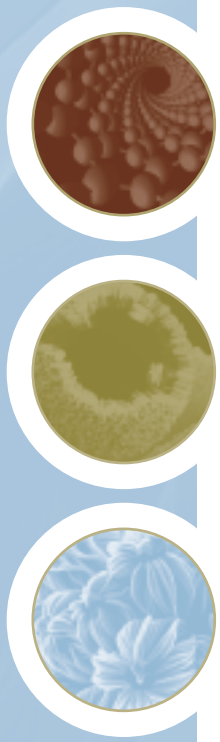
Woodrow Wilson International Center for Scholars

Project on Emerging Nanotechnologies

REGULATING THE PRODUCTS OF NANOTECHNOLOGY:

Does FDA Have the Tools It Needs?

Michael R. Taylor



Project on Emerging Nanotechnologies is supported by THE PEW CHARITABLE TRUSTS

PEN 5
OCTOBER 2006

CONTENTS

Foreword 1
Author's Preface 3
Executive Summary 5
About the Author 11
Introduction 13
Nanotechnology and FDA 13
Potential Risks: What is New about Nanotechnology? 16
FDA's Regulatory Role: Principles from Current Law 18
Evolution of the FDC Act 18
Key Features of the Current Law 20
Regulatory Principles from Current Law 21
Key Elements of a Regulatory Framework for Nanotechnology Products 22
Pre-Market Oversight 22
Post-Market Oversight 23
Overview and Analysis of FDA's Legal Tools for Regulating Nanotechnology Products 25
Cosmetic Ingredients and Products 27
Whole Foods 30
Dietary Supplements 31
GRAS Food Ingredients 33
Food Additives 36
Food Packaging 37
Medical Devices 39
OTC Drugs 41
New Drugs 43
FDA Resources: Current Status and Importance for Safety 45
What FDA Needs To Do 45
FDA's Growing Budget Gap 46
What FDA Is Doing 48
The Consequences of Scarce Resources 49
Conclusion: Gaps in the Tool Kit 51
Recommendations 53
Near-Term Actions 53
Long-Term Legal and Policy Actions 56
Resource Needs 58
Concluding Observation 59
Table 1 Endnotes 60

REGULATING THE PRODUCTS OF NANOTECHNOLOGY:

Does FDA Have the Tools It Needs?

Michael R. Taylor

PEN 5 OCTOBER 2006

The opinions expressed in this report are those of the author and do not necessarily reflect views of the Woodrow Wilson International Center for Scholars or The Pew Charitable Trusts.

Foreword

In 2006, the Food and Drug Administration (FDA) made two important announcements. First, it announced that the agency was holding its first major public meeting on FDA-regulated products containing nanotechnology materials on October 10th in the Washington, DC area. Second, FDA said that it had set up an internal task force to study how to regulate nanotechnology products—focusing on understanding possible adverse health effects from FDA-regulated nanotechnology products and addressing ways to close any knowledge or policy gaps in this area.

Nanotechnology is the ability to do things—measure, see, predict and make—on a scale of atoms and molecules, usually in the realm of 1-100 nanometers. A nanometer is a billionth of meter and a human hair is about 100,000 nanometers in width. As FDA noted in the announcement of its October meeting, due to their small size and extremely high ratio of surface area to volume, nanotechnology materials often have chemical, physical or biological properties that are different from those of their larger counterparts. Because of these novel properties, nanotechnology materials have great potential for use in a vast array of exciting products. However, these special properties may also pose new and different risks for humans and the environment.

According to Lux Research, the nanotechnology industry is expected to grow to $2.6 trillion in manufactured goods by the year 2014.[1] It is a technology which promises to change every facet of people's lives—including important areas under FDA oversight: the prescription drugs, medical devices and therapeutics people rely on; the food and dietary supplements they eat; and the cosmetics they apply. The 2005 market size for nanotechnology drug delivery systems alone is estimated at $980 million, and expected to grow 54% annually over the next five years.[2] Sales of nanotherapeutics, like nanosilver-based wound dressings, were $28 million last year and are expected to increase every year by 62% through 2010.[3] Food industry experts project that nanotechnology will be incorporated into $20 billion worth of consumer products globally by 2010.[4]

With government and industry investing billions of dollars a year in nanotechnology R&D, the stakes involved in FDA "getting it right" in its oversight of nanotechnology are high. The recent and critical assessment by the Institute of Medicine (IOM) of the American drug safety system opened with a quote from business writer Matthew Herper, saying "…FDA has become synonymous with drug safety. In a sense, 'FDA approved' is the brand that the entire $216 billion U.S. drug market is founded upon. Dilute the confidence of the public in the agency, and many billions of dollars in current and potential sales vanish

1. The Nanotech Report 4th Edition. New York, NY: Lux Research, Inc., 2006, p. iii.
2. The Nanotech Report 4th Edition. New York, NY: Lux Research, Inc., 2006, p. 106.
3. The Nanotech Report 4th Edition. New York, NY: Lux Research, Inc., 2006, p. 124.
4. "Study: Nanotechnology in Food and Food Processing Worldwide 2003-2006-2010-2015." Tübingen, Germany: Helmut Kaiser Consultancy, 2006. Available at http://www.hkc22.com/nanofood.html, accessed September 27, 2006.

overnight."[5] The public will expect FDA to likewise ensure the safety of nanotechnology-based products, and these products are already here.

Michael Taylor's report, *Regulating the Products of Nanotechnology: Does FDA Have the Tools It Needs?*, is an extremely important and thoughtful step in helping to ensure that FDA has the strategy, expertise and resources it needs in the area of nanotechnology to "get it right" now.

David Rejeski
Director, Project on Emerging Nanotechnologies

5. Institute of Medicine. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press, 2006, p. 15.

Author's Preface

Nanotechnology is on its way to America's supermarkets, drugstores, and hospitals, promising great benefits to consumers, patients and the economy. Like any new technology, however, the very properties that make nanotechnology different and exciting may pose safety questions that society will demand be addressed.

And, so, nanotechnology is also on its way to the Food and Drug Administration (FDA) – the 100-year-old public health institution on which Americans rely to ensure the safety of many of the products to which nanotechnology is being applied, including cosmetics, foods and food packaging, drugs, and medical devices.

FDA is not "nano ready." This study asks whether FDA is ready, today, for the products of nanotechnology. Does FDA have the tools it needs – legal, resource and scientific – to oversee the introduction of nanotechnology in a way that meets public expectations? The short answer is, unavoidably, no. FDA is missing some of the legal tools it needs, but its readiness for nanotechnology is most seriously hampered by the lack of resources required to respond promptly to products in the market and in the development pipeline.

Gaps exist in FDA's legal tool kit. FDA implements a venerable old consumer protection law, the Federal Food, Drug and Cosmetic (FDC) Act, that has stood the test of time in many respects and has retained its resilience through significant amendments since first being enacted in 1938. Nanotechnology does reveal gaps in FDA's legal tool kit. While there is not a need to start from scratch in providing FDA the legal tools it require to regulate the products of nanotechnology, those gaps do need to be filled if FDA is to provide the oversight people expect. The report analyzes the FDC Act with nanotechnology in mind, identifies gaps, and recommends ways to close them.

FDA lacks necessary resources. The larger issue affecting FDA's readiness for nanotechnology is resources. For the past decade or more, FDA's resource base and overall capacity have been eroded by the pressure of increasing demands and costs of doing business coupled with the failure of Congress and successive administrations to adequately fund even base operations. Just to be able to do what it was doing in 1996 and continue the new activities mandated for it since then, FDA's 2006 budget would have to be 49% greater than it is. Under the President's proposed 2007 budget for FDA, the funding gap between responsibilities and capacity will grow again, to 56%.

This harsh budget reality is a real threat to FDA's ability to effectively oversee nanotechnology. It means among other things that FDA lacks the resources it needs to build its own expertise, to develop the safety-testing protocols and detection methods needed to evaluate new nanotechnology products, to conduct its own risk research, to gather the necessary premarket data required to get ahead of commercialization and to oversee products after they have entered the market.

The potential consequences of not adequately funding these FDA needs are at least twofold. First, FDA may miss potential safety problems or discover them too late to prevent harm, thereby jeopardizing public health and public confidence in nanotechnology.

And second, FDA may lag in providing regulatory guidance and prompt regulatory reviews to product developers, thereby impeding innovation that benefits all.

Neither outcome will be acceptable to the public at large or the regulated industry, but FDA's funding dilemma is stark: devoting resources to nanotechnology means taking resources away from other programs and priorities. I hope the public interest and high stakes surrounding nanotechnology will help prompt action to address FDA's underlying budget crisis. Society cannot fairly hold FDA accountable for delivering on the dual goals of ensuring safety and fostering innovation if it withholds from FDA the means to do the job.

Even within its current authority and resources, FDA can and should take some immediate steps to address the first wave of nanotechnology products now entering the market, including perhaps the most fundamental one of setting the criteria for determining when a nanoscale material is "new for legal and regulatory purposes" and "new for safety evaluation purposes." The distinctive properties of nanomaterials mean that some will pose novel safety questions that are not adequately addressed by safety testing and evaluations performed on conventional versions of the same material. FDA thus should take some immediate steps to prepare itself for regulating nanotechnology products and to deal with cosmetic, sunscreen and food-related applications that are already entering the market. To accomplish this task and to prepare more broadly for its oversight role, FDA needs better access to information about applications of nanotechnology that are in the development pipeline; this report suggests some targeted steps FDA could take to obtain such information.

Though I make a number of recommendations in this report, it will be obvious that I do not have all the answers. I offer an evaluative framework and my own analysis in this report as a starting point. I hope the report will stimulate discussion and debate among FDA officials and FDA's many stakeholders who aspire to effective and efficient regulation of nanotechnology products. Further analysis and active dialogue will be required to get FDA regulation right in this new arena.

Finally, I would like to thank the Project on Emerging Nanotechnologies ("the Project")—a joint initiative of the Woodrow Wilson International Center for Scholars and The Pew Charitable Trusts. I am particularly grateful to its leaders, David Rejeski and Julia Moore, for commissioning this study. They posed the question and turned me loose to begin answering it, leaving responsibility for the content of the report solely in my hands. Likewise, I thank FDA for providing me information on its programs, the people I interviewed for providing their perspectives, and the Project staff and two long-time colleagues of mine, Fred Degnan and Terry Medley, for reviewing it. Finally, the Project's Shilpa Deshpande and Evan Michelson provided crucial research assistance, but they and all others I have mentioned bear no responsibility for the result.

M.R.T.

Executive Summary

Nanotechnology and the Need for Oversight

The question addressed in this paper is whether the Food and Drug Administration (FDA) has the tools it needs to regulate the products of nanotechnology. This question is important because FDA will be charged with overseeing the safety of some of the earliest and most visible applications of nanotechnology – including cosmetics, sunscreens, food packaging, drugs and medical devices – and will be expected to do so in a manner that protects public health, fosters beneficial innovation and provides the basis for public confidence in nanotechnology products.

The extremely tiny, engineered particles of material made possible by nanotechnology are not necessarily hazardous, but they have sufficiently different properties that their safety cannot be assumed based on what's known about the safety of the conventional-size versions of the material.

It is thus reasonable to adopt the presumption that engineered nanomaterials are "new for safety evaluation purposes," which means that until evidence indicates otherwise, they merit careful regulatory oversight by FDA, both before and after entering the marketplace.

Regulatory Principles from Current Law

FDA has a long history of regulating new technologies under the 1938 Federal Food, Drug, and Cosmetic Act (FDC Act), which has been amended many times in response to new technological and public health challenges. The FDC Act remains a resilient legal tool kit for FDA and the source of regulatory principles that properly apply to oversight of nanotechnology products, including these:

- Protecting and promoting public health and the welfare of consumers are the proper drivers of all FDA decision-making, with product safety being FDA's first duty.

- Technological innovation is a valued means to the ends of both protecting and promoting public health and, thus, FDA has a duty to manage its programs in ways that facilitate innovation, consistent with its duty to ensure product safety.

- Public confidence in FDA and the safety and effectiveness of FDA-regulated products are important goals of the regulatory process.

- The public health principle of prevention, implemented through FDA pre-market safety review, properly governs when a product involves intended exposure to a substance that has no prior history of exposure to human beings and no widely accepted and scientifically established demonstration of safety.

- Post-market oversight of FDA-regulated products is just as essential to protecting and promoting public health as pre-market oversight.

Key Elements of FDA Oversight for Engineered Nanomaterials

Based on the above principles drawn from current law, and considering what is known scientifically about engineered nanomaterials, the FDA regulatory system for ensuring the safety of nanotechnology products should be capable of performing certain key functions, pre-market and post-market, including the ability to:

Pre-market Oversight

- Obtain early and adequate information on nanotechnology products under development.
- Define and enforce safety standards for nanomaterials, including the nature and extent of the testing required to satisfy them.
- Place the initial and continuing burden to demonstrate safety on the nanotechnology product's sponsor.
- Review the nanotechnology product's safety prior to marketing and impose conditions as needed to ensure safety.

Post-market Oversight

- Require post-market monitoring and testing as needed to ensure nanotechnology product safety.
- Require timely adverse event reporting.
- Inspect manufacturing establishments and examine records related to nanotechnology product safety.
- Remove from the market nanotechnology products that appear to pose a significant safety hazard or no longer meet the applicable safety standard.

There need not be a "one size fits all" approach to performing these functions; in fact, different approaches can be used for different product categories, as under the current FDC Act. These desired functional elements comprise a useful framework, however, for analyzing the adequacy of FDA's legal tools for regulating nanotechnology products.

The Adequacy of Current Law for Performing Key Functions

Using this framework, the report analyzes the strength of current law as applied to nine categories of nanotechnology-based products that will come under the agency's jurisdiction—

cosmetic ingredients and products, whole foods, dietary supplements, generally recognized as safe (GRAS) food ingredients, food additives, food packaging, medical devices, over-the-counter (OTC) drugs and new drugs.

The results of this analysis, which are summarized in Tables 1 and 2, show that the legal tools provided by the FDC Act vary widely from category to category, with cosmetics and whole foods being subject to generally weaker statutory authorities and medical devices and drugs being regulated under provisions that are stronger in terms of accomplishing the framework's pre-market and post-market functions. Many of these differences reflect implicit congressional judgments about (1) the degree of potential risk posed by various categories – with cosmetics deemed inherently less risky and new drugs inherently more risky – and (2) the nature of the pre- and post-market oversight required to assure safety. Many of these judgments and differences in regulatory approach continue to make sense, while others are challenged by new technologies, such as nanotechnology.

Based on the report's analysis of current law, gaps in FDA's legal authority with respect to nanotechnology products include (1) the lack of pre-market oversight tools for cosmetics, (2) FDA's inability to acquire information about nanotechnology products early enough in their development to prepare properly for their regulation and (3) inadequate authority for post-market adverse event reporting.

The Adequacy of FDA's Resources for Oversight of Nanotechnology

Even more so than legal authority, the issue affecting FDA's readiness to regulate nanotechnology products is resources. For the past decade and more, FDA's resource base and overall capacity have been eroded by the dual pressures of increasing demands and costs of doing business and the failure of Congress and successive administrations to adequately fund even base operations.

Just to be able to do what it was doing in 1996 and continue the new activities mandated for it since then, FDA's 2006 budget would have to be 49% greater than it is. Under the President's proposed 2007 budget for FDA, however, the funding gap between responsibilities and capacity will grow once more, to 56%.

This harsh budget reality threatens FDA's ability to effectively oversee nanotechnology. It means among other things that FDA lacks the resources it needs to build its own nanotechnology expertise, to develop the safety testing protocols and detection methods needed to evaluate new nanotechnology products, to conduct its own risk research, to gather the necessary pre-market data required to get ahead of commercialization and to oversee products after they have entered the market.

The potential consequences of not adequately funding these FDA needs are at least twofold: (1) in products areas where FDA lacks strong pre-market authority, such as cosmetics and dietary supplements, FDA may miss potential safety problems or discover them too late to prevent harm, thereby jeopardizing public health and public confidence in nanotechnology; and (2) for products going through FDA pre-market approval systems, FDA may lag in providing regulatory guidance and prompt regulatory reviews to product developers, thereby impeding innovation that benefits all.

Recommendations

Over the long-term, Congress must address the gaps in FDA's legal authority and resources. In addition, however, there are steps FDA could take now under current law to address nanotechnology products that are already entering or appear close to entering the market. These near-term actions are outlined first, followed by recommendations for longer-term legislative and resource improvements.

Near-Term Actions

- *Establish Criteria for "New for Legal and Regulatory Purposes" and "New for Safety Evaluation Purposes."* The single most important step that FDA should take immediately is to establish criteria and provide guidance to the industry for classifying some nanoscale materials as "new" for legal, regulatory and safety purposes. For nanotechnology products that do not require individual product review and approval by FDA, manufacturers often have to make a threshold determination of whether the product poses a new safety question or otherwise should be considered a new or different material, compared with the conventional form. The conventional form may, for example, have been listed in FDA regulations as a "generally recognized as safe" (GRAS) food substance or as an approved food additive or food contact material. If the manufacturer judges the nanotechnology version to be the same as the listed one, there is no legal requirement to seek FDA pre-market review, and FDA may not become aware of the product until after it enters the market. The burden would then rest on FDA to determine after the fact whether there is a safety or regulatory concern warranting action.

