March 2007

Synthesizing the Ubiquitous:

Venable LLP's White Paper on Nanotechnology Law

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Nanotechnology presents a fascinating study of contrasts. The staggering biological, chemical, physical and engineering questions that nanoparticles raise are matched only by the potential solutions that nanotechnology makes possible. Take, for instance, contaminated soil. Just as many individuals question the effects of engineered nanoparticles on the environment, many others see the value in using nanotechnology to neutralize the contaminants in soil rather than remove it for physical remediation. Similarly, one of the principal benefits of nanoparticles (their small size) also constitutes one of their greatest potential health risks (*e.g.*, potential for penetrating the most sensitive areas of the human body). Consistent with the seemingly inconsistent logic of nanotechnology, what makes nearly inconceivable tiny nanoparticles potentially hazardous is their nearly inconceivable large surface areas. The following paper discusses the many legal principles that affect this ever-evolving environment.

The innovation required to design, manufacture and market a successful nanoengineered product does not end at the store or pharmacy shelf. Ensuring the continued viability of nanotechnology-derived products will require a sound intellectual property platform, protected with the right balance of, among other things, trade secrets and patents. Food, drug and cosmetic manufacturers additionally have to comply with the requirements of the Food and Drug Administration ("FDA"). Manufacturers also will have to create a safe working environment that satisfies the National Institute for Occupational Safety and Health ("NIOSH") and the Occupational Safety and Health Administration ("OSHA"). All byproducts from the manufacturing process will have to be processed in accord with the mandates of the Environmental Protection Agency ("EPA"). Furthermore, standard-setting bodies, such as ASTM International (formerly American Society for Testing and Materials) and International Organization for Standards ("ISO"), are beginning to establish universally known criteria for nanotechnology. Monitoring all of this activity and positioning itself to intervene, if necessary, is the United States Congress. Even surviving this scrutiny does not guarantee success, as jurors faced with an allegedly injured plaintiff or class of plaintiffs ultimately may determine whether a nanoengineered product should have been on the market. The same collaborative effort, forward-thinking attitude and discipline that lead to the discovery of innovative nanomaterials therefore will be necessary to fashion a unified, holistic approach to overcome these legal, regulatory, and commercial hurdles.

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THE FUNDAMENTALS

The Groundwork for Discussing Nanotechnology

"Nanoscience" is the study of how the properties of materials that are between atomic and molecular scale differ from those materials when they exist at larger scales. The "nano" refers to the nanometer measurement ("nm"), which is one billionth of a meter. To put this into perspective, one would have to split a human hair 80,000 times to produce a particle that is one nanometer in width. A human blood cell is approximately 7,000 nm wide and a strand of DNA is approximately two nm wide. A nanoparticle is less than 100 nm in all three dimensions. A nanomaterial is comprised of nanoparticles and is defined as having at least one dimension that is less than 100 nm. By way of example, a platinum/titanium dioxide nanoparticle, a common building block in nanotechnology, has an approximate width of 18 nanometers. Thus, nanoparticles currently being created and used are approximately the size of human DNA.

"Nanotechnology" describes products and processes in which the arrangement of matter is controlled at dimensions of less than 100 nanometers (nm) (less than a ten-millionth of a meter).[1] News stories on the promises and threats of nanotechnology appear regularly. The topic is receiving increased attention by federal regulatory agencies and Congress. There are questions about how nanotechnology-related environmental, health and safety matters will be addressed under existing laws. At the same time, the government and private sector are investing in the development of nanotechnology for many applications.

A. The Commercial and Industrial Interests at Stake

Nanotechnology can and is being used in any number of industries. While nanosized particles exist in nature, nanotechnology generally refers to the manipulation of materials at nanosizes for particular applications. It includes engineering of particles by certain chemical and/or physical processes to create materials with specific properties not displayed in their macro-scale counterparts. It also includes the use of manufacturing processes, such as milling or grinding, to produce nanosized particles that may or may not have properties different from those of the bulk material from which they are developed. Finally, these nanomaterials may be used in many kinds of applications, also under the umbrella of nanotechnology.

Consumer products ranging from cosmetics and pharmaceuticals to building materials and agricultural applications utilize nanoscale materials or components. Nanotechnology is an "industry" that is involved in a vast array of other "industries." The Project on Emerging Nanotechnologies of the Woodrow Wilson International Center for Scholars maintains several comprehensive inventories of interest, including lists of products with nanomaterials; research on environment, health and safety matters; consumer data; and agricultural/food data. *See* www.nanotechproject.org. That entity's consumer product database indicates that over 200 nanotechnology consumer products are currently on the market.

[1] *See* "What is Nanotechnology," National Nanotechnology Initiative, http://www.nano.gov/html/facts/whatIsNano.html, accessed Jan. 30, 2007.

Nanotechnology promises to develop at an exponential rate. According to the National Nanotechnology Initiative ("NNI")—launched in 2001 to coordinate nanotechnology research and development across the federal government—nanotechnology will develop in four distinct phases. The first or current era is characterized by the development of passive nanostructures. The challenge in assessing the toxicological effects of manufactured particles that are the size of DNA is daunting. However, because these structures are passive, their toxicological profile should be the least challenging to assess among the nanosized particles that are expected to be developed. The second phase will be characterized by the development of nanostructures that are used for multi-tasking, such as drug delivery devices and sensors. Nanosized devices conducting multiple tasks will compound the technical difficulty of assessing their toxicological profile since the devices are likely to affect or interact with multiple cell lines, each of which may react differently to particles that are sufficiently small to allow them to enter a cell.

The NNI predicts that the third era of nanotechnology will begin around 2010. That era will feature nanosystems comprised of interacting nanostructures. The last phase of nanotechnology development will include the first integrated nanosystems. Such systems will function very similarly to a human cell, including the development of internal systems.[2]

B. The Potential Health Effects

Somewhat tempering the enthusiasm for nanotechnology-related products are uncertainties about the health effects that could be or are associated with nanoparticles. The potential toxicological effects of nanoparticles are a function of their extremely small size. Nanoparticles have essentially no mass; yet, relative to their mass, they have extremely large surface areas. This is critically important for assessing the potential toxicological effects of nanoparticles. As their size decreases, the surface area of nanoparticles increases. This inverse relationship allows a greater percentage of atoms within a particle to be expressed on the surface of the particle as a function of its size. As more atoms are expressed on the surface, the reactivity between the nanosized particle and its environment increases.

Similarly significant to understanding the realized and potential health effects of nanoengineered particles are basic toxicological principles of exposure and dose. To have an adverse biological or toxicological effect, there must be exposure to an agent. Merely ingesting, inhaling or being dermally exposed to nanosized particles, however, does not mean that they bypassed the body's defensive system and interacted with cells or proteins in the human body. The extent of the actual communication or interaction between nanoparticles and the body's cells and proteins determines the "dose" of nanoexposure that has occurred. A basic principle of toxicology is that there is a dose response relationship. Thus, if nanoparticles are toxic, scientists would expect that the effect will increase as the dose increases. What is not known is whether the "dose" will be a function of the number of particles to which the body has been dosed, their size or their surface area.

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[2] Andre Nel, et al., *Toxic Potential of Materials at the Nanolevel*, 311 Science 622, 622 (Feb. 3, 2006) (appended as Appendix A).

There will be no shortage of exposure to nanoparticles in the future and there will be no shortage of potential avenues of exposure. Foods are currently being developed that utilize nanoparticles. Ingestion of nanoparticles allows for easy penetration and absorption into the digestive tract and subsequently to the blood stream. Nanoparticles also are easily absorbed through the blood stream via inhalation and contact with alveoli. Finally dermal exposures to nanoparticles occur regularly through the use of cosmetics such as sunscreens.

While exposure currently occurs and will increasingly occur as nanotechnology develops, it is not clear to what extent, if any, dosing occurs. The increased surface area and their small size should make nanoparticles very reactive to proteins and cells within the human body. Access to the blood stream makes the passage of nanoparticles through the blood-brain barrier a real possibility.

The leading paradigm to explain the potential biologic effects of nanoparticles involves a generation of reactive oxygen species ("ROS") and resulting oxidative stress. There is some experimental evidence to suggest that certain nanoparticles may induce cells to generate ROS beyond the ability of the antioxidant defenses of cells to neutralize the ROS. When the antioxidant defense system is overwhelmed, inflammation and cell damage result.

By no means do these potential health effects create an impermeable barrier to the development of nanotechnology. Rather, they make plain the importance of remaining abreast of the current scientific, regulatory and legal environments to developing, manufacturing, and monitoring nanotechnology-derived products. Additionally, they create opportunities for nanotechnology-based companies to develop the safety standards, measures and equipment necessary for the industry to proceed through the phases of nanotechnological development. In other words, for every purported or even potential risk created by nanotechnology, a solution likewise may arise from nanotechnology. Perhaps even more important to the continued growth of nanotechnology—be it used in consumer products, pharmaceuticals, food products or safety equipment—is the importance of intellectual property rights to protect the significant investment required to develop these advancements.

