VIRGINIA JOURNAL OF LAW & TECHNOLOGY

SUMMER 2007 UNIVERSITY OF VIRGINIA VOL. 12, NO. 6

Nanotechnology and the FDA

JAMES YEAGLE †

ABSTRACT

Nanotechnology, the use and manipulation of particles on the nano-scale, represents an exploding field of science and a corresponding challenge to the FDA's regulatory framework. The major obstacle to effective regulation is the currently unknown variables that contribute to the toxicology of nano-particles. Until further safety research sheds light on this problem, the FDA cannot approve products containing nano-technology with any confidence unless it requires full phase III testing.

† J.D. University of Virginia School of Law, 2007, BA Physics St. Olaf College 2003. The author can be reached for comment at yeagle_james@yahoo.fr.

TABLE OF CONTENTS

I. INTRODUCTION

¶ 1 The ability to respond effectively to changes in the world is one of the great challenges of any regulatory system. The FDA in particular must deal with the breathtaking pace of technological innovation while working under relatively static statutory authority. Nanotechnology, as an innovation holding tremendous potential but largely unknown risks, poses a critical test of the FDA's ability to respond effectively to change. An exploration of its response to nanotechnology highlights two major conclusions: first, there are serious gaps through which novel and potentially unsafe products can slip; and second, greater knowledge through primary health and safety research is the key to closing these gaps.

¶ 2 Nanotechnology is the science of the small—the extremely small. A nanometer, one billionth of a meter, is about the size of a few atoms put together. A working definition from the National Nanotechnology Initiative defines nanotechnology as "the understanding and control of matter at dimensions of roughly 1 to 100 nanometers… nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale."[1] On the one hand, nanotechnology has been around forever: metabolized drugs go through a phase during which they are nano-sized. What is unique is the relatively new and growing ability to create particles and structures in a controlled

[1] National Nanotechnology Initiative, *What is Nanotechnology*, http://www.nano.gov/html/facts/whatIsNano.html (last visited September 10, 2007).

fashion on the nano scale.

¶ 3 This ability has led to a profusion of new research and applications of previously mundane materials that can take on fantastic properties when delivered in nano-sized particles. Everything from sunscreen to clothing to drugs is, or will be, affected by these developments. A new technology with such large impact unavoidably raises concerns about health and safety. These questions need to be addressed not only because of their substantive concerns, but also because consumer fears can lead to backlashes against technology, undermining its potential to improve people's lives. Consider, for example, the rejection of genetically modified foods in Europe. One study found that only eleven percent of Americans believe that industry self-regulation is sufficient for nanotechnology.[2]

¶ 4 The FDA has a number of different tools with which to approach nanotechnology. Its regulatory mechanisms include regimes for drugs, devices, foods, biologics, and cosmetics. Some of these, like the mechanisms for drugs and high-risk devices, provide safety schemes that can adapt to novel technology with an unknown toxicology. Others, like the mechanisms for some lower risk devices and drug monographs (approved formulae for categories of common drug products), depend for their effectiveness upon an understanding of toxicology that is currently lacking for nanoparticulate products. When products are regulated on the assumption that the toxicological profiles of nanoparticulate versions of compounds like carbon or titanium are the same as their larger chemically identical siblings, the opportunity for unsafe products to get to market emerges. Still other categories, such as cosmetics, present a significant risk for unsafe products due to the agency's general lack of regulatory authority in those areas. Thus the first major conclusion of this article is that there are potentially serious regulatory inadequacies in the face of a novel technology like nanotechnology.

¶ 5 The success of some tools and the failure of others would seem to call for an extension of the successful tools to the unsuccessful domains. Yet regulation itself carries substantial risks by slowing the marketing and development process of commercial products. The regulatory regime for drugs is notoriously expensive and time-consuming to navigate, especially when compared with the regime for devices, for example. For small start-ups with lean capitalization that characterize a field like nanotechnology, such time and expense can spell disaster as money runs out before product marketing can begin. Thus, the safety provided by drug-like regulation is balanced by the lost innovation that could improve people's lives.

¶ 6 A better solution, then, and the one this article endorses, is to create the base of knowledge needed to substantiate the current decision-making mechanisms. Once the fundamentals of nanotoxicity are understood, the FDA can once again judge the safety of one product by the safety record of another similar product. With improved understanding, the FDA can know what characteristics make two products relevantly similar in terms of safety. Thus the second major conclusion of this article is that far more of the current federal budget for nanotechnology research should be used to fund

[2] Robert F. Service, *Consumers Nano-Cautious*, 309 SCI. 1661, 1661 (2005).

programs that build an understanding of nanotoxicity.