  To guide companies in making what amount to market-entry decisions for their particular products, FDA should promptly establish criteria for judging when a nanomaterial is "new" for legal and regulatory purposes, i.e., for purposes of distinguishing it from versions that are already listed in FDA's GRAS, food additive and food packaging regulations or that have been reviewed through the Cosmetic Ingredient Review (CIR). The criteria might be based solely on material size, surface-volume ratios or other physical characteristics, or they could include other properties that FDA might judge relevant. The point is to have a basis for companies to know when they need to come to FDA prior to marketing, versus when they can rely for legal and regulatory purposes on the existing approval, GRAS affirmation or CIR review of the conventional form of the material.

  A necessary extension of clarifying what is "new" for legal and regulatory purposes would be to establish criteria for determining when a nanomaterial should be considered "new for safety evaluation purposes." These criteria presumably would include functional properties that relate to the likelihood that the safety profile of the nanotechnology version would be different from the conventional one. Such criteria would be helpful for all categories of FDA-regulated products as a guide to decisions about the need for toxicity testing beyond what already exists on the conventional form. Another application of such criteria might be to narrow the "new" category so that FDA review of nanotechnology versions of already-approved conventional forms would be required when there is a scientific basis for judging that such review is needed to ensure safety.

- *Resolve the Meaning of "Micronized" in the Over-the-Counter (OTC) Sunscreen Monograph.* FDA's regulation authorizing the use of "micronized" titanium dioxide does not precisely define the term, and some sunscreen product labels claim that nanomaterials are being used. By defining the term "micronized" and clarifying the extent to which the monograph embraces the full range of nanomaterials, FDA would help resolve the status of one of the more visible early products of nanotechnology to enter the market and build confidence that FDA is on top of its regulatory task.

- *Request Cosmetic Companies to Submit Safety Substantiation Data.* An FDA regulation requires cosmetic companies to compile safety substantiation data on their ingredients, but it does not give FDA access to review such data. In order to better inform FDA about the nanotechnology cosmetic products on the market today and the basis for their safety, FDA should request the voluntary submission of substantiation data on all cosmetic products making nanotechnology claims or containing nanomaterials.

- *Provide the Cosmetic Industry Guidance on What Constitutes "Adequate" Substantiation.* While FDA does not currently have legal authority to access a company's substantiation data, the provision of guidance on what constitutes "adequate" substantiation for nanomaterials would at least provide the industry with a common starting point and could contribute to the establishment of a de facto standard of care for the industry.

- *Provide Guidance on When the Use of Engineered Nanomaterials and Their Associated Claims Turn Cosmetics into Drugs.* The labels of some cosmetic products make explicit or implied claims that the products contain nanomaterials that affect the structure or function of the body, which is the legal basis for classifying a product as a "drug." By providing guidance on when the use of engineered nanomaterials and their associated claims in cosmetics make the product a drug, FDA will be asserting its traditional regulatory authority and responsibility for drugs and providing assurance that "cosmetic" ingredients having biological impact receive appropriate review.

- *Call for Data on Food Uses.* In the absence of clear authority to access food industry data on pipeline products, FDA should attempt to access at least some of the food industry's safety-related data by collaborating with industry, perhaps through a trade association, on a voluntary call for data on food uses of nanotechnology.

Legal Authority

- *Call for Data Authority.* To address its need to be informed, FDA should have administrative authority to call for the submission of specified information on emerging technologies and products under its jurisdiction, including products in the development pipeline. The legislation granting such authority should carefully define the purposes for which FDA may call for data and establish criteria and a process so that the requests are focused and targeted.

- *Discretionary Pre-Market Notification Authority.* FDA should be provided rule-making authority to establish interim pre-market notification mechanisms to address emerging and novel technologies. FDA would have the discretion to identify product categories for which pre-market notification would be required, the circumstances that trigger notification and the data that would have to be submitted; a sunset provision should be included.

- *Records Access.* Records access could be achieved by expanding FDA's general inspection authority to include access to safety substantiation data and other safety information, and by granting FDA the ability to request submission of such information in its new authority to call for data.

- *Post-Market Monitoring Authority.* FDA should have authority to require post-market monitoring and surveillance, if needed, to assure the long-term safety of the product.

- *Adverse Event Reporting.* FDA should be given broad authority to devise mandatory adverse event reporting systems that are appropriate for each product category and least burdensome to achieve the legitimate oversight purpose.

Resource Needs

- *Early Warning Information Collection*. Congress should consider funding within the FDA Office of the Commissioner, and in each of the operating centers, focal points for the gathering of "scientific intelligence" to keep FDA abreast of technological developments and to keep the agency involved in discussions occurring within the greater scientific community.

- *FDA Regulatory Research*. FDA's research responsibility is to ensure that proper toxicity-testing protocols are available and that the agency has the scientific knowledge and technical tools, including analytical methodologies, to play its product review and post-market monitoring roles. The $1 million FDA has invested in such research is noteworthy and admirable, but it is not sufficient in light of the array of applications of nanotechnology the agency can expect to confront in coming years.

- *Building FDA's Scientific and Regulatory Staff.* Effective, science-based oversight of nanotechnology products – oversight that understands the safety issues well enough to prevent problems while not unduly slowing innovation – will require specialized scientific expertise and focused effort by regulatory policy makers in all of FDA's programs. Congress should provide FDA the resources to acquire the needed scientific expertise and to bolster the agency's regulatory capacity across all of its programs, at both the policy-making and field oversight levels.

About the Author

Michael R. Taylor is a Professor at the University of Maryland School of Medicine, where he conducts research on policy, resource and institutional issues that affect the success of public health agencies in carrying out their prevention missions. Previously, he was a Senior Fellow and Director of the Risk, Resource, and Environmental Management Division at Resources for the Future. While at Resources for the Future, Taylor co-founded the Food Safety Research Consortium, which he chairs. Prior to Resources for the Future, Taylor served in government, practiced law in Washington and worked in private industry. He was Administrator of the United States Department of Agriculture's Food Safety and Inspection Service from 1994 to 1996; Deputy Commissioner for Policy at the Food and Drug Administration (FDA) from 1991 to 1994; and an FDA staff lawyer and Executive Assistant to the FDA Commissioner from 1976 to 1981. He practiced food and drug law as a partner in the law firm of King & Spalding for 10 years and served as Vice President for Public Policy at Monsanto Company. Taylor has served on several committees of The National Academy of Sciences and currently serves on the Advisory Committee of the Partnership to Cut Hunger and Poverty in Africa and the Board of Trustees of Resolve, Inc. He received his law degree from the University of Virginia and his B.A. in political science at Davidson College.

Introduction

Nanotechnology and FDA

The question I address in this paper is whether the Food and Drug Administration (FDA) has the tools it needs—legal, resource and scientific—to regulate the products of nanotechnology. This question is of increasing importance and timeliness for the many elements of American industry that are investing in this amazing new technology. It is also crucial for the millions of consumers and patients who stand to benefit from the innovative products nanotechnology makes possible and who will want to know that any potential risks are well understood and addressed.

In simple terms, "nanotechnology" is the ability to engineer matter in ways that take advantage of their special properties at the nanoscale.[6] Nanotechnology has far-ranging applications in cosmetics, foods and food packaging, medical products and a host of other areas of great importance to consumers, public health, the economy and the environment. An inventory of manufacturer self-identified consumer products, compiled by the Project on Emerging Nanotechnologies, has identified over 300 such products already available on the market worldwide.

Lux Research, Inc., a commercial research organization, estimates that over $32 billion in products incorporating nanotechnology were sold in 2005, with global research and development spending reaching $9.6 billion.[7] In its *2006 Nanomedicine, Device & Diagnostics Report*, NanoBiotech News estimates that there are currently 130 nano-based drugs and delivery systems and 125 devices or diagnostic tests in preclinical, clinical, or commercial development—an increase of 68% since last year.[8] Over the longer term, Lux Research projects that $2.6 trillion in global manufactured goods will incorporate nanotechnology,[9] or about 15% of total manufacturing output.

The very properties that make engineered nanomaterials beneficial, however, may present novel risks, or at least raise new safety questions—questions that must be understood and addressed if the benefits of the technology are to be fully realized and public health and the environment are to be protected.

As the agency charged with regulating the safety of some of the earliest and most visible applications of nanotechnology—in cosmetics, sunscreens, food packaging, drugs

6. FDA has not formally defined "nanotechnology" but it participates in the National Nanotechnology Initiative (NNI), a White House-led program that coordinates federal agency efforts in nanoscale science, engineering, and technology, and cites the NNI's definition, which considers an activity to be "nanotechnology" if it involves all of the following elements: (1) research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1-100 nanometers; (2) creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and (3) ability to control or manipulate on the atomic scale. Lux Research, Inc. offers this succinct definition of nanotechnology: "The purposeful engineering of matter at scales of less than 100 nanometers (nm) to achieve size-dependent properties and functions." *The Nanotech Report 4th Edition*. New York, NY: Lux Research, Inc., 2006, p. 1.
7. "Nanotechnology in $32 Billion Worth of Products: Global Funding for Nanotech R&D Reaches $9.6 Billion." New York, NY: Lux Research, Inc., May 8, 2006. Available at www.luxresearchinc.com/press/RELEASE_TNR4.pdf, accessed September 27, 2006.
8. *2006 Nanomedicine, Device & Diagnostics Report*. Atlanta, GA: NanoBiotech News, 2006.
9. *The Nanotech Report 4th Edition*. New York, NY: Lux Research, Inc., 2006, p. iii.

and medical devices, all of which will directly affect consumers—FDA will be at the "heart of the action," as it will bear considerable responsibility for answering questions about product safety and potential risks. As with past revolutions in genomics and other technological fields, FDA will be expected by society to ensure the safety of nanotechnology products without impeding innovation or blocking the public's access to the promised benefits. Clearly, the stakes are high: the products FDA regulates account for about 25 cents of every dollar consumers spend.[10] If FDA is successful, we all win. If FDA fails, we all lose.

The extraordinary pace of innovation in nanotechnology makes it timely, if not urgent, to examine FDA's preparedness to play this vital oversight role. Research and product development are proceeding with great speed, and neither science nor the marketplace will wait for years of deliberation over how nanotechnology products should be regulated. Rather, at an accelerating pace, new products will be challenging FDA to set policies and make product-specific decisions that will have a lasting impact on how the safety of nanotechnology is regulated and on how the products of nanotechnology are seen and accepted by the public. This is not an easy challenge, especially since current knowledge about the potential risks of new engineered nanomaterials is limited.[11] FDA will, nevertheless, be expected to acquire knowledge and deploy its regulatory tools in ways that detect and prevent risks while not impeding beneficial innovation.

The timeliness of this report's topic—in FDA's centennial year as a public health regulatory agency—is heightened by broader questions about whether FDA is equipped today to meet the public's high expectations. FDA has a long record and traditionally strong reputation as a science-based public health regulatory agency, with extensive experience overseeing the introduction of new technology. In some ways, nanotechnology is just another in a long line of new technological challenges FDA has faced using the legal tools and resources at its disposal.

But today, FDA is an agency under enormous stress. Its job is being made more difficult every year, not only by promising new technologies in biomedicine and many other fields but also by new public health challenges, from bird flu to bioterrorism, and by the growing and globalizing marketplace for the products FDA regulates. As the job grows larger and more difficult every year, however, the agency's resources are shrinking and its public credibility is eroding.

In relation to the job it is expected to do, FDA has been under-funded for many years. FDA's 2006 budget would have to be 49% greater than it is just to maintain its 1996 base level of activity and continue the initiatives Congress has directed it to undertake. This funding shortfall would continue growing, to 56%, under FDA's proposed budget for 2007.

Public confidence in FDA is also on the decline. A recent Harris poll showed that between 2004 and 2006, the share of the American population holding a positive

10. "An FDA Overview: Protecting Consumers, Protecting Public Health." Rockville, MD: United States Food and Drug Administration, August 2004. Available at http://www.fda.gov/oc/opacom/fda101/fda101text.html, accessed September 27, 2006.

11. Andrew Maynard. *Nanotechnology: A Research Strategy for Addressing Risk*. Washington, DC: Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, 2006.

view of FDA's efforts to ensure the safety, as well as the effectiveness, of new prescription drugs dropped from 56% to 37%.[12] This question of public trust in FDA is not a small matter for nanotechnology companies. In recent congressional testimony, a leading nanotechnology industry analyst from Lux Research noted that firms developing products using engineered nanomaterials could find commercial feasibility blocked by the public perception that these materials are dangerous—even if they are proved safe.[13]

Against this backdrop, nanotechnology provides a revealing and very timely lens through which to examine the bigger picture of FDA's ability to do the job society expects it to do, as affected by the interaction of the agency's legal authority, resources and scientific tools. And this bigger picture is directly relevant to nanotechnology. FDA's legal tools, virtually all of which pre-date nanotechnology by decades, are the essential starting point, but legal authorities are of little value without adequate resources to apply them. Scarce resources also impede FDA's ability to assemble the new scientific knowledge and tools that will be needed to effectively regulate the products of nanotechnology. To really understand and improve FDA's preparedness to regulate in this new arena, it is necessary to look at FDA's legal, resource and scientific tools as an integrated whole.

A truly complete analysis of FDA's tools for regulating the products of nanotechnology is, to put it mildly, a daunting task. FDA implements a voluminous compilation of laws that regulate widely diverse products: lipstick and sunscreens, artificial sweeteners and food packaging, artificial hips and heart valves, cancer drugs and AIDS vaccines, to name a few. FDA regulates the safety *and* proper labeling of all products within its jurisdiction in widely diverse ways, as well as the therapeutic effectiveness of medical devices, drugs and vaccines. Complicating matters further, judgments about the adequacy of FDA's tools necessarily hinge on the particular product category and application of nanotechnology under consideration and a complex mix of legal, policy, scientific, agency resource and social-value considerations.

It is beyond the scope of this paper to tackle all of these issues. As a first step into the thicket, however, I examine in this paper FDA's legal tools and resources for regulating the safety of nanotechnology products. I will analyze the legal tools based on principles that are embedded in the law FDA currently administers—as it has evolved over the past 70 years—as well as my perspective on what the public expects from FDA and what I think is needed to achieve three goals critical to the success of nanotechnology:

- protecting public health;
- fostering innovation; and
- providing the basis for public confidence in the products of nanotechnology.

12. Beckey Bright. "Americans Growing Less Confident in FDA's Job on Safety, Poll Shows" *The Wall Street Journal Online*, May 24, 2006. Available at http://online.wsj.com/public/article_print/SB114831296787359612-uW9Ve_ZtSkQ20zMT5k2fNvR14Uw_20060622.html, accessed September 27, 2006.
13. Matthew M. Nordan. "Nanotech Commercialization Has Advanced, but Government Action to Address Risk Has Not." Testimony before the United States House of Representatives Committee on Science, "Research on Environmental and Safety Impacts of Nanotechnology: What are the Federal Agencies Doing?" September 21, 2006. Available at http://www.house.gov/science/hearings/full06/Sept%2021/nordan.pdf, accessed September 27, 2006.

I will also review the status of FDA's resources and how that affects the agency's ability to achieve these central goals of regulation in the area of nanotechnology. On the basis of this analysis, I will identify gaps in FDA's legal and resource tool kit and make recommendations for filling them.

Some of my recommendations are directed at FDA, which certainly has a leadership role to play in preparing to regulate in this new technological arena. The primary audience for the analysis and recommendations in this paper lies, however, outside FDA, in the political, business, public health and consumer communities that share an interest in seeing that FDA can effectively regulate the products of nanotechnology. After all, the people who work at FDA are keenly aware of what their statutes and resources permit them to do and, from my experience, FDA staff throughout the many centers and offices involved in nanotechnology will work hard to make the best use of the tools they have to carry out their assigned mission.

The question is whether society, acting through Congress and politically accountable officials of the executive branch, has given FDA the tools it needs. I conclude that FDA has many of the legal tools it needs but lacks others, and that it is severely lacking in the resources required to prepare scientifically and otherwise for effective regulation of nanotechnology products and to mount a program in which the public will have confidence. FDA can and should participate in identifying these gaps, but it is for others in society to address them.

Potential Risks: What is New about Nanotechnology?

The starting point for thinking about FDA's tools for regulating the safety of nanotechnology products is an understanding of (and some assumptions about) their potential risks. Much has been written about the special properties of nanomaterials and the state of our knowledge and uncertainty about their potential adverse health effects. The Royal Society & The Royal Academy of Engineering in the United Kingdom, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks and the International Life Sciences Institute in the United States have addressed the issue, as have many others.[14]

I will not recap that growing literature here. As a lay policy analyst, I take this literature at face value and draw the following understandings and assumptions from it:

- Manufactured nanomaterials have physical, chemical and other properties that typically differ from larger-scale materials of the same substance in ways that may affect the way nanomaterials interact with the human body, such as differing absorption patterns and differing abilities to reach certain organs and penetrate cell walls.