NANOTECHNOLOGY IN THE INTELLECTUAL AND COMMERCIAL MARKETPLACE

The Intellectual Property Issues in Nanotechnology

Corporate innovators involved with nanotechnology should be aware of the risks and opportunities presented by intellectual property rights, including patents belonging to others that may block the company's ability to use a desired technology, and patents and trade secrets that can be managed to exclude others from using the company's own nanotechnology.

Nanotechnology is a "disruptive technology," which will "displace older technologies and enable radically new generations of products and processes."[3] By obtaining patents on nanotechnological innovations, a company can realize profit from its research efforts, control the development of a product sector, and establish itself at the vanguard of its field. Innovators recognize the importance of patent protection: in 2005, the U.S. Patent and Trademark Office ("PTO") cumulative class for nanotechnology contained 3162 issued patent and published applications.

Of these, about 23% were classified as chemical inventions.[4] To acquire strategically useful patent portfolios, however, challenges particular to nanotechnology must be understood.

A. Nanotechnology and Trade Secrets

Nanomaterials themselves may be difficult to protect as trade secrets because it may be easy to reverse engineer their composition and shape. But other aspects of nanotechnology can be protected as trade secrets. These may include starting materials, such as precipitated calcium carbonate ("PCC") that are converted into nanoparticles or other nanomaterials, methods of making nanomaterials, and methods of fabricating nanomaterials into composites. These fabrication methods may not be susceptible to reverse engineering, meaning that the materials themselves do not reveal how they were made.

In theory, a trade secret can be maintained indefinitely, but the security measures required impose an ongoing burden. Once disclosed without confidentiality, or published by someone else, the innovation is no longer subject to trade secret protection. Moreover, once a product is sold or in public use, the product and methods of making it become unpatentable in many countries (and in the United States after a one-year grace period).

B. Nanotechnology and Patents

1. General Advantages to Patent Protection

Protection of an innovation by patent is generally more robust than protection by trade secret. A patent holder can exclude others from making, using, selling or importing the patented invention for a period (generally 20 years) from the filing of an application in the PTO. Unlike trade secrets, someone who owns a patent can exclude someone who independently developed the same innovation and may be able to prevent reverse engineering and other research using the patented invention. The patent owner can block someone who was trying to protect an invention as a trade secret in many countries. This right to cut off second movers (and even prior innovators) is of great importance in an intensely researched, emerging field such as nanotechnology.

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[3] *See* "Nanotechnology is Disruptive - What this Means for Manufacturing Sectors with Reference to the UK," Azonano.com, http://www.azonano.com/details.asp?ArticleID=1246, (accessed Jan. 30, 2007).
[4] *See* Richard Elms, A Closer Look: Nanotechnology Class 977, U.S. Patent & Trademark Office Nanotechnology Customer Partnership Meeting, (Mar. 28, 2006).

Although an innovator must disclose the invention when applying for a patent, the innovator can thereafter, without compromising protection, present the information openly to investors, customers, and technical talent, in order to bring new nanotechnology to market.

Companies developing a nanotechnology should seek patent protection as soon as possible. Although the United States has a first to invent system, many rights accrue to the first to file. In a kind of gold rush, early seekers can obtain "blocking patents" on essential nanotechnologies. A patent alone provides the right to exclude others, not necessarily the right to practice an invention; the later patentee therefore may still be blocked by the earlier patentee. The owner of a blocking patent may be able to block or obtain cross-licenses from those who obtain patents on later inventions which depend on the essential nanotechnologies. Through selective licensing, the holder of the blocking patent can leverage an initial research investment across a broad range of products and processes developed by competitors. On the other hand, companies who delay seeking patent protection risk having profits drained through obligatory license fees to holders of blocking patents or being shut out of a market entirely.

2. Patent Practice for Nanotechnology

In prosecuting a nanotechnology patent application, the patent attorney must establish novelty[5] and obviousness.[6] An examiner may assert that a nanostructured product lacks novelty, because the relevant nanostructure was present in an existing product, even though it was not recognized as such. For example, a material may have been recognized as having a desirable technical characteristic, although the mechanism underlying the characteristic was not understood and the initial discovery of the composition may have been serendipitous. Under the doctrine of inherency, the PTO will not grant a patent simply for later identifying the mechanism underlying the characteristic of a known material.[7] However, the examiner bears the burden of demonstrating that the characteristics of a material sought to be patented actually arise from structures already present in a known material.

For example, carbon black has been included in rubber to improve the durability of tires for over 90 years.[8] The structure of fullerenes—carbon molecules evocative of soccer balls and having a diameter of about 1 nanometer—was not determined until the 1980s. Fullerenes were subsequently found to be present in, for example, candle soot.[9]

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[5] 35 U.S.C. § 102.
[6] 35 U.S.C. § 103.
[7] See, Roger E. Schechter & John R. Thomas, Intellectual Property: The Law of Copyrights, Patents and Trademarks § 16.4.3 (2003).
[8] *See* The Handbook of Texas Online: Carbon Black Industry, http://www.tsha.utexas.edu/handbook/online/articles/CC/doc1.html, (accessed Jan. 29, 2007).
[9] *See* Wikipedia: Fullerene, http://en.wikipedia.org/wiki/Fullerene, (accessed Jan. 29, 2007).

Nevertheless, the PTO awarded U.S. Patent Number 5,750,615 to Lukich et al., which was assigned to The Goodyear Tire & Rubber Company, for the "Use of Fullerene Carbon in Curable Rubber Compounds" in 1998. The examiner may have been unable to demonstrate that fullerene compounds in ordinary carbon black were present in a sufficient fraction to meet the criterion specified in the patentees' claim.

A patent claim that specifies a structure having a certain size may be obvious if the structure was previously known, even though the size specified in the prior art was different.[10] To establish that rescaling of what is known is not obvious, one has several options. First, one can argue that, because certain physical phenomena which are insubstantial at larger length scales dominate at the nanoscale, the functioning of the structure at such a small scale would in fact not have been obvious to one of skill in the art at the time of invention. Examples of such phenomena are van-der-Waals forces and the quantum tunneling effect. Second, one can limit the claimed structure, for example, to a specific material. Third, one can claim a new use for a known structure. Fourth, one can claim the process of making the structure, rather than the structure itself, although such a process claim can be more difficult to enforce than an apparatus claim.

The PTO appears not to have strictly applied the doctrine that rescaling is obvious in the context of micro- and nanotechnological inventions. For example, the PTO has granted patents for a micromechanical electromagnetic motor,[11] a micromechanism with a floating pivot,[12] and a microstructure with bumps suspended above a substrate.[13] Recently, the PTO awarded U.S. Patent Number 5,750,615 to Zhang et al., which was assigned to 3M Innovative Properties Company, for "Dental Materials with Nano-Sized Silica Particles."[14] The PTO found a claim to "non-aggregated, non-fumed silica particles [of average diameter less than about 200 nm] having a silane treated surface" valid, even though "silane treated precipitated silica" was discussed in an earlier patent.[15]

A known structure implemented at the nanoscale or a known material in which nanostructures are enhanced may be patentable. Furthermore, a company using a known material (for example, carbon black) may be excluded from using a version of that material (for example, carbon black with greater than a specified percentage of fullerenes) by a competitor who has obtained a patent. The same

[10] *See Gardner v. TEC Systems, Inc.*, 725 F.2d 1338 (Fed. Cir. 1984), *In re Rinehart*, 531 F.2d 1048 (CCPA 1976), *In re Rose*, 220 F.2d 459 (CCPA 1955), discussed in Patrick Ryan, Anticipation and Obviousness in Issues Related to Inventions in Nanotechnology, U.S. Patent & Trademark Office Nanotechnology Customer Partnership Meeting, (Sept. 11, 2003).
[11] U.S. Patent No. 5,327,033 (issued Jul. 5, 1994).
[12] U.S. Patent No. 6,198,180 (issued Mar. 6, 2001).
[13] U.S. Patent No. 5,679,436 (issued Oct. 21, 1997).
[14] U.S. Patent No. 6,899,948 (issued May 31, 2005).
[15] U.S. Patent No. 5,871,846 (issued Feb. 16, 1999).

principles apply with other fillers and nanomaterials, for example, PCC and talc.

The as yet unknown environmental, health and safety effects of nanotechnology inventions provide an opportunity in the sense that beneficial innovative technologies may be more valuable than those that prove to be damaging to health or to the environment. Moreover, if particular standards are set by industry groups or a government agency, it is possible for a patent holder to exert leverage over the marketplace, consistent with antitrust laws. The flip side is that those who do not have a patent position may find themselves blocked from producing materials that comply with such standards by others who have already patented them. Especially in a fast moving field with legal issues yet unresolved, it is wise to develop a diversified portfolio of nanotechnology patents as part of an overall business strategy.

NANOTECH AND FEDERAL REGULATION

A Changing Landscape

A. Overview

The federal government is involved in both nanotechnology research and regulation. Research and development efforts occur in many federal agencies. Investments into federally funded nanotechnology-related activities, coordinated through the NNI, have grown five-fold from $464 million in 2001 to approximately $1 billion in 2005. The federal research effort is described at www.nano.gov.

