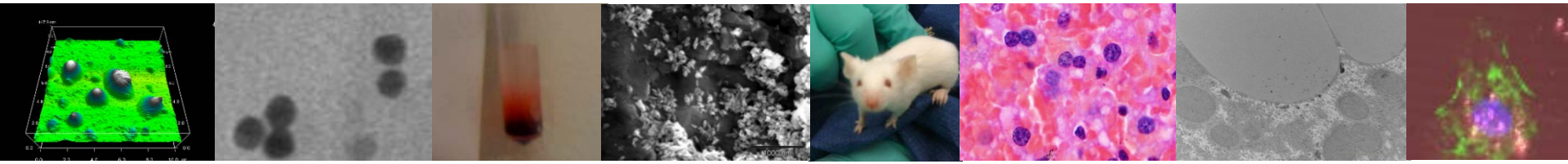
Measuring Exposure Levels of Drug Products Containing Nanomaterials

Katherine Tyner, Ph.D.

CDER/OPQ

US Food and Drug Administration

July 8, 2015



Disclaimer

This talk reflects the views of the author and should not be construed to represent FDA's views or policies The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Agenda

- Considerations for intentional exposure studies
- In vitro examples
- In vivo examples

Agenda

- Considerations for intentional exposure studies
- In vitro examples
- In vivo examples

An Intentional Discussion

- In the majority of instances, the administration of drug products containing nanomaterials means an intentional exposure
  - Unintentional exposure is possible and is part of a robust risk assessment

- Know the exposure has occurred
  - Material
  - Dose
  - Pharmacokinetics/Toxicity (PK/TOX)
  - ADME (adsorption, distribution, metabolism, elimination)

- Detection is still key
  - In vitro
  - In vivo models
  - Clinical

Nanomaterials in Drug Products: CDER Examples

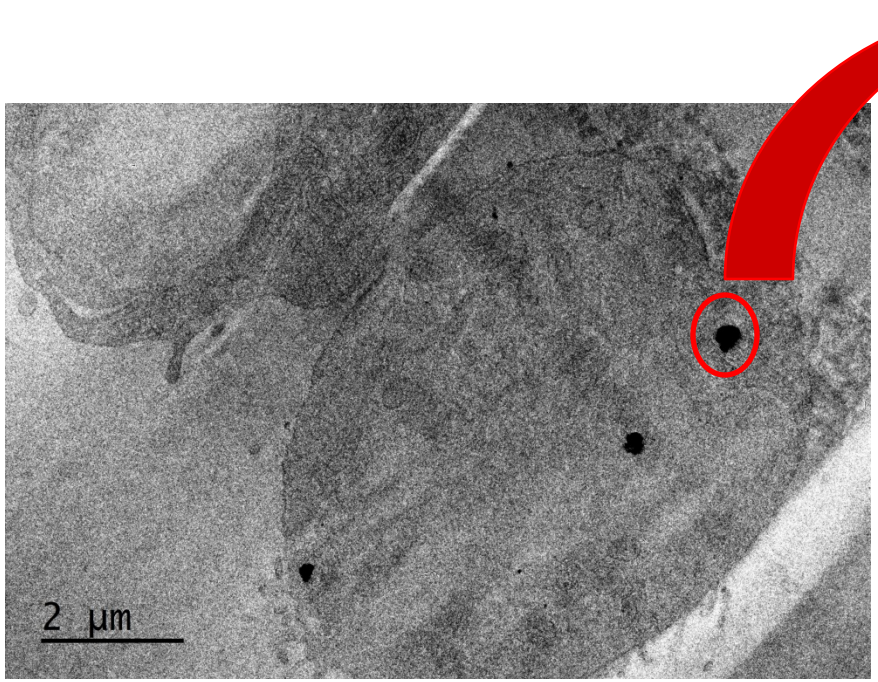
Platform	Example		
	Name	NDA Approval	Indication
Liposome	DOXIL® (Doxorubicin)	1995[1]	Cancer
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999[2]	Anemia
Protein nanoparticle	ABRAXANE® (Paclitaxel)	2005	Cancer
Polymer nanoparticle	MACUGEN® (Pegaptanib sodium)	2004	Macular degeneration.
Emulsion	RESTASIS® (Cyclosporine)	2002	To increase tear production
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegaly
Nanocrystal	TRICOR® (Fenofibrate)	2004[3]	Hypercholesterolemia
Micelle	TAXOTERE®(Docetaxel)	1996	Cancer

