FDA's Regulatory Science Program in Nanotechnology

Science Board Update

October 3, 2012
FDA Nanotechnology Task Force

U.S. Food and Drug Administration
Advancing Regulatory Science

Outline

Why should FDA focus on Nanotechnology?

FDA's Regulatory Science Approach to Nanotechnology

Detailed Review of FDA's Regulatory Science Programmatic Investment Areas

New Legislation relevant to Nanotechnology

Wrap Up

Why should FDA focus on Nano?

National Nanotechnology Initiative

Drug Delivery Systems

Food Applications

NNI Signature Initiatives

Veterinary Medicine

Medical Devices

Dietary Supplements

Nanotechnology-enabled Products

Sunscreens

Cosmetics

Wound Dressings

Why Do We Need Regulatory Science?

- Enable major investments and advances in basic sciences to translate faster into products to benefit consumers
- Protect consumers by applying best possible science to support regulatory activities and decision-making
  - Pre-market review
  - Post-market surveillance
- Keep pace with and fully utilize advances in innovation, while also facilitating development of innovative products that benefit consumers and patients

FDA's Nanotechnology Regulatory Science Plan

http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

Program Management

- Program Administration
- Tracking Projects
- Coordination
- Oversight

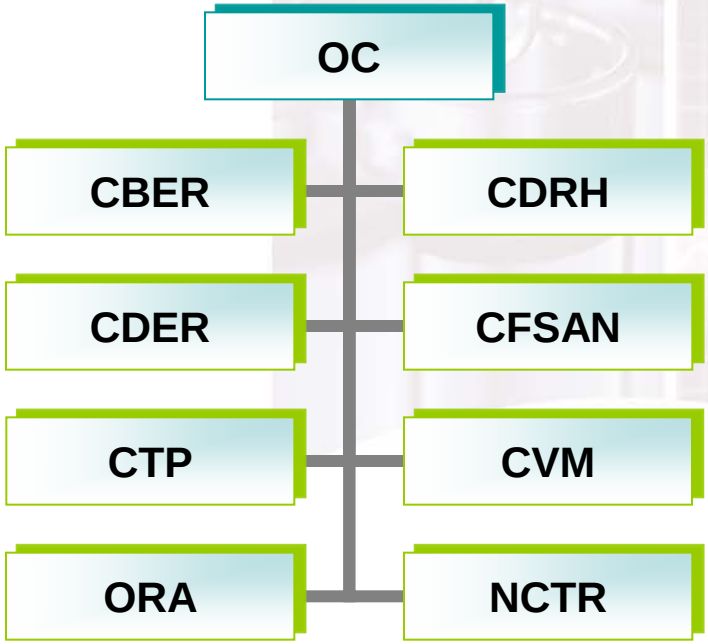
Strategic Partnerships

- Domestic
- International

FDA's Regulatory Science Approach to Nanotechnology

Nanotechnology Coordination

Internal – Nanotechnology Task Force



External (United States Government) – National Nanotechnology Initiative

FDA Programmatic Investment Area	2011	2012	2013	Program
FDA Staff Training	X	X	X	Center Workshops
	X	X	X	Introduction to Nanotechnology online
		X	X	Applied Courses in Nanotechnology online
		(pilot)	X	Hands On Laboratory Course
			X	*Ad hoc* Topic Specific/Product Relevant Review Courses
			X	External Training Opportunities
			X	FDA Nanotechnology Regulatory Science Research Workshop
FDA Core Facilities	X	X	X	Center Specific Laboratories
	X	X	X	NCTR Core Facility
		X	X	White Oak Core Facility
		X	X	FDA Coordination Plan (Safety, Toxicology, Characterization, Manufacturing)
			X	Public Private Partnerships with External Stakeholders
			X	Joint funding Laboratory Facility Projects
FDA Intramural Regulatory Science Research (CORES)	X	X	X	Center Specific Projects
	X	X	X	CORES Program
		X	X	External Peer-Review
			X	Engage Domestic & International Research Opportunities
			X	Additional Product Specific Regulatory Science Research