Twenty-five federal agencies currently participate in the NNI, 13 of which have budgets dedicated to nanotechnology research and development. The other 12 agencies have made nanotechnology relevant to their missions or regulatory roles. Only a small part of this federal investment aims at researching the social and environmental implications of nanotechnology, including its effects on human health, the environment and society. Several federal agencies, including the National Science Foundation ("NSF"), the National Institutes of Health ("NIH"), NIOSH, EPA, FDA and the United States Department of Agriculture ("USDA"), are investing in implications research. These agencies coordinate their efforts through the NNI's Nanoscale Science, Engineering and Technology Subcommittee ("NSET") and its Nanotechnology Environmental Health Implications workgroup ("NEHI"). The President's Council of Advisors on Science and Technology ("PCAST") serves as an advisory body to the NNI.

In September 2006, NSET released a document identifying environmental, health and safety research and information needs related to understanding and management of potential risks of engineered nanoscale materials. The report, entitled "Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials" is attached as Appendix B and is available at www.nano.gov. The purpose of this report was to provide guidance to help direct research to areas that would assist in understanding environmental, health and safety risks of nanotechnology. Approximately $44 million of the FY 2007 federal research budget for nanotechnology is aimed at environmental, health and safety studies.

Among the areas designated for research are instrumentation and measurement protocols, absorption and transport of nanoparticles in the human body, environmental monitoring, workplace exposures, risk management over products' life cycle and risk communication.

On the regulatory side, nanotechnology is of concern in the various federal agencies that regulate products, chemicals, worker exposure, public health and the environment. These agencies are also coordinating efforts as they face the issues of nanosized materials under their statutory and regulatory authorities. It is important to recognize, however, that most of the laws under which nanotechnology is or may be regulated were not enacted for that purpose. For that reason, despite growing interest in the risks and benefits of nanotechnology, there is no comprehensive federal investigation and regulatory program for nanotechnology.

The following are brief summaries of the approaches of several federal regulatory agencies to nanotechnology.

B. Food Products, Pharmaceuticals, Over-the-Counter Drugs and Cosmetics: FDA

At this time, FDA has not established its own formal definition for nanotechnology and has adopted the NNI definition of nanotechnology. The NNI, of which FDA is a member, calls research and technology development "nanotechnology" if it involves: (1) research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1-100 nanometer range; (2) creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and (3) an ability to control or manipulate on the atomic scale. FDA has expanded on the NNI definition only in that nanotechnology relevant to FDA also relates to a product regulated by FDA. To further explore the considerations involving the development and approval of nanotechnology FDA-regulated products, the agency has formed an internal Nanotechnology Interest Group ("NTIG") that is made up of representatives from all of FDA's Centers.

Nanotechnology is also an element of FDA's Critical Path Initiative, a plan to help address the drug pipeline problem by helping to reduce existing hurdles in medical product design and development and to take advantage of innovative science and technologies, such as nanotechnology.

FDA has identified the following FDA-regulated products the agency expects to be impacted by nanotechnology: drugs; medical devices; biotechnology products; tissue engineering products; vaccines; cosmetics; and combination products. Enhanced drug delivery is likely to be the greatest benefit provided by nanotechnology. FDA anticipates that nanotech products will lead to the development of novel and sophisticated applications in drug delivery systems. Enhanced drug properties in the form of increased surface area, solubility, rate of dissolution, oral bioavailability and targeting ability are well within the realm of possibility. In addition, FDA expects nanotechnology to provide enhanced dosing requirement opportunities, such as lower doses administered, better side effect profiles, more rapid onset of therapeutic action (*e.g.,* faster antacid relief from nanotechnology-derived PCC-based antacids) and more convenient dosage forms.

With regard to nanotechnology combination products, multi-component systems may consist of carrier/delivery systems (drug or device), therapeutic agents (drug or biologic), imaging agents or targeting agents. Other examples include implantable microchip-based delivery systems that deliver different drugs under controlled conditions and injectable delivery systems, such as transdermal micro needles.

1. Nanotechnology in the Supermarket: FDA and Food Oversight

The regulation of food products containing nanotechnology materials largely falls under the jurisdiction of the FDA. That agency has responsibility for the regulation of the safety of most food products and principally operates under the Federal Food, Drug and Cosmetic Act of 1938 ("FDCA"), as amended numerous times since its enactment. While the USDA is responsible for the safety of meat, poultry and some egg products, the FDA is responsible for the safety of all other food products.

On August 9, 2006, the FDA announced the formation of an internal task force to study how to regulate nanotechnology products. The task force is to focus on addressing any knowledge or policy gaps in order to help the agency evaluate possible adverse health effects. The task force was specifically assigned to chair a public meeting that occurred on October 10, 2006 to assess the current state of scientific knowledge pertaining to nanotechnology materials, evaluate the effectiveness of the FDA's regulatory approaches, explore opportunities to foster innovation using nanotechnology materials to develop safe products including foods, and continue to strengthen the FDA's collaborative relationships with other agencies. The task force will submit its findings to the FDA Commissioner within nine months of that public meeting.

A diverse group was convened for the public meeting on October 10, 2006. There was a mixed response from the audience about how involved the FDA should be in regulating nanotechnology products. Consumer and environmental groups urged the FDA to take greater action to ensure that products made with nanotechnology materials are safe for humans and the environment. They expressed particular concern with some foods and dietary supplements that are not subject to FDA oversight before they are sold. Others believed that the FDA is doing enough already.

The FDA has historically applied three regulatory goals that should apply to nanotechnology food products: first, to protect the public health; second, to foster innovation; and third, to provide the basis for public confidence in the products of nanotechnology. In pursuit of these goals, the FDA will likely not regulate nanotechnology *per se*. It will instead regulate food products through the application of nanotechnology. The safety of the food products for consumers rests on how the technology is applied to produce particular products and the resulting properties of those products.

Based on this "applied" approach, the FDA regulatory system for ensuring the safety of nanotechnology food products will likely perform pre-market and post-market oversight. Pre-market oversight will place the initial and continuing burden to demonstrate

safety on the nanotechnology product's sponsor. This will require the sponsor to obtain adequate information on nanotechnology products under development. Post-market oversight may involve inspection of manufacturing establishments and examination of records related to nanotechnology food product safety. It will also require the removal from the market of nanotechnology food products that appear to pose a significant safety hazard or no longer meet the applicable safety standard.

Numerous nanotechnology products are found currently in the food industry, with some of the world's biggest companies involved in nanotechnology research and development. Below is a summary of the applicability of the FDA regulatory regime to various categories of nanotechnology food products: whole foods, dietary supplements, generally recognized as safe or "GRAS" food ingredients, food additives and food packaging. Pre-market and post-market oversight varies between product categories. This variance of oversight amongst food product categories may be addressed by the task force when it issues its report to the FDA Commissioner.

a. Whole Foods

This category includes whole food articles such as fruits, vegetables and fish, as opposed to ingredients or intentionally added substances, such as oils, sweeteners, preservatives, color additives and animal drug and pesticide residues. It is doubtful that the regulatory regime for whole foods is likely to play a role in the oversight of engineered nanomaterials and products, but it is a good starting point for understanding the range of approaches the FDA takes to regulate substances in the food supply.

Whole foods are subject only to post-market oversight and to two different safety standards, depending on whether the substance that raises a safety concern is naturally occurring in the food or "added" inadvertently by some human activity. In the former case, such as the naturally occurring toxin solanine in potatoes, the food can be removed from the market only if the FDA can prove that it is "ordinarily injurious" to health. Added substances, such as dioxins, mercury and lead, make food "adulterated" and thus unlawful in commerce if the FDA can prove that the substance is present at a level that "may render" the food "injurious to health." This reflects the Congressional judgment that human interventions are subject to a higher safety standard than nature, as is illustrated in the treatment of GRAS food ingredients, food additives and food packaging.

b. Dietary Supplements

Prior to 1994, the safety of dietary supplement ingredients was subject to regulation by the FDA on the same basis as any intentionally added food substance, which meant that the FDA could require pre-market approval

as a food additive if the supplement ingredients were not GRAS.

Under the 1994 Dietary Supplement Health and Education Act ("DSHEA"), Congress excluded supplement ingredients from the definition of food additive, shifting to the FDA the burden of proof regarding the safety of a wide range of supplements on the market at the time, including vitamins, minerals, herbs and other botanicals, amino acids, and any other substance used to supplement the diet and consumed in pill or other supplement form. The FDA has no pre-market authority over such supplements, but can take court enforcement action to remove them from the market if the agency can prove they "present a significant or unreasonable risk of illness or injury."

For supplements containing "new" ingredients—meaning ones with no history of use in supplement products and no presence in the food supply in the same chemical form—DSHEA requires the sponsor to submit a pre-market notification providing information that the sponsor believes the products "will reasonably be expected to be safe."

c. GRAS Food Ingredients

GRAS food ingredients are regulated under a legal system established by Congress in 1958 to ensure the safety of intentional food additives through careful pre-market testing and FDA review, while avoiding time consuming and costly FDA review of intentionally added substances whose safety is already well established. It thus excludes from the definition of "food additive" and from the pre-market approval requirement intentionally added substances that are "generally recognized as safe" by scientists based on a history of safe use in food prior to 1958 or "scientific procedures," which means the same quantity and quality of evidence required to demonstrate the safety of a food additive.