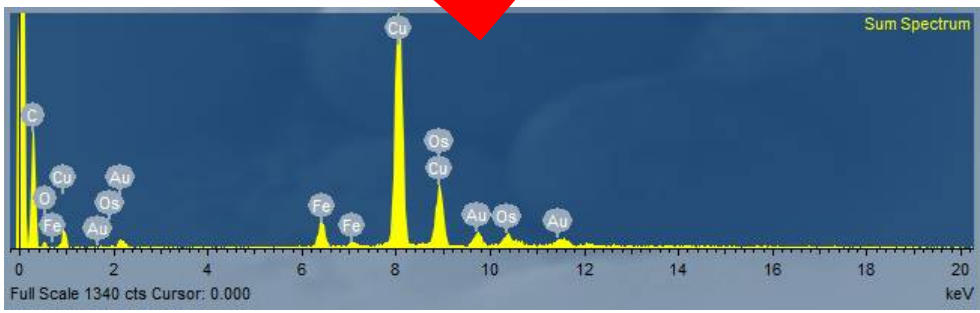
[1] First ANDA approval in 2013
[2] First ANDA approval in 2011
[3] First ANDA approval in 2011

Tyner KT et al. WIRES Nanomedicine and Nanotechnology 2015.

Analytical Methods for Detecting Nanomaterials in Biological Systems

- Non-carbon nanomaterials have methodology for quantification and characterization
  - Detection of elemental signal & visual confirmation
  - Example: ICPMS, TEM/EDS





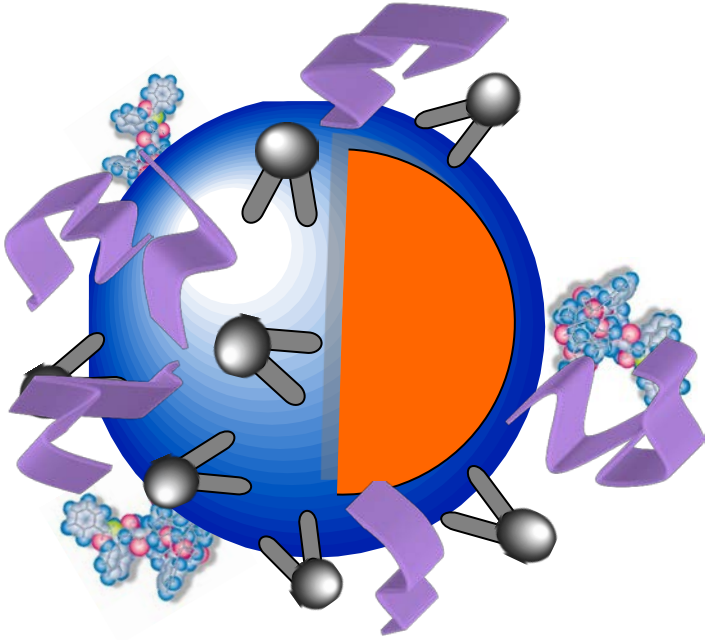
Analytical Methods for Detecting Nanomaterials in Biological Systems

Untreated animal

PK/ADME/Toxicity

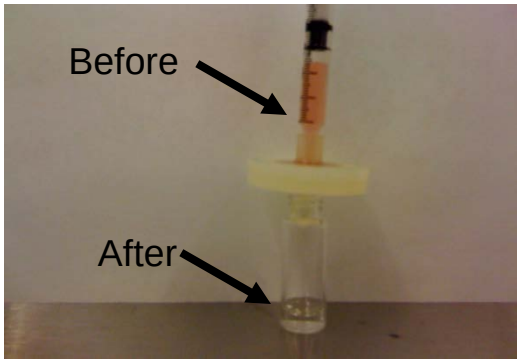
- Pharmacokinetics (PK) is the study of the kinetics of **a**bsorption, **d**istribution, **m**etabolism and **e**xcretion of drugs and their pharmacologic, therapeutic or toxic response in animals and man

