FDA and Nanotechnology for Medical Products

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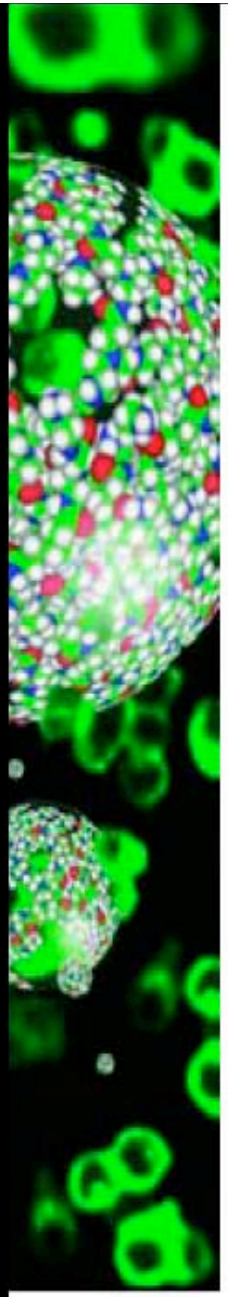
May 7, 2010



Nanotechnology

A Report of the

U.S. Food and Drug Administration

Nanotechnology Task Force

July 25, 2007

The "Nanotechnology Task Force" coordinates policy across centers.

The Centers have their own nano discussion groups.

The 2007 Task Force Report still stands as the policy evaluation for all centers.

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf

Content of the Task Force Report

- Recommendations about definitions
- Synopsis of the state of the science with respect to biological interactions of nanoscale materials relevant to FDA mission
- Analysis and recommendations for science needs
- Analysis and recommendations for regulatory policy needs

Definitions

- No FDA-wide definition of “nano” offered
- Concluded that size is relevant, but not sufficient for regulatory distinction
- At some point, definitions or specifications could be tailored to specific product areas

Task Force Bottom Lines

- Nanoscale materials could be used in most types of products regulated by FDA
- Nanoscale materials present challenges similar to other emerging technologies
- The fact that safety and efficacy can vary with size can complicate the challenges

Bottom Lines (continued)

- Not apparent that nanoscale materials as a group would have more inherent hazard than other materials as a group
- Steps should be taken to better inform FDA reviewers and industry about what is known and expected for analysis of nanoscale materials in products.

NTF Policy recommendations

- Science – FDA needs methods, data, modeling/extrapolation, and expertise
- Regulation
  - Guidance for identification of nano characteristics in product authorization submissions,
  - Guidance for safety/efficacy assessment
  - Issue a “Call” for safety data
  - Address Labeling and Environmental Impacts on a case by case basis

Problem areas for FDA nano regulatory policy

- GRAS food additives
- Dietary supplements
- Cosmetics
- OTC monographs
- Device 510k
- Assuring manufacturing consistency
- Developing assays and metrics relevant to nanomaterials

National Environmental Policy Act (NEPA)

- "Case by case" consideration for nanomaterials with respect to categorical exclusions (CE).
  - A broad policy of NOT allowing the exclusion was not taken.
- Do the 1980's CE arguments and data apply to nanomaterials?
- NEPA revisions by the White House Council on Environmental Quality may force a re-evaluation.

Europe:US

- FDA and EMEA continue to track together on NMs
- Labeling for cosmetics and foods diverging from FDA – similar to biotech foods
- Still possible that “chemical regulation” for NMs will not differ substantially (REACH vs TSCA and TSCA reformed)

Marketed prescription drugs with nanoscale particles (2008)

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	100-1000nm
Emend	Nanocrystal/Aprepitant	Antiemitic	100-1000 nm
TriCor	Nanocrystal/Fenofibrate	Hypolipidemic	
Megace ES	Nanocrystal/Megesterol 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	Lipid coated gas particles	Echography contrast agent	