¶7 This conclusion is supported by one of those rare confluences of industry and environmental interests: the industry fears public backlash if a product turns out to be unsafe, and environmentalists fear the unknown health consequences of a novel technology. A joint op-ed piece published in the Wall Street Journal by Fred Krupp (President of Environmental Defense) and Chad Holliday (CEO of DuPont) articulated the need for increased government spending on safety research:

> Funding to study health and environmental risk represents only 4% of the proposed federal investment in nanotech and becomes vanishingly small when you factor in private investment. Government spending on nanotechnology should be reprioritized so that approximately 10% goes to this purpose. Compared to the estimated $1 trillion market for nanotechnology, this would be a wise insurance policy on such a high-potential investment.[3]

This proposal points to the most effective way to balance regulatory burdens on industry with health and safety concerns: removing the uncertainty surrounding the toxicology of nanotechnology. Once the chemical effects of nanotechnology are known, the regulatory regimes that are now failing to adequately address the unique dangers of nanotechnology will begin to function again.

¶8 This article will begin with an introduction to the field of nanotechnology, its current and future uses, and what is known about its safety hazards. The article will then proceed to analyze each major relevant regulatory regime and its success or failure as applied to nanotechnology. I hope to render this portion both interesting and salient through examples of actual products on the market today. This analysis will conclude that there are devices, monograph-based drugs, and cosmetics on the market today that have unknown toxicological profiles, and therefore represent a risk to public health. This problem is attributable to the regulatory regime combined with lack of knowledge about the unique toxicology of nanoparticles. Thus I conclude that substantial resources should be devoted to understanding this toxicology, and that until then, products should only be approved with great caution.

II. NANOTECHNOLOGY

¶9 Nanotechnology is not so much a field unto itself like biology or physics, but rather an ability to create particles and structures on such a small scale that their very shape begins to take on chemical and biological significance that we would not predict based on the chemical composition alone.[4] Given the diversity of its applications and interdisciplinary nature, it is probably best to introduce the field by example rather than by definition. This is particularly true since size alone does not define the field: water molecules are "nano" in scale, yet making water or water vapor is hardly the radical new field nanotechnology represents.

---

[3] Fred Krupp & Chad Holliday, *Let's Get Nanotech Right*, WALL ST. J., June 14, 2005, at B2.

[4] Robert F. Service, *EPA Ponders Voluntary Nanotechnology Regulations*, 309 SCI. 36, 36 (2005).

¶ 10 Consider carbon, for example. At the macro scale, we know it well as the graphite in sports equipment and the diamonds on jewelry. At the nano scale, chemists and engineers have created new structures out of this same element, such as buckyballs and carbon nanotubes. Buckyballs are an arrangement of sixty carbon atoms into the shape of a soccer ball. While a diamond is relatively inert, buckyballs are strong anti-oxidants.[5] Nanotubes are a diverse array of carbon structures shaped like straws. Nanotubes can be made to conduct electricity like semiconductors or like metals by varying the pitch at which the atoms wind around the straw.[6] The ability to create and control these new structures is at the heart of nanotechnology.

¶ 11 Food packaging is a major area of development using nanotechnology. The integration of nanoparticles can change the nature of plastics, making them stronger, more heat resistant, and less permeable to oxygen—a key feature in food preservation.[7] More advanced applications include use of nanoparticles sensitive to certain food pathogens to trigger a color change in plastic upon contacting a pathogen, making it easy to identify spoiled food.[8] Furthermore, nanoparticulate forms of some elements can act to kill or prevent buildup of microbes. Kodak is developing a plastic to take advantage these properties.[9] Another group has found that the nano form of zinc oxide and magnesium oxide kills microorganisms, and perhaps if added to plastics this could provide another option for safer food packaging material.[10]

¶ 12 Other materials-based applications include the creation of anti-corrosion surfaces that avoid toxic chromates by including nanoparticles that release ions that combat corrosion as it happens.[11] Nanoparticles are also helping to create fire retardants that avoid the use of organic compounds, which actually cause most deaths in fires due to the toxins they release.[12]

¶ 13 Nanoparticles of various forms, often the venerable nanotube, can be made in such a way that they emit an electrical signal when a specific molecule comes in contact with the nanotube.[13] This allows leverage of electrical engineering technologies able to detect and magnify small electrical signals. The combination allows detection of trace compounds with sensitivity far exceeding any current technology.[14] This has potential

---

[5] Lin Am et al., *Carboxyfullerene Prevents Iron-Induced Oxidative Stress in Rat Brain*, 72 J. NEUROCHEM. 1634 (1999).