- ADME
  - Adsorption
    - How it gets in the body
  - Distribution
    - Where it goes in the body
  - Metabolism
    - How the body breaks it down
  - Elimination
    - How the body gets rid of it



PK/ADME Methods & Nanomaterials

- Analytical methods
  - Most popular techniques for small molecules are radiolabeling and bioanalytical techniques
  - Radiolabeling or fluorescently tagging nanomaterials may alter biodistribution
- Common bioanalytical techniques are not always valid for nanomaterials
  - Example: Nanomaterials interacting with filtration step or chromatography columns
- Variety of matrices
  - Blood, urine, feces, on and off-target tissues
- Questions/considerations
  - What is being measured/labeled (drug vs carrier)?
  - Does the nanomaterial remain intact?
    - How are the constituents being identified
  - Is the bioanalytical method appropriate?
    - Controls
    - Testing conditions



Detection and Quantitation of Nanomaterials in Biological Matrices

- HPLC-MS
  - Dendrimers, Polymers, Drugs, Metabolites, Fullerenes
- Capillary Electrophoresis
  - Fullerenes
- Radiolabeling
  - Liposomes, Dendrimers, Polymers
- ICP-MS & Neutron Activation Analysis
  - Metallic Nanoparticles (e.g., Gold)
  - Metal Oxides
- Electron Microscopy
  - EDS, EELS (Detection and confirmation of composition)
- Optical Microscopy
  - Raman, Hyperspectral imaging (Detection)

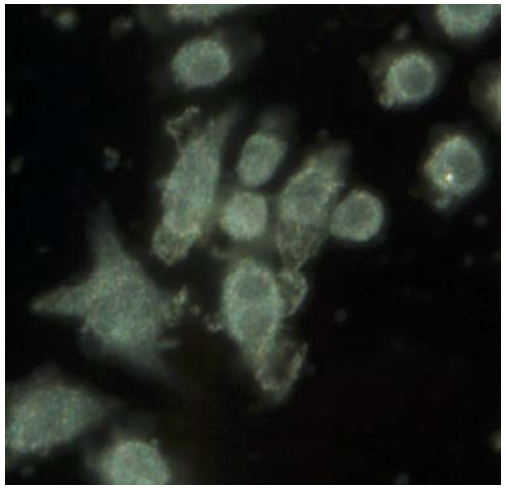
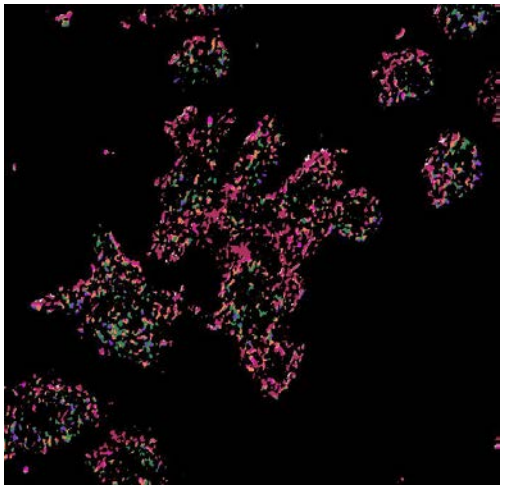
Serum

Serum + Dendrimer

Agenda

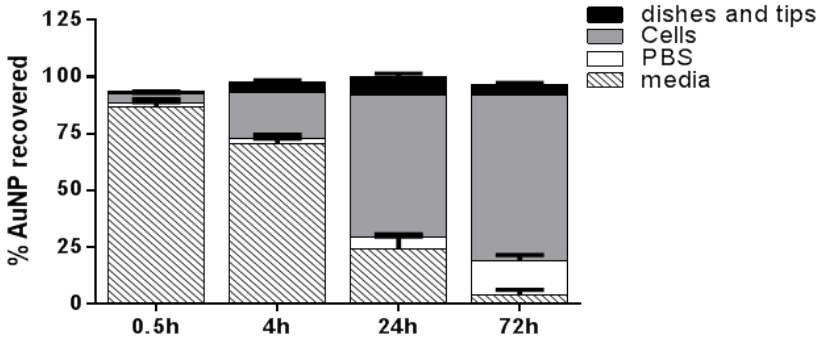
- Considerations for intentional exposure studies
- In vitro examples
- In vivo examples

