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Food and Drug Administration
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ORGANIZATION: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars

SUBJECT: FDA-Regulated Products Containing Nanotechnology Materials [Docket No. 2006N-0107]

The Project on Emerging Nanotechnologies is an initiative launched by the Woodrow Wilson International Center for Scholars and The Pew Charitable Trusts in 2005. It is dedicated to helping business, government and the public anticipate and manage the possible health and environmental implications of nanotechnology. As part of the Wilson Center, the Project on Emerging Nanotechnologies is a non-partisan, non-advocacy organization that collaborates with researchers, government, industry, non-governmental organizations (NGOs), and others concerned with the safe applications and utilization of nanotechnology.

Our goal is to take a long-term look at nanotechnologies; to identify gaps in the nanotechnology information, data, and oversight processes; and to develop practical strategies and approaches for closing those gaps and ensuring that the benefits of nanotechnologies will be realized. We aim to provide independent, objective information and analysis that can help inform critical decisions affecting the development, use, and commercialization of responsible nanotechnologies around the globe.

Both the Wilson Center and The Pew Charitable Trusts believe there is a tremendous opportunity with nanotechnology to "get it right." Societies have missed this chance with other new technologies and, by doing so, forfeited significant social, economic, and environmental benefits.

Nanotechnology is expected to become a transformational technology of the 21st century. It is the world of controlling matter at the scale of one billionth of a meter, or around one-100,000th the width of a human hair. Researchers are exploring new ways to see and build at this scale, re-engineering familiar substances such as carbon and gold in order to create new materials with novel properties and functions.

As the National Science Foundation (NSF) highlighted in a 2000 report, the ability to create novel properties in materials and systems at this scale implies that nanotechnology could eventually have an impact on the production of virtually every human-made object—everything from automobiles, tires, and computer circuits to advanced medicine and tissue replacements—and lead to the invention of products yet to be imagined.[1] Nanotechnology could fundamentally restructure the technologies currently used for manufacturing, medicine, defense, energy production, environmental management, transportation, communication, computation, and education.

We appreciate this opportunity to provide our comments to the Food and Drug Administration (FDA) regarding the relevant scientific, policy, and social issues associated with nanotechnology. By seeking input from various stakeholders and planning this public meeting, the FDA is beginning to take a proactive stance toward the oversight of nanotechnology. We are encouraged by this development.

Over the long term, we anticipate that nanotechnology will play a critical role in making rapid advances in multiple fields, including energy storage, water filtration, and, with respect to medicine, improvements in cancer research and better treatments for diseases, such as Alzheimer's or Parkinson's. However, nanotechnology is currently facing a number of key challenges—the wide and rapid commercialization of consumer products and industrial applications, lack of effective oversight mechanisms, lack of coordinated risk research strategies, and lack of public engagement—that may hinder the development of these promised long-term benefits. Our submission analyzes these crucial issues in depth and highlights specific areas of concern. It also provides a series of recommendations aimed at helping FDA formulate its approach to managing nanotechnology.

In conjunction with these comments, the Project on Emerging Nanotechnologies will also be submitting more-detailed background materials that have resulted from our research and that support the main conclusions presented in this document. These background materials include:

- Nanotechnology commercialization in consumer products—Andrew Maynard and Evan Michelson, *The Nanotechnology Consumer Products Inventory*, March 2006;

- Nanotechnology oversight and governance—J. Clarence Davies, *Managing the Effects of Nanotechnology*, January 2006;

- Nanotechnology public engagement and trust in government—Jane Macoubrie, *Informed Public Perceptions of Nanotechnology and Trust in Government*, September 2005; and

[1] Roco, M.C., R.S. Williams, and P. Alivisatos. *Nanotechnology Research Directions: IWGN Workshop Report*. Berlin, Germany: Springer, 2000, p. iii-iv.

- Nanotechnology risk-related research—Andrew Maynard, "Nanotechnology: Assessing the Risks," *Nanotoday* (1)2: 22-33, May 2006 and Andrew Maynard, *Nanotechnology: A Research Strategy for Addressing Risk*, July 2006.

We hope that, taken together, our comments and these documents will provide useful insight into the critical areas of intersection between nanotechnology and the FDA.

THE LANDSCAPE OF NANOTECHNOLOGY COMMERCIALIZATION AND THE FOOD AND DRUG ADMINISTRATION

We anticipate that a significant proportion of current and future nanotechnology applications will fall directly under FDA's jurisdiction, placing the agency on the forefront of nanotechnology governance. In particular, there are three areas of nanotechnology commercialization that will greatly affect the agency for years to come:

- Consumer product applications, including cosmetics and sunscreens;
- Food applications, including dietary supplements; and
- Medical applications, including drugs and drug delivery devices.

Each of these areas of application will affect the agency in different ways and within different time frames, and may require different oversight mechanisms. Only a concerted effort to identify the potential risks and benefits of these applications early in the product development and commercialization process will allow FDA to ensure that the public's health and safety are protected.

Consumer Product Applications

The most immediate nanotechnology concern for FDA should be consumer product applications. While it would have been difficult to address the development of nanotechnology consumer product applications with respect to FDA just one year ago, a number of reports recently have emerged describing the wide extent of product commercialization.[2] In March 2006, the Project on Emerging Nanotechnologies released the first public inventory of nanotech-based consumer products, indicating that nanotechnology commercialization is occurring more widely and rapidly than anticipated.[3] This suite of already-commercialized products tells us that nanotechnology is here. Products are already being sold, used, and disposed of in multiple ways.

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[2] Maynard, Andrew, and Evan Michelson. *The Nanotechnology Consumer Products Inventory*. Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, March 2006. Available at http://www.nanotechproject.org/index.php?s=reports, accessed June 20, 2006.
Nanomaterials, Sunscreens and Cosmetics: Small Ingredients, Big Risks. Washington, DC: Friends of the Earth, May 2006. Available at http://www.foe.org/camps/comm/nanotech/, accessed June 20, 2006.

[3] See http://www.nanotechproject.org/consumerproducts.
Rick Weiss, "For Now, Nanotechnology Means Little More Than Better Golf Balls," *The Washington Post*, March 10, 2006.

Society's ability to reap the potential long-term benefits of nanotechnology will depend heavily on how we manage the introduction of this first generation of consumer products.

However, this first generation of products is only the beginning. We are about to be inundated with hundreds, if not thousands, of new products that will come under FDA jurisdiction. It is anticipated that more complex products, with large societal implications, will soon be upon us.

In analyzing our nanotechnology consumer products inventory as of June 2006, we found that:

- There are over 275 products on the market. We believe this number is a significant underestimate because the inventory lists only nanotechnology products self-identified by the manufacturer. It does not include the "over 600 raw materials, intermediate components and industrial equipment items" that EmTech Research estimates are currently in use by manufacturers.[4]

- Consumer products are using a range of nano-engineered materials, including carbon, silver, silica, titanium dioxide, and zinc oxide. These products—which include lipstick, moisturizing cream, and shampoo—are designed to be applied directly to the mouth, face, and scalp.

A selection of nanotechnology consumer products
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- Commercialization is already global. We found products from 14 countries, including Mexico, the United Kingdom, France, Germany, Switzerland, Finland, Sweden, China, Korea, Japan, Taiwan, Australia, New Zealand, and Israel, as well as the United States. Nanotechnology will continue to mature in a global digital economy where products can be bought and sold on the Internet and flow quickly across international boundaries through both business-to-consumer and business-to-business Internet transactions.

