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THE FDA AND NANO: BIG PROBLEMS WITH TINY TECHNOLOGY

JESSICA K. FENDER*

INTRODUCTION

Nanotechnology is, simply put, tiny technology. The term refers to technology that either is created on, or capable of manipulating, the nanoscale.¹ Although this field holds great promise, caution must be exercised to ensure the safety and efficacy of products utilizing nanotechnology.

We are in the midst of a nanotechnology revolution. Our understanding of the world changed drastically with the advent of quantum mechanics, when scientists discovered that contrary to the rules of classical physics, matter took on novel and unexpected properties when observed at the nanoscale. Electrons, thought to be discrete particles, could act like waves. Scientists could not pin down both the exact momentum and the position of a particle; one property could not be measured with certainty when the other was accurately measured. Exploring the implications of these strange phenomena led to heady discoveries, and our view of the universe around us changed forever.

It was not until relatively recently, however, that scientists and engineers were able to steer their research in such a way as to take advantage of

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1. Nanotechnology is not a single "technology," because the phrase applies to a wide variety of technologies that could potentially involve manipulation of, or creation on, the nanoscale. The prefix "nano" means "one-billionth"—a nanometer is therefore one billionth of a meter and is denoted "nm." To put this in perspective, a sheet of paper as viewed from the side has a thickness of approximately 80,000–100,000 nanometers. Although the FDA and many other regulatory agencies have not officially adopted a definition of nanotechnology, most informally use the National Nanotechnology Initiative (NNI) definition: Nanotechnology involves (1) the research and technology development at the atomic, molecular, or macromolecular levels, on a scale of about 1–100 nm; (2) the creation and use of structures, devices, and systems that have novel properties and functions due to their size; and (3) the ability to control or manipulate on the atomic scale. U.S. Food & Drug Admin., FDA Nanotechnology—FAQ's, <http://www.fda.gov/nanotechnology/faqs.html> (last visited Apr. 6, 2008) [hereinafter FDA Nanotechnology FAQ].

these queer properties. In 1959, the preeminent physicist Richard Feynman hypothesized that manipulation of individual atoms might be possible. He challenged the scientific community, asking his colleagues “to consider the final question . . . What would happen if we could arrange the atoms one by one the way we want them[?]”²

The world is starting to find out. Though Feynman’s enthusiasm ultimately proved contagious, it was not until the 1980s that the idea became a reality with the invention of the scanning tunneling microscope, or STM.³ The STM is widely described as the first nanotechnology-related invention because the microscope could take advantage of the wave-like properties of electrons to indirectly image and manipulate individual atoms.⁴ Since then, the field has grown by leaps and bounds. Researchers now have a wealth of nanomaterials at their disposal. These include, for example, quantum dots, which are semiconducting nanocrystals; fullerenes, which are spherical carbon cages; and nanowires, which generally are one-dimensional strings of a metallic or semiconducting compound.⁵ These materials can be used in diverse fields such as semiconductor design, biotechnology, materials science, telecommunications, and textiles, because nanotechnology is applicable in just about any field where small size, large surface area, or quantum properties are desirable.⁶

The wide-ranging applicability of nanotechnology-related research has captured the attention of the U.S. government. Federal funding will reach more than \$1.5 billion in 2009,⁷ which is a 50% increase over the amount available in 2005.⁸ In December of 2003, President George W. Bush signed

2. Richard P. Feynman, *There’s Plenty of Room at the Bottom*, in *MINIATURIZATION* (Horace D. Gilbert ed., 1961), reprinted in 60 *J. OF MICROELECTROMECHANICAL SYS.* 60, 65 (1992).

3. Davis Baird & Ashley Shew, *Probing the History of Scanning Tunneling Microscopy*, in *DISCOVERING THE NANOSCALE* 145, 145–46 (Davis Baird, Alfred Nordmann & Joachim Schummer eds., 2004).

4. *Id.* at 146.

5. I say “generally” because nanotechnology terminology is not uniform, and often overlaps. Some terms are too broad to provide any tangible insight into the structure of the molecule. For example, when one searches for the word “nanoparticle” within the “claims” section of a U.S. patent, one will find references to nanoparticles from 1–100,000 nanometers, well into the micrometer range. People also occasionally use the same term to refer to two different materials. For example, one person might refer to a given material as a nanowire, whereas another might call the same material a nanotube. A nanowire is usually defined as above, while a nanotube is generally recognized as having the same carbon connectivity as a fullerene in hollow tube form instead of spherical form. To view images of nanotubes and fullerenes, see PAUL HOLISTER, TIM HARPER & CRISTINA ROMÁN VAS, *CMP-CIENTIFICA, NANOTUBES 7–8* (2003), available at http://nanotechweb.org/dl/wp/nanotubes_WP.pdf.

6. Mark A. Lemley, *Patenting Nanotechnology*, 58 *STAN. L. REV.* 601, 614 (2005).

7. Nat’l Nanotechnology Initiative, Funding, <http://www.nano.gov/html/about/funding.html> (last visited Apr. 4, 2008) [hereinafter NNI Funding].

8. David J. Robeson, *Nanotechnology and the USPTO*, *THE DISCLOSURE*, May 2006, http://www.napp.org/disclosure/2006_Issues/may06.html.

the 21st Century Nanotechnology R&D Act into law, providing \$3.7 billion for nanotechnology research for 2005–2008.⁹ Since 2001, the administration has increased nanotechnology funding by 83%.¹⁰ Most of this funding goes to the National Nanotechnology Initiative (NNI).¹¹ The NNI then portions this funding out to other governmental funding agencies. In 2008, NNI estimates that the Department of Defense will receive the most funding at \$487 million, followed by the National Science Foundation at \$389 million.¹² Other governmental agencies receiving significant funding include the Department of Energy (\$251 million); the Department of Health and Human Services, which includes the National Institute of Health (\$226 million); the Department of Commerce, which includes the National Institute of Standards and Technology (\$89 million); and the National Aeronautics and Space Administration (\$18 million).¹³

Venture capitalists are also funding nanotechnology research. Since 1995, they have invested at least \$2 billion worldwide;¹⁴ some estimate that they invested \$650 million in 2006 alone.¹⁵ This amount, while significant, is dwarfed by the \$1.9 billion that North American corporations invested in nanotechnology research and development in 2005.¹⁶ Clearly, funding from the corporate sector, venture capitalists, and the government illustrates substantial support for nanotechnology.

The availability of funding and the potential financial rewards combine to create a significant incentive to undertake nanotechnology research and development. In the rush to capitalize, the government has not given adequate consideration to the risks that nanotechnology-related products and inventions may pose to public health and safety. Nanotechnology is special in that it is applicable across many fields, but it is this very trait that makes nanotechnology so difficult to regulate. Although the government is largely funding research efforts in the United States, it has not done enough

9. 15 U.S.C. § 7505 (Supp. IV 2004); Press Release, Office of the Press Secretary, President Bush Signs Nanotechnology Research and Development Act (Dec. 3, 2003), available at <http://www.whitehouse.gov/news/releases/2003/12/20031203-7.html>.

10. See Press Release, *supra* note 9.

11. NNI Funding, *supra* note 7.

12. *Id.*

13. *Id.*

14. Press Release, Lux Research, Inc., Venture Capital Pours into Nanotech, but Exits Are Uncertain (Jan. 9, 2006), available at http://www.luxresearchinc.com/press/RELEASE_VC.pdf.

15. Press Release, Lux Research, Inc., Nanotech Venture Capital To Exceed \$650 Million in 2006 (Dec. 4, 2006), available at http://www.luxresearchinc.com/press/RELEASE_VCreport.pdf.

16. LUX RESEARCH, INC., THE NANOTECH REPORT 4TH EDITION: KEY FINDINGS AND TABLE OF CONTENTS, at iii (2006), available at http://www.luxresearchinc.com/pdf/TNR4_TOC.pdf; see Kevin Kelleher, *Nanotech Is Living Large*, THE STREET, Apr. 13, 2006, <http://www.thestreet.com/tech/inter/net/10279136.html> (citing LUX RESEARCH, INC., HOW INDUSTRY LEADERS ORGANIZE FOR NANOTECH INNOVATION (2006)).

to ensure that these efforts will ultimately benefit, and not harm, its citizens. As one critic stated, the government “has acted as a cheerleader, not a regulator, in addressing the nanotech revolution.”¹⁷ In fact, of all the money the federal government has invested in nanotechnology, only about 5% is expressly allocated for environmental, health, and safety research in 2009.¹⁸

The government’s responsibility to invest in environmental, health, and safety research does not arise solely based on its funding of nanotechnology research and development. Nanotechnology squarely implicates many federal regulatory bodies. For example, nanotechnology inventions are patented in the United States Patent and Trademark Office (USPTO), certain nanotechnology products must be approved by the Food and Drug Administration (FDA) before they can be used or offered for sale, the National Institute for Occupational Safety and Health (NIOSH) is supposed to ensure that workers are not exposed to hazardous nanomaterials, and the Environmental Protection Agency (EPA) must monitor nanotechnology products to guarantee that they do not pose an environmental threat. Some of these agencies have already adopted a nanotechnology policy; others are still struggling to define their official stance.

Such is the case with the FDA. Thus far, the FDA has insisted that its present regulatory scheme is adequate to the task of analyzing nanotechnology products.¹⁹ This *ad hoc* approach has been strongly criticized,²⁰ and for good reason. Some have cushioned their criticism of the FDA by pointing out that “nano-enabled drugs and medical devices . . . place burdens on an oversight agency that is already stretched extremely thin.”²¹ Although

17. Kathy Jo Wetter, ETC Group, Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 119 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>.

18. The 2009 proposed budget for the National Nanotechnology Initiative is \$1,527 million; of that, NNI estimates that \$76 million (or 4.9%) will be spent on environmental, health, and safety research. NNI Funding, *supra* note 7; Nat’l Nanotechnology Initiative, NNI Environmental, Health & Safety Issues, <http://www.nano.gov/html/society/EHS.html> (last visited Apr. 4, 2008) [hereinafter NNI, EHS Issues]. This number may be low, since the NNI website states that the figure “does not include substantial research in instrumentation and metrology and on fundamental interactions between biosystems and engineered nanoscale materials, both of which are important in the performance and interpretation of toxicological research.” NNI, EHS Issues, *supra*.

19. FDA Nanotechnology FAQ, *supra* note 1 (stating that “[e]xisting requirements may be adequate for most nanotechnology products that [the FDA] will regulate”); Carol Rados, *Nanotechnology: The Size of Things to Come*, FDA CONSUMER, Nov.–Dec. 2005, at 40, 42 (“For the most part, FDA experts believe that existing regulatory standards are probably adequate for most nanotechnology products. Scientists say that particle size is not the issue. Instead, new tests and standards will be required as new toxicological risks from the new materials are identified.”).

20. *E.g.*, *FDA Told to Watch Nanotech Products for Risks*, MSNBC.COM, Oct. 10, 2006, <http://www.msnbc.msn.com/id/15213085/>.

