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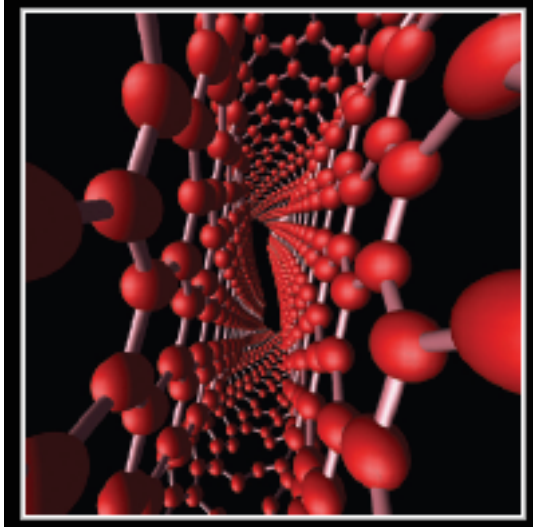


October 31, 2006

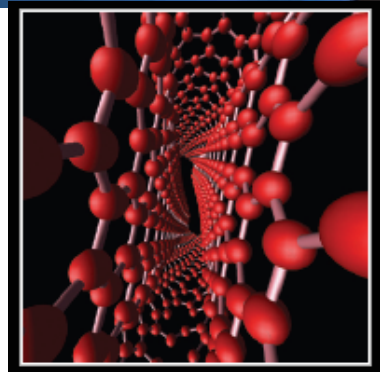
NO SMALL MATTER

Nanotechnology Risks: What Pharma, Biotech and Device Counsel Need to Know Now

A Web/Audio Conference Series

Welcome

…the presentation will begin shortly…



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Nanotechnology Risks: What Pharma, Biotech and Device Counsel Need to Know Now

A Web/Audio Conference Series

Welcome to the first in a series of Arnold and Porter LLP programs on nanotechnology. There will be a Q&A session after the presentation. If a question occurs to you during the panel, press *1 so the operator knows you have a question.

Keep in mind:

- **You do not have to identify yourself when you ask a question.**
- **You may send your question via text to the right of this screen. Only the moderator will see the text and your identity will be remain anonymous.**

Today's Speakers

Arnold & Porter LLP


Donald Beers


Lawrence Culleen


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Nanotechnology – Global Perspective

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No Small Matter – A Nanotechnology Roadmap to Legal, Policy and Regulatory Developments for the Life Sciences

Mapping the Nanotechnology (NT) Policy Landscape

- Why Nanotechnology and Life Sciences?
- US – Shared Global Leadership
  - National Nanotechnology Initiative (NNI) +
  - Multiple USG Players and Programs
  - Non-government Players Emerge
- The Global Context for Law, Policy and Regulation
  - OECD – Emerging Hub for Nanotechnology Regulation and Policy
  - Europe Develops Integrated Approach
  - Asia Sees Nanotechnology as a Core Economic Driver
  - Other Key Actors Make Nanotechnology a National Priority
- The Emerging Agenda: Key Legal, Policy and Regulatory Trends and Developments to Watch for the Life Sciences

Why Nanotechnology (NT)? -- Science and Technology

- **NT = development and application of structures, devices, materials and systems with fundamentally new properties and functions**
- **Size and properties – At nanoscale, properties of materials -- physical, chemical, optical, mechanical and biological -- differ from those at larger scale or from individual atoms/molecules**
  - **Size matters -- especially surface area**
  - **Shape matters – different properties even with same chemical comp**
  - **Other properties matter – exs., charge, surface coatings, structure**
- **Ability to understand and control the fundamental structure and function of matter at nanoscale at <100 nm (one nm = 1 billionth of a meter): the scale at which biological molecules and structures operate in cells**
- **Transformational set of enabling technologies with broad range of applications for the life sciences**

NT -- The Next Industrial Revolution?

- Critical driver of economic growth and development in the 21st Century
- NSF estimates $1 trillion NT market by 2015
- Disruptive, transformational set of science, technologies and applications across more than 16 business sectors
- Life sciences = ~ 20% of NT
- Globalization: $8.6 billion in NT investments in 2004
- Convergence: interdisciplinary and cross-sectoral
- New Business Models and Trends – Collaborative Value Chains, Open Innovation, Vertical Disaggregation, Modularity, Networks, Users

Why Nano? Applications in the Life Sciences

- **Improve existing products, processes and systems**
- **Enable new research strategies, development methods and tools/instrumentation/measurements**
- **Create entirely new products, processes and systems using NT**
  - **New Rx/Dx that combine new delivery devices, sensors, imaging and point-of-care capabilities**
  - **Systems for real-time measurements and assessments**
  - **Combination nanoparticle agents – detect, treat and report on a therapy**
  - **New models – e.g., Synthetic Biology and Systems Biology**
  - **New research tools**

Nanomedicine – A Few Examples

- **Nano-diagnostics:**
  - **Miniaturized, implantable diagnostics**
  - **Point-of-care medical diagnostic devices (1-5 years)**
- **Targeted drug therapies (3-10 years) and drug delivery through cell walls (10-15 years)**
- **Regenerative Medicine**
  - **New generations of tissue engineering and bio-mimetic materials**
  - **Longer-term potential for synthesizing organ replacements or multi-functional new Rx/Dx**
- **Tools for new functionality at the cellular level – exs., enhanced imaging and adaptive biosensors (3-10 years)**
- **NT-based coatings to improve bioactivity and biocompatibility**
- **Genetic tests for more personalized medications and dosages (ex. attaching gold nanoparticles to genetic probes enter CTs)**