Staff Training and Professional Development Program

FDA Programmatic Investment Area	2011	2012	2013	Program
FDA Staff Training	X	X	X	Center Workshops
	X	X	X	Introduction to Nanotechnology online
		X	X	Applied Courses in Nanotechnology online
		X (pilot)	X	Hands On Laboratory Course
			X	*Ad hoc* Topic Specific/Product Relevant Review Courses
			X	External Training Opportunities
			X	FDA Nanotechnology Regulatory Science Research Workshop

Staff Training and Professional Development

Target Audiences

Staff with different needs

- Review Staff
- Research Staff
- Field Staff
- Regulatory Policy Staff

Staff Training and Professional Development

Title: *Introduction to Nanotechnology Science and Regulation at the U.S. FDA*

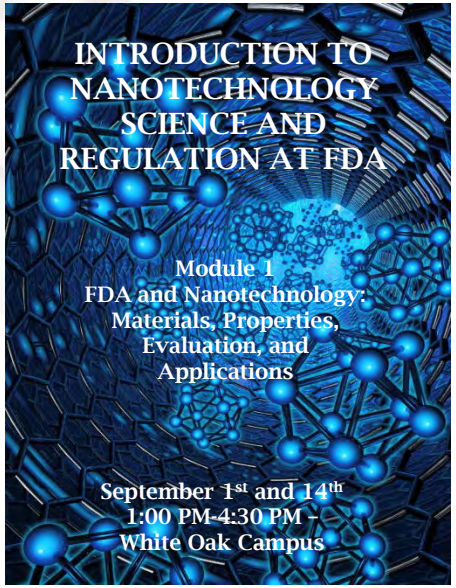
Module 1 – FDA and Nanotechnology: Materials, Properties, Evaluation, and Applications
Module 2 – Nanotechnology: FDA and USG Activities and Perspectives

Time: Fall 2011

Location: White Oak Campus

Hours: 16

Speakers: Outside experts, FDA staff experts, and agency representatives



Staff Training and Professional Development

Title: *Applied Sciences Course in Nanotechnology*

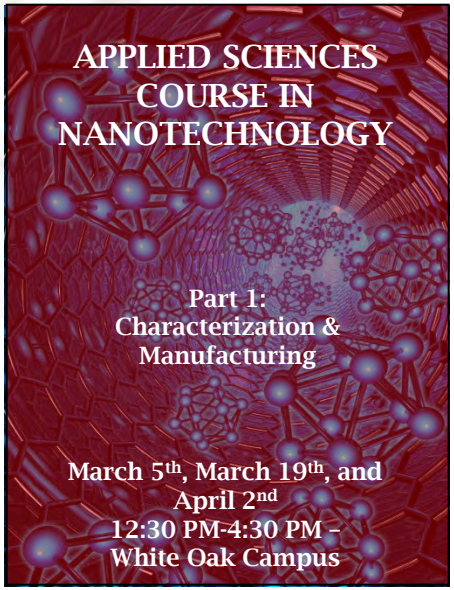
Part 1 – Characterization & Manufacturing
Part 2 – Safety & Toxicology

Time: Spring 2012

Location: White Oak Campus

Hours: 20

Speakers: Outside experts and FDA staff experts



Staff Training and Professional Development

Title: *NCL: Lessons Learned Workshop 2011 @ FDA*

Time: Fall 2011

Location: White Oak Campus

Hours: 8

Speakers: Nanotechnology Characterization Laboratory

Title: *Hands-On Laboratory Course Pilot*

Time: Summer 2012

Location: NCTR Campus

Hours: 16

Focus: Physical-Chemical Characterization of Nanomaterials

Upcoming Staff Training at FDA

- Product Specific/Regulatory Review Seminars
- Hands On Laboratory Course
- FDA Nanotechnology Regulatory Science Research Workshop

FDA Laboratory Facilities

FDA Programmatic Investment Area	2011	2012	2013	Program
FDA Core Facilities	X	X	X	Center Specific Laboratories
	X	X	X	NCTR Core Facility
		X	X	White Oak Core Facility
		X	X	FDA Coordination Plan (Safety, Toxicology, Characterization, Manufacturing)
			X	Public Private Partnerships with External Stakeholders
			X	Joint funding Laboratory Facility Projects