21. *Id.* (quoting David Rejeski, director of the Project on Emerging Nanotechnologies).

the FDA undoubtedly does not have the funding it needs,²² nothing prevents the FDA from taking advantage of valuable information that is freely disclosed by other agencies. The USPTO, for example, recently created a new cross-reference classification number for nanotechnology-related patents. This cross-reference class, Class 977, is evidence that the USPTO thinks an invention relates to nanotechnology and has novel properties that are not the natural result of the invention's small scale. As it stands, if the invention falls under the FDA's jurisdiction, the FDA will treat that invention exactly the same as its large-scale counterpart—despite the USPTO's indication that the invention has unique, nanotechnology-related properties. In this note, I argue that the FDA should use the Class 977 label to identify products that warrant stricter regulatory controls. This label is a simple, inexpensive way to identify products that are likely to require special scrutiny before being released on the market. In addition, due to the manner in which the USPTO defined Class 977, the label applies most often to (and is therefore of greatest use for) those products that would otherwise receive the weakest regulatory oversight from the FDA.

Part I of this note challenges the FDA's premise that nanotechnology-related products pose no special threat by providing evidence that a nanomaterial may have very different physical and toxicological properties than the same material on the macroscale. Part II provides a counterbalance by identifying the unique benefits that may follow from these special properties, and shows how the same property that is harmful in one context can actually prove beneficial in another. Part III details the FDA's current approach to nanotechnology and explains why this approach will not suffice to ensure the public health and safety. In Part IV, the USPTO's approach to nanotechnology is discussed, along with the evolution of Class 977. Part V argues for the applicability of Class 977 to the FDA's regulatory scheme, and further argues that the FDA should use its labeling powers and its Office of Combination Products to ensure the safety of Class 977-labeled products. Finally, Part VI of this note urges the FDA to take decisive action in addressing nanotechnology product safety. Nanotechnology has the potential to transform our lives, but this potential will be wasted if the FDA does not take an aggressive stance in assuring the public that nanotechnology products are safe.

22. MICHAEL R. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES THE FDA HAVE THE TOOLS IT NEEDS? 46–47 (2006), available at http://www.nanotechproject.org/process/assets/files/2705/110_pen5_fda.pdf.

I. BIG PROBLEMS WITH TINY TECHNOLOGY

Nanotechnology is technology created on a very small scale. An atom or molecule created on the nanoscale may have very different physical properties than the same atom or molecule in its naturally occurring state. For instance, most people are familiar with gold—it is yellow, it melts at about 1000°C, and it is (thankfully) non-reactive.²³ On the nanoscale, things look quite different. As one researcher noted, “not one of these ‘facts’ necessarily applies at the nanoscale.”²⁴ For instance, at 5 nm, gold is expected to melt at 830°C, and at 2 nm, it would melt at just 350°C.²⁵ Even the magnetic properties of a material can change—aluminum is not usually magnetic, but it becomes magnetic when individual atoms form a cluster with a diameter of less than 1 nm,²⁶ and at 20–30 nm, aluminum will explode.²⁷ Similarly, at the nanoscale an insulating material may change into a conductor, and a previously insoluble material may become soluble.²⁸ Most importantly, however, the size of a particle does not allow one to predict which, if any, changes in the particle’s “normal behavior” will occur. As a *National Geographic* author described, “It’s like you shrink a cat and keep shrinking it, and then at some point, all at once, it turns into a dog.”²⁹ Physical properties change, and those changes are not limited to properties inherent to small size.

Many reputable sources are expressing concerns regarding nanotechnology safety due to the potential these materials have to exhibit novel, unpredictable properties.³⁰ Although the FDA says that it is “not aware of any adverse safety issues associated with the use of nanotechnology-based materials in FDA regulated products,”³¹ a plethora of scientific evidence

23. Michael Cortie, *The Weird World of Nanoscale Gold*, 37 GOLD BULL. 12, 14–16 (2004) (citations omitted).

24. *Id.* at 14.

25. *Id.* at 16.

26. W. Eberhardt, *Clusters as New Materials*, 500 SURFACE SCI. 242, 244 (2002).

27. Jennifer Kahn, *Nano’s Big Future*, NAT’L GEOGRAPHIC, June 2006, at 98, 100.

28. Delara Karkan, Associate Director, Center for Evaluation of Radiopharmaceuticals, Health Canada, Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 39 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>.

29. Kahn, *supra* note 27, at 103.

30. The American Chemical Society’s Committee on Chemical Safety, for example, is advising chemists to take precautions when working with nanoparticles because “[s]tudies have indicated that low-solubility ultrafine particles are more toxic than larger particles on a mass for mass basis. Because of their tiny size, [nanoparticles] can get deep into the lungs and, once in the bloodstream, may be able to cross the blood-brain barrier.” Am. Chem. Soc’y, Nanotechnology Safety Resources, <http://membership.acs.org/ccs/nano.htm> (last visited Apr. 4, 2008).

31. Randy Lutter, Co-Chair of the FDA Task Force on Nanotechnology, Opening Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 5 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>.

points to the potential dangers of nanotechnology products. Sophisticated computer models provide strong evidence that buckminsterfullerenes (a specific type of fullerene also referred to as C_{60}) will bind and deform double-stranded DNA and prevent the DNA repair mechanism from working correctly.³² When this happens, it can lead to genetic mutations that cause cancer and other diseases.³³ In largemouth bass, buckminsterfullerenes cause an increase in lipid peroxidation, thereby causing cellular damage in the brain.³⁴ Another scientific paper reports that when nanoparticles are taken up into cells, they become coated with proteins.³⁵ This process results in conformational changes, causing normally buried portions of the protein to become exposed. Instead of rejecting the molecule as a foreign body, the cell may instead trigger “inappropriate cellular processes”³⁶ which may prevent a body’s normal immune system from clearing the nanoparticle.³⁷ Carbon nanotubes pose a special threat to the lungs. Mice that inhale single-walled nanotubes experience respiratory deficiencies and cannot clear bacteria from their lungs as efficiently as mice that are not exposed to nanotubes.³⁸ Furthermore, using extremely fine carbon black particles or fine crystalline silica does not have the same effect, indicating that “the biological and toxicological effects of [carbon nanotubes] cannot be predicted by extrapolation of data collected with fine carbon particles.”³⁹ These results provide evidence that there is something exceptional (and not simply size dependent) about the carbon nanotubes themselves.

These are just a few examples of studies that have called attention to the potential risks of nanomaterials. To dismiss these results out of hand

32. Xiongce Zhao, Alberto Striolo & Peter T. Cummings, *C₆₀ Binds to and Deforms Nucleotides*, 89 BIOPHYS. J. 3856, 3856 (2005).

33. See, e.g., Viola Ellison & Bruce Stillman, *Biochemical Characterization of DNA Damage Checkpoint Complexes: Clamp Loader and Clamp Complexes with Specificity for 5' Recessed DNA*, 1 PLOS BIOLOGY 231, 231 (2003); NIH DNA Repair Interest Group, *What is DNA Repair?* <http://www.nih.gov/sigs/dna-rep/whatis.html> (last visited Apr. 4, 2008).

34. Eva Oberdörster, *Manufactured Nanomaterials (Fullerenes, C₆₀) Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass*, 112 ENVTL. HEALTH PERSP. 1058, 1060 (2004). Lipid peroxidation is the process whereby free radicals (atoms or molecules that have an unpaired electron and therefore are highly reactive) “steal” electrons from lipids in the cell membrane, causing cell damage and increased production of free radicals.

35. Iseult Lynch, Kenneth A. Dawson & Sara Linse, *Detecting Cryptic Epitopes Created by Nanoparticles*, SCI. STKE, Mar. 21, 2006, at pe14-1.

36. *Id.* at pe14-3.

37. T. Fettah Kosar, Anna Tourovskaja & Nicholas L. Stucky, *Nanoparticles Administered to the Human Body: Impacts and Implications*, NEWS FROM THE BOTTOM, 2004 (on file with the Chicago-Kent Law Review).

38. Anna A. Shvedova et al., *Unusual Inflammatory and Fibrogenic Pulmonary Responses to Single-Walled Carbon Nanotubes in Mice*, 289 AM. J. PHYSIOL.-LUNG CELL. MOL. PHYSIOL. L698, L698 (2005).

39. *Id.* at L706.

would be to willfully ignore a potential threat to the public. But although these concerns must be taken seriously, the federal government also has an obligation not to overreact to perceived threats. Some have suggested banning further nanotechnology research and recalling nanotechnology products until the safety of such products is conclusively determined.⁴⁰ Such a ban would likely not only be impossible, but irresponsible. There is little doubt that nanotechnologies will drastically improve our quality of life, and banning nanotechnology research entirely would both prevent life-saving products from reaching the market and decimate public confidence in the safe and effective nanotechnology products that will reach (and may already be on) the market.

II. THE BIG PROMISE OF TINY TECHNOLOGY

Researchers and theorists have long painted some truly incredible visions of our future. Nanotechnology will help those visions come to life. For example, NASA is actively considering the use of carbon nanotubes to build an elevator from Earth to space.⁴¹ Perhaps more importantly, nanotechnology is already having a beneficial impact on public health.⁴² Quantum dots are being used to detect precancerous biomarkers, and have proven successful in the early detection of cervical and breast cancer.⁴³ Other nanoparticles may specifically target and destroy cancer cells, leaving healthy cells untouched.⁴⁴ Researchers at MIT are using a self-assembling nanoliquid made of peptides to stop bleeding in less than fifteen seconds, which could significantly reduce the time spent in surgery.⁴⁵ The nanoliquid is applied directly to a wound, and because the liquid is made of

40. E.g., Erich Pica, Friends of the Earth, Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 151 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>; Press Release, ETC Group, Nanotech Product Recall Underscores Need for Nanotech Moratorium: Is the Magic Gone? (Apr. 7, 2006), *available at* <http://www.etcgroup.org/upload/publication/14/01/nrnanorecallfinal.pdf>.

41. Kenneth Chang, *Not Science Fiction: An Elevator to Space*, N.Y. TIMES, Sept. 23, 2003, at F1, F4.

42. Note, however, that many of applications discussed below remain relegated to the laboratory and may not have been approved for use on humans. In addition, some applications, such as the use of quantum dots for tissue imaging, will not require human testing since the tissues are removed and treated prior to being examined under a microscope or similar imaging apparatus.

43. Dawn L. Nida et al., *Fluorescent Nanocrystals for Use in Early Cervical Cancer Detection*, 99 GYNECOLOGIC ONCOLOGY S89 (2005); Jennifer Ouellette, *Quantum Dots for Sale*, INDUS. PHYSICIST, Feb.–Mar. 2003, at 14, 15.