- The different properties and behaviors of engineered nanomaterials do not mean they are necessarily hazardous, but they do mean that the body of evidence used to assess the safety of larger materials cannot

14. See: *Nanoscience and Nanotechnologies: Opportunities and Uncertainties.* London, UK: The Royal Society & The Royal Academy of Engineering, July 2004; *The Appropriateness of Existing Methodologies to Assess the Potential Risks Associated with Engineered and Adventitious Products of Nanotechnologies*. Brussels, Belgium: European Commission/SCHENIHR, March 10, 2006; Gunter Oberdorster, et al, "Principles for Characterizing the Potential Human Health Effects From Exposure to Nanomaterials: Elements of a Screening Strategy," *Particle and Fibre Toxicology* 2005, 2:8.

be assumed to demonstrate the safety of the corresponding nanomaterials.

- Materials produced at the nanoscale vary widely in their properties and in their applications, with the likelihood that, as used, some engineered nanomaterials will pose hazards while others will not. The ability to engineer these materials with precise nanoscale structures—including surface layers and diverse morphologies—adds another layer of complexity to determining which materials will be hazardous and which will be benign.

- For these reasons, judgments about the safety of any particular engineered nanomaterial cannot be based either on the safety of larger-scale versions of the same material or on easy generalizations about nanomaterials as a class; case-by-case safety assessment is required.

- The one generalization that may be appropriate is that nanometer-diameter particles (nanoparticles) bound in a matrix of other material are less likely than unbound or free nanoparticles to be systemically absorbed and distributed and thus are less likely to pose a safety concern, though end-of-life disposal of such bound nanoparticles could present potential risks.

- Finally, it is not clear that existing animal toxicity-testing protocols, on which we rely to assess the safety of most chemicals, can be used in their present form to assess engineered nanomaterials; for example, the traditional measure of dose in terms of the test substance's mass may have to give way to ratios between the surface area of a nanomaterial and its volume or mass.

One way to distill and apply this state of knowledge on the safety of engineered nanomaterials is to adopt the presumption that they are "new for safety evaluation purposes." This is not meant to say that any particular nanomaterial is unsafe. It does mean, however, that, a priori, we just do not know. This presumption is central to the discussion that follows, but it also raises an important definitional issue that FDA and others must address in considering how best to apply FDA's current regulatory tools and to determine whether there are gaps in those tools that need to be filled.

I am using the terms "nanotechnology" and terms such as "nanomaterial" and "nanotechnology product" to refer to techniques and applications that are encompassed within the NNI's definition of "nanotechnology," which includes manipulation and use of matter at the scale of 1–100 nanometers to take advantage of novel properties and functions that occur at that scale. It is under these circumstances that it seems fair and necessary to establish the presumption that an engineered nanomaterial is "new for safety evaluation purposes." Terms such as "nanotechnology" and "nanomaterial" are often used loosely, however, to apply to a broad range of techniques and resulting materials, many of which are properly presumed new for safety evaluation purposes while others may not be. Making clear this distinction, including the criteria for drawing it, should be one of FDA's high-priority tasks, because it is a distinction that does and should play a critical role in FDA's regulatory program.

FDA's Regulatory Role: Principles from Current Law

Evolution of the FDC Act

In analyzing the adequacy of FDA's legal tools for regulating nanotechnology products, it is neither necessary nor wise to start from scratch. FDA has been regulating the application of new and advancing technologies for decades, under a series of congressional enactments going back to 1938, and as FDA's role has evolved over the years, some key principles have emerged concerning FDA's regulatory role and approach. Certainly, each new wave of technology challenges existing principles and approaches and may warrant revising them, as has happened many times over the years, but the proper starting point for this paper's analysis is the role FDA plays under current law.

Constitutionally and functionally, FDA and its mission are creatures of Congress. Established in 1906, FDA is an expert, science-based, regulatory agency whose job is to carry out the public health mission assigned to it by Congress, using the legal tools and resources Congress provides. As an executive branch agency, FDA properly operates within a recognized range of discretion and autonomy, but its job is to implement laws passed by Congress. The principal law under which FDA operates is the Federal Food, Drug, and Cosmetic Act of 1938 (FDC Act), as amended dozens of times in the nearly 70 years since its enactment.

The history of the FDC Act and its many amendments is germane to nanotechnology because it is largely a history of Congress responding to evolving food and medical technologies, to demands from consumers and industry for FDA to oversee the introduction of these technologies and to occasional "crises" that catalyze the politics of legislative reform. As a result, the current FDC Act reveals as well as, or better than, any other source the accumulated and evolving expectations of the American public concerning FDA's role in dealing with the public health consequences of new technology.

The original 1938 law, for example, established the first federal requirements for pre-market safety testing and FDA approval of new drugs in response to the famous Elixir Sulfanilamide disaster, in which the poisonous solvent glycol was used in a cough medicine and killed 107 people, including many children. The 1938 act also gave FDA new authority to establish legal limits on pesticide residues in food in response to public health concerns raised by the wider use of chemical pesticides in agriculture. It also established FDA's first regulatory authority over cosmetics, authorizing FDA to remove a cosmetic product from the market if the agency could prove it was hazardous.

Other instructive examples of society, through Congress, responding to new technology and to evolving public expectations include:

- *The Food Additive Amendment of 1958.* This amendment was enacted in response to the urging of the food industry, which was concerned about public acceptance of the expanding use of chemicals in food processing. Congress required pre-market safety testing and approval of food additives unless they were already "generally recognized as safe" (GRAS) by scientists.

- *The Kefauver-Harris Drug Amendments of 1962.* These amendments were enacted in

response to the growing sophistication of drug development and marketing and sparked by the discovery that the new sleeping pill thalidomide could cause severe birth defects. Congress strengthened the pre-market testing and evaluation of new drugs by requiring that they be tested for effectiveness as well as safety.

- *The Medical Device Amendments of 1976.* These amendments were enacted as medical technology was advancing rapidly to produce sophisticated and life-saving devices and in response to the Dalkon Shield episode, in which many women were injured from use of an intrauterine contraceptive device that had not been adequately tested and was lawfully marketed without FDA approval. Congress required that medical device manufacturers and products be registered with FDA, that FDA be notified prior to any new product entering the market and that new products go through a complete pre-market testing and approval process for safety and effectiveness, unless the sponsor could demonstrate that the product is substantially equivalent to a product marketed prior to 1976.

- *The Dietary Supplement Health and Education Act of 1994.* This act was passed in response to concerns of the dietary supplement industry and its customers that FDA intended to require supplement companies to prove the safety of supplements that already had a history of marketing. Congress classified a wide array of supplements as foods and precluded shifting to the supplement manufacturer the burden of proof on safety with respect to products marketed prior to enactment of the 1994 law. But, Congress also required that ingredients used in a supplement product for the first time after 1994 either have a history of use in food in the same chemical form as those being used in the supplement product or be submitted to FDA prior to marketing along with information substantiating the safety of those ingredients.

- *The Food and Drug Administration Modernization Act of 1997.* This act was passed, in part, in response to concerns that FDA's approval processes for drugs and devices were unduly slowing innovation and market entry of beneficial new products. Congress streamlined the process in various ways while retaining established standards for product testing and FDA's pre-market evaluation of safety and effectiveness.

The foregoing components of the FDC Act deal primarily with FDA's pre-market oversight of the products it regulates. Equally important to FDA's public health role are the inspection, adverse event reporting and enforcement provisions of the law, which empower FDA to discover safety problems with marketed products, to take action to remove specific versions of a product from the market or to ban the product entirely as required to protect consumers and patients. The inherent inability of pre-market testing to reveal all there is to know about the safety and effectiveness of innovative new technologies and applications means that FDA's regulation and oversight is best understood as a continuum, which includes pre-market review and approval but also encompasses FDA's response to problems identified and experience gained throughout the product's lifetime of use.

As with its pre-market authorities, FDA's post-market authorities vary across product categories. For example, during inspections of drug and many medical device manufacturing facilities, FDA has broad access to records relating to the safety and proper manufacturing of

products, while FDA's access to similar records regarding foods is generally conditioned on FDA having a reason to believe that a product poses a serious health hazard. In contrast, FDA has no authority to inspect records related to the safety of a cosmetic product. Similarly, FDA can require drug and medical device manufacturers to report side effects, malfunctions or other adverse events associated with their products, but it has no such authority for foods and cosmetics.

Key Features of the Current Law

What does the history of the FDC Act teach us about its key features? The first, overarching observation suggested by the evolution of the FDC Act is that Congress has built a framework that tailors regulatory standards and processes for new technologies in accordance with broad assumptions about the risks posed by particular product categories and the perceived need for pre-market review and approval of products by government. Importantly, this framework is not built around the underlying technologies themselves. FDA does not regulate polymer chemistry, bioengineering or genomics per se. It regulates the products produced through the application of these technologies. And this is a wise approach, because the safety of products for consumers rests on how the technology is applied to produce particular products and the resulting properties of those products.

While this approach and the current structure of the law have clear strengths, they also have limitations that become most evident when dramatically new technologies come along. For example, most cosmetic ingredients are not subject to any FDA pre-market review for safety based on the assumption, in 1938, that lotions, creams and other materials applied externally to improve appearance pose little safety concern. In 1960, in response to concerns about the safety of coal tar hair dyes, Congress required that color additives used in cosmetics and all other FDA-regulated products be tested for safety and approved by FDA prior to marketing. These broad categorical assumptions about potential risk—pre-market review for colors but none for other cosmetic ingredients—may be sound as a general matter, but do they hold true when engineered nanomaterials are used to enhance the functional properties of non-color cosmetic ingredients?

Similarly, the regulatory structure for food ingredients and food packaging materials established in 1958 is built around the recognition that many natural and manmade materials have a long history of safe use in food or otherwise are generally recognized to be safe. The policy idea is that subjecting every new use of these materials to an FDA pre-market safety review is not necessary to assure safety and not a good use of resources. Does this assumption hold when such materials are manufactured and used at the nanoscale?

Therapeutic drugs and medical devices are generally subject to more comprehensive pre-market safety regulation than cosmetics and foods, but they, too, are regulated in ways that reflect categorical assumptions about risk and the extent of pre-market oversight required to ensure safety. Most over-the-counter (OTC) drugs are regulated under an FDA monograph system that lists drug ingredients that are "generally recognized" by experts to be safe and effective for specific uses, based on a history of safe use or scientific evidence. Products comprised of these ingredients are exempt from the definition of "new drug" and from the individual product licensing requirement that applies to new drugs. For medical devices, the pre-market notification option for "substantially equivalent devices" provides a means to avoid a full-blown pre-market review of a device's safety

and effectiveness based on the assumption that, for these devices, such a review is unnecessary. Does nanotechnology challenge these approaches?

These features of the FDC Act and the law's history give rise to a second broad observation: there is an inherent tension between the imperative to protect the public's health from harm and the goal of promoting public health and consumer welfare in general, by fostering access to innovative new products. This tension is manifest in the complex, highly varied legal framework Congress has created for the wide array of products FDA regulates. It is anything but a "one size fits all" regulatory system. And, in general, this approach makes sense. It reflects the scientific and public health reality that products differ widely in the degree of risk they pose, as well as the political reality that Congress will always seek to balance the need to protect public health and the need to avoid undue restraints on innovation, business activity and consumer choice. Consumers benefit from both careful regulation to ensure product safety and ready access to innovative and beneficial new products.

Regulatory Principles from Current Law

With this background in mind, several regulatory principles emerge from the current FDC Act that I believe should inform FDA's regulation of the products of nanotechnology.

- First, protecting and promoting public health and the welfare of consumers are the proper drivers of all FDA decision-making, with product safety being FDA's first duty.[15]

- Second, technological innovation is a valued means to the ends of both protecting and promoting public health and, thus, FDA has a duty to manage its programs in ways that facilitate innovation, consistent with its duty to ensure product safety.

- Third, public confidence in FDA and the safety and effectiveness of FDA-regulated products are important goals of the regulatory process because they help ensure that the benefits of innovation will be available and accepted in the marketplace without unfounded concerns about product safety and effectiveness.

- Fourth, the public health principle of prevention, implemented through FDA pre-market safety review, properly governs in cases where a product involves intended exposure to a substance that has no prior history of exposure to human beings and no widely accepted and scientifically established demonstration of safety.

- Fifth, and finally, post-market oversight of FDA-regulated products is just as essential to protecting and promoting public health as pre-market oversight.

Now let's consider how these principles apply to nanotechnology.

15. It is important to note that, in the FDC Act and in good public health policy, "safety" is not an absolute. Congress has established a range of safety standards that vary by product category. For food additives, the standard is "reasonable certainty of no harm," with the burden on the sponsor to prove the additive meets this standard. For drugs and medical devices, all of which pose some degree of risk, judgments about safety balance risks and therapeutic benefits. For cosmetics, whole foods, and food contaminants (as opposed to intentional additives)—articles that are not subject to FDA pre-market review—the "safety" standard is in fact a risk standard (e.g., "reasonable possibility of harm") that FDA must prove has been violated in order to remove a product form the market. In all these cases, FDA's job is to implement and enforce the safety standards established by Congress.

Key Elements of a Regulatory Framework for Nanotechnology Products

The final preliminary step before analyzing the adequacy of FDA's legal tools for regulating nanotechnology products is to establish a normative framework for the analysis—to explain what I mean by "adequate." I will do this by laying out the key functional elements of an effective FDA regulatory framework for nanotechnology-derived products, drawing on current law and the principles embedded in it. The elements of the framework are the things I think FDA should be able to do to achieve the three primary goals of ensuring product safety, fostering innovation and maintaining public confidence in the products of nanotechnology.

The importance of spelling out such a normative framework cannot be overstated. A clear understanding of FDA's goals and of what FDA should be able to do to achieve them is essential to analyzing the adequacy of FDA's legal tools, and it should drive any public policy debate about whether to expand or contract FDA's tool kit. Describing this framework is also a way of expressing my judgment about what FDA needs to be able to do to meet the public's expectations concerning government oversight of nanotechnology products. This is ultimately a subjective and political question, of course, to be resolved by Congress, and, like most such questions, it is prone to controversy. By being explicit about my perspective, I hope to stimulate thought and debate, as well as to frame the analysis to follow.

The framework I propose includes pre-market and post-market elements.

Pre-Market Oversight

The common justification for any government pre-market oversight of a new technology is that it is needed to (1) ensure product safety (and possibly effectiveness) in fact, and (2) maintain public confidence in the product's safety based on the assumed objectivity of the government safety review. These two justifications are closely linked.

Without a pre-market review by government or some other objective body, the determination of product safety is left, in the first instance, to the judgment of the company that developed the product and has a commercial interest in marketing it. Most companies take their safety responsibilities very seriously. However, because the interpretation of safety data and the application of safety standards are inherently judgmental affairs, the public has long insisted on pre-market review of health-sensitive products, such as food ingredients, drugs and medical devices, that involve substances having no prior history of exposure to human beings and no widely accepted and scientifically established demonstration of safety. Such a review both increases the likelihood that safety issues will be identified and addressed prior to marketing, and it helps maintain public confidence in the product's safety.

I think this justification for pre-market review applies, in general, to the FDA-regulated products of nanotechnology that are fairly considered "new for safety evaluation purposes." This does not mean that there is a "one size fits all" solution for pre-market oversight and review of nanotechnology

products, as I will discuss later in this paper. It does suggest, however, that FDA should have sufficient pre-market authority to carry out the following activities for nanotechnology products:

1. *Obtain early and adequate information on nanotechnology products in the development pipeline.* Companies that are developing new technologies and product applications always know more about them earlier in the process than FDA does. To prepare for effective and efficient oversight—including making informed determinations on such matters as whether an application is "new for safety evaluation purposes"—FDA needs access to information on products in the development pipeline under conditions that inform FDA while protecting the company's legitimate proprietary interests.

2. *Define and enforce safety standards for nanomaterials, including the nature and extent of the testing required to satisfy them.* One purpose and value of pre-market oversight is that it establishes a level and clearly drawn playing field with respect to safety and a basis for judging that all marketed products satisfy a safety standard that is known to and accepted by society. Typically, Congress expresses safety standards for FDA-regulated products in broad terms, leaving it to FDA to flesh out their operational meaning, including testing requirements.

3. *Place the initial and continuing burden to demonstrate safety on the nanotechnology product's sponsor.* This means the product sponsor must marshal evidence sufficient to demonstrate that its product is safe, in accordance with the applicable safety standard, and respond with data to any significant new safety questions. This is in lieu of the government having to prove that the product falls short of the standard or is hazardous. This element is essential if the goal is to prevent harm rather than react to and correct safety problems after they occur.

4. *Review the nanotechnology product's safety prior to marketing and impose conditions as needed to ensure safety.* A pre-market safety review by FDA provides an objective assessment of whether the product meets the applicable safety standard, thereby increasing the likelihood that the product will, in fact, be safe, and provides a strong basis for public confidence in the product's safety. The procedural nature of the review could range from pre-market notification to a full-blown approval and product licensing regime, but inherent in any credible pre-market review is FDA's ability to impose conditions on the marketing and use of the product, such as compliance with good manufacturing practices (GMPs), as needed to ensure safety.