National Nanotechnology Initiative (NNI) and the 21st Century Nanotechnology R&D Act (12/03)

- US Government NT funding now > $1.5 billion/year (25% of global total); $6.5 billion over 5 years; total US R&D in 2004 = $3.6 billion
- Highly coordinated USG approach
  - National Science and Technology Council (NTSC)
  - Nanoscale Science Engineering and Technology (NSET) Subcommittee
  - OSTP as key chair
- NNI Strategic Plan (2004)
  - Maintain world-class R&D programs
  - Facilitate technology transfer
  - Develop STEM education and skills and support research infrastructure
  - Support responsible development of nanotechnology
- Involves more than 25 different departments and agencies; 13 with R&D budgets for NT

NNI Strategy and the Life Sciences

- **Major focus on the life sciences in NNI**
  - **7/13 "grand challenges" focus on life sciences**
  - **3/4 priority areas for NT investment and R&D involve life sciences (bio-nano, nano-sensors, and modeling/simulations)**
- **Four anticipated generations of engineered nanomaterials:**
  - **1st: Passive Nanostructures (coatings, individual particles)**
  - **2nd: Active Nanostructures (sensors, adaptive functions)**
  - **3rd: Three-dimensional Systems (targeted drugs)**
  - **4th: Molecular Nanosystems and Structures by Design**
- **Key role of Nanotechnology Environmental & Health Implications (NEHI) interagency working group in EHS research and regulations**

Examples of Key NNI Life Sciences Players other than the EHS Regulators

- **NIH/NCI as innovation drivers for basic and translational research with broad range of NT programs; new research models/commercialization steps; broad range of trans-NIH initiatives**
  - CNPlan -- NCI Alliance for Nanotechnology in Cancer (July 2004)
    - Centers of Cancer Nanotechnology Excellence (CCNEs)
    - NT Platform Partnerships for Cancer Research
    - Innovative Technologies for Molecular Analysis of Cancer
    - Nanotechnology Characterization Lab (NCL)
  - NIH Nanomedicine Roadmap Initiative
  - The Cancer Genome Atlas (TCGA) project – major NT role
  - National Toxicology Program (NIEHS/NIH, NIOSH/CDC and NCTR/FDA)
- **National Institute of Standards and Technology (NIST)**
- **NSF – supporting basic research, education and international dialogues**
- **Range of other major USG players in the life sciences -- DoD, DHS, USDA and DOE**

Global Context – Key Drivers and Players

- **Government at four levels**
  - **Multilateral (OECD and UNESCO, plus WHO, CODEX, others)**
  - **Coordinated nanotechnology strategies at national and regional level (EU and most major industrialized countries)**
  - **National authorities with specific functions (ex.,EPA and DEFRA)**
  - **Subfederal (various state/local clusters and infrastructure)**
- **Industry – broad and deep; umbrella groups and 14 sectors**
- **S&T societies and task forces (Royal Society, NAS, etc.)**
- **NGOs and think tanks (Environmental Defense, ETC Group and Woodrow Wilson Center)**
- **New NT intermediaries (CBEN-ICON, Meridian Institute, Vivagora-Nanomonde, Nanoethics Group, NSF Int'l Dialogues)**
- **Alliances – ED and DuPont life-cycle framework to assess risk**

Global Context – OECD as a Key, Emerging Player in Nanotechnology

- **Global Preparatory Workshops and Scoping Meetings (2005-2006)**
  - Environment, Health and Safety of Manufactured Nanomaterials
  - Science, Research and Innovation
  - Biotechnology and Health Innovation
- **OECD Global NT Policy "Scoping Summit" – (Switzerland, 7/06)**
- **Nano as key, new element of OECD work for coming years**
  - Working Party on Manufactured Nanomaterials (London, 10/06)
  - Working Party on Nanotechnology (Seoul, 10/06)
  - Working Party on Biotechnology and Health Innovation (Paris, 2006)
  - Statistics, metrics and methodologies
  - Intellectual Property and Innovation
- **Outreach with China and other BRICS**

OECD – Global Work Program for Key EHS Issues in Working Party on Manufactured Nanomaterials

- **Characterization, Definitions, Terminology and Standards**
  - Establish criteria for the identification, notification and assessment of NT
  - Develop working definitions for EHS regulatory purposes
  - Harmonize standard references for regulatory purposes
- **Testing Methods and Measurement Protocols**
  - Are existing test methods and measurements suitable?
  - Environmental fate and effects (hazard identification, hazard, exposure and risk assessment methods)
  - Human exposure and health effects (hazard identification, hazard, exposure and risk assessment)
- **Risk Assessment -- develop agreed risk assessment protocols**
- **Information sharing, Cooperation and Dissemination of trends, data, research elsewhere and Global EHS Database**
- **Initial regulatory model – harmonization of regulatory practices in chemicals regulatory areas**

OECD WP Manufactured Nanomaterials EHS Work Program for 2007-2008 Includes:

- Hazard-Risk-Exposure terms, standards, research
- Research strategies for understanding the toxicology and biokinetics of nanoscale particles
- Global database development
- Safety testing of a representative set of nanomaterials
- Development of test guidelines for regulators
- Cooperation on voluntary scheme programs