44. Ray Kurzweil, *Reprogramming Biology*, SCI. AM., July 26, 2006, at 38.

45. Rutledge Ellis-Behnke et al., *Nano Hemostat Solution: Immediate Hemostasis at the Nanoscale*, 2 NANOMEDICINE: NANOTECH., BIOL., & MED. 207 (2006); Anne Trafton, *New Material Halts Bleeding*, TECH TALK (Mass. Inst. of Tech., Cambridge, Mass.), Oct. 2006, at 1, *available at* <http://web.mit.edu/newsoffice/2006/techtalk51-5.pdf>.

peptides (which are the building blocks of naturally occurring proteins) the material does not provoke a negative immune response in test animals.⁴⁶ There is even evidence that nanotechnology might ultimately provide a cure for type I diabetes, as one scientist has cured the disease in rats using a nanodevice that releases insulin while blocking antibodies.⁴⁷ Other important nanotechnology applications include treatment of nausea, organ rejection, cholesterol, and loss of appetite due to anorexia or AIDS.⁴⁸

Many features of nanotechnology can be harmful under one set of circumstances and beneficial under another. For instance, one oft-cited concern about nanomaterials is that they may cross the blood-brain barrier.⁴⁹ Nanoparticles used to keep windows clean or food fresh could pose a serious hazard to the consumer if the particles could get into that consumer's brain tissue. On the other hand, a promising drug that seems to work well but lacks efficiency might be "nanosized" to cross the blood-brain barrier, leading to greater functionality for the drug.⁵⁰ Nanosizing a drug can also lead to increased efficiency simply by increasing the surface area of the drug.⁵¹ If drugs can be nanosized to have increased efficacy against viral infections, such a change would benefit both the individual patient (who may take less of the drug or recover more rapidly) and the public at large, because efficient drugs eliminate viruses before they have time to mutate or adapt into new, drug-resistant strains.⁵²

Similarly, buckminsterfullerenes apparently localize in certain tissues (like the brain) to cause harmful side effects,⁵³ much as carbon nanotubes localize and cause harm to the lungs.⁵⁴ But a different nanomaterial may be targeted to a specific area of the body to great benefit. For example, at Rice University researchers are treating cancer using "nanoshells" of gold-

46. Ellis-Behnke et al., *supra* note 45, at 214.

47. Kurzweil, *supra* note 44.

48. All of these drugs have received FDA approval and are commercially available. See Project on Emerging Nanotechnologies, Current Medical Applications, <http://www.nanotechproject.org/inventories/medicine/apps/> (last visited Apr. 4, 2008).

49. The blood-brain barrier is "a naturally occurring barrier created by the modification of brain capillaries . . . that prevents many substances from leaving the blood and crossing the capillary walls into the brain tissues." MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY 133 (11th ed. 2003).

50. Kosar, Tourovskaia & Stucky, *supra* note 37.

51. Elan Drug Technologies, NanoCrystal Technology, http://www.elan.com/EDT/nanocrystal_technology/default.asp (last visited Apr. 4, 2008). See *infra* note 141 for an explanation as to why surface area may affect drug efficacy.

52. Anil Diwan, NanoViricides, Inc., Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 191-92 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>. Viral mutations have created enormous problems in the treatment of illnesses and diseases like malaria and AIDS, as well as the common flu.

53. See *supra* notes 32-37 and accompanying text.

54. See *supra* notes note 38-39 and accompanying text.

coated silica that absorb infrared light; combined with antibodies, the nanoshells localize in tumors.⁵⁵ Once the particles are concentrated in the tumor, the researchers hit the tissue with infrared light, destroying the tumor while leaving non-cancerous tissue untouched. The same nanoshells may have additional uses, such as in welding tissues together to treat a burn victim.⁵⁶ These examples illustrate why a case-by-case evaluation of nanotechnology product safety is needed. One simply cannot draw generalizations about all nanomaterials from the characteristics of one; further, even those characteristics that can be generalized across all nanomaterials may prove useful in certain contexts and dangerous in others.

III. THE FDA'S CURRENT APPROACH

The FDA is an agency within the Department of Health and Human Services, and it is comprised of various centers.⁵⁷ These include, for example, the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Food Safety and Applied Nutrition (CFSAN).⁵⁸ Each of these centers is further divided into several offices. For example, CBER includes an office dedicated to cellular, tissue, and gene therapies and an office for vaccine research and review, among others.⁵⁹ Through these centers, the FDA regulates products accounting for approximately twenty-five cents of every dollar spent by American consumers.⁶⁰ Perhaps this is unsurprising, as the FDA regulates a diverse variety of products including foods and food additives, cosmetics, dietary supplements, animal feeds, pharmaceuticals, medical devices, radiation-emitting electronics, vaccines, blood products, tissues, and sterilants.⁶¹

The FDA's mission, by its very nature, is to engage in a balancing test whereby strict regulatory controls are pitted against the need to get useful and often life-saving products on the market in a timely fashion. The

55. Christopher Loo et al., *Nanoshell-Enabled Photonics-Based Imaging and Therapy of Cancer*, 3 TECH. CANCER RES. & TREATMENT 33 (2004).

56. Andre M. Gobin et al., *Near Infrared Laser-Tissue Welding Using Nanoshells as an Exogenous Absorber*, 37 LASERS IN SURGERY & MED. 123 (2005).

57. U.S. Food & Drug Admin., FDA Organization Charts, <http://www.fda.gov/oc/orgcharts/orgchart.html> (last visited Apr. 6, 2008).

58. *Id.*

59. *Id.*

60. Henry I. Miller, *The Wrong Choice for the FDA*, WALL ST. J., June 26, 1998, at A14.

61. Nakissa Sadrieh, Associate Director for Research Policy and Implementation, U.S. Food & Drug Admin., Address at the Nanobusiness Conference 2005: FDA Consideration for Regulation of Nanomaterial Containing Products (May 24, 2005), slides available at http://www.fda.gov/NANO TECHNOLOGY/powerpoint_conversions/may05.html.

FDA's regulatory scheme is therefore designed for adaptability, and it is built on the recognition that different products require different levels of regulation to ensure the public safety. General adaptability, however, can be stretched only so far before it breaks down, and despite the demonstrably unique properties of nanotechnology-containing products, the FDA states that "[e]xisting requirements may be adequate for most nanotechnology products that [the FDA] will regulate."⁶² The FDA expresses this view because it believes that a new nanotechnology material would be the same size "as the cells and molecules with which FDA reviewers and scientists associate every day. In particular, every degradable medical device or injectable pharmaceutical generates particulates that pass through this size range during the processes of their absorption and elimination by the body."⁶³

While this may be true, the FDA's conclusion that its current regulatory scheme is adequate does not logically follow. First, as illustrated above, the size of a product does not dictate the product's behavior or safety. Size does not necessarily give rise to a particular property; instead, a certain size (on the order of nanometers) provides a strong indication that novel properties may also exist. Second, the nanoscale products with which the FDA claims familiarity are medical devices and pharmaceuticals—products that are often designed to specifically pass through the nanoscale. Some new drugs, for example, are constructed to fit into a protein's "active site" and thereby to either increase or decrease the protein's activity.⁶⁴ These active sites can be even smaller than the nanoscale, on the order of angstroms (or one-tenth as small as a nanometer).⁶⁵ But the pharmaceutical particulates and degradable devices that are approved by the FDA and go on to be successful products are those that survived the FDA's regulatory

62. FDA Nanotechnology FAQ, *supra* note 1.

63. *Id.*

64. An active site is the site on the protein where important activity, such as catalysis of a chemical reaction, takes place. Often, the material upon which an enzyme acts (called a "substrate") will fit into the active site, triggering the protein to perform its normal function. In simplified form, one can envision this mechanism as a "lock and key" model, where the protein is the lock and the substrate that fits into its active site is the key that "unlocks" the protein's activity. Therefore, many researchers work on designing new substrates that would fit in the active site and take the place of the usual substrate. The new substrate could either cause the protein to become inactive or less efficient than the normal substrate (which would be useful if the protein's normal function somehow makes a person ill) or it could increase the protein's efficiency (which would be useful if the protein normally functions to the benefit of the person's health).

65. An angstrom is 10^{-10} meters, where a nanometer is 10^{-9} meters; an angstrom is denoted by the symbol Å. See, e.g., Young Mi Kim & Daniel M. Ziegler, *Size Limits of Thiocarbamides Accepted as Substrates by Human Flavin-Containing Monooxygenase 1*, 28 DRUG METABOLISM & DISPOSITION 1003, 1005 (2000) (providing examples of compounds that about are 4Å in width and 10Å in length and fit into a protein active site).

process—had safety issues arisen due to properties resulting from the product's nanoscale size, that product theoretically would not have received FDA approval. The fact that some products successfully withstood FDA review does not mean that all nanotechnology-related products will likewise be able to withstand such review.

Finally, the FDA's regulatory measures for drugs and medical devices are much more rigorous than for other types of products, such as cosmetics and food supplements, that are just as likely to contain nanomaterials. Any doubts expressed about the adequacy of the FDA's regulatory scheme become even more pressing once one considers that the FDA has little to no regulatory power over these types of products—products that, if they contain nanomaterials, present the same hazards that exist for pharmaceutical or medical device products.⁶⁶

For example, some of the most prominent nanotechnology products on the U.S. market are cosmetics,⁶⁷ which make up more than 15% of the nanotechnology-product market.⁶⁸ These include, for example anti-wrinkle creams such as L'Oreal RevitaLift Double Lifting treatment, which contains “nanosomes” of Pro-Retinol A,⁶⁹ Lancôme's Hydra Zen cream, which contains “nano-encapsulated Triceramides;”⁷⁰ and Zelens's name-brand face cream, which contains C₆₀ molecules.⁷¹ Although cosmetics ostensibly fall under the FDA's regulatory umbrella, they are primarily regulated by the manufacturers themselves.⁷² Indeed, with the exception of color additives, the FDA has no statutory authority to subject cosmetic products to

66. Although the FDA currently does not exercise much regulatory oversight over these types of nanotechnology-related products, this note argues that it is possible for the FDA to do so. For instance, the FDA could use its Office of Combination Products to regulate cosmetics and soaps containing nanomaterials; further, the FDA could strictly enforce its own labeling requirements to promote adequate research into the safety hazards of nanomaterials. These proposals are put forth in more detail below. See *infra* notes 156–161 & 166–171 and accompanying text.

67. TAYLOR, *supra* note 22, at 27.

68. As of April 6, 2008, the Project on Emerging Nanotechnologies had identified a total of 607 nanotechnology-related products, and ninety-five were categorized under “cosmetics.” Project on Emerging Nanotechnologies, Nanotechnology Consumer Products Inventory, <http://www.nanotechproject.org/inventories/consumer/> (last visited Apr. 6, 2008).

69. Liesl Schillinger, *Smart Enough To Understand Your Moisturizer?*, N.Y. TIMES, Dec. 22, 2005, at G3.

70. Lancôme Paris, HydraZen Cream for Normal and Combination Skins, <http://www.lancome-usa.com/skincare/moisturizers/hydra-zen-cream.htm> (last visited Apr. 6, 2008).

71. Project on Emerging Nanotechnologies, Zelens Fullerene C-60 Night Cream, <http://www.nanotechproject.org/inventories/consumer/browse/products/5266/#> (last visited Apr. 6, 2008). The C₆₀ molecule in Zelens cream is the same molecule that has been shown to bind to and deform DNA. See Zhao et al., *supra* note 32.