- This trend in global e-commerce will present new challenges for our oversight system, as products can be shipped, transported, and traded between nations with varying environmental, health, and safety laws. FDA is already experiencing a similar challenge in tracking and regulating the import and distribution of pharmaceutical products from Canada. We anticipate that the agency will face

[4] *External Review Draft Nanotechnology White Paper*. Washington, DC: United States Environmental Protection Agency, December 2, 2005. Available at http://www.epa.gov/osa/pdfs/EPA_nanotechnology_white_paper_external_review_draft_12-02-2005.pdf, accessed June 20, 2006.

similar difficulties in overseeing the global trade of nanotechnology goods over the Internet. The lack of international agreements covering the labeling of products that contain nanomaterials will further complicate this issue, as FDA will have little guidance as to which products actually contain nanomaterials and how nanomaterials might be used to change product performance.

NanoLabels: The Tower of Babel
Ingredient or packaging labels found on a selection of consumer and food products:

On a skin cream:
"optimizes cellular energetic balance using a nanocomplex of multiple intra-cellular transmitters"

On a dietary supplement:
"Nano Calcium Gluconate, Nano Calcium Carbonate, Nano Magnesium Carbonate"

On a sunscreen:
"Our anti-aging ingredients are nano-zinc oxide …"

On a face cream:
"… the first to harness the power of Fullerene C60 in the field of cosmetics"

Some of the most significant and surprising areas of nanotechnology commercialization are occurring with respect to cosmetics (52 products) and sunscreens (16 products), both of which fall under FDA jurisdiction. While sunscreens are regulated as over-the-counter (OTC) drug products—which require the listing of active ingredients, labeling and testing requirements, and cessation of unsupported or misleading terms—the Center for Food Safety and Applied Nutrition (CFSAN) notes that "FDA is only able to regulate cosmetics after products are released to the marketplace."[5,6] CFSAN continues, "neither cosmetic products nor cosmetic ingredients are reviewed or approved by FDA before they are sold to the public. FDA cannot require companies to do safety testing of their cosmetic products before marketing."[7] In short, while the FDA requires sunscreens to be labeled appropriately and—as will be discussed in depth in a later section—requires drugs to undergo a rigorous testing regime prior to being approved for distribution, FDA has virtually no statutory authority to ensure pre-market approval of cosmetics.

As the following table indicates, a simple search of the United States Patent and Trademark Office (USPTO) database shows that a number of cosmetic and personal care product companies, including L'Oreal, Unilever, and Colgate-Palmolive, have applied for patents for the future use of engineered nanosubstances in a variety of cosmetics, including skin creams, nail polishes, hair conditioners, and deodorants.[8]

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[5] "Sunscreen Regulations Finalized." Rockville, MD: United States Food and Drug Administration, May 21, 1999. Available at http://www.fda.gov/bbs/topics/ANSWERS/ANS00955.html, accessed June 20, 2006.
[6] "FDA Authority over Cosmetics." Rockville, MD: United States Food and Drug Administration, March 3, 2005. Available at http://www.cfsan.fda.gov/~dms/cos-206.html, accessed June 20, 2006.
[7] Ibid.
[8] "Patent Full Text and Full-Image Databases." Washington, DC: United States Patent and Trademark Office, June 20, 2006. Available at http://www.uspto.gov/patft, accessed June 20, 2006.

A Sampling of Published Patent Applications and Approved Patents for Nanotechnology in Cosmetics and Sunscreens

Company	Application Title	Key Language/Abstract (relevant claim in bold)	Date Filed	Published Application/ Patent Number
Colgate-Palmolive	Deodorant with small particle zinc oxide	"This invention comprises a one-phase cosmetic composition which can be made as a stick, gel or cream … " " … a small particle size zinc oxide having a **particle size in the range of 20 nanometers-200 microns."**	February 9, 2001	6358499
Unilever	High skin friction cosmetic creams containing dispersed zinc oxide particles as inorganic sunscreen	"A high skin friction cosmetic composition that can provide the consumer-desired sensory properties of traditional vanishing creams, containing solid asymmetric particles and ZnO … " **" … for ZnO the particles appeared well distributed and the size of each particle was about 60 nm … "**	August 21, 2003	20050042187
Estée Lauder	Topical delivery system containing colloidal crystalline arrays	"The system provides a nano-delivery system which permits penetration of actives (both oil- and water-soluble) into the stratum corneum, as well as skin-color correction and unique types of fragrance products … " **" … the silica particles have an average diameter of from about 50 to about 90 nanometers."**	August 20, 2004	20050048089
Johnson & Johnson	Enhancing properties by the use of nanoparticles	"Composite materials comprising nanoparticles functionalized with metals are disclosed. The composite materials may be used in a variety of applications, including in coating compositions, cosmetic and pharmaceutical compositions, absorbent articles, and the like. … " "In one embodiment, the nanoparticles have an **average particle size of about 1 to about 1000 nanometers, preferably 2 to about 750 nanometers**."	November 1, 2004	20050175649
L'Oreal	Cosmetic composition comprising a polyglycerolated silicone elastomer	"These dispersions may especially be in the form of nanoparticles of polymers in stable dispersion in the said fatty phase. In one embodiment the **nanoparticles are between 5 nm and 600 nm in size**."	March 22, 2005	20050220728

A search of the Project's nanotechnology consumer product inventory returns a host of cosmetics currently claiming the use of nanotechnology. For example, L'Oreal is promoting its Plenitude Revitalift Treatment Mask, which contains nanotechnology-enhanced anti-wrinkle moisturizers and exfoliating treatments designed to offset signs of aging skin. With the incorporation of Pro Retinol A, this line of cosmetics claims to introduce nanomaterials within the underlying, base layers of skin. Moreover, the inventory contains products from Barneys New York that have been developed using "several proprietary nanotechnologies, which can be used as a technological platform for creation of multiple products oriented toward enhancement of self-healing processes."[9] In this case, a product identified as a cosmetic is making a health claim. Finally, the Australian firm Advanced Nanotechnology Limited has created a series of nanoscale powders, known as Alusion, for use in lipstick and face powders, along with a transparent version of sunscreen, known as ZinClear, that is reported to contain nanosize particles of the broad-spectrum ultraviolet absorber zinc oxide.

Clearly, many of the cosmetic products we found have high exposure potential, as they are being used directly on the face or body. In short, we are facing a situation in which nano-based products are entering the market at precisely the points where FDA's oversight is imperfect and imprecise and where potential exposure is high. While there are a few available mechanisms to help FDA fill these gaps and loopholes, each is restrictive and disadvantaged by drawbacks, including:

- FDA has recently introduced a reporting system, the Voluntary Cosmetic Registration Program (VCRP), with the hopes that cosmetic manufacturers will voluntarily submit information about both their production sites and ingredients.[10] *However, it remains unclear how many companies that produce nano-based cosmetics will participate in this program, and it is not evident that there is enough incentive for such firms to do so, especially if participation may lead to more stringent nanotechnology oversight.*

- FDA does have some degree of statutory authority under the Federal Food, Drug and Cosmetic Act (FFDCA) to inspect manufacturers of cosmetics. *However, a lack of human and financial resources has hindered the ability of field offices to identify and inspect such firms.*[11]

- Finally, an initial round of basic research is being conducted by a public-private sector initiative that is attempting to determine the toxicity of these and other nanotechnology-related products. Researchers at Rice University in Houston, in conjunction with FDA's CFSAN, are "evaluating the effects" of quantum dots and nanosize titanium dioxide particles on "human and pig

[9] See http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1031.
[10] "Voluntary Cosmetic Registration Program (VCRP)." Rockville, MD: United States Food and Drug Administration, December 1, 2005. Available at http://www.cfsan.fda.gov/~dms/cos-regn.html, accessed June 20, 2006.
[11] "Federal Food, Drug and Cosmetic Act." Rockville, MD: United States Food and Drug Administration, December 31, 2006. Available at http://www.fda.gov/opacom/laws/fdcact/fdcact7a.htm, accessed June 20, 2006.

skin."[12] Such work is a useful preliminary step in determining the long-term health risks, if any, posed by the use of nanoscale-engineered materials in cosmetics. *However, gaps in the research remain. For example, none of the existing studies addresses the life cycle impacts of cosmetics after their use and disposal, such as the impact of nanoscale metal oxide–based sunscreens on aquatic life and habitats.*

Given the uncertainty around risks and regulations, companies may seek comparative advantage by moving now to identify their products as free from nanotechnology. If this occurs, it will force firms using nanotechnology to be more explicit about the risks and benefits, especially if cost premiums are being asked for these new products. The "no-nano" label is a fairly explicit differentiator in a market that is bound to be increasingly confusing for consumers because of the lack of any agreed upon nomenclature for nano-based substances and performance claims.