OECD –Committee on S&T Policy (CSTP): Work on Research, Innovation, IPRs, and Commercialization

- Analyze economic impacts and trends – focus on key applications and evolving business models
- Coordinate science, research and capacity building
- Promote commercialization, IPR, technology transfer and innovation for realizing nanotechnologies' promise
- New Health Innovation initiatives
- Examine human resources, education, and global R&D
- Develop internationally comparable stats and indicators
- Coordinate risk governance for long-term nano growth
- Explore public perceptions, engagement and communication strategies

Europe – EU Integrated Approach to Nanotechnology and Swiss National Strategy

- **$2.4 billion in European R&D in 2004 ($1.7 billion public)**
- ***Towards a European Strategy for Nanotechnology*** **(2004) and Integrated Commission Action Plan (2006) at European-level**
  - **Research, Development and Innovation – especially in FP7**
  - **Infrastructure and Poles of Excellence**
  - **Interdisciplinary Human Resources**
  - **Industrial Innovation**
  - **Integrating the Social Dimension**
  - **Public Health, Safety, Environmental and Consumer Protection**
- **Commission Driven - Key DGs: DG-Health and Consumer Protection, DG Enterprise and DG Research**
- **Switzerland – a global player and a national strategic priority**

Japan – A Major Global Player in NT

- NT R&D = $2.8 billion in 2004 ($900 million public) (FT, 2006)
- Japan expects $238 billion domestic NT market by 2020, with life sciences as $10.3 billion; electronics = $163B
- NT-life sciences one of top 4 priorities in new National Strategy
- Top four NT regulatory/risk concerns: (1) effects on ecosystems; (2) adverse health effects of NT in industrial use; (3) problems in biomedical/health care applications; and (4) problems that arise from cell and gene manipulations enabled by NT (GOJ, 2006)
- Developing NT Roadmap of Risk Assessment
- Key Agencies for Life Sciences: METI, MEXT and MHLW, plus Prime Minister's S&T Council, IPR Council and new NT testing sites
- Beginning to consider ethical issues re NT life sciences applications

China and Asia – China Already #4, and Korea, Taiwan, India and Singapore are All Strong and Eager

- China – already a global leader in new NT companies, NT publications and NT patents; 800 NT companies now
- Targeting life sciences as core areas for NT
- NT markets in China will increase to $145 billion by 2015 (Physorg 2006); 16% global market share
- "Self innovation" and S&T Policy as top economic priorities of government for next 5-10 years
- National Steering Committee for Nanoscience and Nanotechnology (MOST, CAS, NRDC/State Council, SDPC, MOE, NSFC)
- New measures related to research, innovation, standards, IPR and university-industry links (20 university NT centers of excellence)
- Nanomaterials #1; Nano-bio and other life sciences #2

Key Legal, Policy and Regulatory Areas to Watch for the Life Sciences

- Definitions, nomenclature and testing methods
- Regulatory compatibility and adequacy of existing regs
- Risk Governance
- Intellectual property rights
- Standards
- National security
- The science-innovation interface
- Capital formation, investment and tax policy
- Public perceptions, including ethics and dialogues

Harmonization/Disagreements About Definitions, Nomenclature and Testing Methods

- Different definitions for legal, regulatory and policy purposes – and countries (what is nanotechnology?)
- Nomenclatures and classifications differ
  - Metal oxides - Nanoclays
  - Nanotubes - Quantum dots
- Procedures and testing methods
- Reference materials, processes and databases
- Accepted measurement instruments and tools
- Data (advanced in EU and NNI) – comparability; completeness; complementarity; interoperability

Regulatory Compatibility and Signs of Potential Friction – Domestically and Internationally

- Signs emerging of domestic regulatory tensions – EPA, FDA, NIOSH, CPSC, USDA
- Risk assessment methods, test protocols and guidance
- International regulatory disconnects and lack of harmonization in key market drivers
- Precautionary approach to risk v. evidence of harm/risk
- Risks of "NT exceptionalism" and regulatory asymmetry
- "Techno-protectionism" because the stakes are so high
- Convergence threatens regulatory turf wars over jurisdiction, methodologies, and goals

Risk Governance becomes an "A" List Issue for NT – especially for next generation products and services

- **Growing concern with what we don't know about risks and need for much greater EHS research**
  - **NAS: *A Matter of Size* (fall 2006)**
  - **Congressional EHS hearings (9/21/06)**
  - **NNI: *EHS Research Needs for Engineered Nanoscale Materials* (2006)**
  - **Growing media attention**
- **Insurers as a driving force and renewed focus on life cycle analysis**
  - **Asbestos as the cautionary template for insurance companies**
  - **Global reinsurers and others as a new force for increased regulation now**
- **International Risk Governance Council (IRGC) Conceptual Framework and global summit (July 2006)**
  - **Systematic approach to analyzing risks, opportunities and challenges**
  - **Four, overlapping generations of NT products and processes**
  - **Framework based on level of complexity, uncertainty and risk**
  - **Two Key Frames of Reference based on perceived risks -- Frame 1 (classic risk assessment) and Frame 2 (risk concern assessment)**
- **Royal Society Reports and ongoing working groups – shaping the debate**