72. U.S. Food & Drug Admin., FDA Authority Over Cosmetics, <http://www.cfsan.fda.gov/~dms/cos-206.html> (last visited Apr. 6, 2008) [hereinafter FDA Authority Over Cosmetics].

pre-market oversight.⁷³ The FDA states that “[m]anufacturers are not required to register their cosmetic establishments, file data on ingredients, or report cosmetic-related injuries to [the] FDA.”⁷⁴ The FDA cannot authorize a cosmetic product recall, and must depend in large part on the manufacturer to voluntarily remove a dangerous product from the marketplace.⁷⁵ Instead, the FDA attempts to use its misbranding authority to encourage proper substantiation of product safety. If the FDA concludes, through its own examination, that a particular cosmetic product is not safe, the best it can do is use its labeling authority to inform the consumer: “Warning—The safety of this product has not been determined.”⁷⁶ Products that combine cosmetics and drugs (sometimes called “cosmeceuticals”) may slip through the regulatory cracks, because although the FDA claims that “[s]uch products must comply with the requirements for both cosmetics *and* drugs,”⁷⁷ the fact of the matter is that cosmetics that claim to contain nanoparticles “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease [or] articles (other than food) intended to affect the structure or any function of the body of man or other animals”⁷⁸ have not been subjected to pre-market review.

In addition to cosmetics, nanotechnology-related whole foods, generally recognized as safe (GRAS) food ingredients, food packaging, and dietary supplements are also generally not subjected to pre-market review.⁷⁹ If a dietary supplement “presents a significant or unreasonable risk of illness or injury” then the FDA can take the product off the market via court order, but it has no power to regulate the products prior to their release on the market.⁸⁰ Food additives that a manufacturer falsely claims are GRAS may be subjected to pre-market review, but the manufacturer is not required to seek FDA review or to notify the FDA of its marketing plan if *the manufacturer* believes the substance is GRAS.⁸¹ Further, although the Code of Federal Regulations contains a list of substances deemed GRAS by the

73. TAYLOR, *supra* note 22, at 28.

74. FDA Authority Over Cosmetics, *supra* note 72.

75. See 21 C.F.R. §§ 7.40–7.59 (2007) (dealing with recalls generally).

76. *Id.* § 740.10(a).

77. The intended use is established by (1) product claims, such as through advertising, product labeling, or other promotional materials, (2) consumer perception, and (3) the inclusion of drug ingredients, which is established if the ingredients have a “well known (to the public and industry) therapeutic use.” U.S. Food & Drug Admin., *Is it a Cosmetic, a Drug, or Both? (or Is It Soap?)*, <http://www.cfsan.fda.gov/~dms/cos-218.html> (last visited Apr. 6, 2008) (emphasis added).

78. 21 U.S.C. § 321(g)(1)(B)–(C) (2000).

79. Whole foods that incorporate nanotechnology through genetic modification, however, may be subjected to review. TAYLOR, *supra* note 22, at 31.

80. 21 U.S.C. § 342(f); TAYLOR, *supra* note 22, at 32–33.

81. See TAYLOR, *supra* note 22, at 34.

FDA, the regulations only rarely contain any reference to safety data specific to a material's size.⁸² This is no abstract concern, as companies such as Nestle, Kraft, Heinz, and Unilever are investing in food-related nanotechnology research and development—there are already more than 400 companies applying nanotechnology to food in more than 150 different applications.⁸³ Some of these products are already on the market. For instance, one company is using silver nanoparticles in its food containers as an antimicrobial to “reduce the growth of microorganisms,”⁸⁴ and at least forty dietary supplements containing nanoscale ingredients such as iridium, copper, and “nanocolloidal silicate mineral[s]” are available for purchase.⁸⁵

But even for products that receive the most searching FDA review, such as pharmaceutical compounds, nanotechnologies create difficulties. The first of these challenges is a direct result of the way in which the FDA is organized. Assigning a given product to a center is not as easy as it may appear at first blush. Combination products, or products that contain any combination of a drug, a device, and a biological product, are on the rise.⁸⁶

82. See, e.g., 21 C.F.R. pt. 182 (2007).

83. Sean Roach, *Most Companies Will Have To Wait Years for Nanotech's Benefits*, FOODPRODUCTIONDAILY.COM, Aug. 21, 2006, <http://www.foodproductiondaily.com/news/ng.asp?n=69974-nanotechnology-packaging-nano-applications>; see Barnaby J. Feder, *Engineering Food at Level of Molecules*, N.Y. TIMES, Oct. 10, 2006, at C1, C2.

84. For example, Sharper Image is currently marketing the FresherLonger Miracle Food Storage Containers, which use silver nanoparticles “because silver in microscopic particle form is a safe, medically proven antibacterial agent that fights the growth of mold and fungus.” Press Release, Sharper Image, Sharper Image Introduces FresherLonger™ Miracle Food Storage Containers (Mar. 8, 2006), available at <http://www.nsti.org/press/PRshow.html?id=867>. In microscopic particle form, silver may be safe, but there is no mention of whether silver nanoparticles are safe, or if the particles used in the product are actually nanoscale particles. In addition, Sharper Image does not mention the possibility that nanoparticles are used in the product on the FresherLonger product webpage. Sharper Image, FresherLonger™ Miracle Food Storage, http://www.sharperimage.com/us/en/catalog/productdetails/sku_ZN020 (last visited Apr. 6, 2008). This highlights the importance of proper labeling, as a consumer cannot exercise his or her choice to avoid or limit nanoparticle exposure if he or she will not even be informed by the manufacturer that the product contains nanoparticles.

85. Project on Emerging Nanotechnologies, Supplements, http://www.nanotechproject.org/inventories/consumer/browse/categories/food_beverage/supplements/ (last visited Apr. 6, 2008) (listing company descriptions for Nanoceuticals Microhydrin Products and various “Meso” formulations, including formulations containing nanosized iridium, copper, gold, silver, platinum, titanium, and palladium).

86. A combination product, as defined in 21 C.F.R. § 3.2(e), includes:

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) Any investigational drug, device, or bio-

Because “technological advances continue to merge therapeutic products and blur the historical lines of separation between [the] FDA’s medical product Centers,” any one of the three medical product centers (CDER, CBER, and CDRH) could potentially claim regulatory jurisdiction over a combination product.⁸⁷ As each center differs in its regulatory scheme, the destination of a given product can have important consequences for the manufacturer. For example, the application fees differ significantly, ranging from \$281,600 for a pre-market medical device application to \$896,200 for a drug application that requires clinical data.⁸⁸ There are statutory differences in approval times, and anecdotal evidence suggests that manufacturers often believe their product has a better chance of securing approval in one center versus another.⁸⁹ Differences in clinical testing also come into play. For example, CDER and CBER usually require randomized, placebo-controlled studies for certain products, whereas CDRH will allow a variety of different study designs.⁹⁰ This is key for the manufacturer, who is looking to minimize costs, but it also has implications for public safety, as products that should be subjected to the strongest possible review may avoid that review by being assigned to a different center.

The FDA formed the Office of Combination Products, or OCP, in December of 2002 to address these challenges.⁹¹ The OCP is generally charged with overseeing pre-market review of combination products and attempting to maintain consistency in the post-market regulation of those products.⁹² It also works with CBER, CDER, and CDRH to develop regulations and guidelines for combination products. When a combination product application is filed at the FDA, the OCP assigns the product to one of the medical product centers based on the product’s Primary Mode of Action (PMOA).⁹³ It does so in part by considering the applicant’s “request

logical product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

87. U.S. Food & Drug Admin., Overview of the Office of Combination Products, <http://www.fda.gov/oc/combination/overview.html> (last visited Apr. 6, 2008) [hereinafter Overview of OCP].

88. Medical Device User Fee Rates for Fiscal Year 2007, 71 Fed. Reg. 43,784 (Aug. 2, 2006); Prescription Drug User Fee Rates for Fiscal Year 2007, 71 Fed. Reg. 43,780 (Aug. 2, 2006).

89. John Miller, Note, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. 2, 23 (2003), <http://www.stlr.org/html/volume4/miller.pdf> (citations omitted).

90. *Id.* (citing LEWIN GROUP, OUTLOOK FOR MEDICAL TECHNOLOGY INNOVATION: WILL PATIENTS GET THE CARE THEY NEED? 30 (2001)).

91. The OCP was created in the Medical Device User Fee Modernization Act of 2002 § 204, 21 U.S.C. § 353(g) (Supp. IV 2004).

92. Overview of OCP, *supra* note 87.

93. 21 U.S.C. § 353(g)(1).

for designation,” or RFD.⁹⁴ Under 21 C.F.R. § 3.7, the applicant files an RFD setting forth her recommendation as to which center should have primary jurisdiction over her product. The recommendation is based on her perception of the product’s PMOA.⁹⁵ The OCP does not have to follow the recommendation, but as a practical matter, the OCP usually does—an applicant’s recommendation is actually followed 72% of the time.⁹⁶ This symmetry likely stems in part from the fact that if the OCP fails to make its own recommendation within sixty days of the RFD, the applicant’s recommendation will be followed by default.⁹⁷ Therefore, the accuracy of the initial identification of a product’s PMOA may have far-reaching consequences.

Until recently, there was little to assist an applicant in determining a combination product’s PMOA. The FDA did not provide a formal definition, and the very nature of combination products often made it difficult to figure out which action was “primary.”⁹⁸ The director of the OCP, Mark Kramer, explained that there are “products that combine two different things, such as a drug and a device, [and in the future nanotechnology may lead to] . . . products that perform two functions; for example, a single entity’s acting as both a device and a drug.”⁹⁹ In these cases, the combination product may have two different modes of action that are of equal importance. Therefore, in 2005, the FDA attempted to clarify its regulations by providing a definition for PMOA. The PMOA is “the single mode of action of a combination product that provides *the most important therapeutic action* of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”¹⁰⁰ When each mode of action appears equally important, the applicant (or if no recommendation is provided, the OCP) is to follow an algorithm to determine the

94. This recommendation is completely voluntary, but the FDA recommends filing an RFD whenever the classification or assignment of a product is unclear or in dispute. Failure to do so may cause delay, as the FDA will stay any established time periods for agency action during the pendency of the review. 21 C.F.R. § 3.10 (2007).

95. 21 C.F.R. § 3.7(c)(3).

96. 21 C.F.R. § 3.8(b); Suzanne O’Shea, Product Classification Officer, U.S. Food & Drug Admin., Address at AvaMed MTL Conference: Practical Issues in Combination Products: Primary Mode of Action & Request for Designation (May 25, 2006), slides available at http://www.fda.gov/oc/combo/presentations/advamed_files/.

97. 12 C.F.R. § 3.8(b).

98. Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49,848 (Aug. 25, 2005).

99. Erik Swain, *Forging New Regulatory Pathways at FDA*, MED. DEVICE & DIAGNOSTIC INDUS., Sept. 2004, at 58, 60, available at <http://www.device-link.com/mddi/archive/04/09/015.html>.

100. 21 C.F.R. § 3.2(m) (emphasis added).