A No-Nano Label

The May 2006 edition of *Alternative Medicine Magazine* reports that the following companies told the magazine that they have specifically chosen not to use nanoparticles in their products:

Alba Botanica
Avalon Organics
Aveda
Grateful Body
Kiss My Face
MyCehlle Dermaceuticals
Pangea Organics

Concerns about labels, claims, and the possible health implications of nanotechnology consumer products were at the center of a controversy that surfaced in late March 2006 in Germany and Switzerland. A bath and kitchen tile treatment called Magic Nano was recalled from the market after the product caused significant health problems, with over 100 people affected with respiratory problems and six hospitalized with pulmonary edema.[13] Although the Federal Institute for Risk Assessment (BfR) in Berlin concluded that the product did not actually contain nanomaterials and that nanotechnology was not the cause of the reported health problems,[14] the Magic Nano incident illuminated other concerns that could affect regulatory agencies such as FDA if a similar situation were to occur in the United States. For example:

- A lack of disclosure concerning the ingredients in the product prevented a timely resolution of the case and determination of whether and how nanotechnology might have been implicated. A panel of German government experts was unable to determine, in a timely manner, whether nanomaterials were the cause of health

[12] Sadrieh, Nakissa. "FDA Perspective on Nanomaterial-Containing Products," presented at Nanobusiness Conference, New York, NY, May 2005, slide 30. Available at http://www.fda.gov/nanotechnology/powerpoint_conversions/May05_files/800x600/slide1.html, accessed June 20, 2006.

[13] Graber, David, and Pat Phibbs. "German Institute Working to Understand Why 'Magic Nano' Cleaner Caused Ailments." *Daily Environmental Report*, April 12, 2006.

[14] "Nano Particles Were Not the Cause of Health Problems Triggered by Sealing Sprays!" Berlin, Germany: Federal Institute for Risk Assessment, May 25, 2006. Available at http://www.bfr.bund.de/cms5w/sixcms/detail.php/7842, accessed June 20, 2006.

problems because "the distributors of the two sealing sprays were unable to supply the full formulations because information was missing from their upstream suppliers."[15]

- A third-party testing seal (TÜV), highly trusted by the German public, was falsely applied to the product package. The head of the Federation of German Consumer Organizations noted that, "It is irresponsible to give the consumers a mistaken sense of security by falsifying stamps."[16] This case has been referred to the district attorney, and there are calls for a criminal investigation against the manufacturer for suspected violation of Germany's product safety laws. This is analogous to the misuse of the Underwriters Laboratories (UL) symbol in the United States, which has occurred recently with respect to fireplaces,[17] extension cords,[18] and table saws.[19] Further complicating this issue is that these third-party certification bodies test products more for performance than for potential health or environmental risks. Even if such bodies were called upon to test products containing nanomaterials, no clear, agreed-upon test protocols exist.

Image of recalled Magic Nano products

The lack of transparency and the issues with independent testing have serious implications for public perceptions worldwide. In fact, after asking what would help increase public trust in government to manage the risks posed by nanotechnology, the authors of a number of studies conducted around the world reached common conclusions: there is a desire for greater transparency and disclosure and for greater use of third-party, independent safety testing. The Magic Nano case indicates that these desires can be difficult to fulfill—even in a country such as Germany, which has a history of strong environmental and consumer protection laws. Moreover, negatively affected populations may continue to emphatically state, "I blame it on nanotechnology."[20] Though the Magic Nano incident might have been local, the publicity and its impact on public perception can be global.

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[15] "Cause of Intoxications with Nano Spray Not Yet Fully Elucidated," Berlin, Germany: Federal Institute for Risk Assessment, April 12, 2006. Available at http://www.bfr.bund.de/cms5w/sixcms/detail.php/7750, accessed June 20, 2006.
[16] "Nano Poison Scandal: Misuse of a Major German Testing 'Seal of Approval,'" Berlin, Germany: Federation of German Consumer Organizations, April 14, 2006. Available at http://www.vzbv.de/go/dokumente/502/4/17/index.html, accessed June 20, 2006.
[17] See http://www.ul.com/media/newsrel/nr031406.html.
[18] See http://www.ul.com/media/newsrel/nr030106.html.
[19] See http://www.ul.com/media/newsrel/nr040606.html.
[20] Piller, Charles. "Science's Tiny, Big Unknown." *The Los Angeles Times*, June 1, 2006, A1.

Food Applications

While the application of nanotechnology to the food industry—by way of consumables, additives, supplements, production, processing, and packaging—may sound far-fetched, a report by Helmut Kaiser Consultancy concludes the market share of these uses is expected to grow from $7 billion in 2006 to $20.4 billion in 2010.[21] Moreover, the number of companies working in this area is expected to rise from "69 in 2002 to 2004 to several thousands by 2010."[22] In some countries, products using nanotechnology for nutraceutical delivery in foods are already on the market.[23]

Recently, our Project finished the first phase of a study with the University of Minnesota, in which the researchers—Dr. Jennifer Kuzma and Peter VerHage—documented more than 150 government funded research projects where nanotechnologies were being developed for food and agricultural applications. This study generated important information on what products might reach the market first, which oversight mechanisms would be triggered, and who might be exposed to risks. The database is fully searchable and publicly available online.[24] In the future, these investigators will seek to offer a deeper understanding of issues raised by information covered in this database by conducting a series of in-depth case studies that will focus more closely on risks and benefits.

Assembling this database at this point in time, before too many nanotechnology agrifood products have entered into commerce, provides a unique opportunity to better understand what is coming, to think through the potential impacts—both positive and negative—and to begin to engage the public and other key stakeholders in a dialogue about nanotechnologies' use. The public is already becoming increasingly aware of the potential benefits and risks of applying nanotechnology to food. When respondents in Macoubrie's study *Informed Public Perceptions of Nanotechnology and Trust in Government* were asked to indicate areas of interest associated with nanotechnology, both hopes for "safer and better food" and concerns about "nanotechnology's use in food products, packaging, and agriculture" were mentioned on an equal basis.[25]

Given the recent history of public concerns and policy missteps involving genetically engineered food, the introduction of any new technology into food and agricultural products offers public perception challenges for both industry and governments. From the public's perspective, such worries could become linked to a long history of concerns over the presence of chemicals and engineered ingredients in the food

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[21] "Study: Nanotechnology in Food and Food Processing Industry Worldwide 2003-2006-2010-2015," Tübingen, Germany: Helmut Kaiser Consultancy, 2005. Available at http://www.hkc22.com/nanofood.html, accessed June 20, 2006.
[22] Ibid.
[23] See http://www.shemen.co.il/english/nutrition-health.html.
[24] See http://www.nanotechproject.org/index.php?id=50.
[25] Macoubrie, Jane. *Informed Public Perceptions of Nanotechnology and Trust in Government*. Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, September 2005, p. 9 and 11. Available at http://www.nanotechproject.org/reports, accessed June 21, 2006.

supply. Evidence of such a mindset is apparent in that the organic food sector has grown at nearly 20 percent per year since 1990 and now accounts for over $15 billion in sales globally per year.[26] Clearly, there is a growing segment of the public that does not want their food "engineered"—bio, nano, or otherwise—and there are dozens of civil society groups organized to look over the shoulder of transnational food product companies.