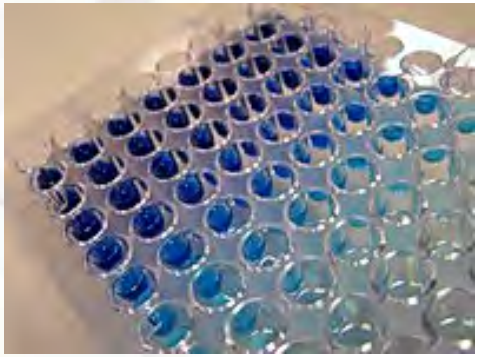
Important Considerations for Regulating Nanomaterial-Containing Products

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

Core Laboratory Facilities

Nanotechnology Regulation Requires:

Equipment + **Personnel** + **Methodologies**

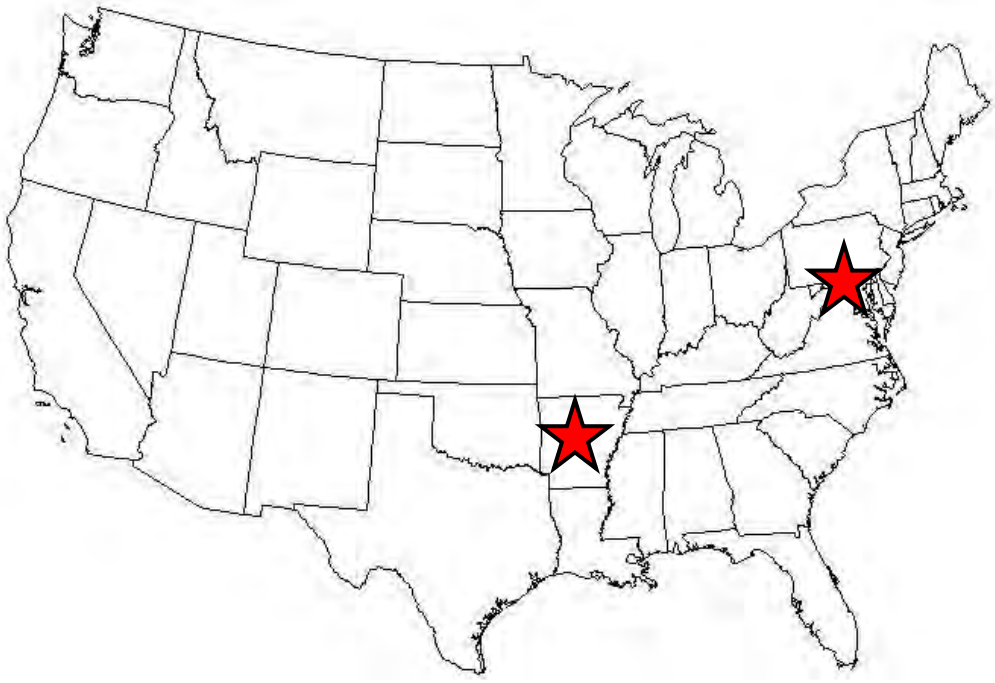


To allow for appropriate:
1) Characterization & Manufacturing Studies and
2) Safety and Biocompatibility Studies

FDA Laboratory Facilities

Purpose: to provide the equipment, expertise, and infrastructure to support nanotechnology regulatory science research within the FDA and collaborating organizations.

Location: two major facilities; White Oak campus, Jefferson AR campus.



Nanotechnology Core Facility: Characterization & Equipment

	TEM (EDS)	SEM (EDS)	AFM	ICP-MS	XRF	Particle Size Analysis	FFF	Surface Area Analysis	Confocal Raman	other
Average particle size, and size distribution	X	X	X			X	X			
Agglomeration and aggregation state		X	X			X	X			
Shape	X	X	X							
Chemical composition and purity	X	X		X	X				X	
Crystal structure										X
Surface area	X							X		
Surface chemistry (reactivity, hydrophobicity, porosity)								X		X
Surface charge						X				
Stability in bulk	X			X		X		X		
Stability in dosing solutions or test media	X		X			X				
Spectral properties									X	X
Endotoxin content and sterility										X
Detection in biological matrices	X	X	X	X	X		X		X	X