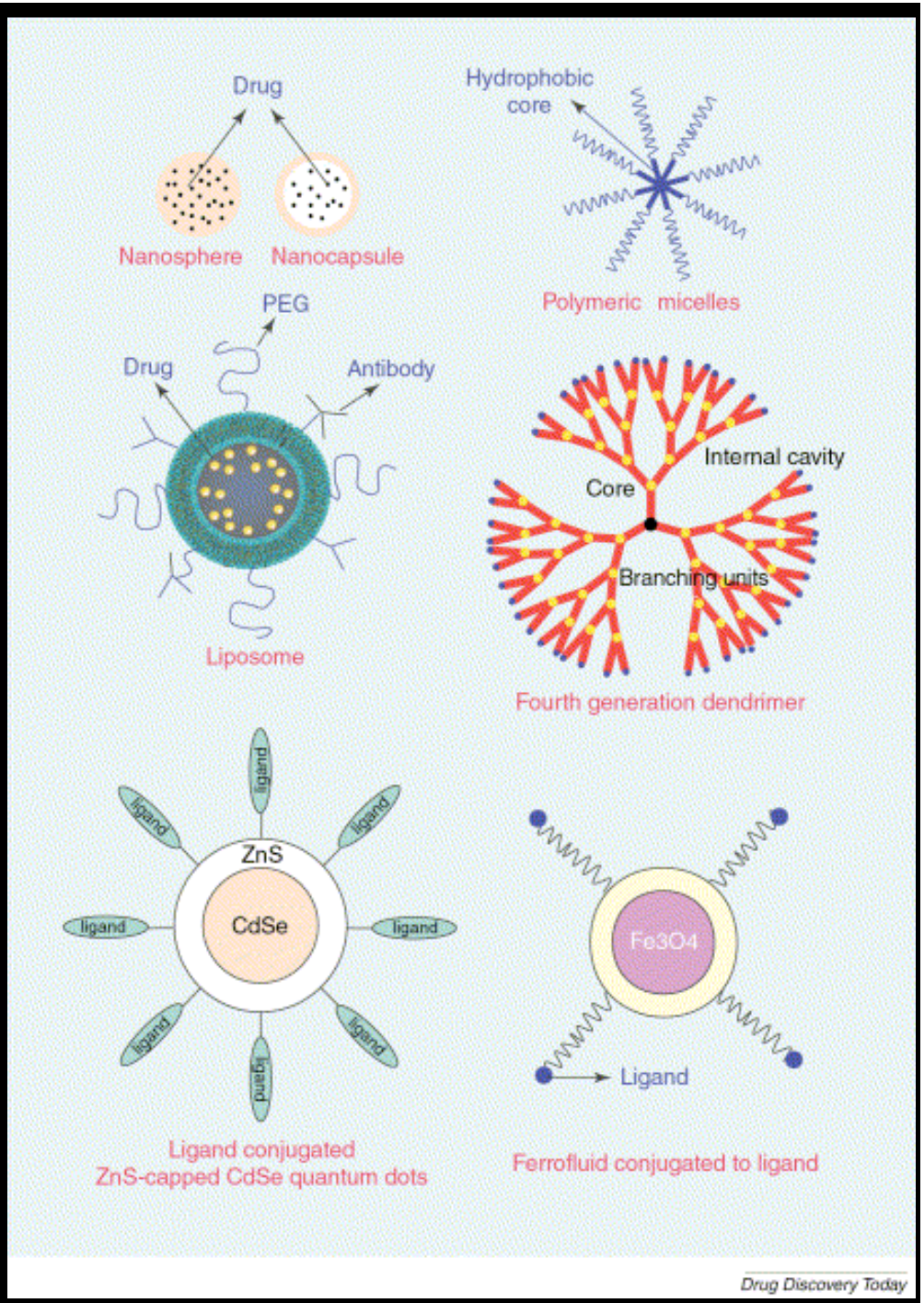
Source: Nakissa Sadreih, FDA

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)

Source: Nakissa Sadreih, FDA



Approved Device Products with Nanoscale Features (2008)

Office of Device Evaluation

- NanoComposite -- Cosmedent Inc. (Dental filling material)
- Filtek Supreme -- 3M ESPE (Dental filling material)
- Simile Nano-Hybrid -- Pentron Labs (Dental filling material)
- Condyloform II NFC (k060565) - Dental filling material - (IVOCLAR VIVADENT, INC.)
- NanOss -- Angstrom Medica (Orthopedic bone filler)
- On-Q Silver Soaker Catheter -- I-Flow Corp (Catheter)
- Silver Bandage -- Curad (bandage)