By law, there is no requirement for a company that considers its food substance GRAS to inform the FDA of its marketing plans or to seek any FDA review. If a company markets based on its "independent" GRAS determination, however, the FDA can challenge that determination in court on the grounds that the substance is not GRAS and thus is an unapproved (and thereby unlawful) food additive. To help avoid such disputes, the FDA, shortly after enactment of the food additive law, issued extensive lists of substances it considers GRAS, and, in the 1970s, initiated a GRAS review program that involved extensive literature reviews and the promulgation of often detailed regulations, including chemical specifications, for additives that the FDA has affirmed as GRAS. In addition to these FDA efforts, commercial customers typically demand from their suppliers documentation that an ingredient or food substance is either FDA-approved as a food additive or GRAS. In the absence of a specific GRAS listing by the FDA, companies frequently

commission panels of scientists to review the available evidence and render a judgment about GRAS status.

It should be noted that, even when the FDA has issued GRAS (or food additive) regulations that appear applicable to the substance, there is room for the exercise of judgment as to whether the substance is covered. For example, the chemical specifications in the FDA's regulations are typically written without regard to material size, leaving open the question of whether a nanoscale version would be covered.

In the late 1980s, agricultural biotechnology presented the FDA a challenge analogous to nanotechnology that was grounded in the food additive-GRAS approach. In 1992, the FDA established a policy for oversight of genetically modified and other "novel," plant-derived whole foods. The policy consisted largely of scientific guidance concerning the determination of whether the genetic modification resulted in a compositional change sufficient to trigger regulation as a food additive. It also included a voluntary pre-market notification procedure under which developers of such foods could submit information to the FDA supporting their judgment that no such change had occurred and thus that the novel food was "substantially equivalent" to its traditional counterpart.

The FDA's biotechnology food policy was an effort to clarify the pre-market safety assessment and approval obligations of product developers and provide an incentive for companies to submit information to the FDA in advance of marketing, despite the lack of any legal requirement that they do so for products they considered GRAS and thus not food additives. This system has worked well to provide the FDA with information about genetically modified foods entering the marketplace, none of which has experienced known safety problems.

d. Food Additives

Substances intentionally added to food—such as spices, flavors, preservatives, emulsifiers and sweeteners—are food additives, unless they are GRAS, and are required to go through a formal FDA safety review and approval process. In this process, the burden of proof is on the sponsor to prove safety. The FDA has full control over testing requirements, and the safety standard is strict: "reasonable certainty of no harm." The process culminates in a regulation setting the conditions under which the additive may be lawfully used. This approach has been criticized for deterring innovation because the standards are stringent and the process is cumbersome, costly and legalistic.

It should be noted that there are other categories of intentionally added substances that are regulated under different sections of the FDCA, such as color additives,

animal drug residues and pesticide residues. The standards and procedures vary in detail but are substantially the same as for food additives. Color additives and animal drug residues are regulated by the FDA. The EPA evaluates the safety of pesticide residues in food and sets tolerances (or legal limits) on the amount that may be present; the FDA enforces the pesticide tolerances.

e. Food Packaging

With companies already claiming that they are using silver "nanoparticles" in food storage containers to keep food fresher and longer and, in the future, to signal when foods are spoiled, food packaging and other food contact materials are among the early applications of nanotechnology that consumers will encounter directly in the marketplace. The primary FDA regulatory concern in this arena is that components of the food contact material may migrate to the food, posing a safety concern or otherwise adversely affecting the quality of the food. Food packaging materials and other food contact substances that are not GRAS are included in the statutory definition of "food additive" and, for most of the years since 1958, have been regulated through the food additive petition process. The result is an extensive and detailed list of regulations, including chemical specifications, prescribing the conditions under which the FDA calls "indirect" food additives, in such categories as adhesives, polymers, adjuvants, production aids and sanitizers, can be safely and lawfully used.

Based on wide agreement that this approach was wasteful of both agency and industry resources, Congress created, in the 1997 FDA Modernization Act, an alternative pre-market notification process as an option for the FDA and the industry in the typical case of low migration and low toxicological concern. Under this approach, the sponsor submits a food contact notification ("FCN") containing information prescribed by the FDA; the FDA then has 120 days in which to review and object if it concludes that the food contact material has not been shown to be safe. If the FDA does not object, the FCN is deemed "effective" and the material can be marketed unless the FDA later determines that the material is no longer safe, in which case the FDA can declare the FCN no longer effective, which revokes its marketing authorization. One distinct feature of this system is that, in contrast to a food additive regulation, which authorizes use by any manufacturer, a FCN covers use of a food contact material only by the entity that submitted it.

2. Nanotechnology in the Pharmacy: FDA and Drug Oversight

a. Currently Approved Nanotechnology FDA-Regulated Drug Products

There are a few nanoscale therapeutics that have been approved by the FDA:

- Gadolinium chelate for MRI imaging (Gd-DTPA Dimeglumine);
- Iron oxide particles for MRI imaging (Feridex);
- NanoCrystal technology products (Rapamune, Emend);
- Liposomes (Doxil, DaunoXome);
- Microemulsions (Cyclosporine); and
- Albumin-bound nanoparticles (Abraxane).

Some examples of approved nanotechnology devices are:

- Silver nanoparticles (anti-bacterial wound dressing);
- Engineered Calcium Phosphate (NanOss TM, duplicates microstructure, composition and performance of human bone); and
- Nanoparticle dental restorative (3M ESPE Filtek).

While the FDA admits that it may not be aware of all of the consumer products on the market that contain nanosized ingredients because of its limited authority over those product categories, *e.g.*, the FDA does not conduct a pre-market review of the safety or efficacy of cosmetics, it is aware and has approved the use of nanotechnology in sunscreens. Sunscreens are marketed as OTC drugs, and oftentimes as combination cosmetic products, containing titanium dioxide and zinc oxide nanoparticles that make the product appear transparent versus opaque. Additionally, the FDA has approved the use of lipid nanoparticles or "nanosomes" used as delivery systems, for controlled release of "active" ingredients in L'Oreal and Estee Lauder cosmetic products.

b. FDA's Regulation of Nanotech Drug Products

Historically, the FDA has approved many products with particulate materials in the nanosize range. Most drugs

are expected to go through a nanosize phase during the process of absorption in the body and, according to the FDA, no safety concerns have been reported because of particle size; however, the FDA is planning additional studies (discussed in brief below) to examine the effects of select nanoparticles on skin penetration. Moreover, it is the FDA's current position that the existing battery of preclinical tests required before a pharmaceutical product is approved is adequate.

The FDA believes that the following criteria for approval provide sufficient assurances of safety and effectiveness because:

- High dose multiples are used;
- At least two animal species are used;
- Extensive histopathy is conducted on most organs;
- Functional tests are conducted (cardiac, neurological, respiratory, reproductive, immune system, etc.); and
- Extended treatment periods are often required (*e.g.*, up to two years for carcinogenicity studies).

Although the agency recognizes that new testing models may be required for nanotech products, there are currently no special testing requirements for such products. Moreover, in the event that research identifies toxicological risks that are unique to nanomaterials, the FDA would likely require additional testing.

Several consumer and environmental groups disagree with the agency's current position on the regulation of the nanotechnology products and have been vocal about what they consider to be a lax approach by the FDA to the potential dangers posed by nanomaterials. In May of 2006, the International Center for Technology Assessment ("CTA") and several other consumer and environmental protection watchdog groups submitted a Citizen Petition to the FDA. A copy of that petition is attached as Appendix C. Among other things, that petition requests that the agency: (1) issue a formal opinion clarifying the agency's stance regarding nanotechnology-derived products; (2) promulgate comprehensive nano-product regulations, including amending FDA regulations to include nanotechnology terminology, nano-specific toxicity testing and mandatory nano-product labeling; (3) amend the sunscreen monograph to address nanoparticle sunscreen ingredients, including the requirement that all nano-sunscreens be considered new drug products, which would require the submission of new drug applications ("NDAs") for approval prior to marketing; (4) declare that nano-sunscreens are an imminent hazard to public health and must be recalled until nano-product

regulations are implemented; and (5) consider human health and environmental impacts related to nano-product regulation, in accordance with the National Environmental Policy Act.

To date, the FDA has not responded to the CTA petition.

c. FDA's Considerations for Nano-Products

There are three categories about which the FDA has expressed uncertainty and concern with regard to the approval, marketing, and regulation of nanotech products.

These three areas involve characterization of the nanoparticles, safety and environmental impact.

1. Characterization Considerations

The FDA has posited several questions to consider for characterization of nanoparticles. Examples of the agency's characterization considerations are: (1) in what forms will the particles (*i.e.*, soluble vs. insoluble particles, liposomes, or nanoemulsions) be presented to the host, cells, and organelles; (2) what are the standard tools used to characterize nanoparticle properties; (3) what validated assays will be used to detect and quantify nanoparticles in drug products and in tissues; and (4) how do we determine long and short-term stability of nanomaterials in various environments. Many other characterization considerations identified by the agency in several presentations by FDA scientists involve identifying the critical physical and chemical properties and their impact on product quality and manufacturing processes.