In Vitro Examples: Is the Method Appropriate? Controls

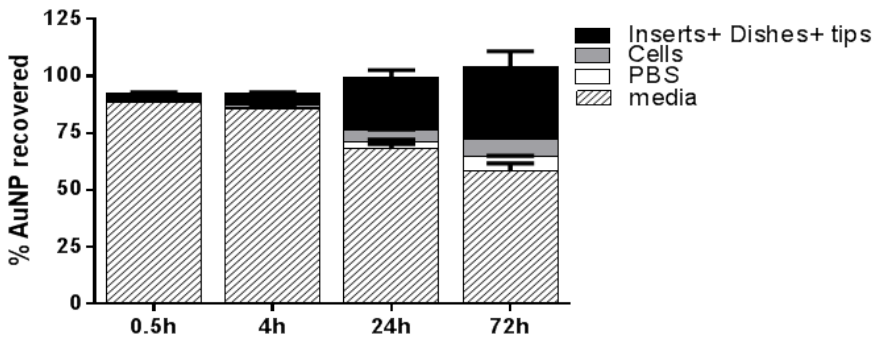
	Hyperspectral Imaging	Positive id
Naïve cells		

In Vitro Examples: Is the Method Appropriate? Design Considerations

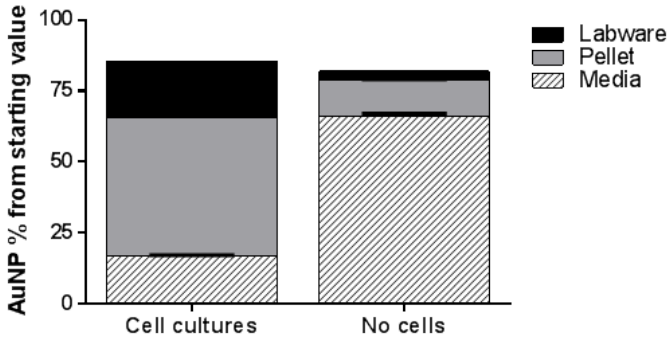
Static-based culture conditions



Inserts-based culture conditions



Suspension-based culture conditions



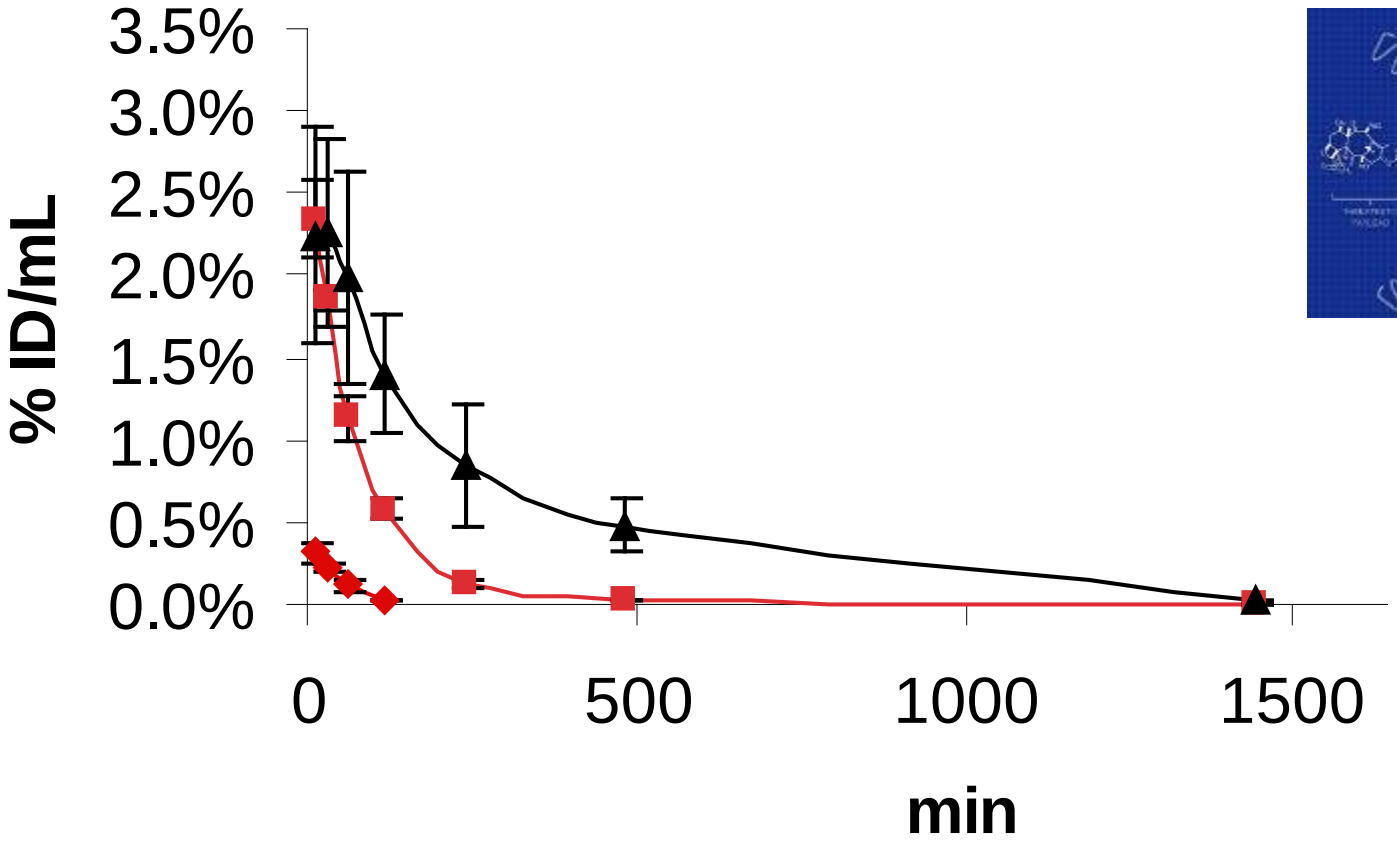