[6] Robert F. Service, *Nanotech Forum Aims to Head off Replay of Past Blunders*, 306 SCI. 955, 955 (2004).

[7] Azonano.com, *Food Packaging Using Nanotechnology Methods: An Overview of 'Smart Packaging' and 'Active Packaging'*, http://www.azonano.com/details.asp?ArticleID=1317 (last visited Apr. 18, 2007).

[8] *Id.*

[9] *Id.*

[10] FoodProductionDaily.com, *Nanotech Discovery Promises Safer Food Packaging*, http://www.foodproductiondaily.com/news/news-ng.asp?n=59980-nanotech-discovery-promises (last visited Sept. 10, 2007).

[11] John Bohannon, *Smart Coatings' Research Shows the Virtues of Superficiality*, 309 SCI. 376, 376 (2005).

[12] *Id*. at 377.

[13] Robert F. Service, *Nanotechnology Takes Aim at Cancer*, 310 SCI. 1132, 1132 (2005).

[14] *Id.* at 1133.

applications to cancer in early detection of its chemical signature.[15]

¶ 14 Nanotechnology also holds tremendous drug delivery potential. A drug compound can be placed inside a nanoparticle (such as the buckyball) which can then be targeted to specific body sites (such as a tumor), allowing for a much more concentrated dose to the tumor than would otherwise be possible.[16]

¶ 15 These and many other applications, some of which will be illustrated in more detail in case studies below, make up the field of nanotechnology. Given the vast potential already illustrated, it should be no surprise that the amount of research money going towards nanotechnology as well as the predicted market are equally vast. It is estimated that the United States alone will spend $3.7 billion between 2005 and 2008.[17] China invested some $500 million between 2003 and 2007, and even countries that typically invest less in research, like Argentina and Brazil, are getting into the field.[18] The reason for this investment is the expectation that nanotechnology will represent a $1 trillion global market by 2010.[19]

¶ 16 Where this money is *not* going is into researching and testing the safety of nanotechnology. Current funding for toxicology research in the United States stands at a paltry $39 million, representing only 4% of the nano-research budget, and even less when private investment is counted.[20] Thus innovation is far outstripping knowledge of the safety of these products.[21] However, enough is known to substantiate concerns that nanoparticles can be toxic for reasons less related to their chemical composition, and more related to their size and shape.

III. POTENTIAL HARM FROM NANOTECHNOLOGY

¶ 17 This article discusses the now familiar nanotube here, not as an example of the potential benefits of nanotechnology, but of the potential harms. What might seem like an innocuous tube of carbon can actually cause cell death due to the creation of free radicals. The studies are currently few, and scientists are far from understanding all the mechanisms of toxicity, but the following is a summary of what is known based on the existing literature.

¶ 18 First, analogies are drawn to studies involving the health effects of fine particles.[22] These studies have shown that the increase in surface area is key to the toxicity of small particles.[23] Consider that of a lump of carbon, only the surface-exposed atoms can

[15] *Id.*
[16] *Id.* at 1134.
[17] Mohamed H. A. Hassan, *Small Things and Big Changes in the Developing World*, 309 SCI. 65, 65 (2005).
[18] *Id.*
[19] *Id.*
[20] Robert F. Service, *Calls Rise for More Research on Toxicology of Nanomaterials*, 310 SCI. 1609, 1609 (2005).
[21] *Id.*
[22] Andre Nel et al., *Toxic Potential of Materials at the Nanolevel*, 311 SCI. 622, 622 (2006).
[23] *Id.*

interact with the outside world. If that lump is broken into pieces that are each only a few atoms thick, then nearly *all* the atoms are exposed and can interact. Furthermore, the chemistry of surfaces can differ from the chemistry of the rest of the solid.[24] Thus simply by decreasing the size, a compound can become more reactive and react in different ways.