PMOA. The algorithm dictates that the product will be assigned to the center that regulates products posing “similar questions of safety and effectiveness;” if no such combination product already exists, the product will be assigned to the center with the most expertise as to those safety and effectiveness issues.¹⁰¹

Two problems arise with the OCP’s method of determining an appropriate regulatory center. First, many have criticized the PMOA algorithm as being entirely too subjective, leading to a lack of consistency, predictability, and transparency.¹⁰² One common example of this subjectivity illustrates the point nicely. Common sense dictates that a drug-eluting stent and a drug-eluting disc should be assigned to the same regulatory center, as both are implantable devices designed for drug release.¹⁰³ However, because the stent’s PMOA would be identified as “opening an artery,” while the disc’s PMOA would be identified as “providing chemotherapy to a tumor,” the FDA would route the drug-eluting stent application to the Center for Devices and Radiological Health and the drug-eluting disc application to the Center for Drug Evaluation and Research.¹⁰⁴

The subjectivity of center assignment is likely to be more pronounced in nanotechnology combination products for two reasons: first, the FDA is still relatively unfamiliar with the implications of products created on the nanoscale and may not be able to determine a nanotechnology product’s PMOA with consistency or accuracy;¹⁰⁵ and second, the attraction of nanotechnology products is due in part to their potential combinatorial nature, making it likely that a higher percentage of nanotechnology products will be classified as combination products as compared to non-nanotechnology products.¹⁰⁶ This in turn makes it more likely that

101. 21 C.F.R. § 3.4(b).

102. Mark Lavender, Note, *Regulating Innovative Medicine: Fitting Square Pegs in Round Holes*, 2005 DUKE L. & TECH. REV. 1, ¶ 36, <http://www.law.duke.edu/journals/dltr/articles/pdf/2005dltr0001.pdf> (citing *Risk Should Drive Combo Product Jurisdiction, Industry Recommends*, DEVICES & DIAGNOSTICS LETTER (U.S. Food & Drug Admin., Rockville, Md.), Dec. 2, 2002).

103. To elute something is to wash it out of a material; here, a drug would first be adsorbed onto either a stent or a disc, and when the stent or disc is placed inside the body the drug “washes out” or dissolves into the person’s system. The word “stent” refers a “short narrow metal or plastic tube often in the form of a mesh that is inserted into . . . an anatomical vessel (as an artery or a bile duct) . . . to keep a previously blocked passageway open.” MERRIAM-WEBSTER’S COLLEGIATE DICTIONARY, *supra* note 49, at 405, 1222.

104. O’Shea, *supra* note 96.

105. In fact, the FDA recently held a public meeting to get input and to learn more about nanotechnology and to learn “*whether* there are new or emerging scientific issues that should be brought to [the] FDA’s attention, including issues relating to safety of nanotechnology materials.” Food and Drug Administration-Regulated Products Containing Nanotechnology Materials; Public Meeting, 71 Fed. Reg. 46,232, 46,232 (Aug. 11, 2006) (emphasis added).

106. See Swain, *supra* note 99.

nanotechnology product applications will be routed through the OCP, and thus that those applications could potentially be assigned to an inappropriate center or that similar applications will be routed inconsistently.

Second, the only combination products addressed under current regulation are those that combine some aspect of a drug, a device, or a biologic. No guidance or consideration is given to unofficial combination products. For example, L'Oreal's anti-wrinkle cream RevitaLift has been classified as a cosmetic despite the fact that it contains "nanosomes of Pro-Retinol A,"¹⁰⁷ and the FDA has very little pre-market regulatory power over cosmetics.¹⁰⁸ One can imagine other products, such as nano-engineered foods or dietary supplements, which could create confusion as to whether the product is a food or a drug. These products are difficult to define, and they raise many of the same concerns that prompted the formation of the OCP in the first place.

The FDA must do something to close its regulatory gaps before the public health is adversely affected. Other agencies have recognized that nanotechnology requires something new, and have adapted in an attempt to fulfill their regulatory duties. One such agency is the U.S. Patent and Trademark Office, or USPTO. Many nanotechnology products are subject to both USPTO and FDA scrutiny, as inventors frequently attempt to secure patent protection prior to submitting their product for FDA approval. Despite the fact that these two agencies often work in tandem, however, their current approaches to nanotechnology-related inventions are at odds. Obviously, the goals of the FDA and the USPTO are quite different—the FDA is concerned primarily with public health, whereas the USPTO focuses on limiting its grant of patent protection to those inventions that meet the statutory requirements. But these differences do not preclude the FDA from adapting USPTO methods that are appropriate to its end, nor do they preclude the FDA from taking advantage of information generated by the USPTO.

107. See *supra* note 69 and accompanying text.

108. See Letter from David Rejeski, Project on Emerging Nanotechnologies, Woodrow Wilson Int'l Ctr. for Scholars, to Division of Dockets Management, Food & Drug Admin. (July 19, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC7-Attach-1.pdf>; TAYLOR, *supra* note 22, at 28.

IV. THE USPTO'S CURRENT APPROACH

Title 35 of the United States Code provides that a patentee must meet various criteria before her invention will receive patent protection.¹⁰⁹ First, the inventor has to show that her invention falls within one of the categories of patentable subject matter, namely that her invention is a “process, machine, manufacture, or composition of matter, or any . . . improvement thereof.”¹¹⁰ Next, the inventor must show that her invention is at least minimally useful.¹¹¹ She must enable her invention by describing it with enough detail that another inventor of average skill in the applicant’s field (a “person having ordinary skill in the art”) can make the invention without undue experimentation.¹¹² She must provide an adequate written description, set forth her perception of the “best mode” or method of making the invention, and particularly point out and distinctly claim her invention under the “definiteness” requirement.¹¹³ Finally, the invention must be novel and non-obvious.¹¹⁴ Only if and when the inventor satisfies all of these criteria will she receive a limited monopoly right in her invention.

Of course, the USPTO does not take it on faith that the patent applicant will satisfy these criteria. Each patent application undergoes a rigorous examination by a patent examiner, a procedure that often takes years.¹¹⁵ The USPTO is structurally organized to ensure that it routes each application to the patent examiner best equipped to determine whether the invention meets the statutory requirements. The patent examiners are divided amongst seven technology centers, each of which is dedicated to a broadly-

109. 35 U.S.C. §§ 101–112 (2000). A detailed discussion of patentability requirements is outside the scope of this note; for a rather more detailed explanation, visit U.S. Patent & Trademark Office, General Information Concerning Patents, <http://www.uspto.gov/web/offices/pac/doc/general/index.html> (last visited Apr. 21, 2008).

110. 35 U.S.C. § 101.

111. *Id.* The utility requirement does not preclude the USPTO from granting patent protection to, for example, an invention that deceives a consumer. *See Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366–67 (Fed. Cir. 1999).

112. 35 U.S.C. § 112.

113. *Id.*

114. *Id.* §§ 102–103. The statute prevents an inventor from receiving protection for something that was already invented by another, or from receiving protection for that which would have been obvious to a person having ordinary skill in the art at the time of his invention.

115. In 2007, the average patent was pending before the USPTO for almost thirty-two months. This time has increased from past years—in 2004, for example, a patent was pending on average for about twenty-eight months. UNITED STATES PATENT AND TRADEMARK OFFICE, PERFORMANCE AND ACCOUNTABILITY REPORT: FISCAL YEAR 2007, at 16 (2007), available at <http://www.uspto.gov/web/offices/com/annual/2007/2007annualreport.pdf>. The increase is undoubtedly due in part to the increase in patent applications being filed each year (355,418 in 2003 to 467,243 in 2007). *Id.* at 109 tbl.1.

defined technology.¹¹⁶ For example, examiners within Technology Center 1600 will examine patent applications relating to biotechnology and organic chemistry.¹¹⁷ Each technology center is further divided into four to eight work groups, which are further divided into art units.¹¹⁸ The art units are the smallest subdivisions within the USPTO, and each art unit consists of about ten to twenty examiners.¹¹⁹

Once a patent application is received, it is assigned to an art unit. The art unit's supervisory patent examiner then assigns the application to a specific examiner. The patent applications are also assigned a primary classification number and a more specific sub-classification number.¹²⁰ These classification numbers serve two functions: first, they assist the USPTO in properly routing the patent applications within the agency, and second, they assist examiners in locating relevant "prior art" (references that relate to the invention and may prove that the invention is obvious or not novel).¹²¹ In addition to the primary classification, the examiner will also list other relevant classification and sub-classification numbers on the face of the patent application for purposes of cross-referencing. When the patent application is published, the primary classification/sub-classification number is called the "PR" or Primary Classification; additional classifications are known as "SR" or Secondary Classifications. Once the patent application is going to issue as a patent, the principle classification is an "OR" or Original Classification; the secondary classifications are known as "XR" or Cross Reference Classifications.¹²² Each art unit is assigned dominion over particular PR groups. The limitations as to which applications are routed to a given art unit allow each examiner to gain substantial expertise in his or her specialized area.¹²³

116. Bruce Kisliuk, Group Director of Tech. Ctr. 1600, U.S. Patent & Trademark Office, Presentation at NC Nanotech 2006: Nanotechnology-Related Issues at the United States Patent and Trademark Office (Mar. 9, 2006) [hereinafter *Nanotechnology-Related Issues at the USPTO*], slides available at <https://files.changemywebsite.com/684462/doc/BruceKisliuk.pdf>.

117. The other technology centers are TC 1700, Chemical and Materials Engineering; TC 2100, Computer Architecture, Software, and Information Security; TC 2600, Communications; TC 2800, Semiconductors, Electrical and Optical Systems and Components; TC 3600, Transportation, Construction, Electronic Commerce, Agriculture, National Security and License and Review; and TC 3700, Mechanical Engineering, Manufacturing, Products. There is also a technology center devoted to design patents, TC 2900. U.S. Patent & Trademark Office, Patent Technology Centers, <http://www.uspto.gov/web/info/pat-tech.htm> (last visited Apr. 6, 2008).

118. E-mail from Bruce Kisliuk, Group Director of Tech. Ctr. 1600, U.S. Patent & Trademark Office, to Jessica Fender, Student, Chicago-Kent College of Law (Jan. 28, 2007, 20:15 CST) (on file with the Chicago-Kent Law Review); *Nanotechnology-Related Issues at the USPTO*, *supra* note 116.

119. E-mail from Bruce Kisliuk, *supra* note 118.

120. USPTO, OVERVIEW OF THE U.S. PATENT CLASSIFICATION SYSTEM (USPC) I-1 (2006).

121. *Id.* at I-2.

122. *Id.* at I-4 to I-5.