2. Safety Considerations

The FDA has enumerated several safety considerations for nanotechnology products. Of particular concern is whether there may be size-specific effects on activity as the particle size gets smaller, *e.g.*, will nanoparticles gain access to tissues and cells that normally would be bypassed by larger particles; if nanoparticles enter tissues, how long will they remain there; how are they cleared from tissues and blood; if they enter cells, what effects will they have on cellular and tissue functions and will they be transient or permanent; and whether there might be different effects in different cell types. Route-specific issues of concern involve: (1) inhalation (local respiratory toxicity, distribution in respiratory tissues, and/or

systemic bioavailability); (2) sub-cutaneous sensitization; (3) ocular intravitreal retention; (4) oral (increased bioavailability); (5) dermal (*i.e.*, increased dermal and systemic bioavailability, increased follicle retention, distribution to local lymph nodes, and phototoxicity); and (6) intravenous (*i.e.*, hemocompatibility, sterility, and different tissue distribution). FDA has also expressed concern about the differences in the absorption and distribution of metabolic elimination ("ADME") for nanoparticles versus larger particles of the same drug.

3. Environmental Considerations

FDA has identified three areas of consideration with regard to the impact of nanotech FDA products on the environment. FDA is interested in: (1) whether nanoparticles can be released into the environment following human use; (2) what methodologies would identify the nature and quantify the extent of nanoparticle-release in the environment; and (3) what might be the environmental impact on other species, such as animals, fish, plants, and micro-organisms.

d. FDA's Current Research Efforts Involving Nanotechnology

Several of FDA's Centers are conducting research to help the agency understand the characteristics of nanomaterials and nanotechnology process, *e.g.*, the Center for Drug Evaluation and Research is researching the development of *in vitro* assays to assess toxicity of selected nanoparticles, as well as research of areas that FDA needs to consider in the regulation of these products. An example of such current research is FDA's collaboration with the other federal agencies, such as the NIH, National Institute of Environmental Health Sciences on studies, as part of the National Toxicology Program, to examine the skin absorption and phototoxicity of nanosized titanium dioxide and zinc oxide preparations used in sunscreens.

e. Industry Considerations for Marketing Nanotech Products

The decision to market products containing nanoingredients, particularly over-the-counter drugs and cosmetics containing nanoingredients, cannot be taken lightly in light of the important issues they pose. For OTC monograph drug products, if a product manufacturer orders nanosized components, such as PCCs, would the performance of the product improve so that it would work more quickly and efficiently? Could this improved performance take the product outside of the safe harbors of the Antacid Products For Over-The Counter (OTC) Human Use (21 C.F.R. pt. 331) (attached as Appendix D) For

example, by nanosizing the surface size of the active ingredient, would this mean that users actually consume greater than the maximum daily dosage allowed under the Antacid Monograph (8 grams of calcium carbonate)?

Would FDA require an approved New Drug Application (NDA) to market the nanosized product? If an NDA were required, would it be practical to market such a product?

For anti-aging cosmetic products, would nanosizing ingredients improve the performance of a cosmetic so that it would improve skin penetration and enhance activity at deeper levels than the skin, *e.g.*, cellular changes that might improve the production of collagen or hormones? Would the enhanced penetration ability of cosmetic ingredients also cause skin sensitization? What would be the effect of continuous inhalation of nanosized ingredients, *e.g.*, cosmetologists' or makeup artists' continual exposure to loose powder in a professional setting? What would the implications of absorption of such particles into lung tissue or the brain over extended time periods? In the case of nano-talc, could enhanced penetration increase carcinogenic risks? In the case of cosmetics, which are very lightly regulated by FDA due to lack of statutory authority, will the courts do more about regulating risks of cosmetics containing nanoparticles than FDA?

For drugs, the use of nano-ingredients appears to hold enormous promise, particularly when they are used over a relatively short period of time to treat serious disease. Already being explored are use of nanoparticles to both diagnose diseases with laser precision such as cancer and target delivery of therapeutics directly to tumor cells, leaving healthy cells intact. In the case of drugs for longer term use, absorption, penetration, and sensitization questions similar to those for OTCs and cosmetics mean that FDA will likely pay closer attention to these issues when reviewing such products for approval.

3. Nanotechnology in the Workplace: NIOSH and OSHA

There are currently no separate worker protection regulatory standards for nanosized materials. Both NIOSH and OSHA are participating in federal research and studies of nanotechnology.

NIOSH released a document, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*, in 2005 which was updated in 2006. This document is attached as Appendix E. The document identifies concerns with production of nanotechnology and has recommendations for worker protection. While this document is not a regulation, prudence dictates that employers manufacturing or processing nanomaterials be aware of the NIOSH document. Most of the recommendations in this document are drawn from guidance for workers handling small

particles that are larger than nanosized, but present similar risks of respiratory or dermal exposure.

NIOSH announced in 2006 that it was establishing an interdisciplinary team to assess health and safety practices at facilities using nanotechnology. The agency has asked entities involved in the manufacturing or use of nanomaterials to volunteer to make their operations available for assessment. NIOSH has also developed a comprehensive library of available information concerning potential occupational hazards related to nanomaterials.

In February 2007, NIOSH released a report, "Progress Towards Safe Nanotechnology in the Workplace," describing the program of its Nanotechnology Research Center. This report summarizes the past and ongoing research, the areas for which additional research is needed, and the steps that NIOSH has taken over the past few years. With respect to management of nanotechnology in the workplace, this report refers to the NIOSH interim guidance on prudent workplace practices and attainment of key roles in facilitating the international scientific discussion.

NIOSH has two additional papers available for public comment on nanotechnology, in what it describes as an information exchange on the topics. These are *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps* and *Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide*. Copies of these papers are attached as Appendices F and G respectively. The NIOSH "Statement on Nanotechnology" is additionally attached as Appendix H.

At this point in time, OSHA is not directly or separately regulating nanomaterials, although it is participating in interagency studies and assessments. OSHA has a Memorandum of Understanding with NIOSH on control banding for nanomaterials. NIOSH will investigate various nanotechnology workplaces to determine whether control banding is appropriate for nanomaterials. If it is, the two agencies will hopefully develop a joint guidance on nanomaterial control banding.

While OSHA is planning guidance activities for nanotechnology, there are no specific occupational health and safety regulations specifically directed at nanoparticles at the moment. Existing OSHA regulations that may apply to nanotechnology include those governing hazard communication, respiratory protection, personal protective equipment, and laboratories.

In addition, there are certain substance-specific standards and permissible exposure levels ("PELs") for certain chemicals that could apply. The agency has 27 comprehensive substance-specific standards and about 400 PELs. In particular, the standards for cadmium, graphite, titanium dioxide, and nuisance dusts are likely to apply to certain nanomaterials.

Although the issue is not resolved, OSHA's hazard communication standard will likely apply to nanotechnology because it requires manufacturers to evaluate the hazards of chemicals they produce or import and share that information with downstream users

through labels and material safety data sheets. The standard also includes "a very large component" on worker training. OSHA has published a draft guidance for the hazard communication standard and is requesting comment. However, this draft guidance does not specifically address nanomaterials. The agency is considering specific hazard communication guidance for nanomaterials.

At this point, OSHA has not determined whether all nanoscale materials should be identified as such on material safety data sheets; whether hazard information for a specific nanomaterial should be conveyed for similar materials; or whether nanomaterials having several components should be treated like mixtures.

These ongoing efforts indicate that NIOSH and OSHA will take increased interest in nanotechnology in 2007 and beyond. Prudence dictates that workplace exposure to nanoparticles be treated in a manner similar to exposure to small particles. This includes the priority of controls described in the NIOSH white paper: engineering controls, administrative controls, and personal protective equipment.

4. Nanotechnology Outdoors: EPA

At EPA, there is ongoing research and general policy towards nanotechnology, as well as some specific regulatory coverage. On the research side, EPA is supporting research into measurement protocols and environmental risks. It is also supporting nanotechnology in environmental clean up technology.

a. Policy

On the policy side, EPA announced in March 2006 that it was working on the development of a "stewardship program" for nanomaterials. This effort will include consultations with experts to identify types of characterization data needed for comprehensive evaluation and appropriate test methodologies to develop these data.

EPA additionally released a final Nanotechnology White Paper on February 15, 2007. A copy of the White Paper is attached as Appendix I. The agency had released a draft of this White Paper in December 2005, and both accepted comments as well as held public meetings for input. The White Paper is a product of EPA's Science Policy Council, and thus focuses primarily on research and research needs. It also identifies why EPA is interested in nanotechnology.

As set out in the White Paper, EPA anticipates that nanotechnology will:

- result in product development with reduced energy and natural resource exploitation;
- improve environmental monitoring and detection technology; and
- improve clean up technologies.

