryScience.

# Regulatory Science Impact

- Regulatory science and research forms the foundation for risk-based evaluation of drug products
  - Review of drug product applications
  - Inspection and surveillance
  - Standards and policy development



- Regulatory science and research impact all drug product areas
  - New drugs
  - Generic drugs
  - Over-the-counter drugs
  - Biotechnology products



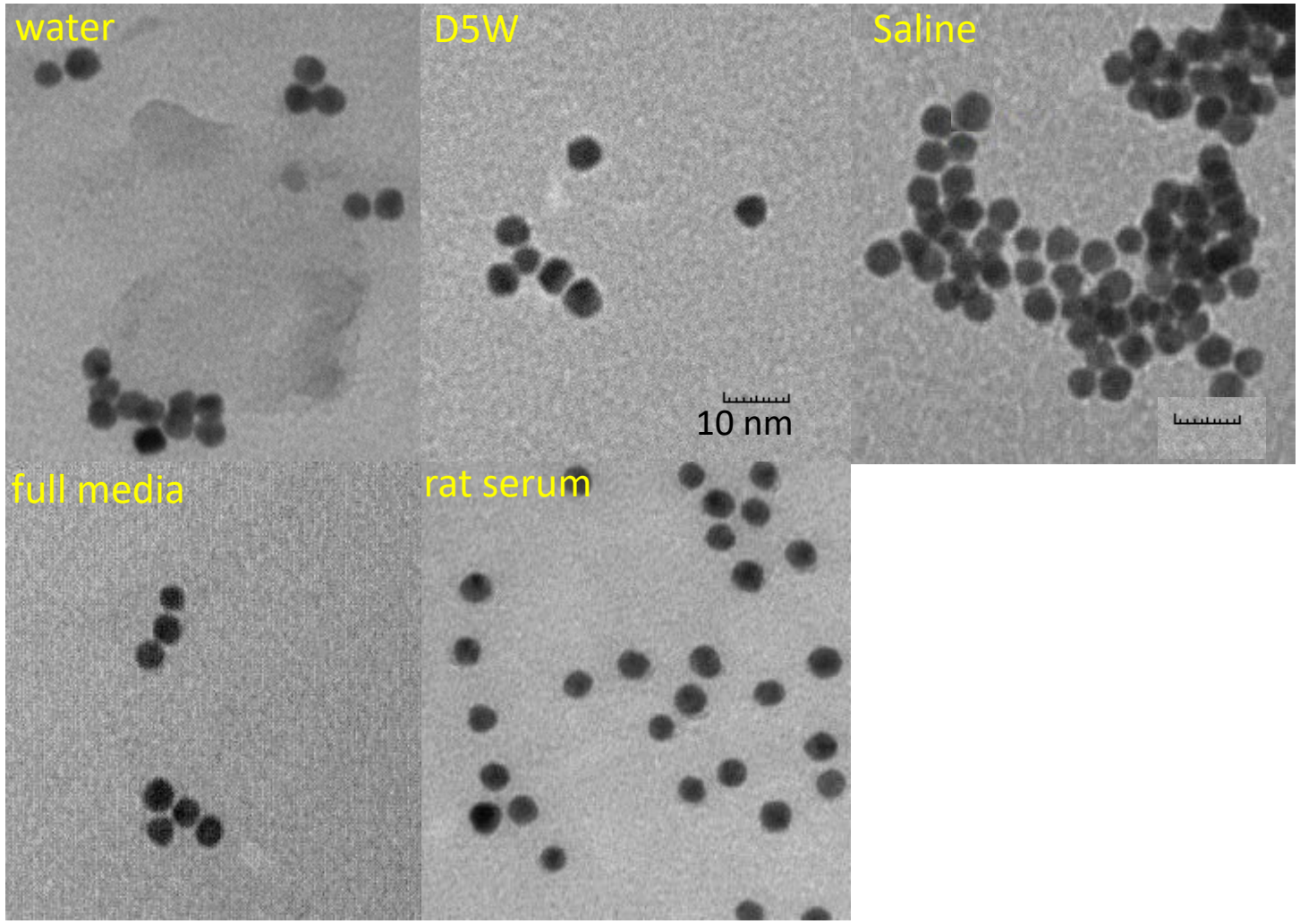

Fisher AC et al. Int. J. Pharm. 515 (2016) 390-402; Tyner KM, et al. Int. J. Cos. Sci. 33 (2011) 234-244