123. E-mail from Bruce Kisliuk, *supra* note 118.

Like the FDA, the USPTO has been affected by the onslaught of nanotechnology-related inventions—by some measures, the USPTO issued upwards of 8600 nanotechnology-related patents in 2003.¹²⁴ Nanotechnology-related patent applications presented unique challenges to the USPTO's organizational scheme. When these applications first began appearing, the USPTO ignored the “nano” aspect of the inventions, and assigned the applications to art units based upon their underlying technologies.¹²⁵ This technique provides insight as to why almost 800 different patent examiners were assigned nanotechnology-related applications between 2001 and 2003—a number representing almost one-fourth of the total primary patent examiners in the USPTO.¹²⁶ Not surprisingly, data like these raised the concern that examiners were not accumulating much-needed expertise in the nanotechnology field.¹²⁷

The problem, however, is that there are serious difficulties present in classifying nanotechnology-related applications. The only unifying theme in nanotechnology is scale. In other words, “the use or inclusion of structural components or objects that are nanoscale occurs in a wide range of technologies, including many with no common ground or common properties attributable to their nano-sized dimension.”¹²⁸ This diversity is illustrated by looking at PR classifications: nanotechnology-related patents can be found in more than 200 different classes.¹²⁹ Complicating matters further, the field continues to lack a unified nomenclature. Some nanotechnology-related applications do not include recognized nanotechnology terms, either because the generic terms do not best describe the invention or because the applicant may write the patent claims to “hide” them from the competition.¹³⁰ Therefore, simply identifying nanotechnology-related applications can be quite difficult.

124. PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., THE NATIONAL NANOTECHNOLOGY INITIATIVE AT FIVE YEARS: ASSESSMENT AND RECOMMENDATIONS OF THE NATIONAL NANOTECHNOLOGY ADVISORY COUNCIL 15 (2005) available at http://www.nano.gov/FINAL_PCAST_NANO_REPORT.pdf; see Dora Marinova & Michael McAleer, *Nanotechnology Strength Indicators: International Rankings Based on US Patents*, 14 NANOTECH. R1, R2 (2003), available at <http://www.iop.org/EJ/toc/0957-4484/14/1>.

125. Blaise Mouttet, *Nanotech and the U.S. Patent & Trademark Office: The Birth of a Patent Class*, 2 NANOTECH. L. & BUS. 260, 260 (2005).

126. Bhaven N. Sampat, *Examining Patent Examination: An Analysis of Examiner and Applicant Generated Prior Art 25* (2004) (unpublished NBER working paper, on file with the Chicago-Kent Law Review).

127. *Id.*

128. M. Henry Heines, “*Nano-Aerobics*” and the Patent System, 4 NANOTECH. L. & BUS. 335, 338 (2005).

129. Sampat, *supra* note 126, at 25.

130. Raj Bawa, *Nanotechnology Patenting in the US*, 1 NANOTECH. L. & BUS. 31, 38 (2004).

The USPTO attempted to face the challenges of nanotechnology, recognizing that its regulatory scheme had to adapt, as it has in the past, to address these concerns. First, the USPTO began identifying nanotechnology-related applications and patents in November of 2001. In 2004, the agency officially created Class 977/DIG.1, a new nanotechnology CR classification.¹³¹ At that time, the USPTO provided a working definition for those patents and applications that met the requirements of Class 977. It also provided a glossary of common nanotechnology-related terms that examiners might encounter (e.g. “nanotube,” “quantum dot,” and “artificial atom”).¹³² Finally, in November of 2005 the USPTO divided the digest into 263 specific sub-classifications.¹³³ As of April 1, 2008, almost 5000 patents and more than 2500 published patent applications were cross-referenced under Class 977.¹³⁴

To be cross-referenced under Class 977, the patent must “relate[] to nanostructure.”¹³⁵ Not only does the invention have to relate to nanostructure, but that nanostructure must “possess[] a special property, provide[] a special function, or produce[] a special effect that is uniquely attributable to the structure’s nanoscale physical size.”¹³⁶ What does it mean to possess a special property or function? The USPTO further explains:

Special properties and functionalities should be interpreted broadly, and are defined as those properties and functionalities that are significant, distinctive, non-nominal, noteworthy, or unique as a result of the nanoscale dimension. In general, *differences in properties and functionalities that constitute mere differences of scale are insufficient to warrant inclusion of the subject matter in Class 977.*¹³⁷

To provide context for this statement, the USPTO provides two non-limiting examples. First, a conductor that possesses “substantially the same electrical properties” on the nanoscale as it possesses on a larger scale would not be classified as Class 977, but a conventional conductor that

131. Robeson, *supra* note 8, at 2.

132. U.S. Patent & Trademark Office, Class 977, http://www.uspto.gov/web/offices/opc/documents/977_classdef.pdf (last visited Apr. 6, 2008) [hereinafter Class 977].

133. Robeson, *supra* note 8, at 3.

134. U.S. Patent & Trademark Office, US Patent Full-Text Database Manual Search, <http://patft.uspto.gov/netahtml/PTO/search-adv.htm> (searching for CCL/977/\$) (last visited Apr. 6, 2008); U.S. Patent & Trademark Office, US Published Application Full-Text Database Manual Search, <http://appft1.uspto.gov/netahtml/PTO/search-adv.html> (searching for CCL/977/\$) (last visited Apr. 6, 2008). The patents were current through April 1, 2008; the patent applications were current through April 3, 2008.

135. Class 977, *supra* note 132, at 1.

136. *Id.*

137. *Id.* (emphasis added).

exhibits quantum confinement¹³⁸ or superconductivity¹³⁹ when created on the nanoscale would be classified under Class 977.¹⁴⁰ Similarly, a catalyst that becomes more reactive on the nanoscale would not be classified under Class 977, *unless* the increased reactivity was beyond that following naturally from the increase in specific surface area.¹⁴¹

Class 977 also exempts some types of inventions outright. For instance, chemical and biological structures are generally classified elsewhere unless they have a particular “nanostructural assemblage” that alters their chemical or physical properties.¹⁴² Otherwise, almost every chemical or biological structure would “relate to nanostructure.” Apparatuses that manufacture nanoscale matter “top down” instead of “bottom up” are generally excluded,¹⁴³ as are inventions that make use of electromagnetic radiation having a wavelength between 1–100 nm.¹⁴⁴ Exclusions such as these ensure that the inventions cross-referenced under Class 977 do in fact relate to nanotechnology in a meaningful sense.

The USPTO did not stop with creating a new classification scheme. Although nanotechnology-related patent applications do not have their own unique art unit¹⁴⁵ the USPTO has taken steps to ensure that its patent examiners can get the support that they need to become proficient in the quirks of nanotechnology. First, every technology center has a number of examin-

138. For an explanation of quantum confinement, see PETER Y. YU & MANUEL CARDONA, *FUNDAMENTALS OF SEMICONDUCTORS* 470–71 (3d rev. ed. 2005).

139. Superconductivity is “a complete disappearance of electrical resistance in a substance[, especially] at very low temperatures.” *MERRIAM-WEBSTER’S COLLEGIATE DICTIONARY* 1178 (10th ed. 2001). See generally MICHAEL TINKHAM, *INTRODUCTION TO SUPERCONDUCTIVITY* (2d ed. Dover 2004) (1996).

140. Class 977, *supra* note 132, at 2.

141. *Id.* Specific surface area is the surface area of an object divided by its volume. As the volume of a particle shrinks, the ratio of surface area to volume increases. For instance, a 3 cm by 3 cm cube will have a surface area of 54 cm² and a volume of 27 cm³—a 2:1 ratio of surface area to volume. If the cube shrinks to a 2 cm by 2 cm cube, its surface area will be 24 cm² and its volume will be 8 cm³—a ratio of 3:1. If the cube shrinks down to the nanoscale, its surface area to volume ratio will naturally be much higher—any increased reactivity will generally not be a result of special nanoscale functionality. However, if the particle had a reactivity much greater than one would predict from the specific surface area, it could properly be classified under Class 977 (assuming it otherwise fit the classification definition).

142. *Id.* at 1. Thus, a fullerene or a nanotube would still be cross-referenced under Class 977.

143. For an illustration of “top down” versus “bottom up” manufacturing in the nanotechnology context, see ROYAL SOC’Y & ROYAL ACADEMY OF ENGINEERING, *NANOSCIENCE AND NANOTECHNOLOGIES* 25 (2004), available at <http://www.nanotec.org.uk/report/Nano%20report%202004%20fin.pdf>.

144. Class 977, *supra* note 132, at 2.

145. Most nanotechnology patents are distributed amongst the following technology centers: Biotechnology and Organic Chemistry; Chemical and Materials Engineering; Semiconductor, Electrical, Optical Systems; and Mechanical Engineering, Manufacturing, and Products. As of January 2006, these TCs examined a total of 92% of all nanotechnology-related patent applications. Nanotechnology-Related Issues at the USPTO, *supra* note 116.

ers that specialize in nanotechnology-related applications.¹⁴⁶ Although theoretically any examiner *could* be assigned a nanotechnology patent application, the majority of the patents are examined by about 100 examiners.¹⁴⁷ Second, the USPTO maintains a non-publicly accessible website for those examiners who do not feel comfortable with nanotechnology. This website includes nanotechnology-related search information, outside web links, and the contact information for seventy patent examiner “points of contact,” or POCs.¹⁴⁸ These POCs are patent examiners who have substantial experience with nanotechnology and have volunteered to assist less-experienced examiners with their research. Finally, between fifty and 100 patent examiners attend nanotechnology-related training every month.¹⁴⁹

In sum, the USPTO recognized that nanotechnology-related inventions required special attention. It promulgated a working definition of nanotechnology which was specifically adapted to its administrative purpose. It created a new cross-reference class, thereby enabling patent examiners to gain experience in nanotechnology and assisting the examiners in identifying useful references. It also established a framework for examiners to get outside help when they desire it, either through POCs or through special training sessions. Although the USPTO continues to receive criticism in its handling of nanotechnology-related patent applications,¹⁵⁰ it has taken a significant step towards ensuring that it can fulfill its regulatory role with this new type of technology.

V. USING CLASS 977 TO THE FDA’S ADVANTAGE

When one considers that the scanning tunneling microscope was invented in the 1980s,¹⁵¹ the USPTO’s delay in classifying nanotechnology-related patents until 2001 may appear overly long. Compared to the FDA, however, the USPTO has moved relatively quickly. The USPTO’s classification scheme should both highlight the weak points in the FDA’s regulatory oversight and provide a guiding light for the FDA as it modifies its

146. E-mail from Bruce Kisliuk, *supra* note 118.

147. *Id.*; see *Where Science and Law Meet: Nanotechnology and Intellectual Property Issues*, MONTHLY FEATURE (Nat’l Cancer Inst. Alliance for Nanotech. in Cancer, Bethesda, M.D.), Oct. 2006, at 1, 3, available at http://nano.cancer.gov/news_center/monthly_feature_2006_oct.pdf.

148. *Where Science and Law Meet*, *supra* note 147; E-mail from Bruce Kisliuk, *supra* note 118.

149. Often, the training takes place at the Atlantic Nano Forum or the American Society of Mechanical Engineers Nanotech Boot Camp. In addition, there are many other nanotechnology training seminars. E-mail from Bruce Kisliuk, *supra* note 118.

150. *E.g.*, Jon Van, *Slow Patent Process Hurts Nanotech Progress*, CHI. TRIB., Oct. 29, 2006, § 5, at 1, 12.

151. Baird & Shew, *supra* note 3, at 145, 145–46.

current approach—but right now, the information generated by the USPTO is going to waste.