*Not a complete list

Source: Subhas Malgan, FDA

Approved Device Products with Nanoscale Features (2008)

Office of Invitro-Diagnostic Device Evaluation and Safety

- Verigene Warfarin Metabolism Nucleic Acid Test, Nanosphere Inc. (Warfarin sensitivity)
- Verigene® F5,F2, MTHFR Nucleic Acid Test (k070597) - Detection of point mutation in human Factor V gene (NANOSPHERE, INC.)
- The GeneSearch™ Breast Lymph Node Assay --- molecular diagnostics assay for breast lymph node testing, Veridex LLC
- CellSearch Circulating Tumor Cell Kit (Epithelial) (k071729) - Detect circulating tumor cells in breast cancer and colon cancer (VERIDEX, LLC)

*Not a complete list

Source: Daya Ranamukhaarachchi, FDA

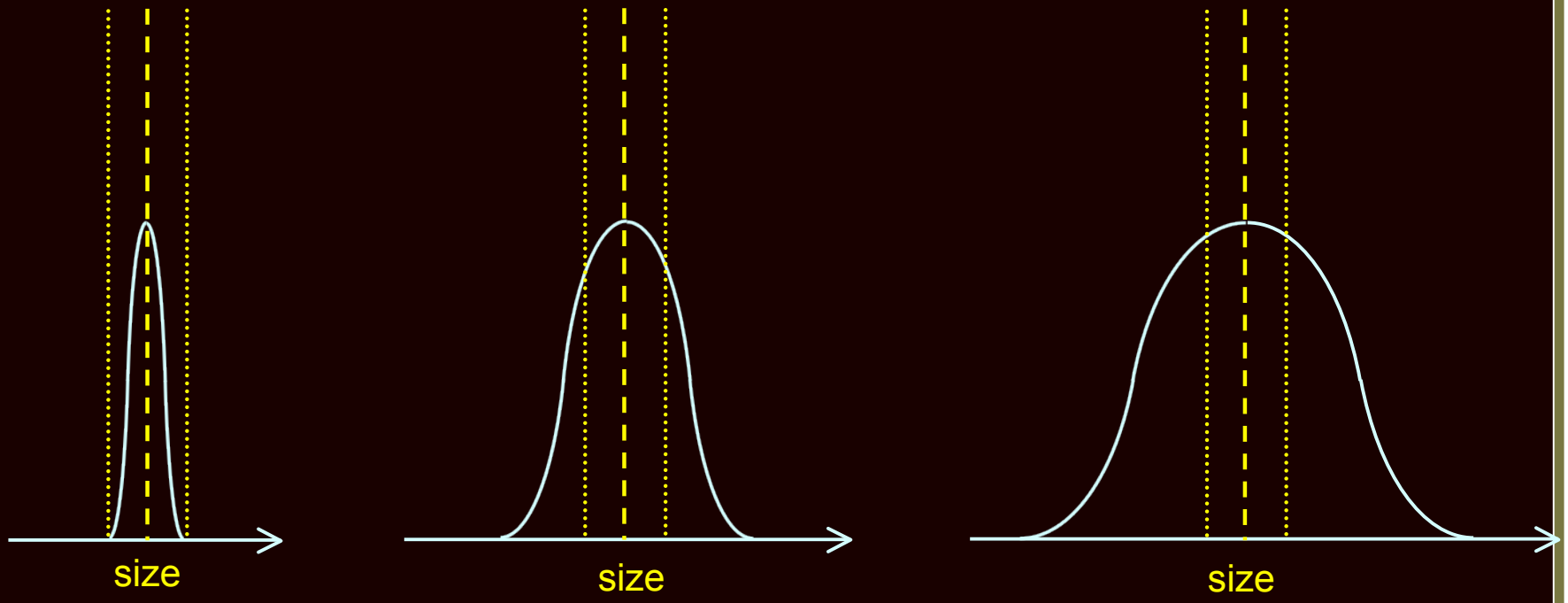
Challenges

- Clear, predictable review pathway
  - Analytic methodologies
  - Preclinical assays
  - Dose assurance (dose metrics)
- Manufacturing/characterization
- Device/Pharmaceutical integration
- Common carriers, Combinatorics

Precompetitive needs "Critical Path"

- Data types – e.g., how to measure size, morphology
- Instrumentation – is there a common need
- Assays – what to validate, what to standardize
- Where are the stumbling blocks?