IPRs Emerging as a Key Issue for NT's Future

- **>1,500 NT patents by 2004 (Huang, 2004) – U.S., Japan and China lead;**
- **Bottlenecks -- 3x increase in NT patents in last 5 years; increased PTO/EPO/JPO delays (up to 4 years); concerns about patent quality**
- **FTO, technology licensing, and technology markets related to NT as an increasing business and university driver**
- **Growing concern about uncertainty, patent thickets, and upstream blocking positions for cumulative and cross-sectoral NT**
- **Collaborative IPR mechanisms under active discussion**
  - **Patent pools**
  - **Standards and new cross-licensing strategies**
- **Ongoing IPR concerns with key NT drivers/markets – China and India**
- **Development of cross-reference art collection of 263 subclasses for NT, designated Class 977 and entitled "Nanotechnology"**

Technology Standards Development Will Shape NT

- **ISO TC 229**
  - Terminology and nomenclature for nanoparticles
  - Metrology and instrumentation for NT
  - Safe practices for occupational uses
  - Possible other EHS aspects of NT
- **Wide variety of national standards-setting bodies (China, UK BSI, German DIN, U.S. ANSI/ASTM)**
- **De Facto Technology Standards**
  - Interoperability
  - Participation and problems
  - FTO
  - Antitrust

National Security Sneaks Up on the Life Sciences as a Major Issue

- **Export Controls – Growing Focus on Nanotechnology**
  - **USG/DOC Nanotechnology Export Controls Review**
  - **Deemed Exports for Corporate and University R&D**
  - **Proposed New China Regulations**
- **Biosecurity and Nanotechnology**
  - **NSABB**
  - **Royal Society and National Academies**
- **Dual-use technologies and wide range of new military applications**
  - **Battlefield medicine**
  - **Biosensors; imaging; arrays**
  - **Bioweapons targeting specific DNA**
- **Growing Concerns that U.S. May Not Lead in NT Global Security**

Science-Innovation Interface Issues

- Balanced portfolio of R&D activities that mix ST, MT and LT goals
- Globalization of R&D
- New research models, federal-state coordination and research/regulatory cooperation (ex., NCI/FDA Agreement)
- Technology transfer and commercialization strategies
- Translational research “from bench to the bedside”
- Evolving university-industry models and consortia
- Shared Infrastructure for NT and Access to NNI Assets
- STEM and Education/Workforce skills constraints in NT

Capital Formation, Investment and Tax Policy

- **Significant increases in venture capital, private equity, and other private investment for NT**
  - **$500 million in venture capital in 2005 (Lux, 2006)**
  - **Corporate R&D = ~ $2 billion+/year**
- **MT/LT proposals to overcome "Valley of Death"**
- **National, regional and state investment strategies**
- **R&D tax credits and various national/local subsidies**
- **Disclosure obligations and issues, including trend to intellectual asset disclosures in Europe and Japan**

The Battle to Shape Public Perceptions and the Understanding of Perceived Risks

- **Four key risk perceptions and communications**
  - **Human development risks and perceptions**
  - **Society structural risks**
  - **Public perception risks**
  - **Transboundary risks and perceptions**
- **Increased focus on Ethical, Legal and Societal Implications (ELSI)**
- **Risk communication strategies evolving**
  - **Information about benefits and unintended effects**
  - **Principles, procedures, monitoring – and results**
  - **Education and training**
  - **Integrated risk communication programs**

FDA Update

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Nanotechnology—What Is Happening at FDA of Relevance to the Drug, Device, and Biotech Industry?

FDA's Understanding of Nanotechnology

- **Materials made in the nanoscale size range can often have chemical or physical properties that are different from those of their larger counterparts. Such differences include altered magnetic properties, altered electrical or optical activity, increased structural integrity, and increased chemical and biological activity.**
- **. . . because of some of their special properties, they may pose different safety issues than their larger counterparts.**
- **FDA Press Release announcing Nanotechnology Task Force, August 9, 2006**

Nanotechnology Developments at FDA

- **May 16, 2006 — International Center for Technology Assessment and other public interest groups petition FDA for various relief related to nanotechnology**
- **August 9, 2006 — FDA announces formation of an internal Nanotechnology Task Force**
- **October 5, 2006 — Woodrow Wilson Center releases white paper on FDA regulation of nanotechnology**
- **October 10, 2006 — FDA holds a public meeting on nanotechnology**

ICTA Petition seeks:

- A formal FDA opinion clarifying the agency's stance regarding nano-products;
- The amendment of FDA regulations to include nanotechnology terminology and comprehensive nano-product regulations, including nano-specific toxicity testing and mandatory nano-product labeling;
- The amendment of sunscreen regulations to address nanoparticle sunscreen ingredients, including the requirement that all nano-sunscreens be considered new drug products;
- The declaration that nano-sunscreens are an imminent hazard to public health and must be recalled until FDA's nano-products regulations are implemented and nano-sunscreen manufacturers submit new drug applications; and
- Agency consideration of human health and environmental impacts related to nano-product regulation, in accordance with the National Environmental Policy Act (NEPA).

Woodrow Wilson Center (Mike Taylor) Report

- FDA needs more resources generally
- FDA should provide guidance on when a nanoscale version of a material should be considered "new" for regulatory and for safety evaluation purposes
- The report suggests that FDA generally has adequate regulatory authority over drugs and devices; may need additional authority over cosmetics.