- Mass balance & control of exposure
- Cell culture conditions influence assay results
- Artificial constraints and/or parameters may influence results

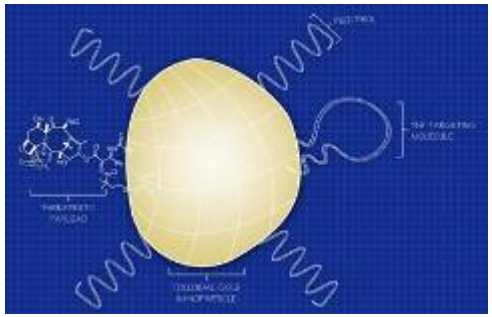
Agenda

- Considerations for intentional exposure studies
- In vitro examples
- In vivo examples

In Vivo Examples

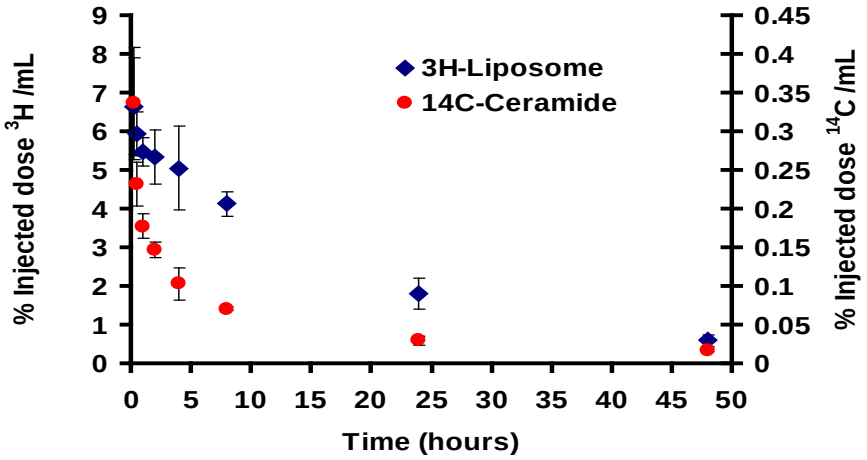
In Vivo Example: What is Being Measured? Complementary Analysis