On the regulatory side, EPA has concerns with environmental and public health consequences of nanomaterials:

- Nanosized particles can act differently both physically and chemically than larger particles and it is not known what unique impacts they may have on human health or the environment either during use or upon disposal.
- Existing risk assessment modeling assumptions and physical modeling techniques may not be applicable.
- It is unclear whether nomenclature and substantive provisions in several of the existing environmental laws and regulations are adequate to address nanomaterials although the White Paper asserts that EPA authority under existing laws that can and will be used.

The EPA White Paper provides some rather detailed descriptions of the "state of the science" with respect to nanotechnology risks. While the document does not present regulatory conclusions or have the force of law, it may be cited by outsiders for the scientific information provided therein.

EPA's White Paper urges those in the nanotechnology business to participate in voluntary pollution prevention and environmental stewardship programs and further urges governmental action to provide assistance and incentives for participation. It also identifies the EPA role in research and development of nanotechnology.

b. Research and Development

EPA is actively participating in nanotechnology development and evaluation. This includes: 1) actively participating in the NNI; 2) funding nanotechnology research through EPA's Science To Achieve Results ("STAR") grant program and Small Business Innovative Research ("SBIR") program; 3) collaborating with scientists internationally in order to share the growing body of information on

nanotechnology; 4) initiating the development of a voluntary pilot program for the evaluation of nanomaterials and reviewing of nanomaterial new chemical submissions in the Office of Pollution Prevention and Toxics; and 5) reviewing nanomaterial registration applications in the Office of Air and Radiation/Office of Transportation and Air Quality.

c. Regulatory Structure

EPA already has assumed regulatory authority over nanosized particles under several of its programs. The existing environmental laws and regulations address, as a general matter, either the receiving medium (*e.g.*, air, water), particular types of products (*e.g.*, pesticides, new chemicals, motor vehicle fuels) or particular kinds of activities (*e.g.*, solid and hazardous waste disposal, hazardous waste clean up.) Because of this, the nanosized particles as a material or product may not be the "trigger" for application of particular environmental regulations. In addition, the environmental programs include a range of exemptions and exclusions that may leave nanomaterials unregulated. Finally, the system of measurements and testing that has developed under most federal environmental programs is ill-suited to measure impacts of nanosized particles. Nonetheless, EPA is already applying its laws in situations involving nanomaterials.

It is prudent, therefore, for the industries involved in nanotechnology to assess their materials and products according to the traditional EPA regulatory system to ascertain whether EPA has any applicable requirements. For example, under the Clean Air Act, EPA must register fuels and fuel additives. The Office of Air and Radiation is processing an application for a diesel additive with nanosized particles. While engineered nanosized particles can be transported by air, the Clean Air Act regime is structured around identification of specific pollutants, classified as criteria pollutants (*e.g.*, ozone precursors, sulfur dioxide) or as hazardous pollutants. Nanosized materials that are among the identified pollutants under the Clean Air Act might be subject to regulation. At this point, however, the standards for measuring air pollution do not generally measure at the nano level, so regulatory changes may be needed to cover such particles.

The Office of Pesticide Programs has authority to register anti-microbial agents under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"). Other agents that serve to kill pests are covered by this law. Anti-microbials have been a relatively active area for use of nanosized particles. To be registered, among other things, the manufacturer or distributor must demonstrate the fate and transport of the anti-microbial. The pesticide program demonstrates one of the difficulties of regulating nanoparticles under current law. Under the pesticide law, EPA has exempted "devices," which would cover equipment or products in which a pesticide is incorporated, rather than released into the environment. Initially, EPA classified many

of the nano-silver-infused products as devices, not requiring registration.

EPA changed its position in reviewing washing machines that inject silver ions—silver atoms stripped of an electron—into the wash and rinse cycles to penetrate fabric and kill bacteria without the need for hot water and bleach. While EPA initially classified this as an exempt device, concerns were raised by some wastewater utility associations, state regulators, and environmental groups that silver ions entering the environment in the wastewater could kill helpful microorganisms like plankton and could possibly harm human health. EPA is now requiring registration of nano silver in most products, which carries with it the requirement to provide information to evaluate the public health and environmental impacts of the nano silver.

EPA also registers all new chemicals under the Toxic Substances Control Act. The agency's Office of Pollution Prevention and Toxics has already been reviewing chemicals with nanomaterials to determine the need for registration. So far EPA has looked at approximately 23 nanosized materials that were submitted to the agency as new chemicals. However, EPA concluded that none had unique or novel properties that would require registration—under the current standards—as a new chemical. That is, having registered the chemical previously, EPA has concluded that the same chemical with engineered nanoparticles need not be registered again. This is in part because the current regulations are not particularly directed at considering differences based on the molecular size of a chemical. The agency is working on TSCA guidance for nanomaterials.

EPA's legal authority with respect to nanotechnology was examined during 2006 by the American Bar Association Section on Environment, Energy and Resources and a series of white papers addressing existing laws and regulations to assess the potential applicability of existing environmental laws and regulations to nanomaterials followed. These papers concluded, as a general matter, that EPA has legal authority to regulate nanomaterials, although in some instances EPA would need to promulgate new regulations. In many instances, although there was legal authority, the regulatory program lacked technology and protocols to measure and monitor nanosized particles. Thus, in order to address the special issues of nanomaterials, EPA will likely have to develop new regulations under one or more of its existing statutes.

It is therefore likely that EPA will continue to expand its review of nanomaterials under existing laws. In addition, the increased interest at EPA in developing protocols that allow evaluation of nanosized materials in programs such as the Clean Air Act will likely direct its research funding. In the interim, the nanotechnology industry has to approach the

EPA regulatory scheme carefully, considering how a material is made as well as how it is intended to be used.

5. Nanotechnology in the Legislature: Congress

The Congress of the United States is beginning to focus more intently on nanotechnology issues. The House Science Committee held a hearing on this issue on September 21, 2006. Both the chair and ranking member of the committee were critical of the limited amount of federal funding being applied to basic research into the potential environmental, health, and safety aspects of nanoparticles. After the 2006 elections, with the changes in Congressional leadership, stakeholders in nanotechnology should expect additional attention to nanotechnology from various committees. It is difficult to predict whether any legislation will be introduced or passed in the near term. It is likely, however, that federal funding for research in nanotechnology will continue.

6. Nanotechnology, as Researched, Applied, and Monitored across Uses: Standard-setting by the ASTM and ISO

Often underlying these legislative and regulatory issues are domestic and international standard-setting organizations that conduct research, review research and establish technical standards for materials and technology.

The ASTM (formerly American Society for Testing and Materials) formed International Committee E-56 on Nanotechnology in 2005 to address a range of nanotechnology issues, including standards for testing and other environment, health, and safety issues related to nanotechnology. This committee recently approved its first standard, E 2456, Terminology for Nanotechnology, which is currently available free of charge from the ASTM International website. ASTM Committee E56 felt that research into the properties, synthesis, and applications of nanostructures was been growing at an exponential rate, and had outpaced the development of a language to describe the chemical compositions and physical forms of these new materials. Documents such as the E56 terminology document define more precisely the language for nanotechnology, and thus ensure effective technical communication within the myriad fields involved in nanotechnology, as well as outreach to the public at large as products containing nanomaterials enter the marketplace. Some of the terms defined in the new standard include nanotechnology, nano-, nanoscale and nanostructured.

In order to facilitate the development of a terminology standard, ASTM International initiated and signed partnership agreements with the Institute of Electrical and Electronics Engineers, the American Society of Mechanical Engineers, NSF International, Japan's National Institute of Advanced Industrial Science and Technology, Semiconductor Equipment and Materials International, and the American Institute of Chemical Engineering. These agreements contain several unique provisions that pertain specifically to Committee E56 and Terminology standard E 2456.

The ISO has also begun work on standards for nanotechnologies. ISO's Technical Committee 229 on Nanotechnologies, also established in 2005, has a long list of projects. Among the top priorities—those that should be addressed over the next one to three years—include developing standard material safety data sheets for engineered nanomaterials; developing standard methods to select the personal protective equipment that workers should wear when dealing with engineered nanomaterials; and developing standard methods to establish occupational exposure limits.

ISO published a January 22, 2006 technical report on inhalation exposure characterization and assessment of ultrafine and nanoparticle aerosols. The report, *Workplace atmospheres—Ultrafine, nanoparticle and nano-structured aerosols—Inhalation exposure characterization and assessment (ISO/TR 27628)*, includes information on the potential health effects of nanoaerosols, sources of occupational nanoaerosols, exposure assessment strategies, particle ensemble characterization methods, size-resolved characterization, online chemical analysis, single particle analysis, and electron microscopy sample collection and preparation. That report makes the following especially notable observations:

- "With only limited toxicity data and negligible exposure data, it is currently unclear how exposure to nanoaerosols should be most appropriately monitored and regulated."

- "At the present time, there is insufficient information to determine which physical exposure metrics—size-selective number, surface area and mass concentration—are most relevant, or which are the most appropriate exposure characterization techniques to use."