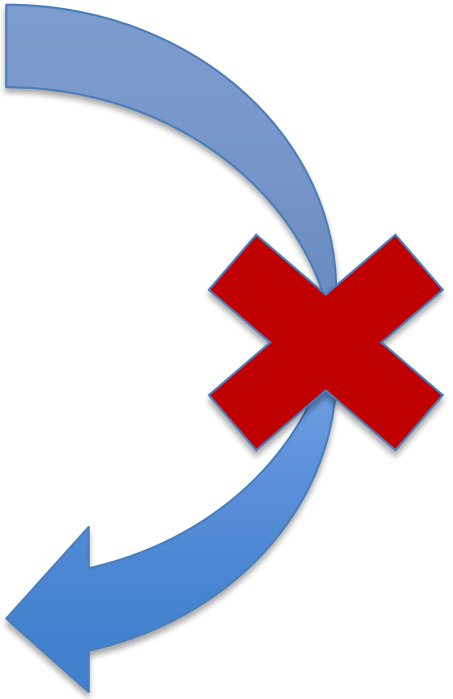
# Regulatory Science Phases for New Technology

- Foundational research
  - What is it?
- Targeted research on issues/limitations
  - What are the failure modes? What is needed?
- Standardization
  - How can it be used?

We are here

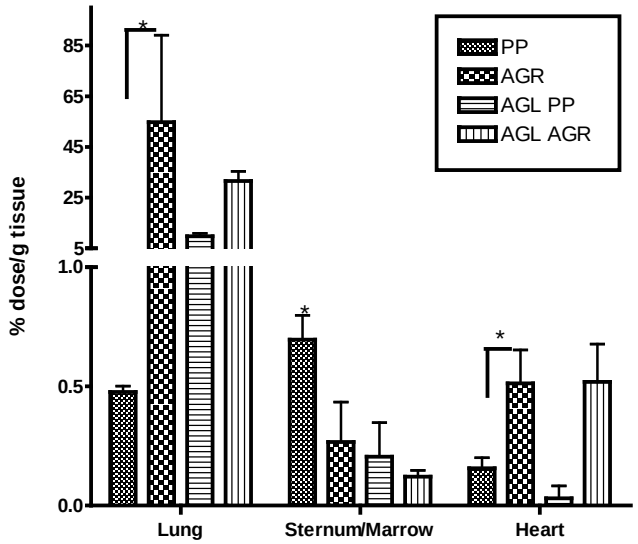
# Foundational Research--Quality

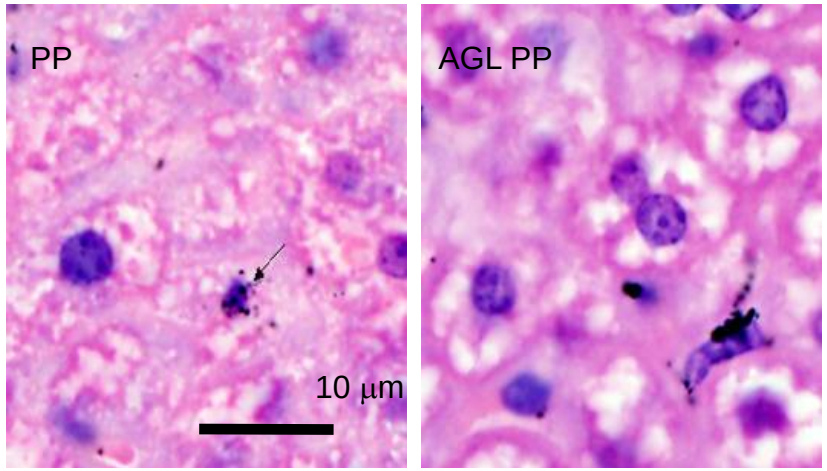


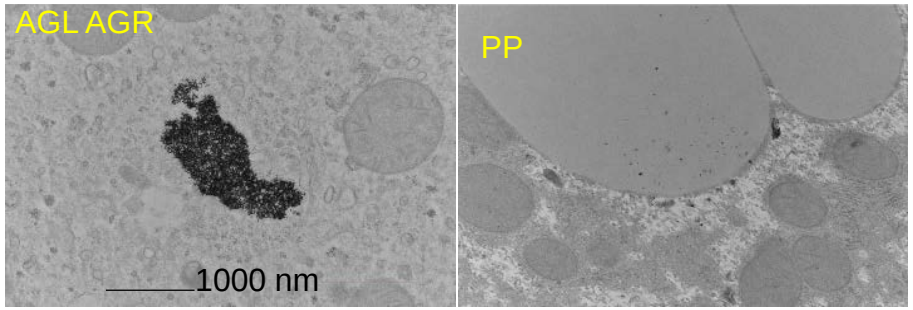



# Foundational Research--Safety

## Self-Associated NP Structures and Biodistribution




- Structures have different biodistribution
- Tissue, cellular and sub-cellular locations
- Potential for different toxicity pathways