¶ 19 Second, one of the primary mechanisms by which nanoparticles cause harm to cells is through the creation of free radicals.[25] Free radicals are highly reactive forms of molecules such as O_2^- that cause damage by reacting with almost anything around them.[26] They can therefore damage DNA or cell proteins by changing their proper functioning chemistry. Human cells have built-in safety mechanisms to combat and neutralize free radicals since they are a natural byproduct of metabolism. The addition of nanoparticles such as nanotubes, however, can create so many free radicals that the cell is overwhelmed and undergoes apoptosis (cell death).[27]

¶ 20 Other recent literature has discovered surprisingly high levels of toxicity in vitro for nanoparticles depending on their solubility (with mildly soluble particles such as zinc oxide and iron oxide being the worst).[28] In fact, these were found to be as toxic to the human and rodent cell cultures as asbestos.[29] While these tests are not directly transferable to the live human context, they do reveal the disturbing possibilities of unknown toxicities of nanoparticles. It is particularly relevant to note that zinc oxide is currently approved for use in sunscreens by the FDA.[30]

¶ 21 One other study of particular relevance to the following discussion found that high concentrations of buckyballs were correlated with brain damage in fish.[31] The mechanism by which this occurs is not fully understood, but it raises concerns. Buckyballs can also be beneficial as an antioxidant, but without knowing how they cause damage, it cannot be predicted under what circumstances they are safe. Note that in the discussion of cosmetics below, creams containing buckyballs are currently marketed as anti-aging lotions.[32]

¶ 22 Other causes for toxicity are unknown. Variables might include "size (surface area, size distribution), chemical composition (purity, crystallinity, electronic properties, etc), surface structure (surface reactivity, surface groups, inorganic/organic coatings, etc), solubility, shape and aggregation."[33] These many variables make it impossible to predict

---

[24] *Id.* at 622-23.
[25] *Id.* at 623.
[26] *Id.* at 624.
[27] *Id.* at 625.
[28] Tobias Brunner et al., *In Vitro Cytotoxicity of Oxide Nanoparticles: Comparison to Asbestos, Silica, and the Effect of Particle Solubility*, 40 ENVTL. SCI. & TECH. 4374, 4379 (2006).
[29] *Id.* at 4378.
[30] Sunscreen Drug Products For Over-the-Counter Human Use; Final Monograph, 21 C.F.R. § 352.10 (1999).
[31] *See* Eva Oberdorster, *Manufactured Nanomaterials Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass*, 112 ENVTL. HEALTH PERSPECTIVES 1058 (2004).
[32] *See, e.g.*, Zelens Day Cream, http://www.zelens.com (last visited Apr. 19, 2007).
[33] Nel, *supra* note 22, at 626.

which particles will be toxic and which will not.[34] Yet such a model is needed since it is impractical to test every particle under all the above variables. This will turn out to be a key problem for the FDA's regulation of nanotechnology.

¶ 23 The purpose of this section is not to prove that nanotechnology is dangerous. In fact, a literature review in the journal *Science* noted that there have not been any clinical demonstrations of toxicity in humans from current applications to date.[35] The point is that we do not know that these products are safe because we do not know what might make them unsafe, and studies have shown that these particles have the potential to be highly toxic. Thus the two major conclusions relevant to the regulation of nanotechnology are (1) it has the capacity to be highly toxic, and (2) reliance on old models for predicting toxicity is invalid.

¶ 24 Having examined the nature, potential value, and potential harm of nanotechnology, I now turn to the response of the FDA to this new technology.

IV. FDA RESPONSE

¶ 25 The FDA defines nanotechnology as including each of three elements:

> 1. Research and technology development, or products regulated by FDA, that are at the atomic, molecular or macromolecular levels, and where at least one dimension, that affects the functional behavior of the product, is in the length scale range of approximately 1 to 100 nanometers.
>
> 2. Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
>
> 3. Ability to control or manipulate at the atomic scale.[36]

Yet the FDA is quick to note that it regulates products and claims about products, not technologies.[37] As a result, the FDA may not even be aware that a product contains any nanotechnology.[38] It further considers its existing testing methodologies generally adequate for application to nanotechnology.[39] The FDA also notes that small size alone is not a safety issue: every metabolized drug goes through a phase in which it is nano-sized.[40] This status quo approach is also present for foods which the FDA announced it

---

[34] *Id.*

[35] *Id*. at 625, 627.

[36] Nakissa Sadrieh, *FDA Perspective on Nanomaterial-Containing Products*, http://www.fda.gov/nanotechnology/powerpoint_conversions/ilsi-hesi-ann-mtg_files/outline/index.html (last visited Apr. 19, 2007).