Post-Market Oversight

As noted earlier, one of the key principles drawn from current law is that post-market oversight of FDA-regulated products is just as essential to protecting and promoting public health as pre-market oversight. No amount of pre-market testing can rule out the possibility of unanticipated safety problems occurring from the actual use of the product. Even the large-scale clinical trials used to assess drug safety and efficacy, which may involve hundreds or even thousands of subjects, are not capable of detecting every low- incidence adverse effect that could occur and be of great public health signifi-

cance when the drug is administered over long periods to millions of people. For health-protection reasons alone, FDA must have the tools to detect and promptly correct such problems.

The ability to deal effectively with safety concerns that might arise post-market is also important to achieving the public health benefits of innovation. Absent that ability, FDA would, in prudence, likely impose more stringent pre-market testing requirements and take an even more cautious approach to its pre-market evaluation, which could substantially delay access to beneficial new products.

With these concerns in mind, FDA should have authority to carry out the following post-market oversight for products of nanotechnology:

1. *Require post-market monitoring and testing of nanotechnology products as needed to ensure safety.* In light of the limitations of pre-market testing and the novelty of the issues that may be posed by certain applications of nanotechnology, FDA should have the authority to require sponsors to actively monitor post-market experience with the product or to undertake formal data collection when needed to provide an adequate assurance of safety. This is in keeping with the on-going responsibility of the sponsor to demonstrate the product's safety.

2. *Require timely adverse event reporting.* Even when special post-market monitoring or testing is not justified, adverse events may well occur after a product enters the market. FDA will never have the resources to detect all such safety-related problems, but, in the normal course of their business, product sponsors are typically the first to learn about them. Significant adverse events should be reported promptly to FDA.

3. *Inspect manufacturing establishments and examine records related to nanotechnology product safety.* The safety of a nano-enabled product may hinge on its quality, purity or other attributes that are affected by how it is manufactured, which is why marketing of most FDA-regulated products is conditioned on compliance with GMPs. To prevent, detect and investigate manufacturing-related safety problems, FDA needs full access to facilities and safety-related records.

4. *Remove from the market nanotechnology products that appear to pose a significant safety hazard or no longer meet the applicable safety standard*. When FDA has reason to believe that a safety problem poses a significant hazard to health, the agency should be able to recall the product through an expeditious administrative process pending final resolution of the safety issue. If FDA concludes upon further analysis that the product no longer meets the applicable safety standard, the sponsor's authorization to market the product would be revoked.

Overview and Analysis of FDA's Legal Tools for Regulating Nanotechnology Products

This section provides a brief overview and summary analysis of FDA's legal tools for regulating nanotechnology products. The analysis is organized around the functional elements of pre-market and post-market oversight described in the preceding section, which I believe are the key elements of a system needed to achieve the goals of protecting public health, fostering innovation and providing the basis for public confidence in nanotechnology products.

A couple of methodological points are in order. First, in this section, the focus of the analysis is on the legal tools themselves and how they contribute to performing each function. I provide my perspective, drawn from experience, concerning the practical effectiveness of FDA's program in each area, but I have not formally evaluated the performance of any program. I also do not consider the impact of scarce resources on the effectiveness of FDA's regulatory programs. I will do that in the next section.

Second, I have used a simplified, four-level rating system—none, weak, moderate, strong—to describe FDA's legal capacity to perform key regulatory functions for nanotechnology products. This will, as intended, provoke debate, and, no doubt, disagreement. My purpose is to provide a succinct basis for comparison of the relative strength of FDA's legal tools across the range of product categories and a starting point for discussion.

As a reference point for the analysis to follow, Table 1 provides an overview of FDA's safety-related legal authorities (pre-market and post-market) for nine categories of products: cosmetic ingredients, whole foods, dietary supplements, GRAS food ingredients, food additives, food packaging, medical devices, OTC drugs and "new" (generally prescription) drugs. This is by no means a complete catalog of product categories regulated by FDA—color additives, animal drugs and biologics, to name a few, are not included—but it includes products that seem most likely to be affected early on by nanotechnology. Table 1 illustrates the diversity of approaches adopted by Congress for regulating these categories of products, ranging from the largely post-market approach for

Nano-Labels: The Tower of Babel

Ingredient or packaging labels found on a selection of cosmetic, personal care and dietary supplement products:

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

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

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

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

TABLE 1. FDA'S SAFETY-RELATED LEGAL AUTHORITIES

	Cosmetic Ingredient[i]	Whole Food	Dietary Supplement	GRAS Food Ingredient	Food Additive	Food Packaging	Medical Device	OTC Drug	New Drug[ii]
Pre-Market Tools									
Establishment Registration	Voluntary	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Product Registration	Voluntary	No	No	No	No	No	Yes	Yes	Yes
Safety Substantiation without Pre-Market Notification[iii]	Optional[iv]	No	No	No[v]	No	No	No	No	No
Pre-Market Notification	No	No[vi]	Limited[vii]	No	No	Yes[viii]	Yes[ix]	No	No
Pre-Market Safety Reviewand Approval By Regulation	No	No	No	No	Yes	Yes[x]	No	Yes[xi]	No
Pre-Market Safety Review and Approval By Product License	No	No	No	No	No	No	Yes[xii]	No	Yes
Mandatory Good Manufacturing Practices (GMPs)	No	No[xiii]	Yes[xiv]	No	No	No	Yes	Yes	Yes
Post-Market Tools									
FDA Judicial Remedies to Remove Risky Products[xv]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Continuing Sponsor Burden to Demonstrate Safety	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Post-Market Monitoring and Testing	No	No	No	No	Limited[xvi]	Limited[xvii]	Yes[xviii]	No	Limited[xix]
Mandatory Adverse Event Reporting	No	No	No	No	No	No	Yes	No	Yes[xx]
Establishment Inspection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Access to Safety Records	No	Limited[xxi]	Limited[xxii]	Limited[xxiii]	Limited[xxiv]	Limited[xxv]	Yes[xxvi]	Yes	Yes
Voluntary Recall	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mandatory Recall	No	No	No	No	No	No	Yes[xxvii]	No	No

TABLE 2. CAPACITY OF FDA'S LEGAL AUTHORITY TO ACHIEVE THE PRIMARY GOALS OF REGULATORY OVERSIGHT FOR NANOTECHNOLOGY PRODUCTS

	Cosmetic Ingredient	Whole Food	Dietary Supplement	GRAS Food Ingredient	Food Additive	Food Packaging	Medical Device	OTC Drug	New Drug
Pre-Market									
Obtain Early Information on Pipeline	None	None	None	Weak	Weak	Weak	Mod-erate	Weak	Mod-erate
Enforce Safety and Testing Requirements	Weak	None	Weak	Moderate	Strong	Strong	Strong	Strong	Strong
Place Burden To Prove Safety on Sponsor	Weak	None	Weak	Moderate	Strong	Strong	Strong	Strong	Strong
Review Safety Prior to Marketing	None	None	Weak	Weak	Strong	Strong	Strong	Mod-erate	Strong
Post-Market									
Require Needed Monitoring and Testing	Weak	None	None	None	Weak	None	Strong	Weak	Mod-erate
Require Timely Adverse Event Reporting	None	None	None	None	Weak	None	Strong	None	Strong
Inspect Facilities and Safety Records	Weak	Mod-erate	Moderate	Moderate	Mod-erate	Moderate	Strong	Strong	Strong
Remove Unsafe Products from Market	Moderate	Mod-erate	Moderate	Strong	Mod-erate	Strong	Strong	Strong	Strong

cosmetics and whole foods to the more intensive combination of pre-market and post-market approaches for medical devices and drugs.

The following analysis briefly describes FDA's approach for each category and the basis for my judgment about the relative strength of FDA's legal capacity to perform the key oversight functions. These judgments are summarized in Table 2.

Cosmetic Ingredients and Products

Overview

Cosmetics are of particular interest for this analysis. As reported in the Project on Emerging Nanotechnologies nanotechnology consumer products inventory,[16] cosmetic products claiming use of nanomaterials are among the most prominent early entries into the U.S. consumer marketplace. Additionally,

16. See http://www.nanotechproject.org/consumerproducts, accessed September 27, 2006. Unless otherwise noted, subsequent examples of nanotechnology products are drawn from this website, which is maintained by the Project on Emerging Nanotechnologies and contains an inventory of manufacturer self-identified consumer products that make express or implied claims for the incorporation of engineered nanomaterials or other applications of nanotechnology.

preliminary data from Japan indicate an additional 87 cosmetics are on the market in that country alone, some of which are sure to end up in global commerce and be subject to the U.S. regulatory system.[17] On the other hand, as was analyzed in J. Clarence Davies January 2006 report *Managing the Effects of Nanotechnology*, FDA's legal tools for regulating cosmetics are among the most limited.

Nanotechnology Cosmetics in the Marketplace

As of October 2006, a search of the Project on Emerging Nanotechnologies nanotechnology consumer product inventory returned 58 specific and general nanotechnology cosmetic products from nine countries, along with 40 products categorized as personal-care products. Many of these cosmetics are designed to be applied to the hair, mouth, eyes, hands and body and are available in cream, spray, liquid and powder forms.

The ensuing analysis of FDA's approach to nanotechnology cosmetics is complicated, however, by FDA's creative use of its legal tools and a longstanding industry self-regulatory program for cosmetic ingredient safety. With the exception of color ingredients, the FDC Act gives FDA no explicit authority for pre-market oversight of cosmetic ingredients or cosmetic products.[18] FDA has only the standard post-market authorities, including the right to inspect manufacturing facilities and seek court action against unsafe or otherwise unlawful products, and can take court enforcement action if a product's labeling is false, misleading or otherwise misbranded. This level of oversight and grant of legal authority occurred in the1938 FDC Act and was based on the assumption that cosmetics (defined to include only products that cleanse, beautify, promote attractiveness or alter appearance) are products that are primarily applied externally, do not affect the "structure or function" of the body in a drug-like way and thus are not likely to pose significant safety concerns.

In the 1970s, as the array of cosmetic ingredients expanded, the potential for dermal absorption, allergic responses and other possible hazards was recognized. FDA made creative use of the aforementioned misbranding authority to establish a "backdoor" safety substantiation requirement for cosmetics. FDA issued a regulation declaring that ingredients and products that had not been "adequately substantiated for safety prior to marketing" would be deemed misbranded unless they bear this warning statement: "Warning – The safety of this product has not been determined."[19] Few if any marketed cosmetic products bear such a warning, implying that their safety has been substantiated based on appropriate testing or other relevant data. FDA does not, however, have authority to access or review the company's substantiation data or other safety-related records.

To support industry compliance with the substantiation requirement, the Cosmetic, Toiletry, and Fragrance Association (CTFA), which is the principal cosmetic industry trade association, established the Cosmetic Ingredient Review (CIR) in collaboration with FDA and the Consumer Federation of America.[20] Funded by CTFA but independently operated, the CIR conducts and publishes scientific reviews on the safety of cosmetic ingredients. The CIR reported in

17. See http://staff.aist.go.jp/kishimoto-atsuo/nano/index.htm, accessed September 27, 2006.
18. See 21 USC 361 et seq.
19. See 21 CFR 740.10.
20. See the CIR website at http://www.cir-safety.org/, accessed September 27, 2006.

August 2006 that 1,300 ingredients have been assessed to date, which it says covers two-thirds of the ingredients most commonly used in cosmetics today. Ingredients passing CIR review are deemed by FDA and the industry to satisfy FDA's safety substantiation requirement.

The CIR is generally regarded as a successful program, as far as it goes, and, as a category, cosmetics are not a major public health concern. The program is voluntary, however, and ingredients that have not gone through the process are beyond FDA's oversight unless and until they are suspected of causing harm. To date, no engineered nanomaterials have gone through the process, but presumably, they will be subject to it at some point in the future.

Another program that addresses safety concerns associated with cosmetics is the Voluntary Cosmetic Registration Program (VCRP). As noted on its website, VCRP is an FDA post-market reporting system for use by manufacturers, packers and distributors of cosmetic products that are in commercial distribution in the United States. It involves registering cosmetic-manufacturing establishments and ingredients using the Cosmetic Product Ingredient Statements (CPIS).[21] In January 2007, CTFA will launch a Consumer Commitment Code, under which companies pledge to make their safety dossiers on cosmetic ingredients available to FDA upon the agency's request.[22]

With this as background, I provide below my judgments about the relative strength of FDA's legal tools for regulating nanotechnology cosmetic products.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **None.** Because there is no requirement for FDA pre-market review and no other incentive or requirement for companies to disclose their research or product development activity, FDA has no legal basis for obtaining this information from them.[23] This is an important issue in the nanotechnology cosmetic arena because of genuine uncertainty about the actual composition and properties of ingredients that are claimed on cosmetic product labels to be produced through or otherwise incorporate the benefits of nanotechnology.

- *Capacity to Enforce Safety and Testing Requirements* – **Weak.** The cosmetic industry deserves credit for the CIR, which is in part a response to FDA's substantiation "requirement." As a matter of FDA's legal authority, however, this functional element is rated weak because the safety substantiation is legally optional, the CIR is voluntary and administered beyond FDA's legal control and cosmetic products bearing nanotechnology claims are on the market without FDA review or knowledge about their actual composition or safety-related properties.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Weak.** FDA's authorities are

21. See http://www.cfsan.fda.gov/~dms/cos-regn.html, accessed September 27, 2006.
22. "CTFA Launches Package of Consumer-Oriented Industry Initiatives at 2006 Annual Meeting." Washington, DC: Cosmetic, Toiletry, and Fragrance Association, March 2, 2006. Available at http://www.ctfa.org/, accessed September 27, 2006.
23. FDA is free to conduct its own research to discover this information, but its capacity to do so is heavily affected by resource constraints, as discussed more fully below.

deemed weak on this element for the same reasons as above, as well as the fact that a product cannot be removed from the market unless FDA can prove that it is potentially injurious or that its safety has not been adequately substantiated.

- *Capacity to Review Safety Prior to Marketing* – **None.** FDA has no authority to obtain and review cosmetic ingredient or product safety data prior to market entry.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **Weak.** FDA has no explicit authority to require post-market monitoring or testing for safety or any other purpose. FDA's safety substantiation regulation contemplates that when a safety question arises post-marketing the company will conduct adequate studies to resolve the question, but FDA's legal capacity in this regard is weak for the same reasons that its capacity to enforce safety and testing requirements pre-market is weak.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no legal authority for this purpose.

- *Capacity to Inspect Facilities and Safety Records* – **Weak.** FDA can inspect facilities, but it has no access to records, other than as provided voluntarily by companies.

- *Capacity to Remove Unsafe Products from the Market* – **Moderate.** FDA has the standard judicial enforcement tools to take a cosmetic product off the market if it can prove it contains a substance that "may render it injurious to users." FDA has no mandatory recall authority for cosmetics, but, because of FDA's power to warn consumers and make other use of publicity when it has concern, the agency typically has good success in obtaining the voluntary recall of products when it brings a safety concern to the attention of a company.

Whole Foods

Overview

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 included in this analysis not because the regulatory regime for whole foods is likely to play a role in the oversight of engineered nanomaterials and products, but rather as the starting point for understanding the complicated range of approaches Congress and FDA have taken to the regulation of substances in or affecting 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.[24] In the former case, such as the naturally occurring toxin solanine in potatoes, the food can be removed from the market only if 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 FDA can prove that the substance is present at a level that "may render" the food "injurious to health." This reflects the congressional

24. See 21 USC 342(a).

judgment that human interventions are subject to a higher safety standard than nature, as will be illustrated further in the discussion below of GRAS food ingredients, food additives and food packaging.

The one arguable exception to the lack of pre-market oversight for whole foods is FDA's policy for regulating genetically modified whole foods derived from plants, which is discussed below under "GRAS Food Ingredients" and not included in the analysis that follows.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **None.** There is, of course, no "pipeline" for most whole foods and all unintentional contaminants and no legal tool for obtaining "early warning" information.

- *Capacity to Enforce Safety and Testing Requirements* – **None.** FDA has no pre-market legal authority over whole foods.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **None.** FDA has no pre-market legal authority over whole foods.

- *Capacity to Review Safety Prior to Marketing* – **None.** FDA has no pre-market legal authority over whole foods.

Post-Market Goals

- *Capacity to Require Needed Monitoring and Testing* – **None.** FDA has no authority to impose monitoring or testing requirements on parties marketing whole foods or otherwise bearing responsibility for the presence of unintended contaminants in foods.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no authority to require adverse event reporting, although FDA's Center for Food Safety and Applied Nutrition (CFSAN) operates a voluntary Adverse Event Reporting System (CAERS).

- *Capacity to Inspect Facilities and Safety Records* – **Moderate.** FDA can inspect facilities where whole foods are processed and stored, collect samples for testing and access safety-related records if it has a "reasonable belief" that the food "presents a threat of adverse health consequences or death."[25]

- *Capacity to Remove Unsafe Products from the Market* – **Moderate.** FDA has the standard judicial enforcement tools that work effectively when FDA can prove that the applicable safety standard has been violated. The recall system, though voluntary, normally works well to remove products from the market when FDA can demonstrate an immediate safety concern.