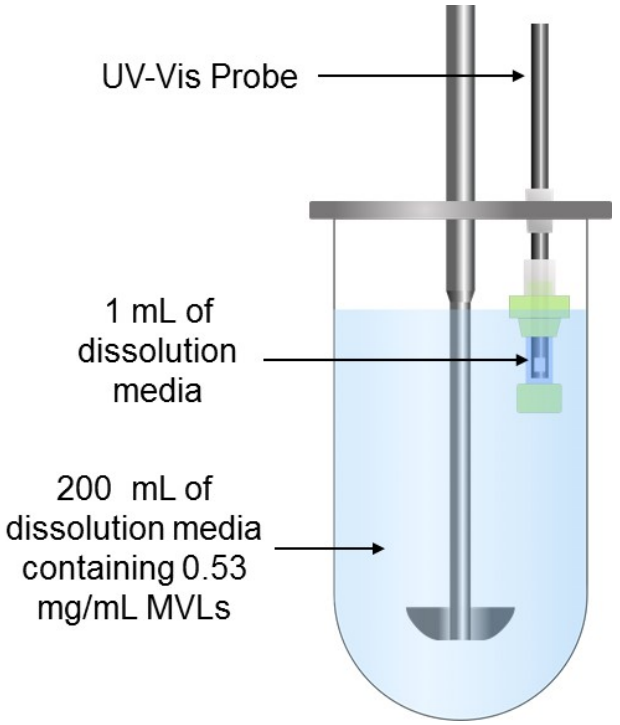


Keene, A.M. et al.,Tissue and cellular distribution of gold nanoparticles varies based on aggregation/agglomeration status. *Nanomedicine.*7(2) 199-209, 2012.

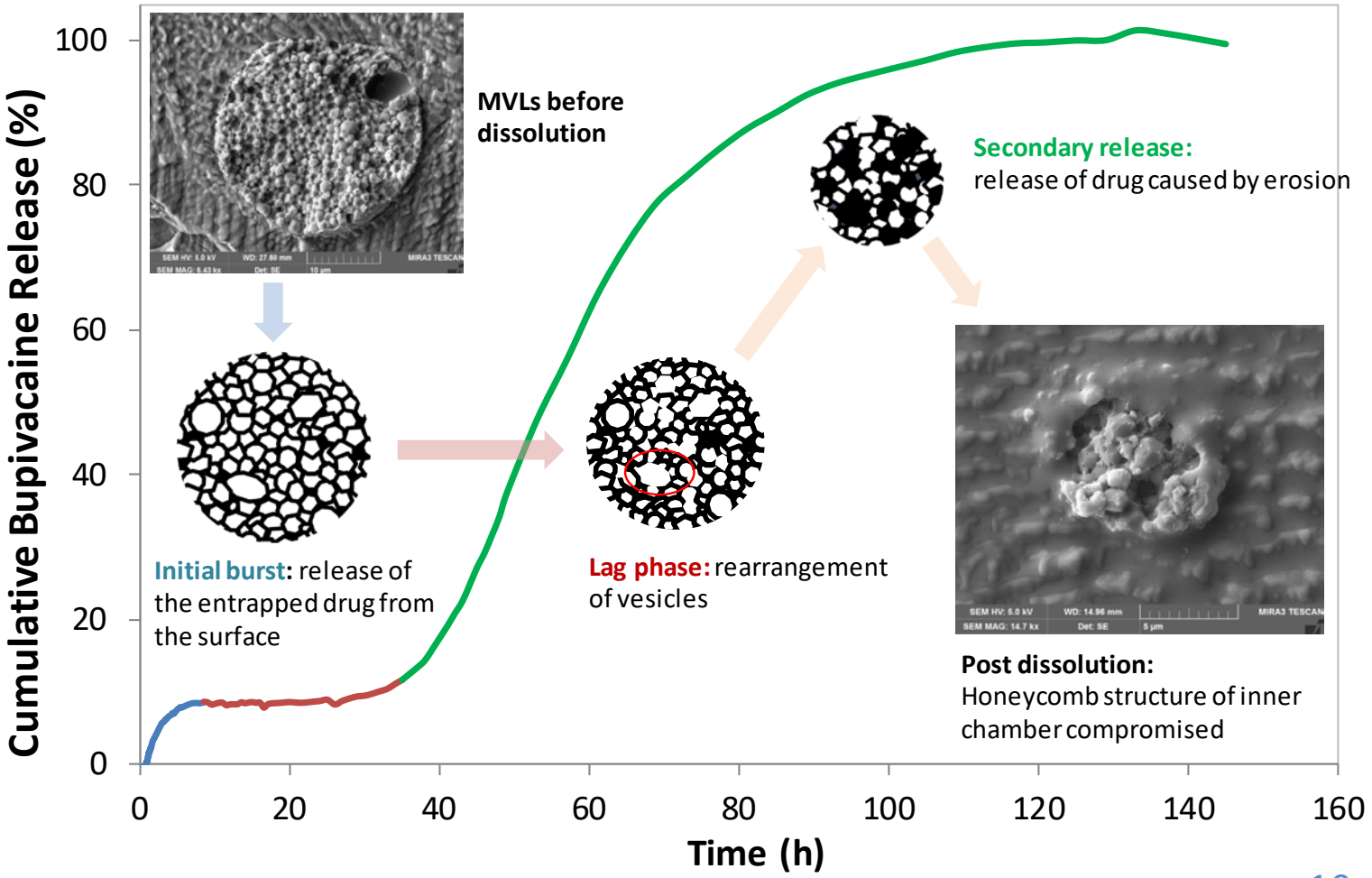
# Targeted Research—Quality; In Vitro Drug Release Test