[37] U.S. Food & Drug Administration, *FDA Regulation of Nanotechnology Products*, http://www.fda.gov/nanotechnology/regulation.html (last visited Apr. 19, 2007).

[38] Norris E. Alderson, *FDA Regulation of Nanotechnology Products*, http://www.fda.gov/nanotechnology/powerpoint_conversions/pcastmar04_files/outline/index.html (last visited Apr. 19, 2007).

[39] *Id*.

[40] *Id*.

would not regulate differently if it included nanotechnology.[41] As if to allay any fears, the FDA also claimed to have developed test methods to determine the biological response to particles, and that it had not discovered any safety concerns.[42] Thus it generally considers that its authority is sufficient and that it need not alter its general approach to marketing approval.

¶ 26 Despite the apparent confidence in its existing procedures, the FDA has commissioned a two-year study of nanotechnology in cosmetics, and has placed nanotechnology on the agenda of its "critical path" project that seeks to pool manufacturers' research to develop standard and inexpensive means of product testing.[43] It is important to note that the agency receives none of the $1 billion in federal funding allocated to nanotechnology research.[44]

¶ 27 The FDA also recognizes—at least in the context of drugs—that nanoparticles may pose unique toxicity and therefore require careful clinical test design to ensure the tests remain valid.[45] Again, though, it generally believes the current battery of preclinical tests to be sufficient due to the high dose multiples used and the reliance on functional tests, among other considerations.[46]

¶ 28 Thus the FDA's response can be characterized as recognizing its current procedures as adequate but verifying this recognition through research assessing the unique safety characteristics of nanotechnology. The FDA has recently concluded a task force project to examine the issues that nanotechnology poses and came in part to a conclusion similar to the one advocated here: the FDA requires more basic research to effectively regulate nanotechnology.[47]

¶ 29 Part of this apparent dichotomy between confidence that existing procedures are adequate and increased scientific attention to potential risks is likely due to criticisms of the agency's lack of response to the technology. It is also an exploding field, and research on the potential dangers is only trickling in, leading the agency to alter its course over time. While the FDA may be correct in asserting that its testing procedures are adequate to the task, the agency does not require all products to be tested. The fundamental problem that I aim to illustrate below is that products have been approved for marketing without product specific testing and without an adequate understanding of

---

[41] *FDA Not Regulating Nanotech Food Differently Than other Food*, FDA WEEK, 2005 WLNR 19418245 (2005).

[42] *FDA Official: Current Regulations Protect Against Nanoparticles*, FDA WEEK, 2005 WLNR 854264 (2005).

[43] *FDA Critics Say Nanotech on "Path" List Signals More Agency Interest*, FDA WEEK 2006 WLNR 4890377 (2006).

[44] *FDA Research: The Foundation for Sound Regulatory Decisions*, FDA CONSUMER 2006 WLNR 3080402 (2006).

[45] Sadrieh, FDA Perspective on Nano-Containing Products, http://www.fda.gov/nanotechnology/powerpoint_conversions/ilsi-hesi-ann-mtg_files/outline/index.html (last visited Apr. 19, 2007).

[46] *Id.*

[47] U.S. Food & Drug Administration, *FDA Nanotechnology Task Force*, http://www.fda.gov/nanotechnology/nano_tf.html (last visited September 10, 2007).

nanotechnology on which to make a judgment of safety based on comparison to similar products.

V. EVALUATING THE FDA'S REGULATORY RESPONSES

¶ 30 Nanotechnology provides a useful example to evaluate the FDA's response to innovation since it is novel and will affect all of the products that the FDA regulates. The major regulatory frameworks examined below are those for drugs (both new drugs and monographs), devices (classes I through III), foods (specifically packaging), and cosmetics. The purpose of looking at each of these is to canvass the range of FDA regulatory frameworks in an effort to determine what works and what fails in the face of radical innovation like nanotechnology. Those frameworks that use specific product testing, like clinical trials for drugs, successfully respond to innovation like nanotechnology because they do not depend on an understanding of the mechanisms of toxicity to reach a valid conclusion. Rather, they measure patient outcomes to judge success of a product. Those frameworks that operate based on assumptions about the mechanisms of toxicity, like the monograph process and devices in some instances, fail to reach valid conclusions because the mechanisms of nanotoxicity are unknown. This leads to the introduction of potentially harmful products into the marketplace as illustrated by the examples below. I conclude that the regulate-by-comparison frameworks serve a valuable cost controlling function, but must be bolstered by a serious commitment to nanotoxicity research to sustain valid comparative conclusions on safety.