However, as noted earlier, food-related products containing nanotechnology are already on the market, including nano-silver food storage systems and refrigerators. One of the biggest areas of application in the food sector appears to be for dietary supplements. A search of the Nanotechnology Consumer Products Inventory returns 12 products categorized as dietary supplements. For example, Health Plus International has developed Spray for Life, a dietary and health supplement advertised to deliver vitamins faster and more evenly into the body through the use of nanomaterials. RBC Life Sciences markets a host of products containing NanoCeuticals™, which claims to be able to "reduce the surface tension of foods and supplements to increase wetness and absorption of nutrients."[27]

Though the use of nanotechnology in such supplements appears to be on the rise, FDA has little statutory authority to test or oversee such products before they come to market. Under the Dietary Health and Education Act, "a firm is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading. The burden of proving safety under the Act is not on FDA, but rather the firm manufacturing or distributing the dietary supplement. This means that dietary supplements *do not need approval from FDA* before they are marketed" (italics added).[28] Companies thus are not required to seek FDA regulatory approval or submit safety test results and, therefore, may bring dietary supplement products containing nanomaterials to market with little oversight. Such a system makes it difficult to track possible negative health effects arising from the use of such nano-engineered products. Any potential side effects emerging from the use of nanomaterials in dietary supplements will remain unknown due to the lack of an approval process that requires the reporting of ingredients or any demonstration of safety or efficacy.

As will be discussed in greater detail in a later section, an improved and more coordinated research strategy will be needed to ensure the public that risks arising from the application of nanotechnology to consumer and food products are appropriately and accurately identified early in the technology development process. All concerned—consumers, industry and government regulators—have a stake in ensuring this outcome.

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[26] Greene, Catherine, and Carolyn Dimitri. "Organic Agriculture: Gaining Ground," *Amber Waves.* Washington, DC: United States Department of Agriculture, February 2003. Available at http://www.ers.usda.gov/amberwaves/feb03/findings/organicagriculture.htm, accessed June 20, 2006. Hansen, Nanette. "Organic Food Sales See Healthy Growth," *MSNBC.com*, December 3, 2004. Available at http://msnbc.msn.com/id/6638417, accessed June 20, 2006.

[27] See http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1123.

[28] "Overview of Dietary Supplements." Rockville, MD: United States Food and Drug Administration, January 3, 2001. Available at http://www.cfsan.fda.gov/~dms/ds-oview.html#what, accessed June 20, 2006.

Medical Applications

It is anticipated that some of nanotechnology's most beneficial long-term applications will occur in the field of medicine in the form of improved drugs, biologics, and devices. Public perception studies indicate that the highest interest in nanotechnology occurs in association with these anticipated medical breakthroughs and health benefits, such as new diagnostic tools or treatments for diseases. Research into these areas is well underway, as nanotechnology is beginning to serve as the basis for new, more effective drug delivery systems and is in early-stage development as scaffolding in nerve regeneration. The National Cancer Institute has invested significant resources to establish the Alliance for Nanotechnology in Cancer in order to help "harness the power of nanotechnology to radically change the way we diagnose, treat and prevent cancer."[29]

Nanometer-silver Cryptomorphic Condom

In addition to these initial investments, the development of commercial medical nanotechnology applications and products is accelerating at a rapid pace. In its *2006 Nanomedicine, Device & Diagnostics Report*, NanoBiotech News estimates that there are currently 130 nano-based drugs and delivery systems and 125 devices or diagnostic tests in preclinical, clinical, or commercial development—an increase of 68 percent since last year.[30] Such domestic trends are being mirrored worldwide, as companies in the European Union and East Asia are also focusing their resources on the medical applications of nanotechnology. For example, in China, an OTC prophylactic product is already being sold under the name Nanometer-silver Cryptomorphic Condom. It is reported that "the condom's antibacterial properties presumably arise from the nano-particles of silver incorporated into the spray."[31]

To provide a sense of the kind of nanotechnology medical applications that are already on the market, a selection of nine currently available nanotechnology drug and drug delivery products approved for use by FDA is presented below.[32] Four of these products employ Elan Corporation's NanoCrystal® Technology that uses "small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary, wet-milling technique" in

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[29] "Mission and Goals—NCI Alliance for Nanotechnology in Cancer." Rockville, MD: National Cancer Institute. Available at http://nano.cancer.gov/about_alliance/mission.asp, accessed June 20, 2006.
[30] *2006 Nanomedicine, Device & Diagnostics Report*. Atlanta, GA: NanoBiotech News, 2006. Available at http://www.nanobiotechnews.com/, accessed June 20, 2006.
[31] Smith, Tony. "Chinese Float Liquid Condom Concept," *The Register*, November 21, 2005. Available at http://www.theregister.co.uk/2005/11/21/china_liquid_condom/, accessed June 20, 2006.
[32] For a more complete listing of FDA-approved nanotechnology medical applications, including those in areas of diagnostics, testing, and drug development, see the *2006 Nanomedicine, Device & Diagnostics Report.*

order to "enable formulation and improve compound activity and final product characteristics."[33] These commercially available products include:

- **Rapamune®**: an immunosuppressant that uses Elan's NanoCrystal® technology to "provide patients with more convenient administration and storage than Rapamune oral solution."[34] It received FDA approval in August 2000.

- **Emend®**: an anti-nausea drug for chemotherapy patients that contains "80 or 125 mg of aprepitant formulated as NanoCrystal® drug particles."[35] It received FDA approval in March 2003.

- **Estrasorb®**: a topical estrogen therapy product that contains estrogen. It is based upon a "patented and proprietary micellar nanoparticles drug-delivery platform."[36] It received FDA approval in October 2003.

- **Megace® ES**: a drug designed to stimulate appetite by using Elan's NanoCrystal® technology "to improve the rate of dissolution and bioavailability of the original megesterol acetate oral suspension."[37] It received FDA approval in July 2004.

- **TriCor®**: a cholesterol-lowering drug that employs Elan's NanoCrystal® technology to provide "the benefits of a simplified, flexible dosing regime and allows for administration with or without food."[38] It received FDA approval in December 2004.

- **Abraxane®**: an injectable suspension used to treat advanced forms of breast cancer. It uses "nanoparticles made of the human protein albumin" in order to boost "the amount of anticancer drug available to kill malignant cells."[39] It received FDA approval in January 2005.

- **Doxil®**: an anti-cancer drug that employs ALZA Corporation's STEALTH® technology that is "composed of lipid nanoparticles that incorporate a

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[33] "Elan: NanoCrystal® Technology." Dublin, Ireland: Elan Corporation, plc, 2004. Available at http://www.elan.com/EDT/nanocrystal_technology/, accessed June 20, 2006.
[34] Ibid.
[35] Ibid.
[36] "Esprit Pharma Acquires Exclusive North American Rights to Estrasorb® Topical Emulsion; Sees Growing Pre-Eminence in Women's Healthcare." East Brunswick, NJ: Esprit Pharma, October 18, 2005. Available at http://www.estrasorb.com/pdf/Esprit-ESTRASORB.pdf, accessed June 20, 2006.
[37] "Elan: NanoCrystal® Technology." Dublin, Ireland: Elan Corporation, plc, 2004. Available at http://www.elan.com/EDT/nanocrystal_technology/, accessed June 20, 2006.
[38] "Elan: NanoCrystal® Technology." Dublin, Ireland: Elan Corporation, plc, 2004. Available at http://www.elan.com/EDT/nanocrystal_technology/, accessed June 21, 2006.
[39] "The Abraxane® Story: A Nanoparticle Platform Delivers Improved Anticancer Activity." Rockville, MD: National Cancer Institute, January 30, 2006. Available at http://nano.cancer.gov/news_center/nanotech_news_2006-01-30e.asp, accessed June 21, 2006.

polyethylene glycol (PEG) coating. This coating helps evade the potential impact of the immune system and enables STEALTH® technology to provide the precise delivery of drugs to disease-specific areas of the body."[40] It received FDA approval in February 2005.