Dietary Supplements

Overview

The nanotechnology consumer product inventory cites numerous examples of dietary supplement products that claim the use of nanomaterials or otherwise refer to nanotechnology in their product claims. It is impossible to know what these claims actually mean, but the suggestion often is that the nanosize of particular materials enhances their absorbability or other functional properties.

Prior to 1994, the safety of dietary supplement ingredients was subject to

25. In the case of seafood and juice products, FDA has issued regulations requiring processors to implement HACCP (Hazard Analysis and Critical Control Points) systems. Based on those regulations, FDA has access to certain records related to the design and operation of such systems. See 21 CFR Parts 120 and 123.

regulation by FDA on the same basis as any intentionally added food substance, which meant that FDA could require pre-market approval as a food additive if the supplement ingredient were not generally recognized as safe (or GRAS). Under the Dietary Supplement Health and Education Act (DSHEA), Congress excluded supplement ingredients from the definition of food additive, shifting to 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.[26] 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."

Nanotechnology Dietary Supplements

As of October 2006, a search of the Project on Emerging Nanotechnologies consumer product inventory returned 16 dietary supplements that claim the use of nanoscale calcium, magnesium and silver to increase the bioavailability of supplements in the body.

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."

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **None.** FDA has no legal tool for accessing information on new technologies and products under development in the supplement industry, and, because most new supplement products are formulated using ingredients that were used in supplements prior to DSHEA, few companies have any need or incentive to bring such information to FDA.

- *Capacity to Enforce Safety and Testing Requirements* – **Weak.** FDA's authority in this regard applies only to new dietary ingredients and, even for these, does not empower FDA to establish testing requirements or a true safety standard.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Weak.** Likewise, the only pre-market safety burden applies to new ingredients, and the requirement is not to demonstrate safety but only to provide the information on the basis of which the manufacturer concludes that the product "will reasonably be expected to be safe."

- *Capacity to Review Safety Prior to Marketing* – **Weak.** FDA's receipt of pre-market notifications provides FDA some information but it does not provide the basis for a full FDA safety review, and FDA is not empowered to block marketing on the basis that it considers the notification inadequate.[27]

Post-Market Goals

- *Capacity to Require Needed Monitoring and Testing* – **None.** FDA has no authority to

26. See 21 USC 321(ff), 342 (f) and 350b.
27. See 21 CFR Part 190.

require post-marketing monitoring and testing of dietary supplement ingredients or products.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no authority for this purpose, though CFSAN's voluntary reporting system, CAERS, applies to supplements.

- *Capacity to Inspect Facilities and Safety Records* – **Moderate.** FDA can inspect facilities where supplements are processed and stored, collect samples for testing and access safety-related records if it has a "reasonable belief" that the food "presents a threat of adverse health consequences or death." DSHEA gave FDA authority to establish GMP requirements for supplements, which presumably would include some record-keeping and access requirements, but the required regulations have not been issued.

- *Capacity to Remove Unsafe Products from the Market* – **Moderate.** FDA's legal capacity here is similar to that for whole foods, which means FDA can go to court to remove a supplement product from the market if it can prove a significant or unreasonable risk of illness or injury. For new dietary ingredients, FDA can go to court if it can prove there is inadequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk.[28] The voluntary recall system is also available.

GRAS Food Ingredients

Overview

The Project on Emerging Nanotechnologies consumer products inventory lists products "powered by nanotechnology" or "utilizing the incredible new nanotechnology" to improve the properties of frying oil and the flavor of cocoa, and a September 2006 report by Jennifer Kuzma and Peter VerHage, *Nanotechnology in Agriculture and Food Production: Anticipated Applications*, offers further documentation that nanotechnology is on its way to the food supply. Similarly, the Helmut Kaiser Consultancy estimates that the nanotechnology food market is growing rapidly and will reach over $20 billion by 2010—about three times its current size.[29] A recent study by Cientifica found over 150 nanotechnology applications currently in the food industry, with some of the world's biggest companies—such as Altria, Nestle, Kraft, Heinz and Unilever—involved in nanotechnology research and development.[30] These findings make the system for regulating

Nanotechnology and Food

An online database categorizing the anticipated applications of nanotechnology in agriculture and food production found 160 projects that cover a wide range of research areas, topics and techniques, including bioprocessing for food, pathogen and contamination detection and smart treatment and delivery systems. The database is availaible at http://www.nanotechnology.org/inventories.

28. See 21 USC 342(f).
29. "Study: Nanotechnology in Food and Food Processing Worldwide 2003-2006-2010-2015." Tübingen, Germany: Helmut Kaiser Consultancy, 2006. Available at http://www.hkc22.com/nanofood.html, accessed September 27, 2006.
30. *Nanotechnologies in the Food Industry.* London, UK: Cientifica, August 2006. Available at http://www.cientifica.com/www/details.php?id=47, accessed September 27, 2006; Sean Roach. "Most Companies Will Have to Wait Years for Nanotech's Benefits." *FoodProductionDaily.com*, August 21, 2006. Available at http://www.foodnavigator-usa.com/news/ng.asp?n=69974-nanotechnology-packaging-nano-applications, accessed September 27, 2006.

substances used in food processing and packaging, including GRAS substances, food additives and food packaging, important to our analysis of FDA's nanotechnology regulatory tools.

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 FDA of its marketing plans or seek any FDA review. If a company markets based on its "independent" GRAS determination, however, 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, FDA, shortly after enactment of the food additive law, issued extensive lists of substances it considers GRAS,[31] 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 FDA has affirmed as GRAS.[32] 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 FDA, companies frequently commission panels of scientists to review the available evidence and render a judgment about GRAS status.

This system generally works very well to assure the safety of substances intentionally added to food. One of its great strengths from a public health and public confidence perspective is that it places the burden to prove safety on the sponsor rather than FDA. Thus, when challenging an independent GRAS determination, FDA need not prove harm but only that safety is not generally recognized; the approval of a food additive can be revoked based solely on an FDA showing that there is an unresolved safety question.

The 1958 food additive amendments to the FDC Act were also intended to foster innovation in food technology by providing a basis for public confidence in the safety of marketed additives. The innovation goal is also evident in the balance struck by inclusion of the GRAS concept. However, the GRAS concept raises an issue, at least from a public confidence perspective, because of its reliance on the judgment of the sponsor as to whether or not a new substance—or a new form or use of a substance—requires FDA approval. Even when 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 FDA's regulations are typically written without regard to material size, leaving open the question of whether a nanoscale version would be

31. See 21 CFR Part 182.
32. See 21 CFR Parts 184 and 186.

covered. In addition, it is almost certainly the case that the safety evaluation underlying the regulation would not have considered the effects at the nanoscale.

In the late 1980s, agricultural biotechnology presented FDA an analogous challenge grounded in the food additive-GRAS regime's inherent flexibility. In 1992, 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.[33] It also included a voluntary pre-market notification procedure under which developers of such foods could submit information to FDA supporting their judgment that no such change had occurred and thus that the novel food was "substantially equivalent" to its traditional counterpart.

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 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 FDA with information about genetically modified (GM) foods entering the marketplace, none of which has experienced known safety problems. The system does not, however, include a full FDA safety review or conclusion about the safety of new products, which has been a factor in the lack of confidence among some U.S. consumers and many in Europe about the safety of GM foods.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Weak.** FDA has no legal tool for accessing information on new technologies and products under development in the food industry. FDA's gatekeeper role under the food additive-GRAS regime gives companies some incentive to provide information during their development process, but the flexibility of the GRAS concept reduces the incentive, and FDA typically gets detailed information about new technologies only when companies are ready or close to ready to market them or submit them for approval.

- *Capacity to Enforce Safety and Testing Requirements* – **Moderate.** Even with the flexibility in the GRAS concept, the laws, and FDA's enforcement leverage, if FDA disagrees with an independent GRAS determination, it has reasonably good capacity to set and enforce safety and testing standards. Over the years, FDA has provided considerable guidance on the testing required to show the safety of GRAS substances and food additives.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Moderate.** As the GRAS concept is written and implemented, sponsors have the ultimate burden to prove safety, which most take very seriously despite their legal flexibility to make an independent GRAS judgment.

- *Capacity to Review Safety Prior to Marketing* – **Weak.** By definition, GRAS substances are not required to go through an FDA pre-market review, though in some cases sponsors have sought GRAS affirmation from FDA prior to marketing.

33. See 57 Fed. Reg. 22984, May 29, 1992.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **None.** FDA has no authority to require post-market monitoring and testing of GRAS food ingredients.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no authority for this purpose, though CFSAN's voluntary reporting system, CAERS, applies to GRAS ingredients.

- *Capacity to Inspect Facilities and Safety Records* – **Moderate.** FDA can inspect facilities where GRAS ingredients are processed and stored, collect samples for testing and access safety-related records if it has a "reasonable belief" that the substance "presents a threat of adverse health consequences or death."

- *Capacity to Remove Unsafe Products from the Market* – **Strong.** FDA's capacity in this regard is strong because, in addition to having all the standard enforcement tools, it need only prove that a safety question exists or that safety is not "generally recognized."

Food Additives

Overview

As outlined above, 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.[34] In this process, the burden of proof is on the sponsor to prove safety, 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 is a strong and effective system for ensuring additives are safe and for providing the basis for public confidence in safety. Some argue, however, that it is a deterrent to 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 FDC Act, such as color additives,[35] animal drug residues[36] and pesticide residues.[37] 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 FDA. The Environmental Protection Agency evaluates the safety of pesticide residues in food and sets tolerances (or legal limits) on the amount that may be present; FDA enforces the pesticide tolerances.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Weak.** FDA has no legal tool for accessing information on new technologies and products under development in the food industry, but FDA's gatekeeper role for food additives provides companies with some incentive to provide information during their development process, especially when novel technologies are involved.

- *Capacity to Enforce Safety and Testing Requirements* – **Strong.** By virtue of its premarket approval authority, FDA has clear

34. See 21 USC 348.
35. See 21 USC 379e.
36. See 21 USC 360b.
37. See 21 USC 346a.

legal capacity to interpret and apply the statutory safety standard, including establishing the testing requirements that give the safety standard its functional meaning.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Strong.** As a matter of law, the burden to prove safety is on the sponsor, and a food additive cannot be marketed until FDA concludes that the sponsor has met that burden.

- *Capacity to Review Safety Prior to Marketing* – **Strong.** This is a central attribute of the premarket approval system for food additives.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **Weak.** FDA has no authority to require post-marketing monitoring and testing of food additives, but on a few occasions FDA has elicited agreements from sponsors to conduct post-market monitoring as a condition of approval. The enforceability of these agreements is questionable.

- *Capacity to Require Timely Adverse Event Reporting* – **Weak.** FDA has no authority for this purpose, though the occasional post-market monitoring noted above has included adverse event reporting, and CFSAN's voluntary reporting system, CAERS, applies to food additives.

- *Capacity to Inspect Facilities and Safety Records* – **Moderate.** FDA can inspect facilities where food additives are processed and stored, collect samples for testing, and access safety-related records if it has a "reasonable belief" that the substance "presents a threat of adverse health consequences or death."

- *Capacity to Remove Unsafe Products from the Market* – **Moderate.** The strong point of FDA's legal capacity in this regard is that it can revoke a food additive approval regulation based solely on a showing that new evidence raises an unresolved safety question. The weak point is that the administrative process involves formal, trial-like proceedings that are resource intensive and time- consuming.

Food Packaging

Overview

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 what FDA calls "indirect" food additives, in such categories as adhesives, polymers, adjuvants, production aids and sanitizers, can be safely and lawfully used.[38] This system has all the strengths of the food additive system as applied to direct

38. See 21 CFR Parts 172–178.

additives, but with typically a much lower possibility for human exposure to chemicals and a lower level of possible safety concern.

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 FDA and the industry in the typical case of low migration and low toxicological concern.[39] Under this approach, the sponsor submits a food contact notification (FCN) containing information prescribed by FDA; 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 FDA does not object, The FCN is deemed "effective" and the material can be marketed unless FDA later determines that the material is no longer safe, in which case 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.

Given the relatively small potential for food safety problems associated with food contact materials, the old food additive regulation system and the new FCN system both provide a high degree of assurance that these materials are safe. Under the old food additive regulation system, however, engineered nanomaterials will raise the same issue presented by GRAS substances and food additives: namely, whether the nanosize form of a previously approved material is covered by the existing regulation. This issue would not arise to the extent manufacturers use the FCN process because each company must submit its own FCN on the specific material it intends to market.

Independent determinations of GRAS status remain an option for developers of new packaging or food contact materials, though the availability of the FCN route reduces the attractiveness of the GRAS option. If pursued, it raises the same issues as GRAS determinations for any other substance. The following analysis applies to food packaging and contact materials for which GRAS claims are not made.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Weak.** FDA has no legal tool for accessing information on new technologies and products under development by the food packaging industry, but FDA's gatekeeper role under the food additive and FCN provisions of law provide companies with some incentive to provide information during their development process, especially when novel technologies are involved.

- *Capacity to Enforce Safety and Testing Requirements* – **Strong.** Whether under the regulation or FCN route, FDA's strong pre-market requirements give it clear legal capacity to enforce the safety standard and set testing and other data requirements.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Strong.** As a matter of law, the burden to prove safety rests clearly on the sponsor.

- *Capacity to Review Safety Prior to Marketing* – **Strong.** This is the purpose and clear consequence of the legal framework for food packaging and food contact materials.

39. See 21 USC 348(h) and 21 CFR 170.100 et seq.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **None.** FDA has no authority to require post-market monitoring and testing, and the voluntary agreement approach that has worked for some direct additives is not likely of practical relevance to packaging and food contact materials.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no authority for this purpose, though CFSAN's voluntary reporting system, CAERS, applies to food packaging and contact materials.

- *Capacity to Inspect Facilities and Safety Records* – **Moderate.** FDA can inspect facilities where food additives are processed and stored, collect samples for testing and access safety-related records if it has a "reasonable belief" that the substance "presents a threat of adverse health consequences or death."

- *Capacity to Remove Unsafe Products from the Market* – **Strong.** As in the case of direct food additives, FDA can revoke a food additive approval regulation for food contact materials or deem a FCN no longer effective without proving harm, only that new evidence raises an unresolved safety question. Under the FCN route, FDA has the further advantage of a simple process for deeming an FCN no longer effective, avoiding the cumbersome process required to revoke a food additive approval regulation.

Medical Devices

Overview

Medical devices have particular potential to benefit from advances in nanotechnology as stronger and more highly functional materials become available for a range of implantable devices, prostheses and diagnostics. As health significance and therapeutic benefit increase, however, so too does the need for vigilance to assure safety, which for devices involves balancing the risks and benefits of the device for the patient.

Nanotechnology Medical Devices

Using information provided by the NanoBiotech News *2006 Nanomedicine, Device & Diagnostics Report,* the Project on Emerging Nanotechnologies was also able to estimate commercialization time frames for two sets of nanotechnology medical applications: cancer-relevant drugs, diagnostic tests and devices; and general drug delivery devices. In terms of drug delivery devices, the Project found 56 products in the pipeline, many of which are in early-stage development or preclinical testing.

The Medical Device Amendments of 1976 establish a comprehensive regulatory scheme that actively addresses the goals of protecting public health, fostering innovation and providing the basis for public confidence. The device amendments provide FDA with a more complete arsenal of regulatory tools than it has for any other regulatory category (see Table 1), including the capacity to tailor the intensiveness of pre-market oversight to the nature of the product, the degree of risk it poses and the nature of oversight FDA thinks the product needs to assure safety and effectiveness.

This system is too complicated to describe in detail here. In a nutshell, however, it requires that any company seeking to market a device product for the first time submit that product for review to FDA unless FDA has exempted that particular type of product from this requirement based on a determination that pre-market review is not needed to

assure safety and effectiveness. In general, only the best-understood and lowest-risk devices are so exempted, and even for these, the manufacturer must register with FDA and list its products with the agency.

For all other device products, the sponsor must submit either a pre-market notification or a full pre-market approval application, which, in either case, requires the sponsor to provide FDA the information it needs to identify issues of safety and effectiveness and, if needed, conduct a full-blown pre-market review of the product's safety and effectiveness for its intended use. FDA approval of new devices, such as ones performing new functions or incorporating new materials or other new technology, typically requires clinical testing, which must also be reviewed in advance by FDA. Under this comprehensive set of pre-market authorities, the incorporation of new nanomaterials to alter the functional properties of medical devices will be subject to careful pre-market review by FDA.

FDA also has extensive post-market regulatory tools, including the traditional inspection and enforcement tools available across the board at FDA, as well as additional authorities, such as the authority to mandate recalls in some cases, require adverse event reporting and post-market surveillance, mandate GMPs and have extensive records access.

Many challenging issues have surrounded FDA's implementation of the device amendments, many of which result from the large number of often small companies and the incredibly rapid pace of innovation. Using its abundant tools in a way that achieves the dual goals of protecting public health and fostering innovation is not easy and may well prove to be a challenge in the case of nanotechnology, but FDA does not lack legal tools.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Moderate.** Though FDA has no explicit authority to access company information on technologies and products under development, its oversight of clinical investigations and strong gatekeeper role provide companies a strong incentive to provide FDA with information on novel technologies well ahead of commercialization.