VI. REGULATORY FRAMEWORK: NEW DRUGS

¶ 31 The FDA regulation of drugs is likely the most successful framework in responding to nanotechnology largely because its methodology has such great capacity to handle innovation. This capacity comes from its testing of specific products and from its outcome-based approach that focuses on whether the patients in the clinical trials are better or worse for having taken the drug. As a result, successful decision-making for approval does not depend on understanding the biological mechanisms by which the drug functions. It is this lack of dependence that makes the process so capable of handling innovation. It must be noted, however, that this capacity comes at a cost: the process can take years and cost hundreds of millions of dollars. Thus, this approach is not practicable for all fields of regulation.

¶ 32 Drugs are defined as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and articles (other than food) intended to affect the structure or any function of the body of man or other animals."[48] Thus, the FDA's jurisdiction turns on the intentions of the manufacturer, which are essentially determined by the claims it wishes to make about its product. Violations of the Federal Food, Drug, and Cosmetic Act (FDCA) include misbranding (labeling that is false or misleading or fails to include or display certain information properly)[49] and adulteration (failure to meet purity or manufacturing requirements, or contamination with

[48] 21 U.S.C. §321(g)(1) (2007).
[49] 21 U.S.C. § 352 (2007).

poisonous or unsanitary ingredients).[50]

¶ 33 The FDCA requires that prior to approval a drug must be shown, by substantial evidence, to be safe and effective.[51] This is generally accomplished through three phases of study. In phase I, the product is tested preliminarily for safety and to determine how the drug is metabolized. Phase II looks for preliminary evidence of efficacy. Phase III involves conducting full clinical trials with a sufficient test population to extrapolate the safety and effectiveness of the drug in the general population. These studies look to answer the question: Does this drug work?

¶ 34 The knowledge base provided by these studies depends on the observation of patient outcomes for its validity rather than on an understanding of the biochemistry of the drug. To be sure, the trials cannot be well-designed without some understanding of the biology underlying the drug's function, and this could be the source of some challenge in dealing with nanotechnology. However, absent hidden deleterious effects, the observation of patient outcomes is valid independent of the underlying biology. Thus the drug evaluation system can continue to function well even where innovation has outstripped understanding.

¶ 35 Two case examples illustrate the types of products regulated under this regime and the success of the approach. This success turns on the fact that the FDA requires phase III trials even where nanotechnology is applied to existing drugs, since it constitutes a reformulation and may require new labeling. Thus nano versions of drugs are treated the same as standard versions; likewise, devices enhanced with nanotechnology are also subjected to a new round of trials.

A. Case Example: Abraxane

¶ 36 Abraxane shows that some of the potential of nanotechnology is already being realized. A leading chemotherapeutic drug, Abraxane is a reformulation of Taxol that avoids most of the dangerous and sometimes fatal side effects associated with Taxol through nanotechnology. These side effects are due mostly to the industrial strength solvent in which the drug is delivered. Abraxane attaches the drug to nanoparticles of protein, avoiding the need for such solvents.[52]

¶ 37 As the drug was a new formulation and also required new labeling, Abraxane was required to submit full phase III clinical trial data. The trial demonstrated improved effectiveness and that pre-medication for the side effects required by Taxol was no longer needed.[53]

¶ 38 The known toxicity of nanoparticles is not so unique or latent as to escape

[50] 21 U.S.C. § 351 (2007).
[51] 21 U.S.C. § 355 (2007).
[52] Arlene Weintraub, *A Nano Drug's Giant Promise*, BUS. WK. ONLINE, Apr. 11, 2005, http://www.businessweek.com/magazine/content/05_15/b3928059_mz011.htm (last visited July 1, 2007); *see also*, Abraxane, http://www.abraxane.com/PAT/index.htm (last visited July 1, 2007).
[53] *Id.*

detection in a full clinical trial. If, for example, the nanoparticles were causing substantial cell death due to free radical production, such effects would have been noticed in the patient population. Note, for example, that the time scale for the study of the toxicity of buckyballs in fish showed effects after only 48 hours.[54] While lower doses of a toxic substance may build up over time, this is a problem with all time-limited clinical trials, and not unique to nanotechnology-based drugs. Thus, the regulatory response to Abraxane can be deemed a success insofar as the decisional process was based on valid information not subject to unexpected toxicities of nanotechnology.