Equipment Core Facilities Use/Outcomes

- Support the conduct of research to establish methods for use by Agency scientists (e.g. quantification of nanomaterial ionization in vitro and in vivo);
- Provide equipment and expertise to conduct specific measurements or assays for FDA scientists;
- Provide within-Agency expertise for confidential consultations regarding nanomaterial characterization or quantification;
- Provide equipment and expertise to train Agency scientists on measurement techniques for nanomaterials (“hands-on”);
- Maintain equipment for use by Agency scientists on projects;
- Augment other existing equipment at each Center.

FDA's CORES Regulatory Science Research Program

(Collaborative Opportunities for Research Excellence in Science)

FDA Programmatic Investment Area	2011	2012	2013	Program
FDA Intramural Regulatory Science Research (CORES)	X	X	X	Center Specific Projects
	X	X	X	CORES Program continuing
		X	X	External Peer-Review
			X	Engage Domestic & International Research Opportunities
			X	Additional Product Specific Regulatory Science Research

FDA's Nanotechnology CORES Program

Collaborative **O**pportunities for **R**esearch **E**xcellence in **S**cience

- Physico-chemical characterization in FDA-regulated products
- Nonclinical modeling of nanomaterials in FDA-regulated products
- Risk characterization information
- Risk assessment
- Risk communication

FDA's CORES Awards

FY11:

Center	PI	Title
NCTR	Dr. Tao Chen	Development and Evaluation of Exposure Dosimetry Methods to Optimize the Standard In Vitro Mammalian Genotoxicity Assays for Engineered Nanomaterials
CBER	Dr. Jan Simak	*In Vitro* Evaluation of Effects of Engineered Nanomaterials on Blood Platelets
CFSAN	Dr. J.J. Yin	Use of Electron Spin Resonance Spectroscopy (ESR) and Biomarkers of Oxidative Damage to Assess the Safety of Nanomaterials Used in Cosmetics

FY12:

Center	PI	Title
NCTR	Dr. Tao Chen	Do Engineered Silver Nanomaterials Varying by Size and Coatings Behave Differently than Bulk Silver in their Ability to Induce Genetic Damage?
CBER	Dr. Jan Simak	*In Vitro* Evaluation of Effects of Engineered Nanomaterials on Blood Platelets
CDRH	Dr. B. Dair	Biological Evaluation and Safety Assessment of FDA-regulated Products with Nano-engineered Surfaces

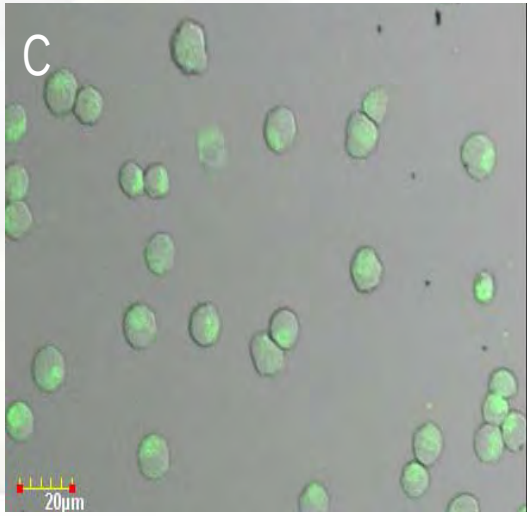
FY11 CORES Project – Tao Chen, Ph.D., D.A.B.T.

Evaluation of the Standard Genotoxicity Assays for Assessing Engineered Nanomaterials

Project Objective: To evaluate whether current mammalian genotoxicity assays are suitable for assessing the genotoxicity of nanomaterials.

Results: The obtained results suggest that the mammalian assays can detect genotoxicity of some nanomaterials, but not the Ames test; however, many factors such as cell uptake of nanomaterials, selection of cell lines, coating, size and aggregation status in relevant media impact the outcome of the assay.

Regulatory Impact: The obtained data can be used for improving guidance to sponsors on preclinical evaluations of genotoxicity of nanomaterials.