- **Acticoat®**: Developed by Smith & Nephew, Acticoat® uses SILCRYST™ Nanocrystals to create wound dressings that **"**offer powerful antimicrobial barrier protection" using "safe bactericidal concentrations of silver with patented nanocrystalline technology."[41] Its Moisture Control system received FDA approval in May 2005.

- **SilvaGard™**: AcryMed, Inc., has begun to license this technology that contains "silver nanoparticle antimicrobial surface treatment for medical devices."[42] It received FDA approval in December 2005.

Using information contained in the *2006 Nanomedicine, Device & Diagnostics Report*, the Project on Emerging Nanotechnologies was also able to estimate commercialization time frames for two sets of nanotechnology medical applications: cancer-relevant drugs, diagnostic tests and devices; and general drug delivery devices. The two timelines—reproduced in the Appendix with the permission of NanoBiotech News—provide an overview of the number of products that are in various stages of development, from preclinical testing through FDA approval.

For each stage of the regulatory approval process, time frames were estimated as to when the various delivery systems and cancer drugs, diagnostic tests and devices are expected to be commercialized. The number of years allocated to each phase of the regulatory approval process is based upon the "Phases of Product Development" guide assembled by Dr. Dale E. Wierenga and C. Robert Eaton.[43] The number corresponding to each phase of development represents the number of drugs or products currently in that stage or estimated to be commercialized during that time frame.

As shown in the timelines, there are a total of 77 drugs, delivery systems, diagnostic tests and devices related to cancer and 56 products related to drug delivery.[44]

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[40] "ALZA: STEALTH® Liposomal Technology." Mountain View, CA: ALZA Corporation, September 16, 2006. Available at http://www.alza.com/alza/stealth, accessed June 21, 2006.
[41] "Smith & Nephew Acticoat® Product Line." Largo, FL: Smith & Nephew, Inc. Available at http://wound.smith-nephew.com/us/Standard.asp?NodeId=2867, accessed June 21, 2006.
[42] "AcryMed Fighting Infections, Healing Wounds." Beaverton, OR: AcryMed, Inc., 2006. Available at http://www.acrymed.com/, accessed June 21, 2006.
[43] Wierenga, Dale E., and C. Robert Eaton. "Phases of Product Development." Available at http://www.allp.com/drug_dev.htm, accessed June 21, 2006.
[44] For the cancer timeline, one product listed in the *2006 Nanomedicine, Device & Diagnostics Report* was not listed because of unknown time to commercialization. Additionally, three additional products were included that are based upon Elan Corporation's NanoCrystal® Technology that were not listed in the *2006 Nanomedicine, Device & Diagnostics Report.* For the drug delivery timeline, one product listed in the *2006 Nanomedicine, Device & Diagnostics Report* was not listed because of unknown time to commercialization. Additionally, three additional products were included that are based upon Elan

Drug delivery devices related to cancer are appropriately included in both timelines. A majority of items in both timelines (52 for cancer and 46 for drug delivery) are in early-stage development or preclinical testing. Additionally, there are some phases of the approval process (with respect to cancer, phase III clinical testing, and with respect to drug delivery, FDA review process) for which products have yet to enter. Again, as indicated by the more than 250 entries in the *2006 Nanomedicine, Device & Diagnostics Report*, these timelines include only a fraction of the actual number of nanotechnology medical applications currently in the pipeline.

As these medical applications proceed through the regulatory system, they will face a more thorough regulatory review than either cosmetics or dietary supplements. As J. Clarence Davies notes in his January 2006 report, "the process for approving drugs, biologics, and medical devices works reasonably well."[45] When exercised correctly, FDA's more substantial regulatory authority for medical applications appears not to require as much adjustment as does the regulatory authority for certain consumer product and food applications. Davies concludes that in the event of the development of a new law focused on nanotechnology, medical applications would most likely not need to be included, since such applications are already sufficiently covered by existing statutes.

However, FDA could face additional resource challenges that go beyond statutory authority. As is the case with other federal agencies tasked with overseeing nanotechnology developments, questions related to whether the agency has sufficient expertise, budgetary resources, or access to enough risk-related research will arise. As will be described in greater detail in a later section, the FDA also faces significant public perception and trust problems stemming from previous difficulties regulating new technologies in the drug and medical device areas. All these issues must be addressed to ensure that FDA's ability to regulate new nanotechnology products is not weakened or undermined by a narrow approach to the problem.

KEY NANOTECHNOLOGY CHALLENGES FACING THE FOOD AND DRUG ADMINISTRATION

Clearly, there are various barriers to nanotechnology's acceptance that may make it difficult for the technology to deliver its promised benefits.

First, there is a *lack of effective oversight mechanisms* to manage the potential risks posed by emerging nanotechnologies. Without such integrated management systems in place, the government runs the risk of playing regulatory catch-up with the rapid advance of nanotechnology commercialization.

Corporation's NanoCrystal® Technology that were not listed in the *2006 Nanomedicine, Device & Diagnostics Report.*

[45] Davies, J. Clarence. *Managing the Effects of Nanotechnology.* Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, January 2006, p.13. Available at http://www.nanotechproject.org/reports, accessed June 21, 2006.

Second, there is a *lack of coordinated research strategies* into the potential environmental, health, and safety risks posed by nanotechnology. In the absence of a strategic research framework, it will be difficult for the science community to investigate the downsides of the technology and to reach conclusions about how to assess and manage risk. Without this knowledge, it is hard to see how responsible nanotechnologies can be developed efficiently.

Third, there is a *lack of public engagement*, leading to *low trust in government and industry* to manage potential risks associated with nanotechnology. These negative public perceptions may continue to grow if appropriate steps are not taken to ensure the safety of the materials in nanotechnology goods.[46]

Lack of Effective Oversight Mechanisms

Something is going right: nanotechnology is starting to become commercialized in the areas of drugs, medical devices, food, and consumer products. However, as the Magic Nano case in Germany illustrates, nanotechnology's public perception could be harmed if an adequate oversight regime fails to be developed and implemented.

Although agencies have been meeting to discuss oversight and the Environmental Protection Agency (EPA) has begun developing a voluntary data collection program, the government's overall approach on the regulatory side so far has been ad hoc and incremental, with little vision. It is particularly worrisome that many nanotechnology-based consumer products, such as cosmetics and dietary supplements, are entering the market in areas with scant government oversight. The U.S. government approach has been limited by the following:

- Insufficient consideration of how nanotechnology impacts the Federal Food Drug and Cosmetic Act;

- A focus on single statutes, such as the Toxic Substances Control Act, rather than on an integrated, multi-statute approach;

- A focus on products more than on the facilities where production occurs and processes are used;

- A general lack of concern with the full life-cycle impacts of emerging nanotechnologies (an approach recommended in the 2004 U.K. Royal Society Report);[47] and

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[46] Macoubrie, Jane. *Informed Public Perceptions of Nanotechnology and Trust in Government*. Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, September 2005. Available at http://www.nanotechproject.org/reports, accessed June 21, 2006.

[47] *Nanoscience and Nanotechnologies: Opportunities and Uncertainties.* London, U.K.: The Royal Society and Royal Academy of Engineering, July 2004. Available at http://www.nanotec.org.U.K./finalReport.htm, accessed June 21, 2006.

- Inadequate discussion of the resource constraints to effective oversight (for instance, do the relevant agencies have the personnel, expertise, and financial resources needed for enforcement or testing?).

Most important, we have not looked forward to consider where nanotechnology is heading. Instead, we assume that decades-old risk management policies and analogies to the past will help us respond to the risks of the future. Today, nanotechnology is largely chemistry and materials science. But it is quickly becoming chemistry, materials science, and biology. After that, we will be dealing with multi-functional machines operating at the interface of classical and quantum physics, and, eventually, the convergence of nanotechnology, biotechnology, information technology, and cognitive science.