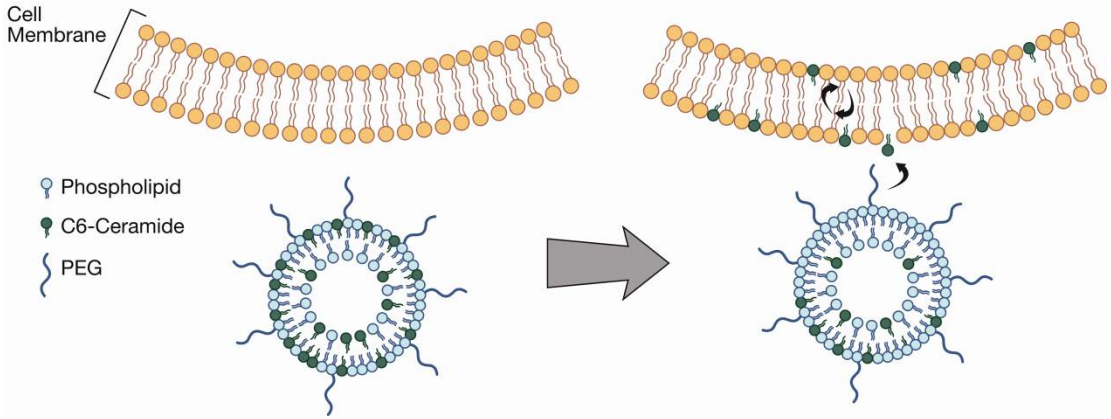


TNF-Au NP PK in rats, [TNF] by ELISA; [Au] by ICP-MS

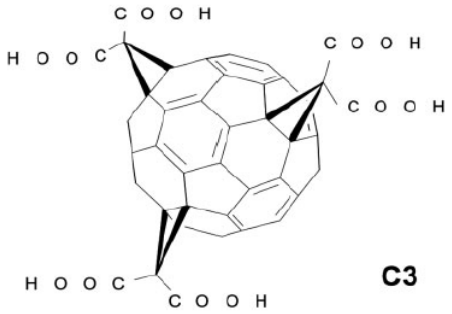
In Vivo Example: Does the Nanomaterial Remain Intact? Dual Labeling

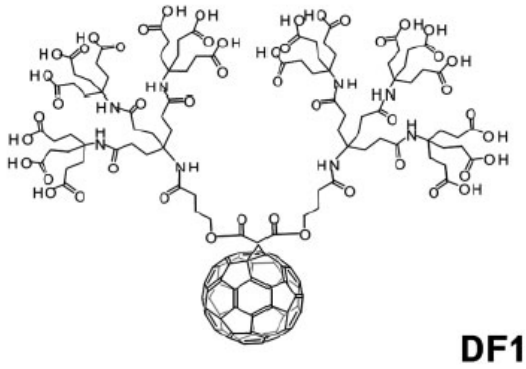


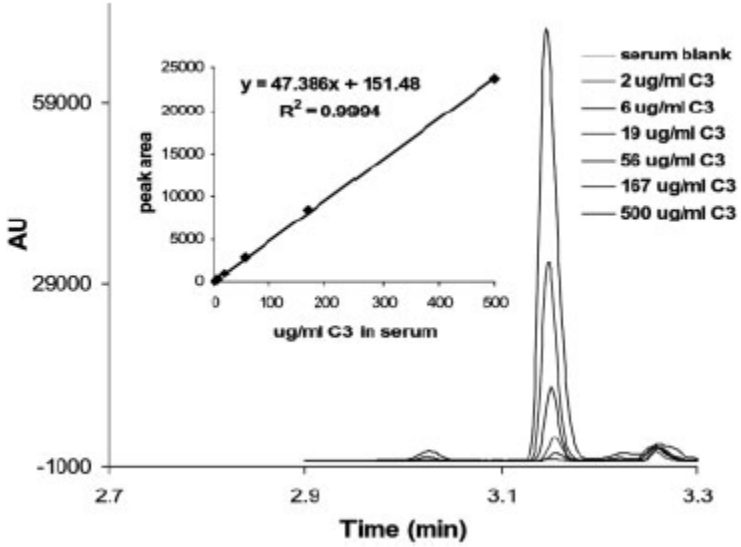
	V_d (mL*kg^{-1})
	Mean ± SD
Ceramide	1020 ± 478
Liposome	63 ± 19