FDA Open Meeting

- FDA made no new announcements
- Presentations were generally informative but not confrontational
- No strong push for more regulation of nanomaterials used in drugs or devices
- Question about the definition of nanotechnology — Is a 100 nanometer cut-off meaningful?
- Question about labeling medical devices as containing nanoparticles.

What does this all mean for the drug and device industries?

- **FDA**
  - **is listening**
  - **is interested**
  - **is not likely to make any radical changes in its regulation of drugs or devices because it reasonably believes that it does not need to do so**
- **If there is FDA regulatory change, it is more likely to come in areas where FDA exercises less regulatory oversight —cosmetics, OTC drugs.**

Nanotechnology and Drugs Approved under NDAs or BLA's

- **With premarket review authority, FDA can assure safety and functionality of nanoparticles used in drugs**
- **What might "fall through the cracks"?**
  - **New versions of active ingredients, formulated for better bioavailability**
  - **Inactive ingredients considered safe in non-nano form.**
- **Potentially difficult issues**
  - **Inhaled products**
  - **Derm products**

OTC Monograph Drugs

- **Nanoparticle active or inactive ingredients could be used in drugs covered by OTC monographs**
- **There is a question about what the term "micronized" means in the OTC suncreen monograph. FDA permitted micronized titanium oxide as an ingredient**
- **Inactive ingredients need only be suitable and safe for use, 21 C.F.R. 330.1(e)**

What about devices?

- **Use of nanotechnology in devices approved under PMAs will be shown safe and effective by required testing.**
- **For 510(k)s, it is less clear how much, if any, testing may be required. Does the change to nanoscale change the technological characteristics of the device? That will depend on the device.**

What is ahead for FDA regulation of nanotechnology in drugs and devices?

- **FDA sees its charge at this point as to "encourage the continued development" of safe and effective FDA-regulated products.**
- **If there is a safety problem attributed to a product of nanotechnology, it is predictable that FDA's emphasis will change quickly from encouragement to consumer protection.**

EU Perspectives

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European Perspective:

What is the primary focus of European regulatory policies?

Nanotechnology or Nanobiotechnology

- **The debate started in late 2002 following Commission's Communication on life sciences for Europe**
  - **Regulation of emerging technologies**
- **Certain key reports published by the Commission addressing:**
  - **Risks associated with use of nanotechnologies in various sectors**
  - **Mapping out the parameters for future regulatory control**
  - **European strategy for nanotechnology setting out the policy agenda and the potential impact on biotechnology, information/communication, healthcare etc.**

Other developments

- **UK Royal Society and Royal Academy of Engineering (2004). Nanoscience and nanotechnologies: opportunities and uncertainties**
- **UK Government Response to Royal Society and Royal Academy of Engineering Report (2005)**
- **European Science Foundation foresight study on nanotechnology**
- **European Technology Platform on Nanomedicine: Vision paper and Basis for a strategic research agenda for Nanomedicine**

EU Definition of nanotechnology

- **Production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around 0.2nm (2 Å) up to around 100 nm**

Current EU regulatory thinking

- **Likely that nanotechnology will be regulated more appropriately under sector-specific rules focussing on the potential risks associated with the product characteristics**
  - **Development of sector non-specific regulatory framework if there is a need to do so (e.g. GM).**

Sector specific laws

- **The legal test for placing healthcare products on the market is similar with public health protection**
  - **Medicinal products: risk/benefit**
  - **Medical devices: conformity with essential requirements and general product safety**
  - **Cosmetic products: no damage to human health under normal or reasonably foreseeable conditions of use**
  - **Food: not injurious to health or unfit for human consumption**
- **Post-market surveillance or monitoring**
- **Communications**
  - **Proper labelling**
  - **Product inserts**

European Medicines Agency

- **Indicated in its Reflection Paper (June 2006) that nanotechnology based products are regulated as medicinal products rather than as medical devices**
  - **Seemingly relying on a new provision set out in the new pharmaceutical legislation to classify borderline products as medicinal products**
  - **Innovation Task Force set up primarily to address regulation of emerging technologies**

European Medicines Agency

- **"Nanomedicine" is defined to mean the application of nanotechnology with the view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale**

- **In terms of regulatory approach, reference is made to the approval of certain medicinal products in the EU based on liposomal products, polymer-protein conjugates, polymeric substances or suspension (including colloids)**

- **Regulation will be based upon an assessment risk/benefit balance with particular focus on risk management**

EU regulatory attitude

- **Precautionary principle underpins EU regulatory policy**
- **The principle received judicial endorsement by the European Court of Justice in matters concerning BSE, GM and use of antibiotics**
- **The purpose of the principle is to manage scientific uncertainties in a given set of circumstances**

Risk assessment must be transparent and thorough (European Court of Justice in Pfizer case)

- **"Thus, in order to fulfill its function, scientific advice on matters relating to consumer health must, in the interests of consumers and industry be based on the principles of excellence, independence and transparency … It follows that a scientific risk assessment carried out as thoroughly as possible on the basis of scientific advice founded on the principles of excellence, transparency and independence is an important procedural guarantee whose purpose is to ensure the scientific objectivity of the measures adopted and preclude any arbitrary measures."**

EPA and OSHA Update

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Environmental Protection Agency and work place practice requirements that will be important for producers and users of nano-scale materials