We need a systemic analysis across agency statutes and programs, across agencies, and across the international landscape. This analysis should include existing regulations, voluntary programs, information-based strategies, state and local ordinances, and tort law. All these measures need to be evaluated not only in terms of their applicability to nanotechnology today but also in terms of their efficacy in 5 or 10 years. We need an oversight blueprint that is proactive, transparent, and, for industry, predictable both now and into the foreseeable future.

Lack of Coordinated Research Strategies

There are currently no coordinated research strategies designed to help agencies such as the FDA address the potential environmental, health, and safety (EH&S) risks posed by nanotechnology. In the absence of such a strategy, it will be difficult for the public or for small- and medium-size companies to learn about the downsides of the technology and reach conclusions about how to assess and manage risk. Additional research on potential workplace hazards, environmental implications, and human-health impacts needs to be done and made readily available to small- and medium-size nanotechnology corporations.

Over the past 15 years, scientific data on the EH&S impacts of nanostructured materials have been growing slowly. However, research results on the implications of purposely manufactured nanomaterials have been readily available only for the past 5 years.[48] Though much of the research undertaken so far has raised more questions than answers, a number of key points have emerged, including:

- Since engineered nanomaterials show behaviors that depend on their physical and chemical structures, risk assessment paradigms that have been developed based on traditional, bulk chemistry alone may no longer be valid.

[48] Oberdörster, Günter, Eva Oberdörster, and Jan Oberdörster. "Nanotoxicology: An Emerging Discipline Evolving for Studies of Ultrafine Particles," *Environmental Health Perspectives*, July 2005, 113(7): 823-839.
Maynard, Andrew, and Eileen Kuempel. "Airborne Nanostructured Particles and Occupational Health," *Journal of Nanoparticle Research*, 2005, 7: 587-614.

- Inhaled, nanometer-structured, insoluble particles can elicit a greater response in the lungs than their mass would suggest, indicating mechanisms of action that are dependent on particle size, surface area, and surface chemistry, among other properties. However, information on the structure-related behaviors of nanomaterials in the body is lacking.

- Inhaled, nanometer-diameter particles may leave the lungs through non-conventional routes and affect other parts of the body, including the cardiovascular system, liver, kidneys, and brain. Very little is known about the impact of engineered nanomaterials on these organs.

- Nanometer-diameter particles may be able to penetrate the skin in under some circumstance, although this is still an area of basic research and the chances of penetration appear to be low for healthy skin. The potential for nanostructured particles present in cosmetics and other skin-based products to do harm may be low, but remains unknown.

- Virtually nothing is known about the hazards of engineered nanomaterials ingested as food additives or by accident.

To date, the majority of research on the EH&S implications of nanotechnology has focused on relatively basic engineered nanomaterials. As nanomaterials move from simple to complex materials and on to active and multi-functional materials, major knowledge gaps need to be filled before useful quantitative risk assessments can be carried out and before comprehensive, life cycle risk management strategies can be developed.

A number of groups have developed, or are developing, lists of research priority areas and questions of interest. These organizations include EPA,[49] the National Institute for Occupational Safety and Health (NIOSH),[50] Environmental Defense,[51] the Semiconductor Research Corporation and the Chemical Industry Vision 2020 Technology Partnership,[52] and the Project on Emerging Nanotechnologies.[53] Despite the

[49] *External Review Draft Nanotechnology White Paper*. Washington, DC: United States Environmental Protection Agency, December 2, 2005. Available at http://www.epa.gov/osa/pdfs/EPA_nanotechnology_white_paper_external_review_draft_12-02-2005.pdf, accessed June 20, 2006.
[50] *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps*. Washington, DC: National Institute for Occupational Safety and Health. September 28, 2005. Available at http://www.cdc.gov/niosh/topics/nanotech/strat_planINTRO.html, accessed June 21, 2006.
[51] Denison, Richard A. "A proposal to increase federal funding of nanotechnology risk research to at least $100 million annually." Washington, DC: Environmental Defense, April 2005. Available at http://www.environmentaldefense.org/documents/4442_100milquestionl.pdf, accessed June 21, 2006.
[52] Semiconductor Research Corporation and Chemical Industry Vision 2020 Technology Partnership. "Joint NNI-ChI CBAN and SRC CWG5 Nanotechnology Research Needs Recommendations." Available at http://www.chemicalvision2020.org/ pdfs/chem-semi%20ESH%20recommendations.pdf, accessed June 21, 2006.
[53] Maynard, Andrew. *Nanotechnology: A Research Strategy for Addressing Risk.* Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, July 2006.

diversity of these organizations, these gap analyses are generally in broad agreement on the areas requiring further research and development. Common themes include toxicity (human and environmental), exposure and material release and dispersion, health outcomes, epidemiology, measurement and characterization, control of exposure and emissions, safety hazards, risk management models, and product life cycle analyses.

However, more needs to be done to engage small- and medium-size businesses in setting research agendas and in identifying knowledge gaps. Without such involvement, EH&S research may not be able to adequately address and provide substantial answers to many risk management questions that will emerge in both the near and long-term future for these companies. Therefore, an effective, forward-looking, internationally accepted, EH&S research strategy that takes into account small- and medium-size businesses needs to be developed to fill this gap.

Lack of Public Engagement and Low Trust in Government and Industry

We know from public surveys and polls that the government and industry will have to win the public trust on nanotechnology. The emergence of viable markets depends on strong and growing consumer confidence.

However, in the midst of nanotechnology's commercialization, publics throughout the world remain largely in the dark. A major study, funded by the NSF and conducted in 2004 by researchers at North Carolina State University (NCSU), found that 80 percent to 85 percent of the American public has heard "little" or "nothing" about nanotechnology.[54] This is consistent with similar polling results in Europe and Canada.[55] Anecdotally, some researchers believe that an even higher percentage of the public remains uninformed about nanotechnology. These same citizens are now encountering nanotechnology products in their local stores or on the Internet. The public will increasingly have to make sense of competing claims, complex science, and emerging risk research, all with little or no preparation or support. Into this mix enter an increasing number of NGOs interested in shaping public opinion in various directions, some of which may have large strategic implications for business and government.[56]

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[54] Cobb, Michael D., and Jane Macoubrie. "Public Perceptions about Nanotechnology: Risk, Benefits and Trust." Raleigh, NC: North Carolina State University, 2004. Available at http://www2.chass.ncsu.edu/cobb/me/past%20articles%20and%20working%20papers/Public%20Perceptions%20about%20Nanotechnology%20-%20Risks,%20Benefits%20and%20Trust.pdf, accessed June 21, 2006.

[55] *Nanotechnology: Views of the General Public*. London, United Kingdom: BMRB Social Research, BMRB/45/1001-666, January 2004. Available at http://www.nanotec.org.uk/Market%20Research.pdf, accessed June 21, 2006.
Einsiedel, Edna. "In the Public Eye: The Early Landscape of Nanotechnology among Canadian and US Publics," *First Impressions: Understanding Public Views on Emerging Technologies.* Ottawa, Canada: Government of Canada, 2005: 99-117. Available at http://www.biostrategy.gc.ca/CMFiles/CBS_Report_FINAL_ENGLISH249SFD-9222005-5696.pdf, accessed June 21, 2006.

[56] Since 1990, more than 100,000 new citizens' groups have been established around the world. Trust in many of these groups has increased in direct proportion to decreasing confidence in government and

In 2005, the Project on Emerging Nanotechnologies commissioned a report by Senior Associate Jane Macoubrie, who co-authored the NCSU study in 2004. This report, *Informed Public Perceptions of Nanotechnology and Trust in Government*, provides an in-depth look at American attitudes toward nanotechnology.

It indicates that U.S. consumers, when informed about nanotechnology, are eager to know and learn more. They generally are optimistic about nanotechnology's potential contribution to improve quality of life, especially in regard to major advances in health and medicine. The key benefits the public hopes for are major medical advances, particularly greatly improved treatment for cancer, Alzheimer's, and diabetes.