B. Case Example: Elan NanoCrystal

¶ 39 Biotechnology company Elan has developed a method to transform many existing drugs into nanoparticulate form.[55] By reforming the drug compound into nanocrystals (not changing its chemical composition), the drug can be suspended in water in such a way that it behaves as if it were in solution. This overcomes the challenge many drugs face: if they are insoluble in water, finding an effective delivery system can be difficult to impossible. Also, by increasing the surface area, the smaller particles can actually make the drug more potent at lower doses (increased bioavailability).[56]

¶ 40 Johnson & Johnson decided to use this technology to reformulate its schizophrenia drug. By reducing the particle size to below 200 nanometers the new formulation overcomes the solubility challenge faced by the original formulation. The FDA required phase III clinical trials for the new formulation, which are ongoing. Again, as a result of a full clinical trial where the well-being outcomes of patients are measured, the FDA can find the new formulation safe with the same confidence it does any other drug formulation.[57]

VII. REGULATORY FRAMEWORK: MONOGRAPH DRUGS

¶ 41 Not all drugs are regulated as new drugs requiring clinical trials. The 1962 amendments to the FDCA first granted the FDA the power to require pre-market approval, and added the 505(d) command that a drug not be approved unless shown safe and effective by substantial evidence (hence the phase III trials requirement). However, by this time there were so many over-the-counter drugs already on the market without any official FDA approval that pulling them all and demanding new drug applications would have been impractical and disastrous.

¶ 42 The FDA created the monograph process to respond to this problem. It would categorize the hundreds of thousands of products into groups and define an approved set of ingredients for each category. Even this process has proved extremely time

[54] Eva Oberdorster, Manufactured Nanomaterials Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass, 112 ENVTL. HEALTH PERSPECTIVES 1058 (2004).

[55] Elan.com, *Nanocrystal Technology*, http://www.elan.com/EDT/nanocrystal_technology/ (last visited July 1, 2007).

[56] *Id.*

[57] Elan.com, *Elan's Proprietary NanoCrystal Technology is Used by Johnson & Johnson*, http://www.elan.com/News/2005/20050112.asp (last visited September 10, 2007).

consuming, as the final rule promulgating the monograph for sunscreen did not emerge until 1999.[58]

¶ 43 The sunscreen monograph was actually delayed for a short time as the industry discovered the possibility of using nano-sized zinc and titanium oxides in sunscreens. In 1998 the FDA issued a proposed amendment to the monograph to include such oxides and called for comments and data.[59] The 1999 final rule approved the use of zinc oxide and titanium oxide. In its discussion of the data in support of including zinc oxide, the FDA focused almost exclusively on the studies demonstrating effectiveness under various conditions. It devoted only these words to safety:

> Based upon the Panel's evaluation of zinc oxide as a skin protectant and the long history of use of zinc oxide in various drug and cosmetic products, the agency continues to believe that there are no safety concerns regarding the use of zinc oxide as a sunscreen active ingredient in concentrations up to 25 percent.[60]

This cursory treatment of zinc oxide indicates that the agency primarily considered the history of safety of larger forms of zinc oxide, not nanoparticles. This conclusion is supported by transcripts of a meeting discussing the FDA's response to nanotechnology. In it, an FDA scientist noted that size is not typically considered a factor in characterizing a substance such as zinc oxide.[61] Furthermore, the scientist commented that the FDA was now in the process of working with National Center for Toxicology Research to investigate the potential toxicity of zinc oxide in sunscreens.[62] This again indicates that the unique properties of nano-sized zinc were not considered during the monograph process. Yet it is precisely the unique nanoparticulate properties of zinc and titanium oxides of which manufacturers seek to take advantage. At that size, these compounds become transparent yet retain much of their UVA and UVB protection.[63]

¶ 44 The problem with this decision-making process is that it relies on an understanding of the mechanisms by which zinc oxide might be toxic. The known historical uses had not proved toxic, yet even if some of these included nano-sized zinc, the FDA had insufficient data to judge it to be safe. The small amount of toxicological data available points to the highly variable toxicity of nanoparticles. Without knowing what variables predict toxicity, it is impossible to know whether one formulation of zinc is similar to another in ways relevant to comparing toxicity. For example, perhaps when zinc oxide is coated with another substance it is quite harmless, but when uncoated it is highly toxic. Therefore, the sunscreen formulation would have to require that coating in order to render the product safe. Or perhaps one-hundred nanometer zinc particles are

[58] Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph, 21 C.F.R. §§ 310, 352, 700 & 740 (1999).