U.S. Environmental Protection Agency Overview

- **EPA is an active participant in National Nanotechnology Initiative (Government-wide working groups)**
- **Has issued no new regulation, or proposals regarding:**
  - **Emissions or Disposal of nano-scale materials**
  - **Pre-manufacture notification of production of nano-scale substances**
- **General areas of focus within EPA:**
  - **Funding of Research & Development Efforts - focus on beneficial uses and environmental risks of nanotechnology**
  - **Consideration of Potential Regulatory Approaches and Initiatives - TSCA and the Voluntary Nano-scale Materials Stewardship Program (NMSP)**
  - **Participation in appropriate bodies (e.g. I.S.O)**

EPA Considering Potential Regulatory Approaches: Toxic Substances Control Act (TSCA)

- **Regulation of Nano-scale chemical substances under current TSCA framework**
  - **TSCA § 5 New Chemicals and New Uses**
  - **TSCA § 4 Testing**
  - **TSCA § 8 Information Gathering**
  - **TSCA § 6 Existing Chemicals - (e.g., carbon, silica)**
- **Potential Issue: "New" versus "Existing Chemical" - lack of nomenclature and classification standards**
  - **"Significant New Use Rules" – SNURs**
- **EPA Expects to Release a "Position Paper" on the "New-ness" Issue "Soon"**
  - **EPA has been receiving notifications pursuant to TSCA's new chemicals requirement**

EPA Voluntary/Non-Regulatory Initiatives

- **Voluntary Nanoscale Materials Stewardship Program (NMSP)**
- **Currently under development - Industry ability to influence scope, characteristics of program**
- **Risk Management Focus with Record Keeping and Reporting**
- **Conference Held in DC October 19-20, 2006**
- **Will Voluntary Programs Become the "Standard of Care"?**

EPA Regulatory Approaches: Toxic Substances Control Act (TSCA)

- **Caution – Some TSCA requirements that presently apply to existing nano-scale chemicals:**
  - **TSCA § 8(c) - Recordkeeping of "allegations" of "significant adverse reactions" to health or the environment required.**
  - **TSCA § 8(e) - Reporting of "substantial risks" required.**
  - **TSCA § 8(d) and § 8(a) - Submission of unpublished health and safety studies and other information may be compelled.**
- **Of Course - - TSCA § 5 Applies to Truly "New" Chemical Substances (i.e. Not on Inventory)**
  - **PMNs being submitted**
  - **EPA has requested additional data on these**

Other EPA Activities

- Federal Insecticides, Fungicides, and Rodenticides Act (FiFRA)
- Household and Agricultural Products
- Includes Antimicrobials
- Registration Applications Being Reviewed

Consumer Product Safety Commission

- **Has jurisdiction over consumer products generally (many FDA products excluded)**
- **Federal Hazardous Substances Act**
  - **Labeling and "ban" on "hazardous" children's products**
- **CPSA – substantial product hazards**
  - **Recalls, reports, responses**
- **CPSC Nanomaterial Statement**

Nanotechnology and Safety in the Work Place

- **OSHA - no current standards**
- **NIOSH – July 2006 publication**
  - **identified/compiled potential health and safety concerns**
  - **preliminary guidelines for working with engineered nanomaterials**
  - **Currently under peer review**
- **Potential risks to human health - inhalation, ingestion, dermal absorption**
- **Much more research needed to identify and understand impact of occupational exposures on worker health**

NIOSH Preliminary Recommendations - Establish Risk Management Program:

- Evaluate hazard posed by nanomaterial based on available data
- Assess worker exposure to determine degree of risk
- Educate and train workers in proper handling of nanomaterials
- Establish criteria and procedures for installing and evaluating engineering controls (e.g., exhaust ventilation)
- Develop procedures for determining the need and selection of personal protective equipment (e.g., clothing, gloves, respirators)
- Systematically evaluate exposures to ensure control measures are working properly
- Institute other good work practices (e.g., cleaning of work areas using HEPA vacuum, wet wiping)

Do Not Overlook Non-Governmental Nanotechnology Standards Development. Examples Include:

- **ASTM International Committee E56 on Nanotechnology**
- **ISO Technical Committee (TC) 229**

These have the potential to be representative of the "standard of care" too

Be Aware of Other, Voluntary Industry Initiatives

- **DuPont and Environmental Defense**
- **Others**
- **Benchmarks for Your Own Programs/ Possible Standards of Care**
  - **Requires a firm foundation in "good science"**
  - **Have an awareness of litigation perspectives**

Guarding the Promise of Nanotechnology

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Nanotoxicology:

What are the risks, what is the evidence, and what should you be thinking about.

What are the Concerns?