A novel in vitro release testing (IVRT) method has been developed to understand the drug release mechanism in bupivacaine multivesicular liposomes.

**Reverse-dialysis with in-situ fiber optic UV monitoring**

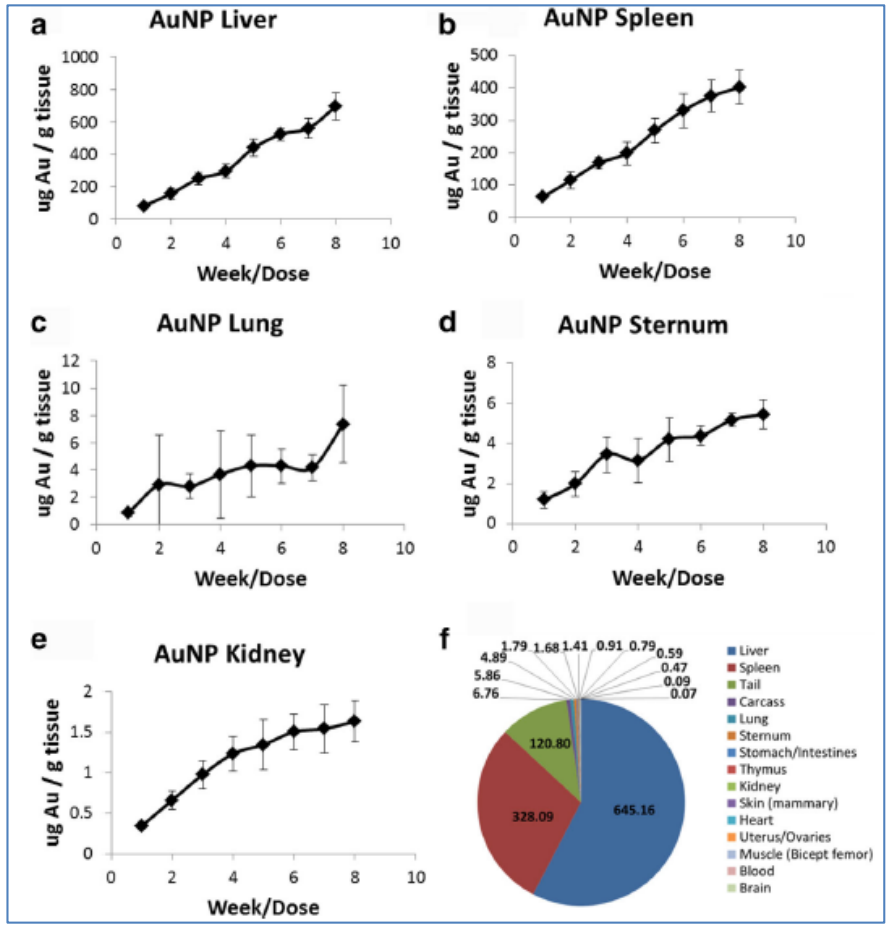



JCR volume 294 Cover Story!