Macoubrie also found that FDA fared particularly poorly in terms of public trust in the agency's ability to manage nanotechnology risks. A number of worrisome trends were illuminated and a variety of concerns were voiced, including:

- Respondents lowered their level of trust after learning more about FDA's functions in the government;

- Respondents referred to historical analogies and parallels between nanotechnology and FDA's difficulties in previous instances of product oversights, such as Vioxx and other medical applications;

- Respondents perceived negative influences from Congress and industry, which the public believes could undermine and weaken effective regulatory protections.

In short, Macoubrie's examination indicated that FDA's ability to manage risks posed by nanotechnology created some of the respondents' most significant concerns.[57] Macoubrie's findings indicate that FDA's actions are going to be critical to the introduction of nanotechnology in food and agriculture products and that both government and industry are going to have to take steps to win the trust of consumers.

The Project's report findings track closely with work done in 2004 by University of East Anglia researcher Nick Pidgeon for Great Britain's Royal Society. Pidgeon found there were few among the British public who knew much about nanotechnology, although those who did know about it were generally optimistic about its benefits.[58] However, this optimism was tempered by a significant amount of suspicion about

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industry. See Bonini, S. M., et al. "When Social Issues Become Strategic," *McKinsey Quarterly*, 2006, Number 2.

[57] Macoubrie, Jane. *Informed Public Perceptions of Nanotechnology and Trust in Government*. Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, September 2005, p. 13. Available at http://www.nanotechproject.org/reports, accessed June 21, 2006.

[58] *Nanotechnology: Views of the General Public.* London, U.K.: BMRB Social Research, January 2004, BMRB/45/1001-666. Available at www.nanotec.org.U.K./Market%20Research.pdf, accessed June 21, 2006.

industry's intentions and skepticism about the government's commitment to effective oversight.

For policy makers, the take-home messages that emerge from these studies are quite clear:

- Consumers want more information about nanotechnology's uses as well as greater engagement in shaping how the technology is developed.

- There are low levels of trust in government and industry to manage any risks associated with nanotechnology. There is little support for industry self-regulation or voluntary agreements. A majority of the public believes that mandatory government controls are necessary.

- People have clear ideas about how to improve trust. They want government and industry to practice *due diligence* to ensure manufacturing and product safety. In both the U.S. and U.K. studies, this translated into strong support for research and safety testing *before* products enter the market and a focus on better understanding of the products' long-term effects both on people and on the environment.

Conceivably, negative health or environmental effects reported to be caused by nanotechnology-based cosmetics could create a public backlash if regulatory agencies such as FDA are viewed as not heeding such advice. Such a response would not only have a negative impact on the nanotechnology industry but would also reinforce public mistrust of government and undermine confidence in the government's ability to manage new technologies effectively.

There is still time to inform public perceptions about nanotechnology and to ensure that nanotechnology is developed in a way that citizens—as well as the insurance industry, corporate investors, NGOs, and regulatory officials—can trust. However, with the production of nanosubstances ramping up and with more and more nanotech-based products pouring into the marketplace, this window is closing fast.

Worries are already being voiced that public input will now be used simply as a "tokenistic add-on" rather than as a valuable policy-making tool.[59] Coordinated education and engagement programs will be needed, supported by both government and industry. Public engagement programs will have to be structured to reach a wide range of consumers. To cut across age, gender, and socioeconomic status, it must use non-traditional media, such as the Internet, blogs, and podcasts, as well as print, radio, television, and film

[59] Saleh, Anna. "Critics Say Nanotech Plan Sidelines Public," *ABC Science Online,* April 28, 2006. Available at http://www.abc.net.au/science/news/health/HealthRepublish_1625988.htm, accessed June 21, 2006.

RECOMMENDATIONS FOR THE FOOD AND DRUG ADMINISTRATION

To address the challenges outlined above, there are a number of steps FDA should consider as it moves forward in formulating its approach to managing nanotechnology. The goal of these recommendations is to ensure the benefits overweigh the risks, firms have a clear path to market, and public confidence grows.

- **Conduct risk research in front of product flows to both inform oversight and regulatory strategies with good science and to provide important information on risks and benefits to the public.** There has been a surprising consensus among industry, trade associations, think tanks, and environmental NGOs concerning the urgent need for more EH&S research funds and the need to make sure these funds are strategically allocated to deal with existing *and* emerging risks. For instance, although the Project on Emerging Nanotechnologies has indicated that ingestible nanotechnology products are already on the market—along with a number of promised applications in the agriculture and food sectors—there is no research on the impacts of nanomaterials in the gastrointestinal tract. Given the lag time between the initiation of research and the results, greater efforts need to be made to place research on environmental, health, and safety concerns further "upstream" in the product development process. Such research needs to be coordinated at a global level, since the commerce in nanotechnology materials and products is, and will continue to be, worldwide.

- **Develop an oversight system that is transparent, efficient, and predictable.** Such a system is essential if commercialization of the products of nanotechnology is to succeed. Companies are often confused about the regulatory intentions of the government, investors and insurers are insecure, and the public is suspicious. Davies notes that "nanotechnology is difficult to address using existing regulations," since they "either suffer from major shortcomings of legal authority, or from a gross lack of resources or both."[60] Short of new legislation, which must be seriously considered, there is much more government and industry can do to provide adequate oversight on emerging products. One approach is applying a portfolio-of-initiatives strategy to key product areas.[61] Using cosmetics as an example, one could assemble a portfolio that combines FDA's Voluntary Cosmetic Registration Program (VCRP)[62], the Cosmetic, Toiletry & Fragrance

[60] Davies, J. Clarence. *Managing the Effects of Nanotechnology.* Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, January 2006. Available at http://www.nanotechproject.org/reports, accessed June 21, 2006.

[61] The use of a portfolio-of-initiatives approach is often recommended as a strategy for dealing with uncertainty. See Bryan, Lowell. "Just-in-time Strategy for a Turbulent World," *McKinsey Quarterly*, 2002 Special Edition, or Courtney, Hugh. *20/20 Foresight: Crafting Strategy in an Uncertain World.* Cambridge, MA: Harvard Business School Press, September 2001.

[62] "Voluntary Cosmetic Registration Program (VCRP)." Rockville, MD: United States Food and Drug Administration, December 1, 2005. Available at http://www.cfsan.fda.gov/~dms/cos-regn.html, accessed June 20, 2006.

Association's (CFTA) Cosmetic Ingredient Review (CIR)[63], labeling guidelines, and consumer education efforts by industry and government. Such a multi-faceted system could be used to fast-track the review of key nanomaterials, such as carbon fullerenes, that are already being used in high-exposure cosmetic products. Integrating industry, government, and association efforts would bolster the insufficient level of human resources that exist in the regulatory agencies.[64] Such a portfolio-based approach requires not only an integration of initiatives but also a constant evaluation of progress and a willingness on the part of government and industry to make midcourse corrections if necessary.