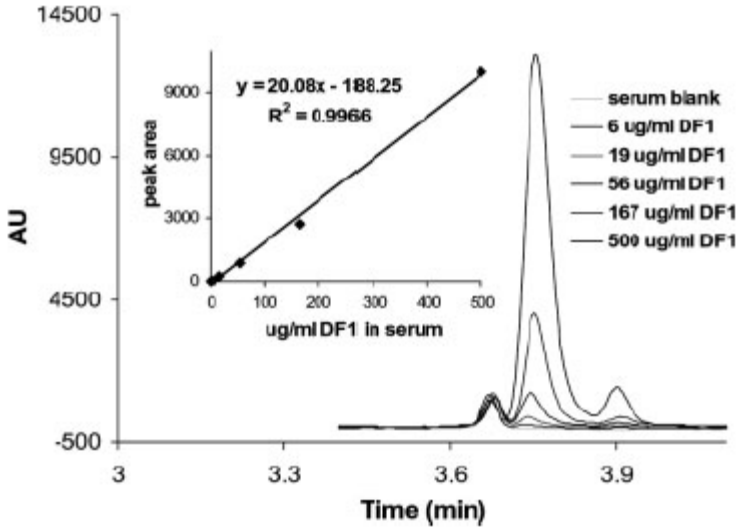


In Vivo Example: Is the Method Appropriate? Capillary Electrophoresis

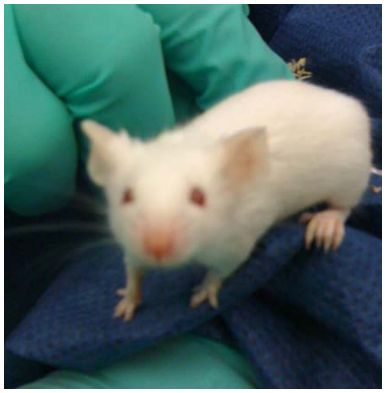


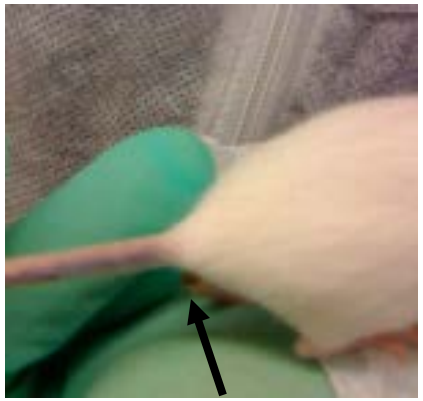


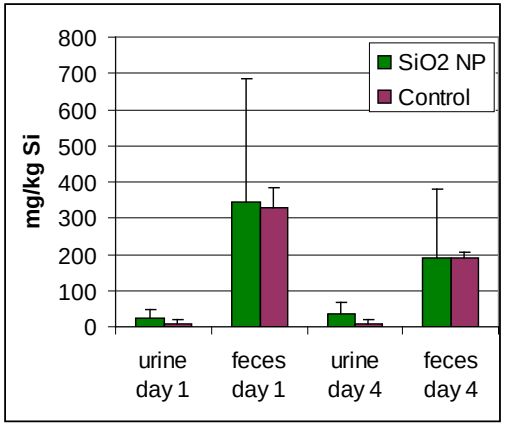




In Vivo Example: Is the Method Appropriate? Testing Considerations







- Detection
- Limits of detection
- Limits of quantification
- Nanomaterial interference
- Appropriate controls
- Well-designed studies

Conclusions

- PK/ADME determination for drug products containing nanomaterials is an evolving area
- Techniques & methods exist to detect nanomaterials within biological tissues
  - Multiple endpoints/methods
- Multiple issues and/or considerations may confound method development and analysis
  - Appropriate controls
  - Well designed studies
- Regulatory science projects continue to address these issues
  - Collaboration opportunities!

Acknowledgements

- Dr. Anil Patri, Director, NCTR-ORA Nanotechnology Core Facility

- The Nanotechnology Characterization Laboratory

- The authors would like to acknowledge the FDA White Oak Nanotechnology Core Facility for instrument use, scientific and technical assistance