- *Capacity to Enforce Safety and Testing Requirements* – **Strong.** FDA's strong and flexible pre-market oversight tools provide ample authority and practical leverage to interpret and enforce the risk-benefit safety standard.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Strong.** The burden to prove safety rests as a general matter on the sponsor, unless FDA has made its own judgment on the safety and effectiveness of a particular type of device and exempted it from the pre-market submission requirements.

- *Capacity to Review Safety Prior to Marketing* – **Strong.** FDA has full but flexible authority to conduct pre-market safety reviews as needed.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **Strong.** FDA has explicit authority to require post-market surveillance for devices whose failure would be reasonably likely to have serious health consequences.[40]

- *Capacity to Require Timely Adverse Event Reporting* – **Strong.** FDA has explicit and

40. See 21 USC 360l and 21 CFR Part 822.

broad authority to require adverse event reporting for devices.[41]

- *Capacity to Inspect Facilities and Safety Records* – **Strong.** FDA has broad authority to inspect device manufacturers, including for compliance with mandatory GMPs, and to require the provision of agency access to records related to assuring the safety and effectiveness of devices.

- *Capacity to Remove Unsafe Products from the Market* – **Strong.** FDA can effectively withdraw a company's marketing authorization, whether granted under the pre-market notification or full pre-market approval route, based on new information raising a significant safety question,[42] and it has a broad range of other post-market remedies, including mandatory recall authority, to deal with emergent safety problems.

OTC Drugs

Overview

In general, FDA regulates human pharmaceutical products under a comprehensive set of pre-market and post-market controls. The FDC Act defines the term "drug" broadly to include products that diagnose, treat and prevent disease, as well as those that affect the structure or function of the body for other purposes (not including food purposes). Any "new drug" must be approved on an individual product basis prior to marketing. In a manner similar to the food additive provisions of the FDC Act, however, products are excluded from the definition of "new drug" if they are "generally recognized as safe and effective" (GRAS/GRAE) for their intended use.[43]

Nanotechnology in Sunscreens

As of October 2006, a search of the Project on Emerging Nanotechnologies Consumer Product Inventory contained 18 specific and generic nanotechnology sunscreens from the United States, United Kingdom and Australia.

To implement the GRAS/GRAE element of the FDC Act and address the regulatory status of OTC drugs, FDA initiated in 1972 a monograph system under which FDA reviews the safety and effectiveness of active ingredients and issues regulations listing—by category of intended OTC uses—the ingredients that can lawfully be incorporated in drug products based on FDA's conclusion that they are generally recognized as safe and effective for their intended uses.[44] Most OTC drugs are regulated under this system. Products formulated using these "monographed" active ingredients and "safe and suitable" inactive ingredients, and labeled in accordance with the monograph, are not considered "new drugs" and thus are not subject to the requirement for a new drug application and the issuance of a product-specific approval as a prerequisite for marketing. On the other hand, as a general rule, FDA considers any drug *not* covered by a monograph to be a "new drug."

41. See 21 USC 360i and 21 CFR Part 803.
42. FDA does not have explicit statutory authority to administratively revoke marketing authorizations granted under the pre-market notification procedure, but it has on occasion issued revocation letters and has ample other post-market authorities to remove such products from the market, including publicity, if it believes there is a safety concern.
43. See 21 USC 321(g) and (p) and 21USC 355.
44. See 21 CFR Part 330 et seq.

In addition to these basic provisions defining the terms of market access for drugs, the FDC Act gives FDA a range of other pre-market and post-market authorities (see Table 1), including company registration and product listing, oversight of clinical trials, mandatory GMPs, adverse event reporting for "new drugs" and access to company records related to product safety. The drug provisions of the FDC Act lack some of the post-market authorities Congress has provided for medical devices, such as comprehensive authority to require post-market surveillance, but, in general, the legal tool kit for drug regulation is strong.

The GRAS/GRAE concept, as implemented through the OTC monograph program, gives rise, however, to at least one issue that will be important to how engineered nanomaterials are regulated. Like FDA's GRAS affirmation regulations for food substances, the OTC monographs typically list active ingredients by name and may include purity and other specifications (often incorporating by reference standards adopted by the U.S. Pharmacopeia), but ordinarily without reference to material size. Thus, it becomes a matter of interpretation whether a nanoscale version of a listed ingredient is properly considered within the monograph and thus lawful to market.

This issue has already arisen in a petition by the International Center for Technology Assessment (ICTA) filed with FDA regarding the sunscreen monograph, which lists titanium dioxide as an active ingredient.[45] When reduced to very small size, titanium dioxide continues to provide protection from ultraviolet light but it does not scatter light and thus becomes clear on the skin (rather than white), which is cosmetically advantageous. While companies are using "micronized" materials of titanium dioxide, which FDA has said fall within the monograph, they are also releasing products that are making "nano" claims. "Micronization" refers to a process of grinding materials down rather than a particle-size classification, and may or may not lead to the production of nanosize particles. Since FDA has not precisely defined the term "micronize," it is not clear exactly what size materials are being used in the marketplace or whether they pose safety questions different from those addressed in establishing the monograph.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Weak.** FDA has no legal tool for accessing information on new technologies and products under development by the OTC drug industry, but the need to comply with the OTC monograph system gives companies some incentive to provide information during the development process, especially when novel technologies are involved.

- *Capacity to Enforce Safety and Testing Requirements* – **Strong**. The OTC monograph system, backed up by the FDC Act's new drug authority, provides FDA ample authority to set and enforce safety standards and testing requirements.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Strong.** If FDA believes there is an unresolved safety question about an approved OTC ingredient, it can propose to amend the monograph on that basis, effectively shifting the burden to prove safety to the product sponsor(s) either through the OTC rule-making process or new drug approval process.

45. See 21 CFR Part 352.

- *Capacity to Review Safety Prior to Marketing* – **Moderate.** Individual OTC product formulations that are within a monograph are not required to be submitted for review by FDA, but "monographed" active ingredients have all been reviewed for safety and effectiveness by FDA through the monograph process.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **Weak.** FDA has no explicit legal authority to require post-market monitoring and testing of monographed OTC drug products, though, in the event of a safety question, it can use the possibility of removing an ingredient from the monograph as a tool for eliciting information from manufacturers.

- *Capacity to Require Timely Adverse Event Reporting* – **None.** FDA has no explicit legal authority to require adverse event reporting by manufacturers of monographed OTC drug products and does not do so.

- *Capacity to Inspect Facilities and Safety Records* – **Strong.** FDA can inspect manufacturing facilities, including for compliance with mandatory GMPs, and can access records related to product safety.

- *Capacity to Remove Unsafe Products from the Market* – **Strong.** FDA can, through rulemaking, remove an active ingredient from the monograph based solely on a showing that available data no longer demonstrate safety.

New Drugs

Overview

New drugs (both pioneer or brand name and generic) require approval by FDA through the new drug application (NDA) process, or abbreviated NDA (ANDA) for generics. This process results in a company- and product-specific approval to market the product in accordance with conditions and under a detailed label approved by FDA. FDA is empowered to oversee human-safety and efficacy testing of new drugs and to require prior to marketing the submission of extensive information on all aspects of a drug's composition, safety and effectiveness. FDA thus has ample legal authority to address any safety question that might arise pre-market with respect to the application of nanotechnology.

FDA also has considerable post-market authority, as outlined in Table 1 and below, though its lack of broad authority to require post-market surveillance and testing has been cited recently by the Government Accountability Office (GAO) as a gap in FDA's authority that affects oversight of drug product safety.[46]

Nanotechnology in Pharmaceuticals

In its submitted comments to FDA, the Project on Emerging Nanotechnologies has identified at least nine currently available nanotechnology drug and drug delivery products that have already been approved for use by FDA. Many of these drugs are designed to more effectively target and treat a range of diseases, from high cholesterol to breast cancer, and cause fewer side effects.

46. *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process.* Washington, DC: United States Government Accountability Office, GAO-06-402, March 2006. Available at http://www.gao.gov/new.items/d06402.pdf, accessed September 27, 2006.

Pre-Market Functions

- *Capacity to Obtain Early Information on Products in the Pipeline* – **Moderate.** Despite the lack of a specific legal tool for accessing information on new technologies and products under development by the drug industry, companies facing the NDA process have a significant incentive to provide FDA with the information the agency needs to understand and efficiently review new products especially when novel technologies are involved.

- *Capacity to Enforce Safety and Testing Requirements* – **Strong.** The NDA process gives FDA complete authority in this regard.

- *Capacity to Place Burden to Prove Safety on Sponsor* – **Strong.** The NDA process places the burden of proof on safety on the applicant, and, if a safety question arises post-approval, the burden rests on the NDA holder to resolve it.

- *Capacity to Review Safety Prior to Marketing* – **Strong.** No new drug can enter the market without FDA approval.

Post-Market Functions

- *Capacity to Require Needed Monitoring and Testing* – **Moderate.** As reflected in Table 1, FDA has clear legal authority to require post-market testing for safety only in limited circumstances, involving primarily follow-up on expedited approval of lifesaving drugs based on surrogate end points and testing of approved drugs for use by children. Nevertheless, FDA's strong leverage through the NDA process provides companies an incentive to produce data FDA thinks are necessary to sustain continued approval of a marketed drug.

- *Capacity to Require Timely Adverse Event Reporting* – **Strong.** FDA has clear authority to require adverse event reporting for new drugs.

- *Capacity to Inspect Facilities and Safety Records* – **Strong.** FDA can inspect manufacturing facilities, including for compliance with mandatory GMPs, and can access records related to product safety.

- *Capacity to Remove Unsafe Products from the Market* – **Strong.** FDA can revoke approval of an NDA based on a showing that safety and effectiveness are no longer demonstrated, and NDA holders typically respond voluntarily once FDA concludes revocation is necessary.

FDA Resources: Current Status and Importance for Safety

FDA's legal tools are essential to its success, but they are not sufficient in and of themselves. They need to be well implemented, which takes human and financial resources. The harsh budget reality at FDA, however, is that the agency's resources are in steady decline in relation to the responsibilities it has been given to do, and the resources it does have are spoken for, mostly by programs and activities that are commanded by law or public health priority. FDA simply lacks any significant cushion of resources it can draw upon when new challenges arise. To its credit, FDA is doing things to prepare for and respond to the challenge of nanotechnology, but the scarcity of resources is a severe constraint on the agency's ability to do what it needs to do to meet the public's expectations.

In this section, I will outline some of the things FDA needs to be doing now and in the near future to prepare for and effectively oversee the coming wave of nanotechnology products; describe the current state of FDA's budget and what FDA is doing within that budget; and make a few points about the consequences of not having enough resources to do the job.

What FDA Needs To Do

Meeting public expectations regarding the regulation of nanotechnology or any novel technology requires both preparation and action. The preparatory steps FDA should take involve, generally, building its knowledge base, expertise and technical tool kit, and, on that basis, developing guidance for companies that will be seeking to understand and meet FDA's requirements. Examples of such preparatory activities include:

- *Learning more about applications of nanotechnology that are in the pipeline or market.* The purpose here is to be able to understand for planning purposes the kinds of nanotechnology applications that are likely to be coming so that safety and regulatory issues can be identified and prepared for and the agency can assure the public that it is on top of this emerging field. This could involve scientific intelligence gathering through public sources, surveys of firms and academic researchers, tracking and analysis of products on the market and direct outreach to leading companies. It should encompass all areas covered by the agency—drugs, biological products, cosmetics, medical devices and foods.

- *Developing the necessary in-house scientific expertise to understand and evaluate the products of nanotechnology.* FDA already has much general expertise in fields related to nanotechnology—in chemistry, physics, material science and engineering—but the novelty of the technology and its rapid advance will demand specialized expertise FDA does not have in-house. Meeting this need will require a combination of training and new hiring, both of which are expensive.

- *Developing the safety evaluation and analytical tools required to assess particular nanotechnology products.* This may be FDA's most resource intensive and critical need. It will be resource intensive because these tools will

have to be built on a foundation of research and experimentation. For example, the current battery of in vitro models, animal bioassays and clinical trial methods used for chemical safety testing assume conventional and much larger material size, with doses being measured in mass per unit of body weight or similar measures. For nanoscale materials, which are thought capable of going places in the body that conventional materials cannot reach and behaving differently as a function of their small size, current toxicology tools may not be adequate. Likely, some are and some are not. Someone has to do the work to know the difference.

- *Developing necessary scientific and regulatory guidance.* In all product categories, clarity by FDA internally and with product developers about criteria for product testing, data submission and review is essential to making good public health decisions and facilitating innovation. Nanotechnology, like any new technology, will involve learning by doing and an evolution in FDA's understanding and requirements. Early effort, in collaboration with the external scientific community, to develop guidance that is as clear as possible will pay big dividends.

In addition to supporting these preparatory activities, FDA needs resources so that it can take action in the near term to get in front of future regulatory issues, as well as address products that are already entering the market. As discussed in the Recommendation section of this report, cosmetic, sunscreen and food packaging applications of nanotechnology are in the market today and present regulatory issues that flow from FDA's lack of an airtight pre-market handle. FDA could take steps using current legal authority to get ahead of these issues, though that would require management and staff time that are in short supply.

Longer term, as more products emerge and go through the pre-market approval systems at FDA, highly expert staffing will be needed in headquarters and the field if FDA is to provide meaningful post-market oversight on such matters as responding to adverse event reports and conducting GMP inspection.

FDA's Growing Budget Gap

Where will FDA get the funds for the preparatory and regulatory actions outlined above? That question is hard to answer in light of FDA's extremely difficult budget situation.

The simple fact is that for at least the past decade, FDA's annual appropriation has fallen short of what the agency would need just to keep doing what it had been doing the year before, including continuing the newly mandated activities that the administration and Congress regularly put on FDA's plate. According to analyses prepared by FDA,[47] the agency's 2001 budget would have had to be 26% greater than it was just to stay even with its 1996 budget. By 2006, this budget gap had grown to a stunning 49%, meaning that just to be able to do what it was doing in 1996 and to continue the new activities mandated since then, FDA's 2006 budget would have to have been 49% greater than it is. Under the President's proposed 2007 budget for FDA, the gap grows again to 56%.

This harsh budget reality stems from the fact that about 80% of FDA's budget goes for

47. Table presented in connection with FDA briefing for consumer groups on "FDA Financial Realities," March 10, 2006 (copy on file with author).

costs directly associated with personnel, including salary, benefits and rent for office space and other facilities. These costs rise on average 5.8% per year for reasons beyond FDA's control, such as congressionally mandated pay raises and increasing health insurance, rent and other facility costs. Congress, however, routinely fails to fully fund these increases, which means that to cover them, FDA must either reduce staffing levels or reduce already tight operating budgets—the money for research, grants and contracts, travel and other activities through which FDA staff do their current jobs and prepare for new challenges, such as nanotechnology.

The impact of this resource erosion at FDA is seen most acutely at its Center for Food Safety and Applied Nutrition (CFSAN), which oversees cosmetics as well as the dietary supplement, food packaging and other food-related applications of nanotechnology that are already entering the market. Just since 2003, CFSAN's total staff has declined from 950 to 850, with a further decline to 817 projected in 2007.[48] At the same time, CFSAN's operating budget, which covers a vast array of food safety and nutrition activities, as well as cosmetics, has declined from an already-modest $47.5 million to $30 million and is projected to be $25 million in 2007.

As documented in a recent Institute of Medicine report, FDA's drug safety program is another important activity that is hampered by FDA's widespread scarcity of resources for activities that are not financed through the user fee programs recently enacted to support the new drug and medical device pre-market review programs.[49]

FDA's resources are not only increasingly scarce and shrinking in relation to need, but they are also already spoken for. The tasks being performed by FDA staff are determined by congressional mandate or earmark—such as the operation of pre-market approval programs, mandatory GMP inspections or new initiatives such as bioterrorism prevention, pandemic preparedness and drug safety; by activities reflected in FDA's own public health priorities, such as blood safety or preventing food-borne illness; or by the demands of industry and other external constituencies. When a new challenge such as nanotechnology comes along, FDA's managers find their resources already deployed elsewhere, and they are deployed for real reasons.

No one would argue that FDA's current resource allocation is in any sense perfect, but anyone who wants FDA to step up its efforts on nanotechnology has to recognize that that means taking resources away from some other activity. There simply is no reserve or pool of discretionary funds available to managers to respond to new problems.

Shifting resources in response to new problems is what managers do in any organization, but FDA is in such a strained financial situation that absent a nanotechnology safety crisis, I believe significant shifts are unlikely to occur. The problem with this scenario is that for lack of resources, FDA may miss the opportunity to prepare in ways that could help *prevent* a crisis and all of the adverse consequences such a crisis would have for the future of nanotechnology.

48. Of these, about 30 "full time equivalents" ("FTEs") are available to the Office of Cosmetics and Colors, the great majority of whom work on the statutorily mandated color certification program, leaving only a handful of employees at CFSAN to oversee the multi-billion dollar cosmetic industry.
49. Institute of Medicine. *The Future of Drug Safety – Promoting and Protecting the Health of the Public.* Washington, DC: The National Academies Press, September 2006.