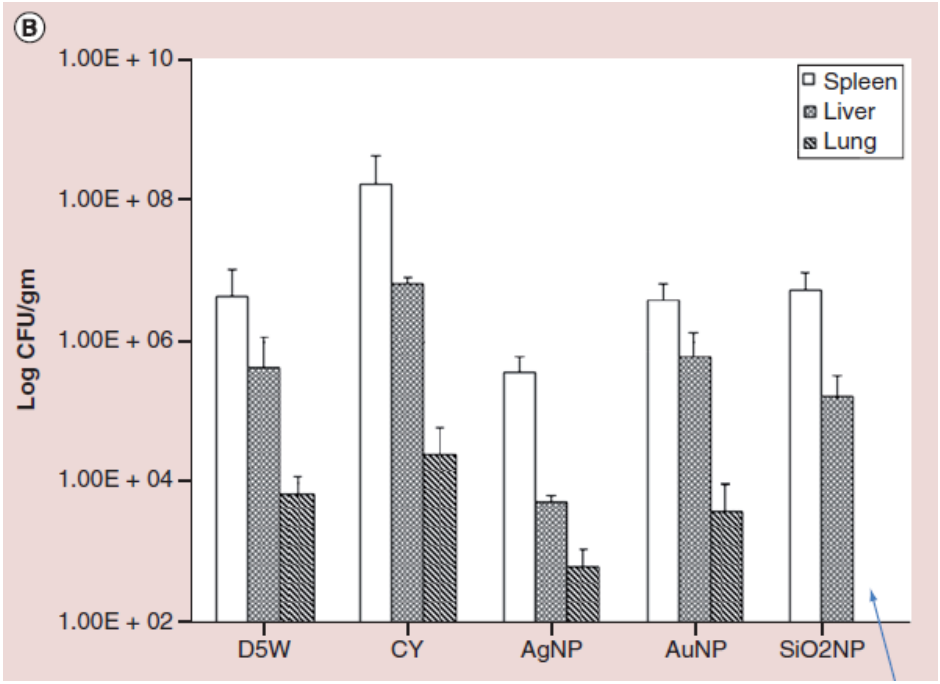



S. Manna, et al. *J of Controlled Release. 294, p279-287*

# Targeted Research--Safety




Durable nanoparticles repeat administration combined with secondary challenge




Weaver et al. Particle and Fibre Toxicology (2017) 14:25; Khan S et al. Nanomedicine (2017) 12:17

# Standardization—Suggested Minimal Characterization of Nanomaterials circa 2013

- Agglomeration/aggregation
- Chemical composition
- Crystal structure/crystallinity
- Particle size/size distribution
- Purity
- Shape
- Surface area
- Porosity
- Surface charge
- Surface chemistry (composition and reactivity)
- Endotoxin content
- Solubility
- Stability
- Concentration
- Zeta potential
- Surface energy
- Catalytic properties
- Dustiness
- Oleophilicity/hydrophilicity
- Grain size
- Photocatalytyic activity
- Octanol-water partition coefficient
- Redox potential
- Radical formation potential

*Card and Magnuson, J. Food Sci., 74, vi-vii, 2009; MinCHAR project; www.characterizationmatters.org*
*http://www.toxicology.org/isot/ss/nano/docs/Ostraat_guest_presentation.pdf*

# Standardization—Suggested Minimal Characterization of Nanomaterials circa 2019

**ALWAYS**

- **Chemical composition**
- **Average particle size**
- **Particle size distribution**
- **General shape and morphology**
- **Stability, both physical and chemical**