By cross-referencing an application or a patent under Class 977, the USPTO provides public notice that the invention has novel properties *which are not the natural result of small scale*. But that same invention, once submitted to the FDA for approval, will be treated exactly as its large-scale counterpart. Worse, if the invention is a cosmetic, soap,¹⁵² or otherwise GRAS, it will be placed on the market with little to no FDA oversight. The fact that two regulatory agencies with different mandates might regulate particular products differently is not surprising, but in this case it is unacceptable. It is the FDA, not the USPTO, that is charged with looking after the public health and safety; yet when the USPTO provides the equivalent of a warning sign—Class 977—on a patented product, the FDA continues to state that its current regulatory scheme should be adequate.

The USPTO's Class 977 label can and should be used by the FDA to identify products that warrant stricter regulatory controls.¹⁵³ Many pharmaceutical products that are patented at the USPTO will not be cross-referenced under Class 977, since the class definition exempts chemical and biological structures that do not have unique nanotechnology-related properties.¹⁵⁴ Medical devices are more likely to be classified under Class 977,¹⁵⁵ but as already noted, medical devices and pharmaceuticals are two

152. The FDA has a very particular definition of "soap" and a soap product that "consists of detergents or primarily of alkali salts of fatty acids and is intended not only for cleansing but also for other cosmetic uses, such as beautifying or moisturizing" will be treated as a cosmetic. If the soap makes no claims to beauty treatment but instead makes a medical claim (such as curing dandruff) it may be regulated as a drug. Soap that makes no claim beyond cleansing is regulated not by the FDA, but by the Consumer Product Safety Commission. Harold Hopkins, *All that Lathers Is Not Soap*, FDA CONSUMER (U.S. Food & Drug Admin., Rockville, M.D.), Feb. 1979, available at <http://www.cfsan.fda.gov/~dms/cos-215.html#update>; U.S. Food & Drug Admin., *Is it a Cosmetic, a Drug, or Both? (or is it Soap?)*, <http://www.cfsan.fda.gov/~dms/cos-218.html> (last visited Apr. 6, 2008) [hereinafter *Cosmetic, Drug, or Soap*].

153. See, e.g., Petition from the Int'l Ctr. for Tech. Assessment, et al., to the U.S. Food & Drug Admin. 64–68 (May 17, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06p0210/06p-0210-cp00001-01-vol1.pdf> (arguing that nanotechnology inventions that have received U.S. patent protection should be considered novel substances, thereby requiring new drug applications prior to FDA approval). But see Bridget A. O'Leary Smith, *Everything New Is Old Again: Patentable Novelty of Nanoscale Chemical Materials Does Not Imply Newness Under the TSCA and the FDCA*, 4 NANOTECH. L. & BUS. 457, 470 (2007) (arguing that "the patentable novelty of nanoscale chemicals is simply not the proper standard to trigger . . . [new drug] requirements for them" in part because the converse is not true, namely, that "a substance that is *not* new under the Patent Act should *not* be subject to health and safety regulation under the FDCA or TSCA," but recognizing that "this is not to say that nanoscale drugs . . . should not be regulated as new drugs under FDCA or that nanoscale chemicals should not be regulated as new chemical substances under the TSCA").

154. Class 977, *supra* note 132, at 1.

155. The following query yielded 53 patents on April 6, 2008: CCL/977/\$ and SPEC/"medical device." U.S. Patent & Trademark Office, US Patent Full-Text Database Manual Search, <http://patft.uspto.gov/netahtml/PTO/search-adv.htm> (last visited Apr. 6, 2008).

categories of FDA-regulated products that already undergo relatively in-depth pre-market safety testing. The USPTO's Class 977 label is arguably somewhat less useful for these products.

On the other hand, the Class 977 label can be quite useful for the FDA in areas where its regulatory oversight is otherwise at its weakest, such as in cosmetics and soaps. Inventions like these fall squarely within Class 977. L'Oreal Paris, for example, holds twenty-seven patents that are cross-referenced under Class 977.¹⁵⁶ Of these, twenty-one contain the words "cosmetic" or "dermatological" in the title, and another claims to "combat[] blemishes on and/or ageing of the skin" using a composition that can be disbursed by polymer nanocapsules.¹⁵⁷ Johnson and Johnson has invested in a cosmetic composition patent cross-referenced under Class 977,¹⁵⁸ as has Unilever.¹⁵⁹ There are Class 977 patents that claim new body wash compositions¹⁶⁰ and those that nanosize GRAS compounds.¹⁶¹ This provides strong evidence that the Class 977 label effectively identifies a subset of products that are related to nanotechnology and that are not subject to FDA pre-market review.

Obviously, the FDA cannot ensure the public safety by simply subjecting Class 977 inventions to stricter scrutiny: not all inventions move from the USPTO to the FDA; the USPTO issues patents on products that may pose nanotechnology-related health hazards, but are not cross-referenced under Class 977; and some products are regulated by the FDA without the inventor first filing for a patent. Class 977 simply brings into focus the fact that current FDA standards are inadequate to ensure nanotechnology product safety, and that valuable information generated by one agency is being ignored when it could be used to inform the FDA's next steps.

One of the most important things the FDA can do is to propagate its own definition of nanotechnology.¹⁶² Not only would a working definition assist the agency in shaping its policy, but it would assist product manufacturers in determining when they must comply with the FDA's existing regulatory mechanisms. Michael Taylor, of the Project on Emerging

156. *Id.* (searching "CCL/977/\$ and AN/loreal").

157. *Id.* (searching "CCL/977/\$ and AN/loreal and TTL/(cosmetic\$ or dermatologic\$)"). The specific patent referred to above is U.S. Patent No. 5,670,487 (filed June 20, 1996).

158. U.S. Patent No. 6,544,531 (filed Nov. 9, 1999).

159. U.S. Patent No. 5,814,343 (filed Feb. 21, 1996).

160. *E.g.*, U.S. Patent No. 6,303,109 (filed Mar. 3, 1999).

161. *E.g.*, U.S. Patent No. 6,001,336 (filed Dec. 29, 1997).

162. This recommendation has been made in some form by a number of groups. *E.g.*, Petition from the Int'l Ctr. for Tech. Assessment, *supra* note 153.

Nanotechnologies, has convincingly argued that the FDA should provide criteria for two subcategories: “new for legal and regulatory purposes,” and “new for safety evaluation purposes.”¹⁶³ He explains:

To guide companies in making what amount to market-entry decisions for their particular products, [the] 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 [the] FDA’s GRAS, food additive and food packaging regulations or that have been reviewed through the Cosmetic Ingredient Review (CIR). . . . The point is to have a basis for companies to know when they need to come to [the] 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

[The criteria for “new” for safety evaluation purposes] 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.¹⁶⁴

The Class 977 cross-reference should be considered by the FDA and manufacturers alike to indicate that the product is new for both legal and regulatory purposes and for safety evaluation purposes. The cross-reference classification indicates that another governmental agency, while using a definition of nanotechnology that closely resembles the National Nanotechnology Institute’s definition (which the FDA has not officially adopted, but did take part in developing),¹⁶⁵ identified a special functionality, property, or effect in the product that is particularly attributable to its nanotechnology-related aspect. Many products beyond those cross-referenced under Class 977 would qualify under whatever criteria the FDA adopts, but this method provides a starting point with the benefit of providing a bright line rule for manufacturers seeking to comply with FDA regulations, and providing the FDA with an easy way to identify potentially harmful products.

Of course, identifying nanotechnology-related products as “new” for legal or safety purposes will not create the desired effect unless the product is going to be regulated differently than it would have been regulated without the “new” label. In the case of a nanosized GRAS product, for example, classification as “new” has an immediate impact—the nanosized version of the GRAS product will no longer be recognized as safe. But for other prod-

163. TAYLOR, *supra* note 22, at 8.

164. *Id.*

165. FDA Nanotechnology FAQ, *supra* note 1.

ucts, more than the “new” label is needed. It would be a meaningless exercise for the FDA to classify a nanoparticulate-containing skin-firming lotion as “new” if the result is that the lotion remains classified as a cosmetic, because that cosmetic would still not be subject to pre-market regulation.

There are two potential solutions to this problem. First, the FDA could use its labeling power to encourage manufacturers to conduct safety research on their products. For instance, the FDA can consider a cosmetic product containing even one ingredient “whose safety [has not been] adequately substantiated prior to marketing” to be technically misbranded unless it contains a warning label.¹⁶⁶ The FDA should enforce this labeling requirement for Class 977 products immediately. To do so would create a strong incentive for cosmetic manufacturers to substantiate their products’ safety by funding new research. Even manufacturers of nanotechnology-containing cosmetics that are already on the market can be pressured into substantiating their products’ safety. For cosmetics having a “history of use,” once an ingredient’s safety is brought into question the manufacturer must provide a warning label unless (1) there was previous substantiation of the product’s safety, (2) the new information does not demonstrate a human health hazard, and (3) “[a]dequate studies are being conducted to determine expeditiously the safety of the ingredient or product.”¹⁶⁷ This begs the question as to what “adequate substantiation” actually means, but if the FDA adopts a working definition of nanotechnology and creates a list of criteria for classifying products as “new” for various purposes, manufacturers would have greater clarity as to what is required of them. Either way, manufacturers would research the effects of Class 977 products on public health and safety. Further, if these requirements alone do not suffice, the warning labels may create enough public pressure to coerce manufacturers into substantiating product safety. Companies have bowed to pressure in the past when consumers have expressed concern about the lack of product regulation. In 2005, for instance, L’Oreal and Revlon agreed to eliminate from nail polish and other cosmetics certain chemicals suspected of causing cancer, birth defects, and infertility after groups like the Breast Cancer Fund pressured the companies to do so.¹⁶⁸

Second, the FDA should use the Class 977 cross-reference to create a presumption that the product is likely to fall within more than one of its regulatory categories. Such a product might, for example, meet the defini-

166. 21 C.F.R. § 740.10(a) (2007).

167. *Id.* § 740.10(b)(1)–(3).

168. See Laurel Naversen Geraghty, *Should You Worry About the Chemicals In Your Makeup?*, N.Y. TIMES, July 7, 2005, at G3.

tion of both a cosmetic and a drug, or the product might be an “official” combination product that combines aspects of a drug, a biologic, or a medical device.¹⁶⁹ In the case of “official” combination products, the FDA can continue to use its method of identifying the product’s PMOA to assign it to the appropriate office. Upon the identification of an “unofficial” combination product (i.e. a product that combines aspects of more than one regulatory category but does not meet the definition provided in 21 C.F.R. § 3.2(e)), the FDA should strongly enforce its own requirement that the product meet the standards set forth for both regulatory categories.¹⁷⁰ Since, as the FDA notes, “[a]pplications for new drugs must demonstrate the product’s safety and efficacy or the product’s bioequivalence to a previously approved drug product,” this would provide additional insurance that at least some of the Class 977 products would be subject to health and safety research.¹⁷¹

VI. A CALL TO ACTION

The FDA needs to act before more nanotechnology products are placed on the market without adequate oversight. Not only does the FDA undermine its own position as a public protector, but its failure to address nanotechnology when other regulatory agencies are doing so undermines those agencies’ abilities to fulfill their mandates. For instance, the EPA has published an external review draft of a white paper on nanotechnology, provided numerous grants and funded research on nanotechnology’s impact on the environment, and held workshops and conferences on nanotechnology.¹⁷² The NIOSH has likewise published a “strategic plan” for dealing with gaps in nanotechnology health and safety knowledge, and published a paper that reviews what NIOSH currently knows about nanoparticle toxicity and control.¹⁷³ This document requests input from “occupational safety and health practitioners, researchers, product innovators and manufacturers,

169. 21 C.F.R. § 3.2(e).