What FDA Is Doing

To its credit, in traditional FDA fashion, despite the lack of any new resources or formal reallocation of resources, FDA is not just sitting back. The Office of Science in the Office of the Commissioner has been designated as the focal point for nanotechnology at FDA, and, along with program staff in FDA's operating centers, has been making presentations to stakeholders about how nanotechnology products fit into the agency's existing regulatory program. The agency has a nanotechnology page on its website that contains information of this kind.[50]

The Office of Science has also been coordinating several efforts among FDA scientists, working internally and with other agencies, to learn more about nanotechnology, develop research agendas and priorities and consider regulatory approaches.

For example, FDA is an active member of the inter-agency Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the Committee on Technology, under the National Science and Technology Council (NSTC). This administration-led group coordinates among agencies involved in the development of nanotechnology products. It includes a Nanotechnology Environment and Health Implications (NEHI) Working Group, which the FDA representative chairs.

Internally, FDA has established the FDA Nanotechnology Interest Group (NTIG), whose members are review-level scientists from all the FDA centers. The NTIG considers the development and approval of nanotechnology products through discussions and sharing of issues that the centers are experiencing in their discussions with product sponsors and review of submissions. The NTIG meets quarterly and has an invited outside speaker at each meeting to present to the group his or her perspective on issues and approaches to the use of nanotechnology in development of FDA regulated products.

The FDA Acting Commissioner, Dr. Andrew C. von Eschenbach, also announced in August 2006 the creation of the FDA Nanotechnology Task Force, which is an internal task force charged with determining regulatory approaches for nanotechnology that address innovation, safety and effectiveness concerns. On October 10, 2006, FDA is holding a public meeting to seek information about the kinds of new nanomaterial-based products under development in the product categories FDA regulates and whether there are emerging scientific issues that should be brought to FDA's attention, including issues related to the safety of engineered nanomaterials.

FDA is also collaborating with outside bodies on specific issues, including the National Cancer Institute (NCI) and National Institute of Standards and Technology (NIST) on the application of nanotechnology to cancer diagnosis and treatment, and with international standard-setting bodies on the development of terminology, nomenclature, metrology and characterization of nanomaterials.

In addition to these coordination and dialogue activities, FDA's centers are conducting a limited program of research related to nanotechnology product safety and effectiveness. FDA is devoting about 16 staff years and $1 million to this research, much of which involves the potential for dermal

50. See http://www.fda.gov/nanotechnology/, accessed September 27, 2006.

penetration by nanoparticles and development of methods for assessing the toxicity of engineered nanomaterials. While seemingly well targeted and useful, this research is spread over five FDA centers and is at best a first step by these centers to build the scientific knowledge needed to regulate engineered nanomaterials.

Unfortunately, the only source of new research funding for nanotechnology among federal agencies is the National Nanotechnology Initiative (NNI). The President's 2007 budget request for the NNI's research program is $1.278 billion, of which $44 million is allocated to seven agencies for research on environmental, health and safety issues.[51] None of that money is allocated to FDA, even though a growing number of nanotechnology-based products fall directly under FDA's oversight.

The Consequences of Scarce Resources

The internal discussion and coordination, the public meeting and the research FDA is undertaking to prepare for nanotechnology are worthy efforts, but they are limited. They are the things FDA can do to address a new challenge when it has no new resources and no reserve or contingency on which to draw.

These activities involve busy program managers and staff adding nanotechnology to the long list of issues for which they are already responsible. The October 10 public meeting will help give visibility to nanotechnology as an important issue for FDA, but it is a fairly passive way to build FDA's knowledge base and will generate only the information parties choose and are willing to give in a public setting, which may or may not be the information FDA needs.

Finally, FDA deserves credit for reallocating some of its limited research capacity to address very immediate safety-related questions, such as the dermal-absorption properties of nanotechnology cosmetic ingredients, but the scale of the effort seems small.

I see two possible, broad consequences of FDA proceeding at this pace.

1. **In product areas where FDA lacks a strong pre-market review handle, such as cosmetics, dietary supplements and GRAS food ingredients, the commercial reality of products in the marketplace will get too far ahead of FDA's knowledge about what is out there and of its ability to assure the public that the products are safe.** There is always the possibility this could result in an actual safety problem, but there is an equal or greater risk of undercutting public confidence and willingness to accept nanotechnology. Just one visible safety incident with a marketed product—whether the risk is real or perceived—is often enough to prompt the press and public to ask: Where is FDA? What has it done to assure the safety of this product? Unsatisfying answers to those questions will be a blow to public confidence in nanotechnology and in FDA.

51. See National Science and Technology Council. "The National Nanotechnology Initiative – Research and Development Leading to a Revolution in Technology and Industry, Supplement to the President's FY 2007 Budget." Washington, DC: Office of Science and Technology Policy, July 2006. The analysis by Maynard (n. 13, supra) of federal research highly relevant to addressing the health risk of engineered nanomaterials identifies just $11 million allocated across five agencies in 2005—none of which is associated with FDA.

2. **Products coming through the premarket approval systems, such as food additives, medical devices and new drugs, will be delayed.** To play its market gatekeeper role in a way that protects consumers from harm and facilitates beneficial innovation, FDA needs to know as much or more about the safety- and effectiveness-related aspects of nanotechnology as do the engineers and other scientists developing it. Without such knowledge, FDA might miss a safety issue, and it certainly runs the risk of long delays in the review process. When the regulatory system places the burden to prove safety on product sponsors, ignorance about safety or how to assess it is almost as much of a constraint on innovation as actual safety concerns. If FDA does not have a scientifically sound basis for concluding a product is safe, the regulatory response will be either "no" or extended delay until the scientific understanding matures.

In the end, it all comes back to public expectations for FDA's role in overseeing the introduction of nanotechnology products. If the public expects FDA to have an expert understanding of the technology and a credible basis for assuring the safety of nanotechnology products before they enter the market, this requires resources. If the public expects a post-market ability to learn actively from actual in-use experience, including adverse events, and be prepared to act when problems occur, this, too, requires effort and resources that FDA would today have trouble mustering.

I think these are the expectations of a large segment of the American people. With these expectations in mind, I outline in the Conclusion and Recommendations sections some actions FDA could take within its current authority to help meet them, as well as some ways in which society, through Congress, can better equip FDA to do the job people expect it to do.

Conclusion: Gaps in the Tool Kit

As noted in the Introduction of this report, nanotechnology could possibly be seen as just another new technology and another new challenge for FDA. FDA has managed its way through such challenges in the past and, one might argue, will find a way to do it again. Thus, one could conclude that no special effort or enhancement of FDA's capacities is needed to deal with the emergence of nanotechnology as a commercially significant technology.

I disagree. Nanotechnology is emerging rapidly as a potentially transforming technology across virtually every product category FDA regulates. Its enormous potential to benefit consumers and patients will be realized, however, only if its safety is understood and reasonably assured *and* if people have confidence in its safety. The public expects FDA to play an active role on both counts.

For these reasons, I think FDA's capacity to regulate nanotechnology needs special attention and action. While FDA has most of the legal tools it needs to regulate most of the products of nanotechnology, significant gaps in authority remain, especially in these areas:

- **Pre-Market Oversight of Cosmetics.** Cosmetics, obviously, comprise the product category for which FDA's legal arsenal is most lacking if the agency is to play a meaningful pre-market oversight role rather than simply react to products and, possibly, problems after they appear in the marketplace. While there is currently little, if any, affirmative evidence that the cosmetic products making nanotechnology-related claims in the marketplace today are unsafe, there is also very little information in the public domain, or available to FDA, about the exact composition, including material size and properties, of these claimed nanotechnology products or about the testing that has been done to assess their safety.

- **Acquiring Information about New Nanotechnology Products.** The ability to simply acquire information about nanomaterials and nanotechnology products that are in development or newly in the market is another gap in FDA's legal tool kit, but one that cuts widely across the agency's programs. The Federal Trade Commission (FTC) has authority to request and even subpoena information to support its unfair competition investigations, and the Environmental Protection Agency (EPA) can "call in" data from companies to support its safety evaluations of pesticides, but FDA has no legal tools to acquire information to help it anticipate safety concerns about products it will be expected to regulate efficiently and effectively.

- **Adverse Event Reporting.** Likewise, FDA lacks authority to require adverse event reporting on marketed products by manufacturers, except with respect to medical devices and new drugs. This hampers FDA's ability to detect patterns and investigate safety problems that arise post-market, ideally in time to take the corrective and preventive actions needed to protect public health and maintain public confidence. The broad question that needs consideration with regard to adverse event reporting and information gathering in general is how FDA can come to know what it needs to know in time to do what it needs to do.

While Congress should consider legislation to address these and other possible gaps in authority, FDA's resource crisis is at least as great, if not greater, a constraint on the agency's ability to meet public expectations as its lack of legal tools. Whether for research and other information gathering, providing science-based guidance to industry or using the legal tools it has, FDA's resources are seriously deficient and need sustained attention and improvement in the coming years to deal effectively not only with nanotechnology but also with a host of other public health, innovation and public-confidence challenges.

Recommendations

The recommendations presented below include ideas for addressing the gaps in FDA's legal authority and resources outlined above, thus better equipping FDA to oversee nanotechnology and other new technologies over the longer term. I also see a pressing need for FDA to consider some near-term actions that it could take, within its current authority and resources, to address some of the nanotechnology products now entering the market and to demonstrate the agency's ability to stay ahead of the product-introduction curve. I will first recommend some of these shorter-term actions and then address longer-term legislative and resource needs.

Each of the recommendations that follow deserves much more analysis and thought than I have been able to give them in this overview report, and this list is by no means exhaustive. My hope with these recommendations is, first, to illustrate that there are actions FDA *can* take, and ways society *can* better equip FDA, to meet society's expectations, and, second, to stimulate thinking and debate on these issues.

Near-Term Actions

My near-term recommendations relate primarily to cosmetics and food-related product categories: dietary supplements, GRAS substances, food additives and food packaging. The central goals are to provide guidance to the industry on some critical questions that affect the regulatory status and pathway of many nanotechnology products and to help FDA obtain the information it needs to stay abreast of this market and be prepared for its regulatory job.

Establish Criteria for "New for Legal and Regulatory Purposes" and "New for Safety Evaluation Purposes"

In the end, safety evaluations of engineered nanomaterials and products involve case-by-case assessment and judgment. For nanotechnology products that do not require individual product review and approval by FDA, however, manufacturers often have to make a threshold determination of whether the product poses a new safety question or otherwise should be considered a new or different material, compared with the conventional form. The conventional form may, for example, have been marketed as a dietary supplement or listed in FDA regulations as a GRAS substance or as an approved food additive or food contact material. If the manufacturer judges the nanotechnology version to be the same as the listed one, there is no legal requirement to seek FDA premarket review and FDA may not become aware of the product until after it enters the market. The burden would then rest on FDA to determine after the fact whether there is a safety or regulatory concern warranting action.

FDA should thus promptly provide companies guidance for making what amount to market-entry decisions. The primary need is to establish criteria for judging when a nanomaterial is "new" for legal and regulatory purposes, i.e., for purposes of distinguishing it from versions that are already listed in FDA's GRAS, food additive and food packaging regulations or that have been reviewed through the Cosmetic Ingredient Review (CIR). The criteria might be based solely on material size, surface-volume ratios or other physical characteristics, or they could include other properties that FDA might judge relevant. This is for FDA to determine. The point

is to have a basis for companies knowing when they need to come to FDA prior to marketing versus when they can rely for legal and regulatory purposes on the existing approval, GRAS affirmation or CIR review of the conventional form of the material.

A necessary extension of clarifying what is "new" for legal and regulatory purposes would be to establish criteria for determining when a nanomaterial should be considered "new for safety evaluation purposes." These criteria presumably would include functional properties that relate to the likelihood that the safety profile of the nanotechnology version would be different from the conventional one. Such criteria would be helpful for all categories of FDA-regulated products as a guide to decisions about the need for toxicity testing beyond what already exists on the conventional form. Another application of such criteria might be to narrow the "new" category so that FDA review of nanotechnology versions of already-approved conventional forms would be required when there is a scientific basis for judging that such review is needed to ensure safety.

Currently, the science needed to set these criteria may be lacking, especially to define when a nanomaterial is "new for safety evaluation purposes." Nevertheless, addressing these threshold questions, which are at the heart of determining the regulatory status of many engineered nanomaterials and the testing needed to ensure their safety, is fundamental to FDA's job. Moreover, simply embarking on the process of setting the criteria, which should involve the external scientific community and the industry, would stimulate necessary discussion and better definition of the scientific issues that require further research. Leaving these issues unaddressed will foster uncertainty, leave companies to make their own decisions based on criteria of their choosing and make orderly oversight of the rapidly developing market for nanotechnology products difficult, if not impossible.

Resolve the Meaning of "Micronized" in the OTC Sunscreen Monograph

Related to the definition of "new" is the specific question of what forms of titanium dioxide are allowed under the OTC drug monograph for sunscreens. The preamble to the monograph states that "micronized" forms of titanium dioxide had been considered in establishing the monograph and thus are covered, but the term "micronized" was not defined.[52] By defining this term and clarifying the extent to which the monograph embraces the full range of nanomaterials, FDA would help resolve the status of one of the more visible early products of nanotechnology to enter the market, thereby building confidence that FDA is on top of its regulatory task.

Request Cosmetic Companies to Submit Safety Substantiation Data

FDA's safety substantiation program for cosmetics[53] requires companies either to "adequately" substantiate the safety of their ingredients or to provide a label statement warning that the safety of the product has not been determined. An increasing number of cosmetic products are on the market bearing nanotechnology claims or reporting formulations using nanoscale ingredients, and with

52. See "Sunscreen Drug Products for Over-The-Counter Human Use; Final Monograph." Rockville, MD: United States Food and Drug Administration, 64 Fed. Reg. 27666, May 21, 1999.
53. See 21 CFR 740.10.

labels that do not bear the warning statement. Presumably, this means that the companies have in hand or can cite "adequate" safety substantiation data. The regulation does not provide for FDA access to the substantiation data, and FDA's general inspection authority does not authorize access to cosmetic company records.

In order to better inform FDA about the nanotechnology cosmetic products on the market today and the basis for their safety, FDA should request the voluntary submission of substantiation data on all products making nanotechnology claims or containing nanomaterials. The agency should provide appropriate confidentiality protection for the information. FDA should take care in formulating the scope of the request, including whether it covers all products bearing any nanotechnology-related claim or just claims for products whose nanomaterials satisfy some FDA criteria, such as the criteria for "new." By establishing this flow of information from the cosmetic industry, FDA will not only be better informed but also have a much more secure basis on which to assure the public of the products' safety and/or judge whether additional regulatory tools or initiatives are needed to inform the agency and protect consumers.

Provide the Cosmetic Industry Guidance on What Constitutes "Adequate" Substantiation

Cosmetic companies marketing products that contain engineered nanomaterials do so today without the benefit of FDA guidance on what it takes to adequately substantiate their safety. The scientific basis for substantiating the safety of some cosmetic ingredients is no doubt unclear and still evolving, but because nanotechnology products are a present reality, FDA should provide some guidance on the nature of the data that should be generated and criteria for evaluating the data. For example, product-specific dermal penetration and potential hazard tests would seem an appropriate core data element of a substantiation package, with products found to achieve penetration requiring further study and evaluation.

While FDA does not currently have legal authority to access a company's substantiation data, the provision of such guidance would at least provide the industry with a common starting point and could contribute to the establishment of a de facto standard of care for the industry. As recommended below, the credibility of FDA's oversight of nanotechnology cosmetics longer term may require giving FDA authority to review a company's substantiation data.

Provide Guidance on When the Use of Engineered Nanomaterials and Their Associated Claims Turn Cosmetics into Drugs

Products that are ostensibly cosmetics but contain ingredients that are intended to "affect the structure or function of the body" are drugs and must satisfy the FDC Act's standards for drug safety and efficacy. Some nanotechnology cosmetics bear such claims, for example, by stating that a product is "bioactive" and "facilitates the increased growth of collagen." By providing guidance on when the use of engineered nanomaterials and their associated claims make the product a drug, FDA will be asserting its traditional regulatory authority and responsibility for drugs and providing assurance that cosmetic ingredients having biological impact receive appropriate review.

Call for Data on Food Uses

As with cosmetics, FDA does not ordinarily have access to food company records and

safety-related data. Nevertheless, many companies are investing in nanotechnology research and development and presumably developing considerable knowledge about the safety and other properties of engineered nanomaterials that would be relevant to FDA's regulatory and public confidence roles. FDA should attempt to access at least some of this information by collaborating with industry, perhaps through a trade association, on a voluntary call for data on food uses of nanotechnology. Again, FDA would have to determine a reasonable scope for the information requested, including the products covered and the nature of the information FDA seeks, and provide appropriate confidentiality.