Publications:

1. Li, Y et al: ***Mutat Res – Gen Tox En***, 2012
2. Mei N et al: ***Environ Mol Mutagen***, 2012
3. Woodruff et al: ***J Appl Toxicol***, 2012 (in press)

FY11 CORES Project – Jan Simak, Ph.D.

In Vitro Evaluation of Effects of Engineered Nanomaterials on Blood Platelets

Project Objective: Develop a panel of in vitro assays for evaluation of effects of nanomaterials on blood platelets and investigation of platelet interactions with selected nanomaterials.

Results: 1) Design an on-going research validation of the panel of in vitro assays

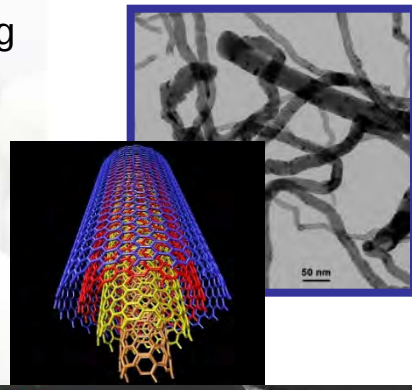
2) Elucidate a mechanism of platelet activation by carbon nanotubes

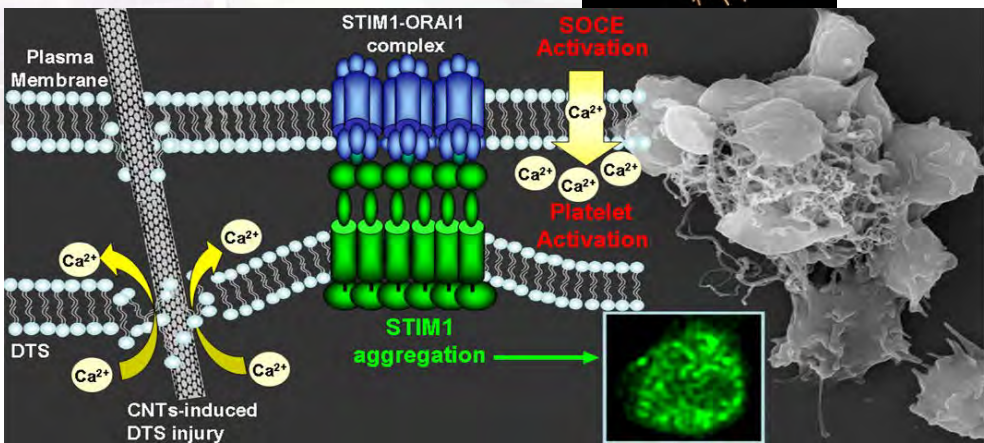
3) Elucidate nanoparticle size/charge effects on interactions with platelets in a PAMAM dendrimer model

Regulatory Impact: 1) Availability of in vitro tests for preclinical safety assessment for nanotechnology products

2) Risk communication and understanding thrombogenicity of carbon nanotubes

3) Tools for prediction of thrombogenicity based on size/charge characteristics of nanoparticles



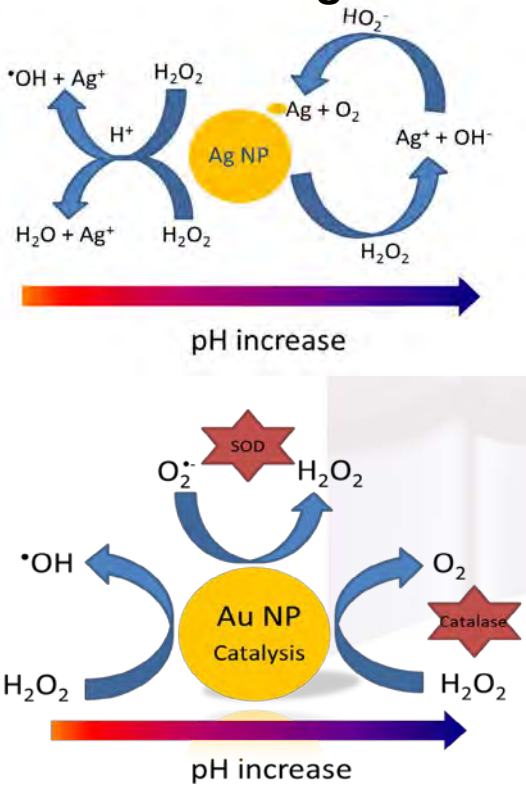


Publications:

1. Simak J. In: ***Handbook of Immunol. Prop. Of Eng. Nanomaterials***, 2012 (in press)
2. Lacerda SH et al: ***ACS Nano***, 2011
3.Dobrovolskaia MA et al: ***Mol Pharm***, 2012

FY11 CORES Project – Jun-Jie Yin, Ph.D.

Use of Electron Spin Resonance Spectroscopy (ESR) and Biomarkers of Oxidative Damage to Assess the Safety of Nanomaterials Used in Cosmetics



Schematic presentation of Ag NPs and Au NPs triggering the generation of hydroxyl radicals and oxygen controlled by pH.

Project Objective Using ESR, to develop rapid and predictive tests to screen nanomaterials for their ability to generate reactive oxygen species (ROS). The focus is on nanomaterials used in cosmetics.

Results: Using ESR, we observed that both Au and Ag NPs could enhance the generation of hydroxyl radical and oxygen in biologically relevant systems. Also, we found that Au NPs showed SOD like activity, i.e., reduced levels of superoxide. These results may provide insights for evaluating the biosafety and risks associated with Au and Ag NPs in commercial applications.

Regulatory Impact: The development of methods for identifying FDA regulated products that may contain nanomaterials and which may increase levels of oxidative intermediates under physiological conditions.

Publications:

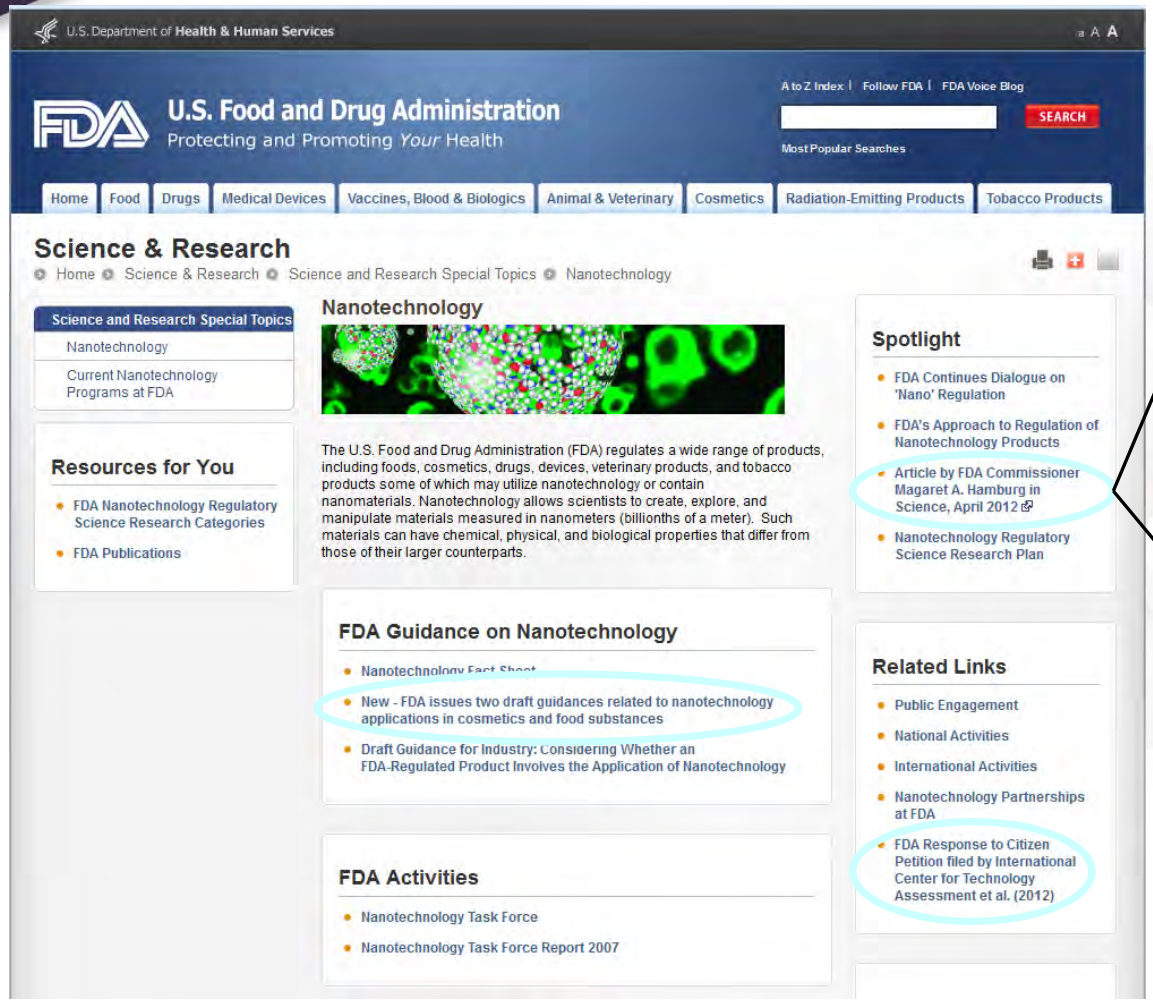
1. On Ag NP***: Biomaterials*** (2012) 33:7547-55.
2. On Au NP: ***Biomaterials*** (under review)