- **"At the moment, nobody has died from engineered nanomaterials. To our knowledge nobody has even gotten sick…" ***
- **So what are the health and safety concerns?**

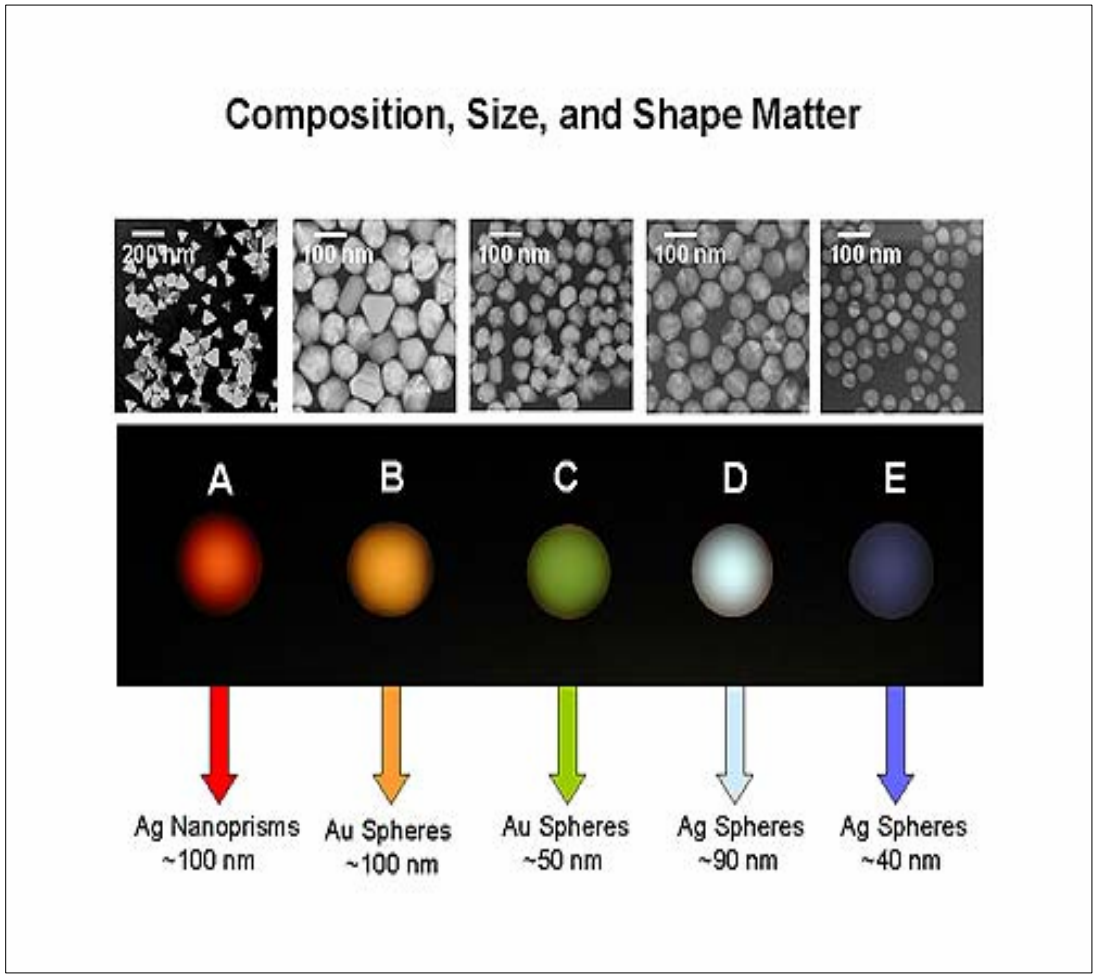
  Due to the unique physicochemical properties of nanomaterials and early toxicological evaluations, there are scientifically sound reasons to believe that some nanomaterials may have potentially serious implications for environment, health, and safety **(ENVIRON)**

- **"We have an opportunity to try to mitigate potential risks before they get significant" ***

*** SOURCE: Andrew Maynard, Project on Emerging Nanotechnologies**

Why Could Nanomaterials Be Toxic?

- **Physicochemical Properties**
  - **Aggregation**
  - **Shape**
  - **Size**
  - **Solubility**
  - **Surface area**
  - **Surface charge**
  - **Surface coatings**



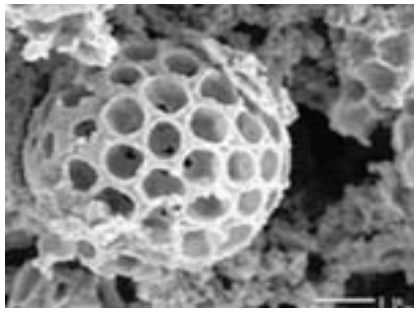
Gold and silver nanoparticles are physically different at different sizes down the nano-scale in color and shape (Northwestern University).

Nanotoxicology

- **Evidence sparse, but relevant to humans:**
  - **Nanoparticles enter the body via inhalation, possibly skin contact/penetration, ingestion**
  - **Inhaled particles may be transported via blood to other organs**
  - **Workers exposed to fine and ultrafine particles exhibit lung function decrements – exact cause uncertain**
  - **Engineered nanoparticles remain to be studied**
    - **Truly may be new substances (not previously encountered)**
    - **Some may be designed not to aggregate or agglomerate**

What Evidence Do We Have Now?