170. Cosmetic, Drug, or Soap, *supra* note 152.

171. FDA Nanotechnology FAQ, *supra* note 1.

172. U.S. ENVIRONMENTAL PROTECTION AGENCY, NANOTECHNOLOGY WHITE PAPER (2007), available at <http://es.epa.gov/ncer/nano/publications/whitepaper12022005.pdf>; U.S. Environmental Protection Agency, Nanotechnology, <http://es.epa.gov/ncer/nano/factsheet/> (last visited Apr. 6, 2008).

173. NAT’L INST. FOR OCCUPATIONAL SAFETY AND HEALTH, APPROACHES TO SAFE NANOTECHNOLOGY: AN INFORMATION EXCHANGE WITH NIOSH (2006) [hereinafter NIOSH, SAFE NANOTECHNOLOGY], available at http://www.cdc.gov/niosh/topics/nanotech/safenano/pdfs/approaches_to_safe_nanotechnology_28november2006_updated.pdf; Nat’l Inst. for Occupational Safety and Health, Strategic Plan for NIOSH Nanotechnology Research, http://www.cdc.gov/niosh/topics/nanotech/strat_plan.html (last visited Apr. 6, 2008).

employers, workers, interest group members, and the general public.”¹⁷⁴ These agencies admit that they do not have all the information that they need, but they are nevertheless taking steps toward establishing an interim framework for regulation while the necessary information is acquired. If the FDA does not act, nanotechnology products released on the market may adversely impact not only the health of consumers, but the health of the nation’s environment and the health of its workers.

Another concern is that if the FDA does not act quickly to regulate nanotechnology products, the public will lose confidence in the products’ safety. Ensuring that the public gets accurate information about nanotechnology is not only important for consumers, but key for manufacturers as well, because public perception can dictate whether a market will exist for the products of nanotechnology. The FDA’s mission is more than simply regulating new products and protecting the public health. The FDA is also responsible for “helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.”¹⁷⁵ Public confidence in the FDA as an administrative agency has fallen over the last few years.¹⁷⁶ The FDA must counter this perception with regard to nanotechnology products in particular, because “[p]erceived risks may very well constitute the tipping point that will decide whether nanotechnology succeeds.”¹⁷⁷

One has only to think back to genetically modified corn to realize the impact that public perception has on product success.¹⁷⁸ In that case, the EPA approved a strain of corn that was resistant to a particularly threatening insect, but was not harmful to other insects, humans, or animals. Four years later, a paper in the journal *Nature* claimed that the genetically modified corn pollen harmed monarch butterfly larvae.¹⁷⁹ Immediate public outcry followed, and the European Union banned the corn entirely.¹⁸⁰ Later

174. NIOSH, SAFE NANOTECHNOLOGY, *supra* note 173, at ix.

175. U.S. Food & Drug Admin., FDA Mission Statement, <http://www.fda.gov/opacom/morechoices/mission.html> (last visited Apr. 6, 2008).

176. Press Release, Harris Interactive News, The FDA’s Reputation with the General Public Is Under Assault (May 26, 2006), available at <http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=1060>. In 2004, for instance, 56% of people felt that the FDA did a “good or excellent” job in ensuring that innovative products get to the market quickly; in 2006, the numbers were roughly reversed, with 70% having a negative view of the FDA’s ability to do so.

177. Emmanuelle Schuler, *Perception of Risks and Nanotechnology*, in DISCOVERING THE NANOSCALE, *supra* note 3, at 279, 283. See generally JANE MACOUBRIE, INFORMED PUBLIC PERCEPTIONS OF NANOTECHNOLOGY AND TRUST IN GOVERNMENT (2005), available at <http://www.wilsoncenter.org/news/docs/macoubriereport.pdf>.

178. Schuler, *supra* note 177, at 279, 280–81.

179. John E. Losey, Linda S. Rayor & Maureen E. Carter, *Transgenic Pollen Harms Monarch Larvae*, 399 NATURE 214 (1999).

180. Schuler, *supra* note 177, at 279, 280–81.

studies contradicted the earlier results, but neither publication of those studies nor the EPA's statement of confidence in the safety of the corn could save it.¹⁸¹

In the regulatory vacuum that exists at the FDA, there is the risk that a single negative incident like that seen with genetically modified corn could completely undermine public confidence in nanotechnology and derail future efforts at new product development.¹⁸² The now-infamous incident with "Magic Nano" underscores the point. Magic Nano was an aerosol glass and ceramic tile sealant marketed in Germany.¹⁸³ It was recalled just three days after being released on the market, after approximately 100 consumers reported symptoms such as difficulty with breathing and chest pains. A few weeks later, German regulatory authorities released tests showing that Magic Nano contained no nanoparticles whatsoever. By that point, however, nanotechnology's reputation had taken a hit. As yet, no American product has created a similar scare. One could easily occur, and regardless of whether that scare is justified or not, it will impact the public's willingness to use nanotechnology products. Even though there may be no "inherent risks or toxicities associated with nanomaterials, the public's perception of that is not going to be realized until . . . studies are promoted in concert transparently with the development of novel materials."¹⁸⁴ If the FDA creates a strong regulatory network and can assure the public that nanotechnology products are being carefully monitored, nanotechnology will be able to survive and thrive where genetically modified foods could not.

CONCLUSION

The FDA is struggling to come to terms with nanotechnology. That being said, it has taken some important steps towards fulfilling its obligation to protect the public health and safety. For instance, the FDA has formed a nanotechnology interest group, where representatives from each

181. *Id.* at 279, 281.

182. See also Kenneth David, Michigan State University, Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 73–74 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf> (describing how the delay in engaging the public hurt genetically modified foods in Britain).

183. Barnaby J. Feder, *Technology's Future: A Look at the Dark Side*, N.Y. TIMES, May 17, 2006, at G4.

184. Stacey Harper, Oregon State University, Remarks at the Public Meeting on Nanotechnology Materials in FDA Regulated Products 75–76 (Oct. 10, 2006), *transcript available at* <http://www.fda.gov/nanotechnology/meetings/transcript.pdf>.

center meet to discuss nanotechnology-related issues.¹⁸⁵ These groups “provide a level of coordination of review for the various product types . . . [, identify and define] the regulatory challenges in the various review disciplines, [then work to] propose a path forward.”¹⁸⁶ The FDA also held its first public meeting on nanotechnology in October of 2006, where it heard from a diverse group such as Friends of the Earth and the Cosmetic, Toiletry, and Fragrance Association.¹⁸⁷ Within its own centers, the FDA is beginning to conduct nanotechnology research, and is collaborating with the NIH and NIEHS on studies examining the toxicity and absorption of nanosized titanium dioxide and zinc oxide in sunscreens;¹⁸⁸ it also participates in the National Science and Technology Council’s Subcommittee on Nanoscale Science, Engineering and Technology.¹⁸⁹

In addition, the FDA created a Nanotechnology Task Force in 2006; after the FDA’s public meeting on nanotechnology issues, the Task Force released a report on its findings.¹⁹⁰ While adhering to the FDA’s stance that “nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies,” the Task Force took a vital and long-overdue step by recognizing that nanotechnology may create special problems, “both because nanotechnology can be used in, or to make, any FDA-regulated product, and because, at this scale, properties of a material relevant to the safety and . . . effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range.”¹⁹¹ The Task Force noted that for many of the products discussed above, such as GRAS products and cosmetics, “the agency’s oversight capacity is less comprehensive” and the FDA may need to take

185. Press Release, FDA Forms Internal Nanotechnology Task Force (Aug. 9, 2006), *available at* <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01426.html>; U.S. Food & Drug Admin., Nanotechnology, <http://www.fda.gov/nanotechnology/> (last visited Apr. 6, 2008).

186. FDA Nanotechnology FAQ, *supra* note 1.

187. U.S. Food & Drug Admin., Draft Agenda: Public Meeting on Nanotechnology Materials in FDA Regulated Products, <http://www.fda.gov/nanotechnology/agenda1010.html> (last visited Apr. 6, 2008).

188. FDA Nanotechnology FAQ, *supra* note 1.

189. *Id.*

190. NANOTECHNOLOGY TASK FORCE, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION (2007), *available at* <http://www.fda.gov/nanotechnology/taskforce/report2007.pdf>.

191. *Id.* at ii. The report also states that “[t]here may be a fundamental difference in the kind of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way that testing is performed,” *id.* at 13, and expressed some concern about the lack of predictability in biological interactions, since “particle size range or particle concentrations [which could cause an adverse] increase in reactivity . . . would depend on adaptive responses of the affected biological system . . . and, therefore, would be difficult to predict in the absence of test data.” *Id.* at 10.

additional steps to ensure product safety.¹⁹² The report, which was endorsed by the Commissioner of the FDA,¹⁹³ makes a number of key recommendations, including that the FDA actively monitor research into the hazards of various nanoscale materials, develop standards for characterizing nanoscale materials, reassess the way in which nanotechnology-related combination products are assigned to FDA centers, and issue guidance to product manufacturers.¹⁹⁴

Each of these actions should be applauded, but the fact remains that the FDA is simply not doing enough to address the challenges that it admits exist.¹⁹⁵ Other agencies, such as the USPTO, have propagated working definitions and rules to address the unique aspects of nanotechnology-related products and inventions. The FDA should take advantage of the information generated by the USPTO, as well as other agencies, to help it fulfill its role in ensuring the public health and safety. By taking a few small steps now, the FDA can do its part to ensure that American consumers reap the big rewards of tiny technology.

192. *See id.* at iii, 33–34.

193. Memorandum from Andrew C. von Eschenbach to the Deputy Comm'r for Policy and the Associate Comm'r for Science (July 23, 2007), *available at* <http://www.fda.gov/nanotechnology/taskforce/report2007.pdf>.

194. NANOTECHNOLOGY TASK FORCE, *supra* note 190, at 14, 18, 20, 30–34.

195. *See supra* note 191 and accompanying text. As the FDA put it:

Issues that [the] FDA anticipates include: The likelihood that many of the nanotechnology products that the Agency regulates will be Combination Products (i.e., drug-device, drug-biologic, or device-biologic products). Because [the] FDA regulates products based on their statutory classification rather than the technology they employ, [the] FDA's regulatory consideration of an application involving a nanotechnology product may not occur until well after the initial development of that nanotechnology. Because [the] FDA has limited regulatory authority over certain categories of products, the Agency may have limited authority over the use of nanotechnology related to those products. For example, there is no premarket approval of cosmetic products or their ingredients, with the exception of color additives.

FDA Nanotechnology FAQ, *supra* note 1.