Wrap Up

FDA Advances in Nanotechnology

- **Science**
- **Regulatory Research**
- **Staff Training & Professional Development**
- Policy
- Communication

Additional Activities



POLICYFORUM

SCIENCE AND REGULATION

FDA's Approach to Regulation of Products of Nanotechnology

A broadly inclusive initial approach may become more nuanced in light of experience, scientific information, and public input.

Margaret A. Hamburg

The U.S. Food and Drug Administration (FDA) has long encountered the combination of promise, risk, and uncertainty that accompanies new technologies. This is equally true for nanotechnology, which engenders both excitement and concern owing to the rapidly evolving science and range of applications. The very changes in biological, chemical, and other properties that make some applications so exciting may also present new questions about how to predict, identify, measure, and monitor possibly harmful effects.

FDA is generally responsible for overseeing the safety and effectiveness of drugs and devices for humans and animals and of biological products for humans, and the safety of foods (including food additives and dietary supplements), color additives, and cosmetics. The agency conducts these oversight functions under a variety of laws and regulations, which establish the specific premarket and/or postmarket oversight mechanisms applicable to a particular class of products (1). We focus below on identifying FDA products that involve nanotechnology, evaluating products that contain nanomaterials, and ensuring a responsive regulatory framework, which may be tailored to specific products as necessary.

Identifying Nanomaterials for Regulation

FDA's regulatory science priorities are focused on issues relevant to oversight of products subject to its regulations. Identifying nanomaterials is an important first step. Materials can exhibit new physicochemical properties at nanoscale dimensions (2), and properties that are attributable to size can be seen or retained even when the material or end-product may not necessarily exist entirely within the nanoscale (3–7). Although one definition for "nanomaterial" may offer meaningful guidance in one context, that definition may be too narrow or broad in another. For this reason, FDA is not at this time adopting a regulatory definition of nanotechnology. Instead, it is initially taking a broadly inclusive approach to considering whether FDA-regulated products contain nanomaterials or involve nanotechnology.

FDA recently issued a draft guidance for industry on this topic (8) proposing that when evaluating whether an FDA-regulated product contains nanomaterials or involves nanotechnology, FDA and its stakeholders should consider the following: Does an engineered material or end-product have at least one dimension in the nanoscale range (~1 to 100 nm)?; or does it exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimensions, even if these dimensions fall outside the nanoscale range, up to 1 μm? Structures such as agglomerates and aggregates are of interest in this context (3), as are coated, functionalized, or hierarchically assembled structures (4). This initial broadly inclusive approach may become more nuanced in light of experience, available scientific information (including the agency's own regulatory science research), and public input, which will inform any future agency issuance of regulatory documents or public communication efforts. There may also be an opportunity to pursue approaches specifically tailored to FDA's various product areas.