- **Studies of humans exposed to ambient (non-engineered) nanoparticles:**
  - **Carbon black, titanium dioxide, iron oxides, silica; ultrafine pollutants**
- **Animal lung studies**
  - **"Instillation" rather than "inhalation" – relevant to humans?**
  - **Do inhaled nanoparticles deposit in lungs, then reach bloodstream?**
- **Skin penetration studies**
  - **Research equivocal – recent flexing studies positive**
  - **Nanoparticles in topical cosmetics not absorbed**
- **Ingestion studies**
  - **Ingested nanoparticles may be absorbed in GI tract**
- **Translocation**
  - **Nanomaterials' uptake into the brain, liver, and kidney**



Gaps in Toxicological Studies

- Few specific nanomaterials have been investigated, and only in a few organ systems
- Toxicity of engineered nanomaterials is unknown, and different congeners or structures may have different toxicity
- Generalizing from studies of ambient, or non-engineered nanos may not be valid

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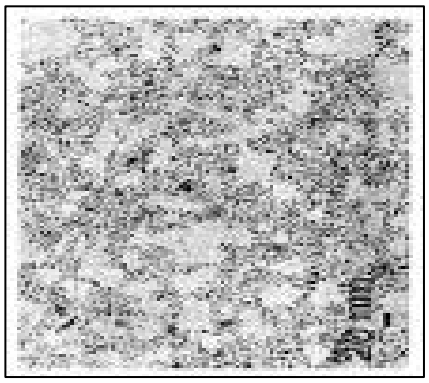


Fine Particles

(3,000-100 nm)

Nanoparticles

(< 100 nm)

Pragmatic Approaches

Recommended Approach

1. **Know the science**
2. **Best occupational health practices**
   - **Eliminate, reduce, protect**
   - **Conservative approaches to manage uncertain risks**
3. **Adaptive management**
   - **Strategies for safe production and use**
   - **Experience with potent compounds, virulent strains, and radioactive substances**
4. **Generate data to address anticipated questions**

Scientific Information Resources

- **Dozens of reports are generated that might be important… or not!**
  - **How to identify most relevant and scientifically valid reports?**
  - **How can engineers, business managers, financiers and decision-makers access and evaluate key health and safety information?**
- **NanoHealth Reviews Database:**
  - **Searchable public database**
  - **Plain-language summaries of latest toxicological and health science developments**
  - **Summaries authored by qualified experts in relevant field**
  - **University-based, with multi-institutional collaboration**
  - **Launch by end of 2006/beginning 2007**

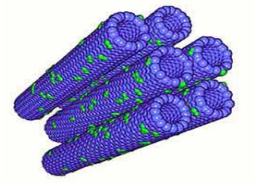
Employee / Exposure Database

- **Until human health data are generated, much uncertainty remains**
- **Epidemiological approaches needed for:**
  - **Rapid identification of hazards and risks**
  - **Detecting early stages of chronic effects / small risks**
- **Standard database structure for nanomaterial producers and users**
- **Highlights:**
  - **Inventories materials, products, work locations**
  - **Accounts for protective measures/controls, changes**
  - **Identifies employees by work tasks and locations**
  - **Standard format facilitates future pooling (anonymity of employees maintained) and analyses**
  - **Preserves key data for future epidemiological research**

Managing Uncertainty

- **Fortunately, integrated approaches exist**
  - **Science-based**
  - **Pragmatic**
  - **Draw on experience with known hazardous materials**
- **Much research is underway**
  - **New information needs to be evaluated, synthesized**
  - **Collaborative approaches across industries and internationally**

Many of the uncertainties we now face can be managed, guarding the "promise" of nanotechnology



Product Liability

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Preventing and Limiting Product Liability for Nanotechnology Risks

Product Liability Claims Involving Medical Products

- **Strict Liability, Negligence, Breach of Warranty**
  - Failure to warn (pre- and post- sale)
    - Breach of express warranty
    - Fraudulent misrepresentation
  - Design defect
  - Manufacturing defect
- **Damages Claims**
  - Punitive Damages
  - Deceptive Trade Practices violations (treble damages)
  - Medical Monitoring
  - Fear of future injury
- **Proximate and "but for" cause of personal injury**

Types of Product Liability Claims

- **Failure to Warn**
  - Reasonably foreseeable risks of the product
  - Learned intermediary defense
- **Design Defect**
  - Comment K "unavoidably unsafe" exception to strict liability
  - Risk/Utility of product
- **Manufacturing Defect**

Hindsight Assessments of Company Conduct: Problematic Scenarios

- Inadequate research and testing
- Inadequate disclosure of known or reasonably knowable risks in warning labels or marketing materials
- Withholding information from the FDA or other regulators
- Noncompliance with industry or regulatory standards
- Failure to modify design in light of newly revealed risks
- “Bad” documents and email

Nanotechnology: A Unique Risk Profile

- **Evolving scientific and medical knowledge**
  - **Exposure possible via skin, inhalation, ingestion**
  - **Nanoscale materials may cross the blood-brain barrier**
  - **Some nanoscale materials appear to aggregate in the body similar to asbestos**
- **Evolving industry standards and practices**
- **Evolving regulatory standards**
- **Little evidence of disclosure of nanoparticle content or potential risks in current products**

Even though no nanotechnology-based products have caused personal injury to date . . .

- Lack of industry and regulatory standards for nanotechnology creates potential for hindsight judgments
- Evolving knowledge creates greater opportunities for "junk science" based claims
- Greater potential for design defect claims
- Potential for latent, undetected exposure in absence of studies
- Complex causation scenarios could lead to highly individualized, case-by-case litigation

Preventing and Limiting Product Liability for Nanotechnology Risks

- Keep abreast of evolving scientific and medical knowledge in the field
- Comply with industry standards and best practices
- Comply with applicable statutes, regulations and recommendations for product development and marketing
- Develop and ensure compliance with internal policies and procedures
- Closely monitor post-sale product complaints and adverse event reports and respond appropriately
- Remember that compliance alone will not eliminate potential liability; conduct must be reasonable in light of all the circumstances