Additionally, the report's overall aim is "to provide generally accepted definitions and terms, as well as guidelines on measuring occupational nanoaerosol exposure against a range of metrics." By doing this, the report attempts to address an immediate need and establish an essential step for developing future exposure measurement standards for nanoaerosols. Although a long-term goal, there will continue to be efforts by ASTM International Committee E-56 towards nanotechnology standards other than definitions.

NANOTECHNOLOGY IN THE COURTROOM

Litigation and Risk Management

A. Overview

Although considered the engine for the next industrial revolution, nanotechnology poses litigation concerns akin to those involving a former juggernaut for the manufacturing industry—asbestos. That pliant, remarkably insulating "miracle mineral" was once incorporated into products ranging from consumer products to commercial turbines. Isolated case reports prior to the 1930s raised some concerns about the potential health hazards that asbestos could pose, but manufacturers, workers using asbestos products, and consumers generally considered the mineral to be safe. This misperception resulted from, among other things, the different perspectives that the public, government, legal system, and industry had about product testing and technical limitations in identifying the warning signs of possible trouble. If one believes the American plaintiffs' bar, that misperception also resulted from the industry's and insurance companies' manipulation of publicly distributed research results. Once occupationally exposed workers developed life-ending illnesses, however, the adverse health effects associated with asbestos were discovered. The legal ramifications of that discovery reverberate today. As one may have observed based on what has occurred with companies faced with asbestos personal injury litigation, merely being named in one case can lead to others being filed against that defendant. Even though billions of dollars have been spent defending and resolving asbestos-related personal injury claims, some of the world's most prominent asbestos suppliers no longer exist, and the workers who faced the most risk have died (some for reasons unrelated to asbestos), therefore, the litigation continues with little end in sight.

B. Nanotechnology on the Scales of Justice: The Present Defense

The same themes on which plaintiffs in asbestos personal injury litigation rely also would resonate in any personal injury action filed against a manufacturer of a nanotechnology-derived product. Drowning out the difficulties in limiting worker and consumer exposure to nanoparticles, the absence of technology to monitor some nanoparticles, and the absence of any long-term, reliable epidemiological evidence that would support the notion that nanoparticles pose any inherent risk of adverse health effects are the heavy investments of venture capitalists, *Fortune* 500 companies, small startups, and even the federal government in commercially developing nanotechnology. There are scores of consumer, automotive, or health products incorporating the fruits of research into nanotechnology and many more are in the pipeline. Observers see the next wave of nanotechnology-derived products taking tremendous strides in the pharmaceutical, biomedical, and electronics markets. Yet, these same stakeholders spend comparatively little examining the risks associated with nanotechnology. By way of example only, Andrew Maynard, the chief science advisor for the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars, estimates that as little as $11 million of the more than $1 billion that the United States government invests in nanotechnology research focuses on nanotechnology's potential risks.

Current knowledge of the health effects associated with nanoparticles paints an uncertain picture. As discussed earlier, nanoparticles generally become more chemically reactive, become less predictable, and have a higher surface-to-mass ratio with decreasing size. Some studies confirm that, although they may behave differently, nanoparticles pose no more health risk than the larger particles from which they are derived. Yet, like asbestos, any health effects associated with nanoparticles may not be known for many years. Well-respected scientists recognize the potential for nanoparticles to cause adverse health effects:

> The unusual physiochemical properties of engineered [nanomaterials or "NM"] are attributable to their small size (surface area and size distribution), chemical composition (purity, crystallinity, electronic properties, etc.), surface structure (surface reactivity, surface groups, inorganic or organic coatings, etc.), solubility, shape, and aggregation. Although impressive from a physiochemical viewpoint, the novel properties of NM raise concerns about adverse effects on biological systems, which at the cellular level include structural arrangements that resemble NM in terms of their function. Indeed, some studies suggest that NM are not inherently benign and that they affect biological behaviors at the cellular, subcellular, and protein levels. Moreover, some nanoparticles readily travel throughout the body, deposit in target organs, penetrate cell membranes, lodge in mitochondria, and may trigger injurious responses.

Andre Nel, et al., *Toxic Potential of Materials at the Nanolevel*, 311 Science 622, 622 (Feb. 3, 2006) (attached as Appendix A).

A handful of small *in vivo* and animal studies suggest that nanoparticles may pose a greater health risk than the macroparticles from which they are derived. *E.g.*, Charles Reynolds and Lynne Radke, *Don't Laugh Now . . . Four Torts You May See before the End of 2005* 47, FOR THE DEFENSE 54 (July 2005) (describing reports of nanopollutants reaching vulnerable lung tissue, animal studies suggesting significant health problems from considerable exposures, studies demonstrating that nanoparticles can accumulate in areas of the body, and inflammation and scarring identified in rats exposed to nanotubes). Well-respected organizations, such as Swiss Re and Britain's Royal Society and Royal Academy of Engineering, also have noted the tremendous economic potential and potential for adverse health effects posed by nanoparticles. A copy of the Swiss Re report, "Nanotechnology: Small matter, many unknowns" is attached as Appendix J and a copy of the Royal Society and The Royal Academy of Engineering report, "Nanoscience and nanotechnologies: opportunities and uncertainties" is attached as Appendix K. The Royal Society has even gone so far as to suggest that manufacturers should presume that nanoparticles are hazardous until proven otherwise.

Other risks associated with nanoparticles are inextricably tied to their benefits. By way of example, the blood-brain barrier constitutes a substantial hurdle to delivering modern therapeutics to the brain. Nanotechnology-derived drug delivery systems presently under development could enable healthcare providers to deliver exact amounts of pharmaceuticals directly to the areas requiring treatment, including, but not limited to, the brain. This technology also will antiquate the "carpet-bombing" typically employed with modern pharmaceuticals, resulting in potentially less toxicity.

Developing pharmaceuticals that permeate many of the body's natural defenses and that directly deliver concentrated doses, however, creates the potentiality for considerable side effects and liability. These new technologies additionally are being principally developed in oncology, a discipline focused on a physically sensitive population in need of effective treatment.

C. Nanotechnology as the Future . . . of Products Liability or Mass Tort Litigation?

Thus far, nanotechnology-related litigation has focused on patent, intellectual property, and garden-variety commercial disputes. Like other product manufacturers, however, nanotechnology-based companies will face the same growing pains associated with distributing breakthrough products. For example, "Nano Magic," a household glass and ceramic tile sealant in an aerosol can sold in German supermarkets and discount stores, was recalled after four days on the market. That short market life yielded nearly 100 reports of health problems ranging from difficulty in breathing to hospitalization and a product warning being issued by German authorities. Subsequent investigation revealed that the product may not have even contained nanoparticles—a significant development but for the fact that some still consider these inauspicious events as the first time that health concerns necessitated a recall of a nanotechnology-derived product. Had that same chain of events occurred in the American market to a publicly traded product manufacturer, a securities action based on a drop in the manufacturer's stock price when the recall was announced, a stockholder derivative action based on the directors' and officers' purported misconduct in permitting the product to go onto the market, consumer fraud actions, personal injury actions filed by plaintiffs with whom the company could not settle, and a potential class action from purchasers who were not physically harmed by the product, but who nonetheless seek compensation, would not be surprising. Coverage disputes with the manufacturer's insurer, regulatory actions, and even deceptive advertising actions filed by competitors also would not be outside the realm of possibility.

That is not to say that nanotechnology's role in current personal injury litigation is purely hypothetical. The diesel exhaust litigation may provide some indication of the direction in which nanotechnology-related personal injury litigation is headed. A number of FELA and product liability cases have been filed over the past five years alleging a variety of health effects from exposure to diesel particulate matter ("PM"). Since most of the epidemiological and *in vitro* data pertain to larger sized "fine" particulate matter (defined as having diameter greater than 2.5 micrometers), the litigation has not focused on ultrafine particulates that are in the nanosized range. Nonetheless, asserting that such studies reveal a causal connection between diesel exhaust and various respiratory- or cardiac-related health events, mine workers, truck drivers, and diesel engine mechanics have filed claims under workers' compensation acts, the Federal Employers' Liability Act, and/or the Locomotive Inspection Act.

Those claims have led to mixed results, as some courts have found sufficient evidence to warrant awards and others have not.[16] Diesel truck and engine manufacturers likewise have been sued in a few personal injury cases, but typically as part of benzene litigation and involving occupational exposures.

Asbestos and diesel exhaust only roughly approximate the potential litigation that nanotechnology could spark. Defending personal injury litigation may present additional issues to address. For example, naturally occurring particulate matter, such as diesel exhaust, settles comparatively rapidly. By contrast, man-made nanoparticles may be designed to remain airborne longer, avoid aggregation, disseminate faster, expose a wider range of individuals, and reach more protected areas of the body in those individuals. Potential plaintiffs also may not be hindered in proving exposure: unlike diesel exhaust emanating from many different sources, the sources of engineered nanoparticles are much easier to attribute to a specific source.