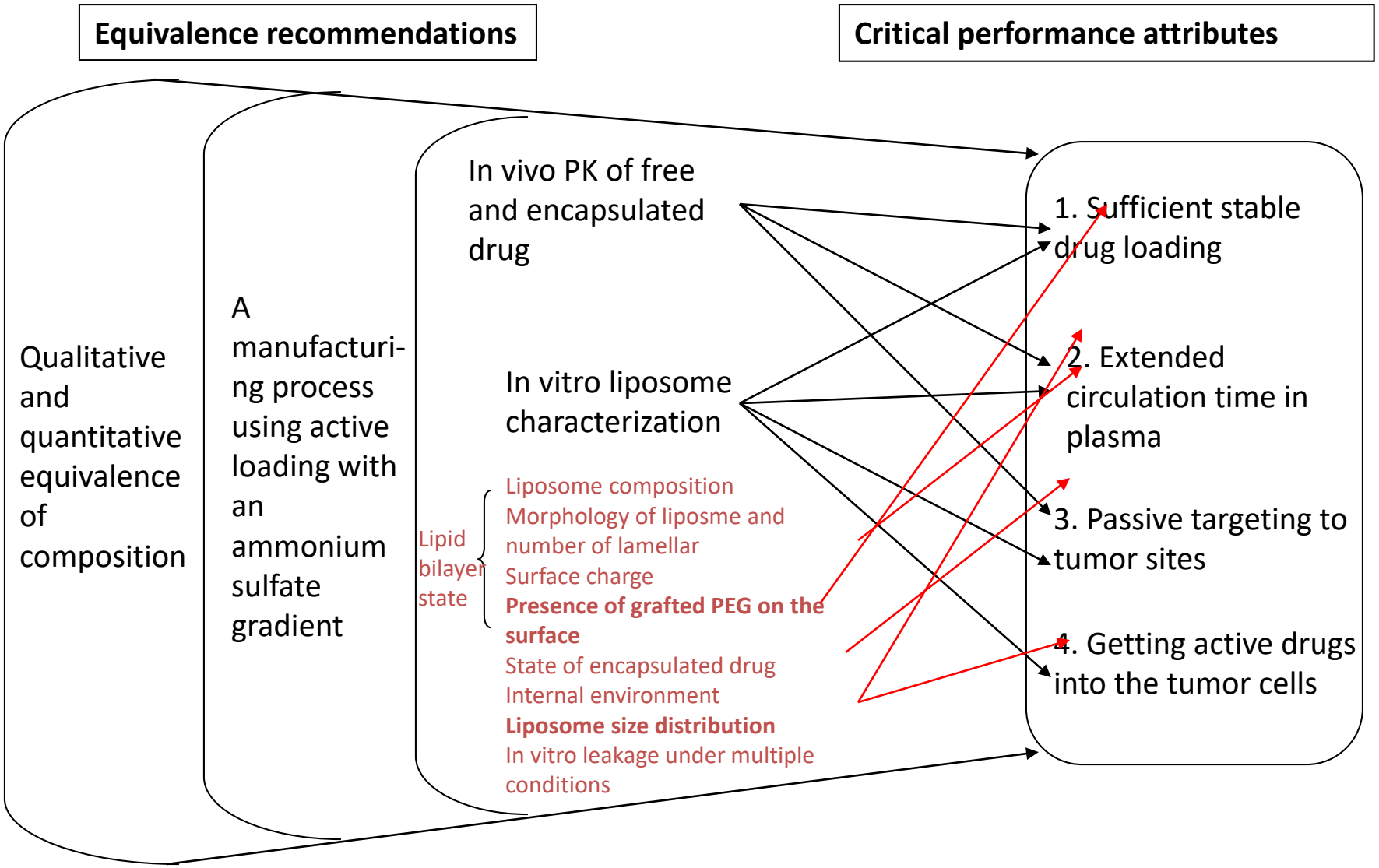
**SOMETIMES**

- Assay and distribution of any active ingredient
  - Associated with the nanomaterial and free in solution
- Structural attributes that relate to function
- Surface properties
- Coating properties
  - Including how coatings are bound to the nanomaterial

- Porosity
- Particle concentration
- In vitro release
- Crystal form
- Impurities
- Sterility and endotoxin levels

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf

# Standardization--Characterization with a Purpose




Liposome Drug Products: Slide from W. Jiang, FDA

# FDA Nanotechnology Standard Participation

- Prioritize nanotechnology standards based on Agency needs
- Assist in the development of standards
- Consolidate FDA comments for nanotechnology standards up for review.

# FDA Nanotechnology Standard Participation

- ASTM International
  - E56 Committee on Nanotechnology
- International Organization for Standardization
  - TC 229 Nanotechnologies
- Organisation for Economic Co-operation and Development
- United States Pharmacopeia (USP)
  - USP Joint Sub-committee on Nanotechnology

# Conclusions

- Regulatory science forms the foundation of science-based regulatory decisions
- Regulatory science can be divided into phases that contribute from the basic understanding of a technology to the development of standards
- Nanotechnology can serve as an example of how to address and incorporate new technology into a regulatory setting
- Standards work is ongoing. Participation is welcome!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