- **Increase resources for public engagement by orders of magnitude and rapidly accelerate public engagement activities.** This request for comments and decision to hold a public meeting is a good first step. However, attendance at and participation in such meetings is limited to a few industry, government, and NGO stakeholders and does not take into account the wider public's desire for information and engagement. The wait to begin engaging the public about nanotechnology has lasted far too long. Successful commercialization in the fields of FDA-relevant consumer products, food, and medicine will be impossible without strong consumer confidence. How consumers find out about nanotechnology, from whom, and with what messages will be critical to nanotechnology's long-term success. Key impressions formed over the next two years will affect consumer confidence far into the future. The "21st Century Nanotechnology Research and Development Act" requires the government ensure that **"**public input and outreach … be integrated into the Program by the convening of regular and ongoing public discussions, through mechanisms such as citizens' panels, consensus conferences, and educational events."[65] However, nothing along these lines has occurred in over a year and half. The first meeting on this topic took place at the end of May 2006, and its purpose was to discuss *how* to structure public engagement, not to actually engage the public. An effective, nationwide public engagement program around nanotechnology would cost a minimum of $3–$5 million. It is not clear who in the government is prepared to fund such an endeavor. The longer the wait the greater the danger that the public will see such efforts as disingenuous, "after the fact," and tokenistic.[66]

These three steps should be taken together, properly resourced, and integrated. Frankly, with products flowing into the market at an increased rate, we do not have a lot of time. Technological innovation has no "pause button" that government can

[63] "Cosmetic Ingredient Review." Washington, DC: Cosmetic Ingredient Review, 2006. Available at http://www.cir-safety.org, accessed June 21, 2006.
[64] Though the federal government has continually maintained that it has sufficient statutory authority to deal with nanotechnology, it has said nothing about the resources needed to back up existing statutes, which are as critical to success as the statutes themselves.
[65] "21st Century Nanotechnology Research and Development Act," S. 189, Washington, DC: United States Congress, 2003. Available at http://thomas.loc.gov, accessed June 21, 2006.
[66] This problem occurred in the U.K. after the government launched a project on public engagement around genetically modified food (GM Nation), after such products were already on the market.

conveniently push to create time for research, testing, policy deliberation, or a few more public meetings. By the time there is a settlement on nomenclature for the first generation of nanomaterials, the next generation will be here; by the time the risks of early-stage nano-based substances have been characterized, newer, more complex materials will be on the market. Without better foresight, answers will be received for yesterday's questions.

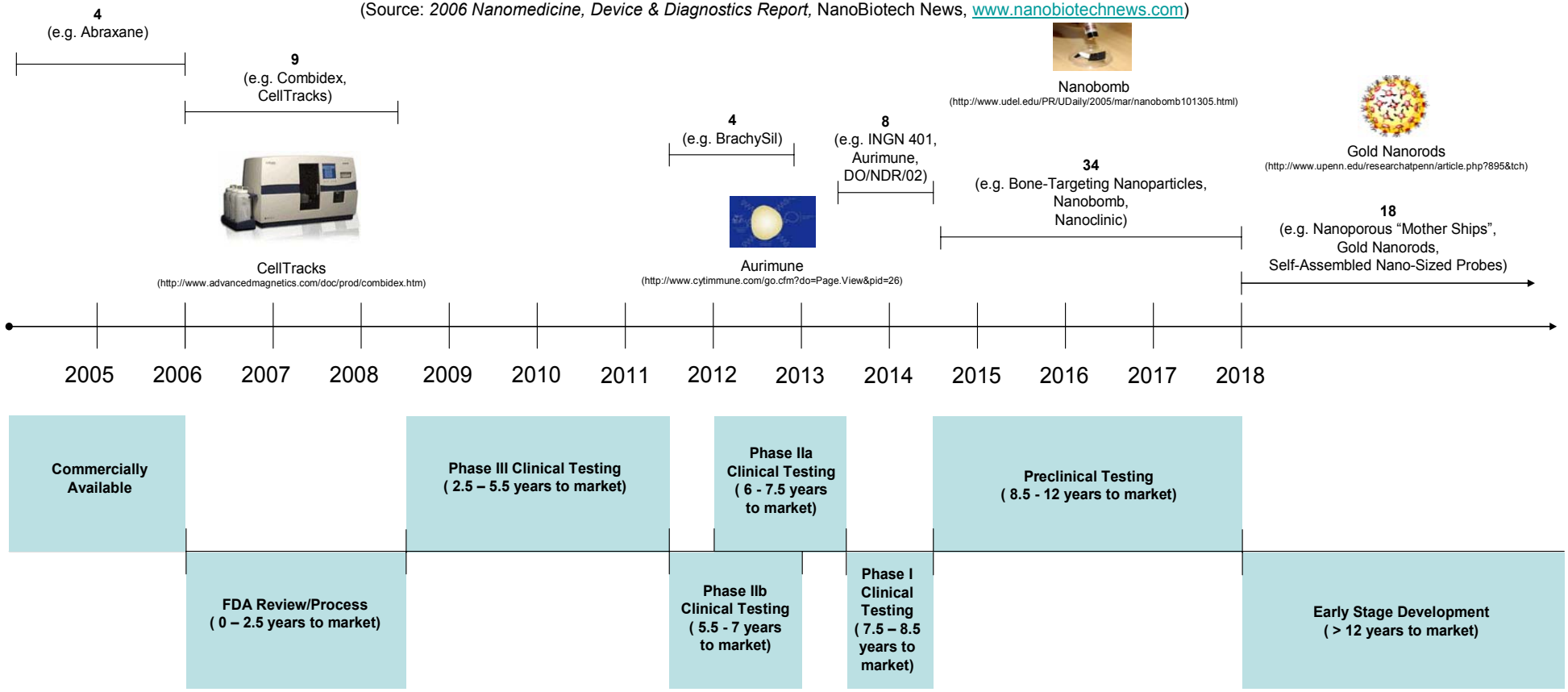
* * *

The Project on Emerging Nanotechnologies expects that a wide array of nanotechnology developments in fields of interest to FDA—from healthier, safer food products to improved cancer treatments—to enter the market over the coming years. These applications will have a variety of uses and could potentially save a great number of lives. Nanotechnology is already moving from being used in passive structures to active structures and may soon aid in the formation of molecular systems that will be strikingly similar to living systems. These predictions have great significance not only by highlighting state-of-the-art nanotechnology research and development but also in helping FDA realize that it may soon face a dramatic increase in the number of nanotechnology products that fall under its jurisdiction. The most important challenge at the present time is to figure out how to encourage the development of this remarkable technology while minimizing any downsides that may occur along the way.

In closing, the Project on Emerging Nanotechnologies applauds FDA for taking this first step. We hope that an open, fruitful, and productive dialogue will emerge through the ideas presented in these comments and through discussions at the public meeting. In the long run, key social and economic benefits will occur only if society succeeds in overseeing nanotechnology innovation effectively and efficiently. FDA will play a significant role in this process. To do that, there needs to be a concerted effort to place new people, resources, and ideas behind an expanded national nanotechnology initiative.

Appendix: Nanomedicine Timelines

Estimated Commercialization Timeline For Select Nanotechnology Cancer Applications
Total: 77
(Source: *2006 Nanomedicine, Device & Diagnostics Report,* NanoBiotech News, www.nanobiotechnews.com)



Estimated Commercialization Timeline For Select Nanotechnology Drug Delivery Applications

Total: 56

(Source: *2006 Nanomedicine, Device & Diagnostics Report*, NanoBiotech News, www.nanobiotechnews.com)

4
(e.g. Nanocrystals used in Rapamune, Emend, TriCor, and Megace ES)

Emend
(http://www.prestonhunt.com/hd/pics/59%20Emend.jpg)

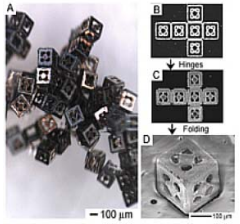
1
(e.g. PRINT)

1
(e.g. NPI 32101)

NPI 32101
(http://www.nucryst.com/product_pipeline.htm)

4
(e.g. Biological Nanoparticle, Transferrin-Coated Nanoparticles)

30
(e.g. NX-300, Nanocomposite Drug Carrier)



Self-Assembling Cubes
(http://www.jhu.edu/news/home05/dec05/cubes.html)

16
(e.g. Self-Assembling Cubes, Fortifying Nanovehicles)

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

Commercially Available

FDA Review/Process (0 – 2.5 years to market)

Phase III Clinical Testing (2.5 – 5.5 years to market)

Phase IIb Clinical Testing (5.5 - 7 years to market)

Phase IIa Clinical Testing (6 - 7.5 years to market)

Phase I Clinical Testing (7.5 – 8.5 years to market)

Preclinical Testing (8.5 - 12 years to market)

Early Stage Development (> 12 years to market)