What does “impurity” mean for a nanomaterial when size determines properties?

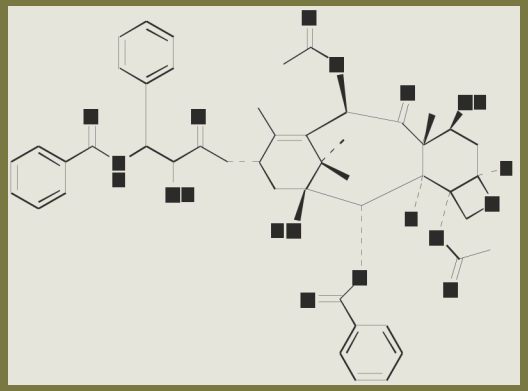


100% within range

50% within range
50% impurity?

10% within range
90% impurity?

New versus Old Methods

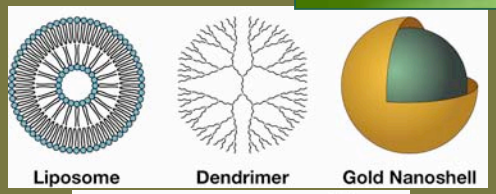


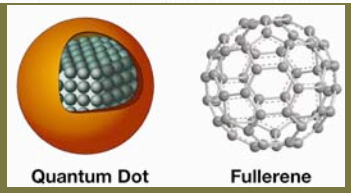
Small Molecules

- Elemental analysis
- Mass Spec
- NMR
- UV-Vis
- IR
- HPLC
- GC
- Polarimetry

Physicochemical Parameters

- **Composition**
- **Physical properties**
- **Chemical properties**
- **Identification**
- **Quality**
- **Purity**
- **Stability**





Nanomaterial

- Microscopy (AFM, TEM, SEM)
- Light scattering (Static, Dynamic)
- SEC, FFF
- Electrophoresis (CE, PAGE)
- Zeta sizer
- Fluorimetry

Same parameters – different/additional characterization methods

What FDA is doing

- Guidance to industry
  - Foods
    - What to report
    - How to assess safety
    - What is a “new” manufacturing change
  - Codification of the Nano Task Force report
- MaPP guidance to reviewers (CDER)
- OTC monograph comment/revision (sunscreens)
- Looking for places to add data requirements

The Center for Foods is leading FDA policy development

- CFSAN guidance requires nanoscale data
- Is developing guidance on manufacturing process changes that will apply to NMs
- Is developing guidance on safety assessment (tox testing) for NMs
- These guidances are pressuring CDER, CBER, CDRH to do something similar

MaPP guidance for CDER to begin capturing nanoscale data

- MANUAL OF POLICIES AND PROCEDURES for nanomaterials, in final review
- Existing data on size will be captured in standard formats
  - No new data questions in the MaPP
  - But the next step is probably a guidance change that asks for data on size and surface characteristics
- Data collection will allow recognition of nano products and coordinated reviews

Nanotechnology Characterization Laboratory (National Cancer Inst)

- “reduce the cost and risk associated with the development pathway by standardizing the pre-clinical efficacy and toxicity testing and to facilitate the regulatory review process.”