D. Bolstering the Case for Nanotechnology-related Product Manufacturers

Notwithstanding the uncertainty about nanotechnology-related risks, manufacturers can take effective steps now to limit their liability. A principal step is incorporating the latest scientific, medical, epidemiological, and health-related knowledge about nanoparticles into product design, material safety data sheets, and occupational environments. Aside from ensuring a cutting edge product and a safe working environment, American law requires the investment of this time, energy, and effort. For example, products liability laws generally obligate product manufacturers to adhere to the "state of the art." In other words, to the extent that experts in the many disciplines that comprise nanotechnology recognize that readily available tests, reasonable

[16] *See, e.g., Hager v. Norfolk & Western R. Co.*, No. 87553, 2006 WL 3634373, at *9 (Ohio App. Dec. 14, 2006) (affirmed $250,000 jury verdict in favor of former railroad employee who asserted that he had occupationally related asbestosis and his workplace exposures to asbestos, silica, and diesel exhaust had aggravated his Kartagener's disease, but remanding for unrelated reasons); *King v. Burlington N. & Santa Fe R. Co.*, 2005 WL 4122174, at *2-*6 (Neb. Dist. Ct. Oct. 17, 2005) (granting motion to exclude expert offering to opine that occupational exposure to diesel exhaust caused multiple myeloma based on absence of supporting epidemiological evidence and proffered expert's failure to perform reliable differential diagnosis); *Dunn v, Metro Area Transit*, No. A-02-323, 2002 WL 31819591 (Neb. App. Dec. 17, 2002) (affirmed workers' compensation award to retired mechanic for mass transit organization who alleged that diesel exhaust exposure caused his chronic obstructive pulmonary disease and specifically upheld admission of treating physician's opinion linking this exposure to plaintiff's COPD); *Fiore v. Consolidated Freightways*, 659 A.2d 436, 460-61 (N.J. 1995) (reversing award to freight deliverer for allegedly diesel exhaust-related cardiac injuries due to workers' compensation court's application of inappropriate burden of proof for establishing claims and remanding case for additional proceedings); *Manis v. Peterbilt Motors Co.*, No. 01S01-CV-00065, at *2 (Tenn. App. May 8, 1995) (workers' compensation finding that diesel fumes aggravated employee's pre-existing lung and respiratory conditions upheld and degree of claimant's disability increased from 30 percent to 60 percent); *Missouri Pac. R.R. Co. v. Navarro*, 90 S.W.3d 747, 758 (Tex. App. 2002) (excluded proffered expert opinions that railroad employee's occupational exposure to diesel exhaust could cause multiple myeloma due to, among other things, inability to identify supporting studies and disregard of studies demonstrating no relationship between diesel exhaust and multiple myeloma); *see also West Virginia ex rel. City of Martinsburg v. Sanders*, 632 S.E.2d 914, 920-21 (W. Va. 2006) (writ of prohibition granted and trial court reversed for refusing to dismiss medical monitoring case against City of Martinsburg based on firefighters' exposure to diesel exhaust from fire engines or emergency vehicles).

alternative designs for a product, or effective warnings can reduce health hazards, product manufacturers will be presumed to have that same knowledge. A company's emphasis on research and development therefore should not stop once a nanoengineered product is introduced into the market nor should it simply meet the standards set by its competitors.

Product manufacturers also may want to consider partnering with well-credentialed experts to remain knowledgeable about nanotechnology and to test product safety. To be sure, in-house product testing provides invaluable insight on product safety. In-house monitoring of the conditions, if any, that employees exposed to nanoparticles develop also could constitute an invaluable resource of knowledge. Protecting against institutional bias and validating a manufacturer's decision to introduce a product incorporating nanotechnology into the market nonetheless may necessitate outside consultants. Independent testing facilities can provide valuable guidance on product design, product safety, and compliance with prevailing standards. Several universities also have established well-respected departments focusing on nanotechnology and may provide other resources.

These are not burdens that product manufacturers must bear alone. Professional associations, trade associations, and other groups should consider aggregating their efforts to address these issues. Andrew Maynard even recommends that the nanotechnology industry follow the example set by the Health Effects Institute, a revolutionary organization that is funded by industry and the federal government and that has had a tremendous impact on research into the health effects associated with particulate pollution. Such an organization could provide the long-term perspective and focus necessary to conduct well-constructed research addressing nanotechnology-related concerns. These organizations additionally may play a critical role in refuting unfounded, but understandable, concerns associated with nanotechnological advancements; one need only note the on-going public worries about genetically engineered foods to understand the importance of transparency and maintaining a public discourse about nanotechnology. In organizing these efforts, product manufacturers need to proceed carefully so as to avoid raising antitrust and other concerns associated with concerted joint corporate action.

Manufacturers also should take care to ensure the independence of third-party researchers and avoid any appearance that the testing is performed to generate a specific result. Instead, the emphasis should be on generating reliable results that can be replicated. For drug, biologics, and medical device manufacturers, commissioning such testing during product development is part of obtaining FDA approval and should be considered during the post-marketing stage as well. Other product manufacturers may consider these independent tests to be an additional product development expense, but the alternative should be considered: if the manufacturer of Nano Magic had commissioned well-controlled product testing before putting its product onto the market, the consequences of its decisions could have been different.

Although unquestionably different from consumer exposure, nanotechnology-derived product manufacturers also should pay close attention to employee exposures. Again, the past provides invaluable guidance: the first indications that asbestos may be related to adverse health consequences arose from those who worked with that mineral on a daily basis. The health of employees and others with disproportionate

exposures to nanoengineered materials thus may provide signals of adverse health effects. To the extent possible, product manufacturers should incorporate monitoring mechanisms to detect exposure, investigate the availability of reasonable filtering technology to limit nanoparticle exposure, and, again to the extent reasonable feasible, incorporate employee protections uniformly to protect delivery persons, cleaning personnel, and others who may be exposed to nanoparticles in the workplace.

Insofar as no product manufacturer can eliminate risk, close attention also should be paid to passing risk appropriately. There is some basis to conclude that products liability policies will cover personal injury claims arising out of nanoengineered products, employers may assume that workers' compensation policies will cover employee claims, and the insurance industry has not adopted a "nanotechnology exclusion." Annabelle Hett, *Nanotechnology: Small Matter, Many Unknowns, Swiss Re* 8 (2004) (attached as Appendix J) (discussing need for insurance industry to evaluate and calculate risks associated with nanotechnology: "Given the heterogeneity and global dissemination of nanotechnically manufactured products, and the fact that they are being sold—and are generally covered by existing treaties in insurance already—this is no easy task."). Some commentators question the coverage available for nanotechnology-based personal injury claims, pointing to the same provisions that insurers and asbestos manufacturers have litigated for decades, *e.g.*, "trigger, fortuity, and the applicability of the pollution exclusion." Joseph A. Ziemianski, et al., *Emerging Property & CGL Ins. Claims Trends*, 742 PLI/Lit 251, 309 (May 2006). Once again, closely monitoring the manner in which the insurance industry handles nanotechnology-related personal injury claims over the next few years and remaining diligent so as to ensure the reasonableness of a manufacturer's decision to keep a product incorporating nanotechnology on the market are critical to preventing ruinous liability. Just as with any product manufacturer, nanotechnology-related product manufacturers also should consider appropriate indemnification and contribution agreements along the distribution chain to defer risk.

Of course, aside from these nanotechnology-specific observations, manufacturers of nanoengineered products should incorporate the measures expected of any reasonable corporate citizen faced with potential products liability exposure. Tried and true principles of responsible corporate governance, such as maintaining appropriate corporate formalities, establishing compliant document retention policies, and appropriate disclosures to federal entities, the public, and investors, apply to any product manufacturer. Some of these responsibilities naturally flow from the actions that good corporate citizens take to ensure corporate responsibility. Other responsibilities may not be so patent, thereby necessitating the advice of solid legal counsel.

APPENDICES

A: Andre Nel, et al., *Toxic Potential of Materials at the Nanolevel*, 311 Science 622 (Feb. 3, 2006)

B: Nanoscale Science, Engineering, and Technology Subcommittee, Committee on Technology, National Science and Technology Council, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (Sept. 2006)

C: Petition of International Center for Technology Assessment, et al., to the United States Food and Drug Administration (No. CF 1978N-0038/CP17) (filed May 17, 2006)

D: Antacid Products For Over-The Counter (OTC) Human Use Monograph, 21 C.F.R. pt. 331 (2007)

E: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Draft, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* (July 2006)

F: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Nanotechnology Research Program, Draft, *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps* (Sept. 28, 2005)

G: National Institute for Occupational Safety and Health. Draft, *Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide* (Nov. 22, 2005)

H: NIOSH Position Statement on Nanotechnology: *Advancing Research on Occupational Health Implications and Applications*, available at http://www.cdc.gov/niosh/topics/nanotech/position.html, accessed Mar. 5, 2007.

I: United States Environmental Protection Agency, Science Policy Council, *Nanotechnology Workgroup, Nanotechnology White Paper* (Feb. 2007)

J: Annabelle Hett, *Nanotechnology: Small Matter, Many Unknowns*, Swiss Re 8 (2004)

K: The Royal Society & The Royal Academy of Engineering, *Nanoscience and nanotechnologies: opportunities and uncertainties* (July 2004)