By taking on these issues and reaching out for industry information on nanotechnology products, FDA would be playing a proper leadership role and establishing the credibility of its regulatory oversight role. While these actions do not require new legal authority, they do require resources that FDA currently lacks. Thus, in recommending these actions, I speak as much to those who control FDA's budget as I do to those with regulatory responsibilities: if gathering information and providing guidance of the kind outlined here are appropriate means for meeting public expectations for oversight of nanotechnology products, FDA should be provided the resources to do the work.

Long-Term Legal and Policy Actions

Beyond immediate actions it can take under current law, FDA's ability over the longer term to meet public expectations in its oversight of nanotechnology products probably requires some statutory change. I will outline a few ideas in this section aimed at enhancing FDA's authority to be informed and provide appropriate pre-market and post-market oversight. The issues that may justify legislative change are not, however, unique to nanotechnology. Thus, ideally, legislative change that might be prompted by nanotechnology would be crafted to enhance FDA's ability to deal with any emerging technology.

Importantly, however, I do not propose changing the basic structure and approach of the FDC Act, with its various regulatory frameworks for different product categories reflecting the varying degrees of oversight judged by Congress to be appropriate for products ranging from hand cream to cancer drugs. In particular, though the cosmetic category is the least intensively regulated, I do not see a pressing need for sweeping change to, for example, require mandatory pre-market approval of all cosmetic ingredients. FDA certainly needs access to cosmetic industry safety data and some flexible new tools to deal with new cosmetic technology, but, for most cosmetic ingredients, the current system appears to work reasonably well in most cases.

A final prefatory note: parties concerned about FDA's effectiveness should not be afraid to seek legislation. A common reservation about the legislative route is that when going into the process, one never knows for sure what the outcome will be. While that may be true enough, in our system Congress is the sole source of FDA's authority and other tools for doing its job. If parties become afraid to legislate, FDA is left with tools that may be outdated and simply insufficient to do what the public expects, which leaves FDA unprepared to do its job. On a subject such as nanotechnology, the legislative system works best if parties with a common interest can come together on a common agenda. In any event, if the public wants FDA to do its job well in a changing world,

parties should not shy away from asking Congress to provide the necessary tools.

As a starting point, I recommend consideration of five new or expanded tools to enhance FDA's oversight, both pre-market and post-market.

Call for Data Authority

One of FDA's greatest limitations in preparing to regulate products of nanotechnology or any rapidly emerging technology is its lack of early, detailed, product-specific knowledge about how the technology is being applied. That knowledge is essential in order to prepare scientifically to make decisions that are sound from the perspective of protecting public health and timely from the perspective of facilitating innovation. And, without the ability to be knowledgeable about emerging technologies, FDA has difficulty establishing the credibility of its oversight.

To address its need to be informed, FDA should have administrative authority to call for the submission of specified information on emerging technologies and products under its jurisdiction, including products in the development pipeline. The legislation granting such authority should carefully define the purposes for which FDA may call for data and establish criteria and a process so that the requests are focused and targeted. Confidentiality of trade secrets and other proprietary information must be carefully protected.[54]

Discretionary Pre-Market Notification Authority

While I believe the basic structure of current law works well in most cases, the effectiveness and credibility of FDA's oversight of novel technologies is reduced when the system allows for market entry without any prior safety review by FDA. FDA lacks such a review opportunity for cosmetics, most dietary supplements, GRAS food ingredients and OTC products or reformulations marketed for the first time by a company.

To address this issue, FDA should be provided rule-making authority to establish interim pre-market notification mechanisms to address emerging and novel technologies. FDA would have the discretion to identify product categories for which pre-market notification would be required, the circumstances that trigger notification and the data that would have to be submitted. The goal would be to give FDA the basis for assessing whether the product satisfies the applicable statutory safety standard; still, such a mechanism would be a notification process, not a full pre-market approval. If FDA believes the product does not satisfy the safety standard, it could block marketing by objecting to the notification.

Such mechanisms should be authorized as interim measures, such as for a period of five or ten years, so that FDA can effectively oversee the introduction of the novel technology without establishing a permanent new regulatory regime. During this period, FDA and other parties could assess whether any additional oversight is needed on an ongoing basis.

Records Access

For cosmetics, most dietary supplements and GRAS ingredients, FDA has no general authority to examine company records related to the safety of the product. This includes the data underlying cosmetic safety substantiations, unless based on the voluntary Cosmetic Ingredient Review. Without such access, FDA is constrained in its ability to

54. Precedents for FDA use of the call-for-data tool, albeit without explicit statutory authority, lie in its implementation of the OTC monograph program and the Drug Efficacy Study Implementation (DESI) program following enactment of the 1962 drug efficacy amendments to the FDC Act.

detect and assess possible safety issues and has little basis for assuring the public that particular products meet applicable safety standards.

The proposed call for data and pre-market notification tools would go a long way to remedy this problem by giving FDA access to the safety information on which the company relies for marketing its products. Absent these tools, FDA's general inspection authority for cosmetics and foods should be expanded to allow access to safety substantiation data for cosmetics and other information in company records related to the safety of cosmetics, foods, GRAS ingredients, food additives and food packaging.

Post-Market Monitoring Authority

FDA's lack of general authority to require post-market monitoring has been highlighted recently by the GAO in the context of FDA's oversight of drug safety. The issue has broader application, however, to the range of circumstances involving FDA-regulated products where novel and beneficial technologies are entering the market, notwithstanding the inherent inability of pre-market testing to fully assess possible long-term effects across large populations of consumers or patients. In these cases, FDA should have authority to require post-market monitoring and surveillance if needed to assure the long-term safety of the product. Implantable medical devices incorporating innovative nanomaterials provide one possible example of where such monitoring might be justified.

The authority should be built into FDA's pre-market approval systems across the board. However, the burden should be on FDA to justify invoking it in particular cases, and it should be invoked only for well-defined purposes and where it will be feasible to produce information that can help assure the safety of the product.

Adverse Event Reporting

Currently, FDA can mandate adverse event reporting only for prescription drugs and medical devices. Across the board, however, FDA's inability to know what the sponsor knows about adverse events is an unnecessary obstacle to FDA being able to provide effective post-market oversight. There are many issues about how to manage adverse event reports, and making good use of them requires a serious investment in staff time and information management systems. But, information about what may have gone wrong with a product or its use is basic to FDA's ability to protect health and vouch for the safety of products.

FDA should be given broad authority to devise mandatory adverse event reporting systems that are appropriate for each product category and least burdensome to achieve the legitimate oversight purpose.

Resource Needs

In general, for reasons discussed elsewhere in this paper, Congress needs to reverse the decline in FDA's resource base and to rebuild FDA's capacity to meet the public's expectations. In doing so, Congress should make some provision for FDA's ability to respond to the challenges posed by emerging new technologies.

Fund "Early Warning" Information Collection

There have been calls for many years to invest more in maintaining and building FDA's science base, which includes the staff and facilities to keep up with rapid scientific advances in all quarters of FDA's jurisdiction. Doing this is certainly a large part of being prepared to

regulate novel technologies. In addition, however, Congress should consider funding within the Office of the Commissioner, and in each of the operating centers, focal points for the gathering of "scientific intelligence" to keep FDA abreast of technological developments and to keep the agency involved in discussions occurring within the greater scientific community. While there are offices that are tasked with this responsibility, their operating budgets, and thus resilience to respond to new developments, are terribly thin. Congress should increase this funding.

Fund Regulatory Research

The burden should be on product sponsors to test the safety of their products. FDA's research responsibility is to ensure that proper toxicity-testing protocols are available and that the agency has the scientific knowledge and technical tools, including analytical methodologies, to play its product review and post-market monitoring roles. FDA's $1 million investment in such research is noteworthy and admirable, but it is not sufficient in light of the array of applications of nanotechnology the agency can expect to confront in coming years.

Build the Scientific and Regulatory Staff

Effective, science-based oversight of nanotechnology products—oversight that understands the safety issues well enough to prevent problems while not unduly slowing innovation—will require specialized scientific expertise and focused effort by regulatory policy makers in all of FDA's programs. Congress should provide FDA the resources to acquire the needed scientific expertise, so that being prepared to oversee nanotechnology does not require depriving other FDA programs of the scientific resources they need.

FDA also needs to add regulatory capacity across all its programs, at both the policy-making and field-oversight levels. Providing scientifically sound regulatory guidance to industry is one of the most important things FDA can do to stay in front of any potential safety issues posed by nanotechnology products. FDA needs a field force that can conduct inspections, respond to problems and do the other "bread-and-butter" things that are needed for an effective and credible regulatory program. In the end, FDA's capacity to provide timely guidance and to do these other things is impaired by the scarcity of its resources.

Concluding Observation

Americans expect a lot of the Food and Drug Administration. Food and cosmetics are to be safe. Medical products are to be safe and effective. And FDA is to achieve this without impeding technological innovation or the prompt introduction of new products. FDA has a long history of rising to this challenge, never perfectly but almost always with an earnest effort and creative use of the tools at its disposal. This, of course, is FDA's responsibility.

But society has a responsibility, too. Society – citizens, businesses, and organized interest groups – created FDA and the expectations surrounding it. And only society, acting through the political process, can give FDA the tools it needs to do its job. Nanotechnology is yet another important challenge for FDA that brings into question whether the agency is equipped to do what is expected.

At present, FDA is not fully equipped, in either its legal authority or resources, which means society has a responsibility to act – to be clear about its expectations and to give FDA the tools it needs to meet them. FDA should continue its resourceful use of the tools it has and help lead the discussion of what more it needs to be successful, but the rest is up to others.

Table 1 Endnotes

i. This category includes all cosmetic ingredients except color additives, which are regulated under separate authority in a manner similar to food additives.

ii. For simplicity's sake, this table omits FDA's authorities for animal drugs and therapeutic biologics, which are regulated under separate but similar, and in some respects overlapping, statutory provisions.

iii. This includes only cases in which, by statute or regulation, FDA has established a specific requirement that a product's sponsor independently substantiate safety prior to marketing but without a requirement that that substantiation be submitted to FDA.

iv. By regulation, FDA provides that cosmetic ingredients and products "shall be adequately substantiated for safety prior to marketing," but provides the option, in the absence of safety substantiation, of stating on the label: "Warning – The safety of this product has not been determined."

v. Intentionally added food substances that are "generally recognized as safe" are exempt from the definition of food additive and from the requirement of pre-market approval. If FDA has not formally recognized the GRAS status of a substance, companies commonly assemble information to demonstrate GRAS status, but there is no legal requirement that they do so, and, in the event of a safety concern, the burden of proof is on FDA to demonstrate that the substance is not GRAS and thus a food additive.

vi. FDA has established a voluntary pre-market notification procedure for "novel foods" that has been used routinely by developers of genetically modified whole foods to inform FDA in advance of marketing that the developer has reviewed the safety of the food and considers it substantially equivalent to the traditional food for safety purposes. This procedure does not involve a full FDA safety review or result in an FDA conclusion on the safety of the product.

vii. This requirement applies only to dietary supplements containing "new dietary ingredients," which are defined as those that were not marketed in the United States prior to October 15, 1994, and only if the new dietary ingredient has not been present in the food supply in a chemically unaltered form. 21 USC 350b.

viii. Components of food packaging materials and other food contact substances are "food additives" if there is a reasonable expectation they will migrate to food, unless they are GRAS. Rather than submitting full food additive petitions, however, sponsors of food contact substances have the option of submitting a pre-market notification substantiating safety, which, if FDA does not object, provides the legal basis for marketing the substance.

ix. Pre-market notification is the vehicle for market entry of medical devices that are "substantially equivalent" to a previously marketed "predicate device" or are subject to an FDA-promulgated performance standard.

x. This applies if FDA decides the pre-market notification does not adequately demonstrate safety or if the sponsor otherwise chooses to submit a food additive petition.

xi. Most OTC drugs are regulated by FDA under a monograph system that includes FDA review of the safety and effectiveness of their active ingredients and the issuance of regulations listing, by category of intended OTC uses, the ingredients that can lawfully be used based on FDA's conclusion that they are generally recognized as safe and effective for their intended uses. Products formulated using these active ingredients and "safe and suitable" inactive ingredients are not considered "new drugs" and are thus not subject to the requirement for a new drug application and the issuance of a product-specific license as a prerequisite for marketing. 21 CFR Part 330.

xii. New medical devices that are not substantially equivalent to predicate ones and not subject to a performance standard, or that are otherwise deemed a "Class III" device, can be marketed only after full FDA review and approval of that specific device product.

xiii. FDA has issued GMP regulations for foods (21 CFR Part 110), but these are not backed up by any statutory provision making compliance with GMPs a prerequisite for marketing. This means that the burden remains on FDA to prove that a product is unlawfully contaminated or otherwise "adulterated," not merely that it has violated the GMP regulation.

xiv. FDA was authorized in 1994 to issue regulations mandating GMPs for dietary supplements but has yet to do so.

xv. For all the product categories FDA regulates, the FDC Act authorizes FDA to go to federal court to obtain an order seizing particular lots of product that FDA is prepared to prove are in violation of the FDC Act for safety or any other reason. FDA can also seek an injunction barring future shipments of violative products and can pursue criminal prosecution for violations of the FDC Act. In criminal investigations, FDA can gain access to safety-related records and other company-held information if there is probable cause that the records are evidence of a crime.

xvi. The FDC Act contains no express authority to require post-market monitoring or testing of an approved food additive, but FDA has on occasion elicited a sponsor's agreement to conduct monitoring for adverse events as a condition of approval. FDA has also by regulation established a seldom-used procedure for requiring additional studies on a marketed additive when a safety question has arisen, as a condition of continued marketing of what FDA calls an "interim" food additive. 21 CFR Part 180.

xvii. Id.

xviii. For certain high-risk devices, FDA can, on a case-by-case basis, require product manufacturers to conduct "post-market surveillance" for the purpose of collecting data that can reveal unforeseen adverse events or "other information necessary to protect public health."

xix. FDA can require post-market testing as a prerequisite for marketing in two limited situations. The first is under the accelerated approval program, which provides for the approval of drugs for serious or life-threatening illnesses based on surrogate end points of effectiveness provided the sponsor conducts post-market studies to verify safety and effectiveness. 21 CFR Part 314, Subpart H. The second, and even more unusual, case is when human-efficacy studies on a drug are not ethical or feasible. 21 CFR Part 314, Subpart I. FDA can also require post-approval testing of marketed drugs if needed to assess the safety and effectiveness of those drugs for use by children. 21 USC 355c(b).

xx. Sponsors of new drugs are required to report to FDA within 15 days any adverse event coming to their attention that is both serious and unexpected, and to report all other adverse events on a quarterly basis. 21 USC 355(k) and 21 CFR 310.305.

xxi. FDA may inspect safety records only if it first has a "reasonable belief" that the food "presents a threat of serious adverse health consequences or death." 21 USC 350c(a).

xxii. FDA may inspect safety records only if it first has a "reasonable belief" that the supplement, which is by law deemed a food, "presents a threat of serious adverse health consequences or death." 21 USC 350c(a).

xxiii. See note 11.

xxiv. Id.

xxv. Id.

xxvi. As a general matter, FDA inspectors can access safety-related data on any medical device that is "restricted" to use only on the prescription of health practitioners or that is otherwise subject to use conditions to assure its safety. 21 USC 704(a). In addition, FDA has broad authority to require device manufacturers to collect and report safety-related data, and its inspectors have access to those data as well. 21 USC 704(e).

WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS
Lee H. Hamilton, President and Director

Board of Trustees
Joseph B. Gildenhorn, Chair
David A. Metzner, Vice Chair

Public Members
James H. Billington, The Librarian of Congress; Bruce Cole, Chairman, National Endowment for the Humanities; Michael O. Leavitt, The Secretary, U.S. Department of Health and Human Services; Tami Longabergr, Designated Appointee within the Federal Government; Condoleezza Rice, The Secretary, U.S. Department of State; Lawrence M. Small, The Secretary, Smithsonian Institution; Margaret Spellings, The Secretary, U.S. Department of Education; Allen Weinstein, Archivist of the United States

Private Citizen Members
Carol Cartwright, Robin Cook, Donald E. Garcia, Bruce S. Gelb, Sander R. Gerber, Charles L. Glazer, Ignacio E. Sanchez

The **Project on Emerging Nanotechnologies** was launched in 2005 by the Wilson Center and The Pew Charitable Trusts. It is dedicated to helping business, governments, and the public anticipate and manage the possible human and environmental implications of nanotechnology.

The Pew Charitable Trusts serves the public interest by providing information, advancing policy solutions and supporting civic life. Based in Philadelphia, with an office in Washington, D.C., the Trusts will invest $204 million in fiscal year 2006 to provide organizations and citizens with fact-based research and practical solutions for challenging issues.

The **Woodrow Wilson International Center for Scholars** is the living, national memorial to President Wilson established by Congress in 1968 and headquartered in Washington, D.C. The Center establishes and maintains a neutral forum for free, open and informed dialogue. It is a nonpartisan institution, supported by public and private funds and engaged in the study of national and international affairs.

Project on Emerging Nanotechnologies

One Woodrow Wilson Plaza
1300 Pennsylvania Ave., N.W.
Washington, DC 20004-3027

T 202.691.4000
F 202.691.4001
www.wilsoncenter.org/nano
www.nanotechproject.org