NCI/NCL Approach

- “Incubator” for companies to develop preclinical data
- Collaborate with National Institute on Standards and Technology on methods
- Form communication channels with FDA
  - Reviewers
  - Researchers (NCTR, CDER, CBER, CDRH)
  - Policy makers

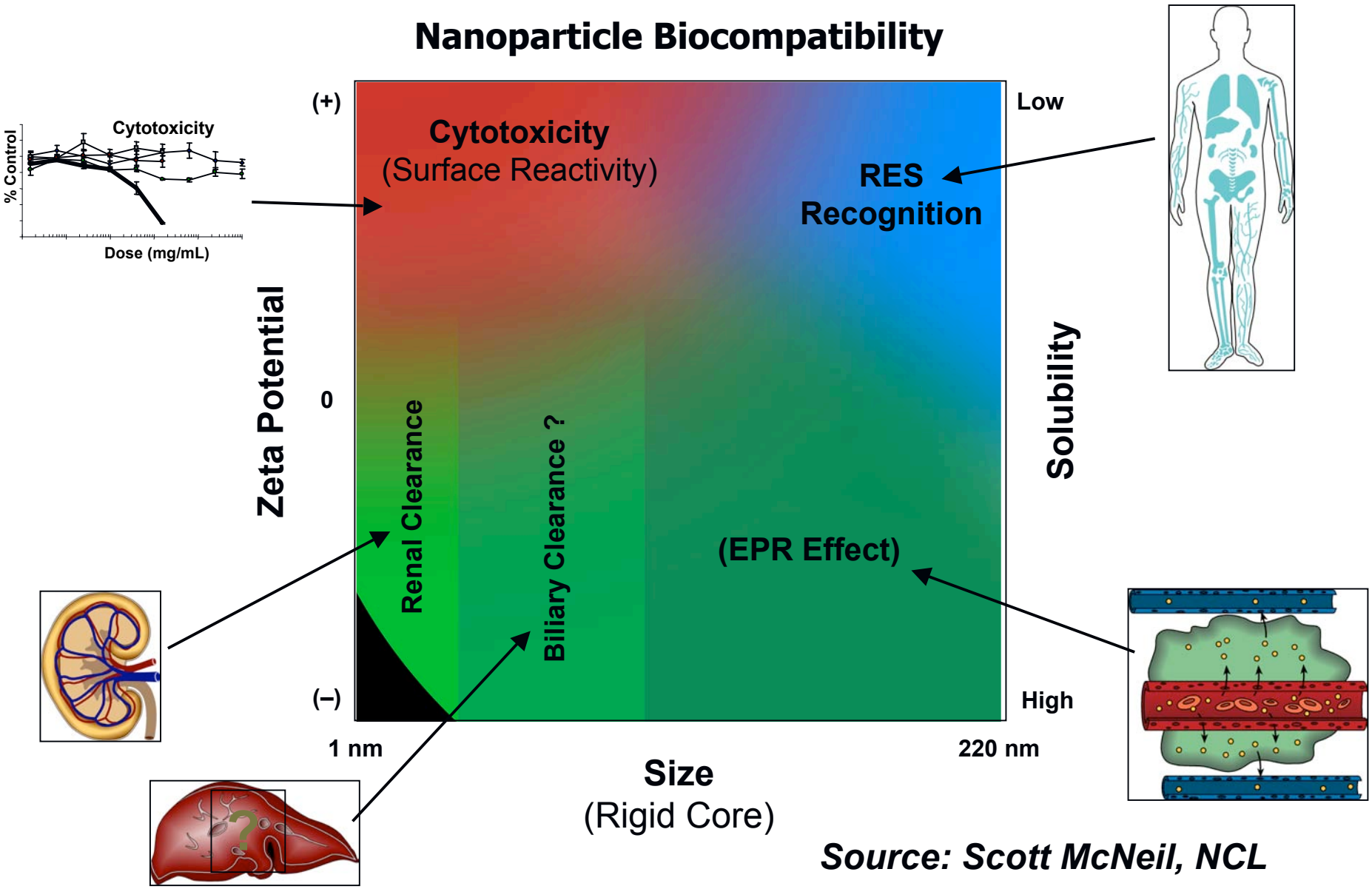
NCL Assay cascade

- http://ncl.cancer.gov/working_assay-cascade.asp
- Has the effect of developing guidance for FDA on how to test NMs
- Same methods for each partner
  - Particle characterization
  - In vitro and in vivo assays
- Convey what is discovered to standard methods

Some of what has come up at NCL

- How you measure and report size affects what “the size” is and its utility for predicting biological response
- Tracking carrier and payload for NMs can be challenging
- “particle pharmacokinetics”

Trends: Biocompatibility



Source: Scott McNeil, NCL

Thank you

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