Until then, industry and developers should keep both of these broad size- and property-related factors in mind when considering whether their products might fall within FDA's attention for nanomaterials and are encouraged to consult with the agency early in their development process to resolve any uncertainties.

Evaluating Products Containing Nanomaterials

Whether a product is subject to premarket review (e.g., new drugs, biological products, certain devices, and food and color additives) or not (e.g., cosmetics), industry is required to ensure that the product satisfies applicable safety standards and complies with other applicable requirements. Substantiation of safety requires scientific evidence. The FDA Nanotechnology Task Force made recommendations for a staged approach to determining whether current tests are adequate to support risk management decisions and where they are not, to collect data and update procedures (9). Of particular importance are the following:

- routes of exposure, including inhalation, dermal absorption, and ingestion (e.g., as related to cosmetics and foods), as well as exposure media (e.g., air, water, and food).
- properties related to absorption, distribution, metabolism, and excretion (ADME) (e.g., as related to drugs). Because biological interactions may be influenced by size changes, this may require additional analytical techniques capable of determining physical characteristics (e.g., size or aggregation) not previously assessed for tissue samples collected in ADME studies.
- size, size distribution, surface charge, surface properties, particle interactions, particle behavior, purity, stability, and general batch-to-batch variability. The new properties of materials and products that involve nanomaterials or applications of nanotechnology may require additional product-specific testing and manufacturing controls.

For FDA, regulatory science addresses these questions and involves developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products, to help evaluate whether products are appropriate for marketing (10). FDA plans to continue to invest in a regulatory science program that includes such areas as nanomaterial characterization, in vitro and in vivo modeling, and product-focused research. There may be areas of application that deserve special attention, such as cosmetics, for which there is no premarket review that requires industry to provide the agency with product-specific data. For these products, better characterization of nanotechnology-based products—as well as the development and evaluation of models for predicting safety, effectiveness, and quality—will help industry fulfill their responsibility to ensure product safety before marketing and will help FDA in its postmarket surveillance. There may also be product-specific research needs in areas such as novel medical products for serious diseases. FDA is sharing information, coordinating its activities, and combining resources through interactions with other U.S. agencies, such as through the interagency National Nanotechnology Initiative (11). FDA is also participating in pub-

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FDASIA Legislation Relevant to Nanotechnology

Section 1126 of FDASIA, 21 USC 399e

GENERAL.—The Secretary of Health and Human Services (referred to in this section as the ‘‘Secretary’’) shall intensify and expand activities related to enhancing scientific knowledge regarding nanomaterials included or intended for inclusion in products regulated under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) or other statutes administered by the Food and Drug Administration, to address issues relevant to the regulation of those products, including the potential toxicology of such nanomaterials, the potential benefit of new therapies derived from nanotechnology, the effects of such nanomaterials on biological systems, and the interaction of such nanomaterials with biological systems.

FDA Programmatic Investment Area	2011	2012	2013	Program
FDA Staff Training	X	X	X	Center Workshops
	X	X	X	Introduction to Nanotechnology online
		X	X	Applied Courses in Nanotechnology online
		(pilot)	X	Hands On Laboratory Course
			X	*Ad hoc* Topic Specific/Product Relevant Review Courses
			X	External Training Opportunities
			X	FDA Nanotechnology Regulatory Science Research Workshop
FDA Core Facilities	X	X	X	Center Specific Laboratories
	X	X	X	NCTR Core Facility
		X	X	White Oak Core Facility
		X	X	FDA Coordination Plan (Safety, Toxicology, Characterization, Manufacturing)
			X	Public Private Partnerships with External Stakeholders
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FDA Intramural Regulatory Science Research (CORES)	X	X	X	Center Specific Projects
	X	X	X	CORES Program
		X	X	External Peer-Review
			X	Engage Domestic & International Research Opportunities
			X	Additional Product Specific Regulatory Science Research

Online Resources

FDA Nanotechnology Website

http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

FDA Nanotechnology Regulatory Science Plan

http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

FDA Program Summaries

http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm309672.htm

NNI Strategic Plan

http://www.nano.gov/node/581