[59] Sunscreen Drug Products for Over-the-Counter Human Use; Amendment to the Tentative Final Monograph; Enforcement Policy, 63 Fed. Reg. 56584 (Oct 22, 1998) (to be codified at 21 C.F.R. pt. 352).

[60] *Id.*

[61] Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Advisory Committee for Pharmaceutical Science 266 (Apr. 14, 2004), http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.pdf.

[62] *Id*.

[63] Sunscreen Drug Products for Over-the-Counter Human Use, 63 Fed. Reg. at 56584.

safe but twenty nanometer zinc particles are not, meaning that the size of zinc would have to be defined in the monograph. The agency itself noted that zinc oxide and titanium oxide ranged across this size spectrum and did not address the potentially different toxicities.[64] Yet the monograph contains none of these or any other variables; it merely allows zinc oxide to be used in concentrations of up to twenty-five percent.[65]

¶ 45 Subsequent research into the toxicity of zinc oxide and titanium oxide, the two approved ingredients in sunscreen, underlines the potential for error in this type of decision-making process. A 2001 study of titanium oxide found two major sources of toxicity in sunscreen applications: the creation of radical hydroxyl groups and direct DNA damage.[66] Both of these processes resulted from interaction with sunlight, which is, of course, the purpose of sunscreen. The hydroxyl groups are formed when the titanium absorbs sunlight, but more importantly the researchers found that the titanium could catalyze DNA damage when illuminated.[67]

¶ 46 A study published in 2005 found that titanium oxide could be toxic even in the absence of light.[68] Critically for the purpose of this article, it found that 200 nanometer particles did not cause damage while twenty nanometer particles did.[69] Thus particle size, a variable recognized by the FDA but ignored for its impact on safety, can in fact matter. It further found another variable unrelated to size that changed the toxicity of nanoparticles of titanium oxide.[70] This again points out the flaws in judging a substance safe based on comparison to like substances when there is insufficient understanding of precisely what makes one compound relevantly like another.

¶ 47 The Royal Society produced one final report of particular note. This comprehensive survey of nanotechnology noted the use of nanoparticles in sunscreen and that "it is clear that nanoparticles have different properties to the same chemical at a larger scale, and the implications of these different properties for long-term toxicity to the skin require rigorous investigation on a case by case basis."[71] The report did not find that such sunscreens were necessarily dangerous since current evidence does not indicate that the particles penetrate below the upper level of the skin, though it offered the caveat that damaged skin (sunburned for example) may offer more opportunity for such penetration.[72] The report further noted a lack of sufficient evidence about zinc oxide in particular, and its known phototoxic effects on mammalian cells' DNA.[73] The Royal

---

[64] *Id.*

[65] *Id.*

[66] *See* Nick Serpone et al., *Deleterious Effects of Sunscreen Titanium Dioxide Nanoparticles on DNA: Efforts to Limit DNA Damage by Particle Surface Modification*, 4258 PROCEEDINGS OF THE SOC'Y OF PHOTO-OPTICAL INSTRUMENTATION ENG'RS 86 (Catherine J. Murphy ed., 2001) (2001).

[67] *Id*.

[68] Jia-Ran Gurra et al., *Ultrafine Titanium Dioxide Particles in the Absence of Photoactivation Can Induce Oxidative Damage to Human Bronchial Epithelial Cells*, 213 TOXICOLOGY 66 (2005).

[69] *Id.*

[70] *Id.*

[71] ROYAL SOC'Y & ROYAL ACAD. OF ENG'G, NANOSCIENCE AND NANOTECHNOLOGIES: OPPORTUNITIES AND UNCERTAINTIES 43 (2004), *available at* http://www.nanotec.org.uk/report/chapter5.pdf.

[72] *Id.* at 44.

[73] *Id.*

Society recommended further study on the possibility of nanoparticle skin penetration and the propensity of these particles to generate free radicals.[74]

A. Drug Conclusion

¶ 48 New drugs utilizing nanotechnology, and reformulations of existing drugs, are not so novel as to undermine the clinical phase III trial required by the FDA to demonstrate safety and effectiveness. The capacity of this approach to handle innovation stems from its focus on *outcomes* for determining validity rather than relying on understanding and predicting the mechanisms of toxicity. This has allowed exciting new drugs onto the market without compromising the FDA's gate-keeping role in determining safety.

¶ 49 The monograph process suffers, however, since it does not demand individual testing of products. Therefore approval of an ingredient is based not on measured outcomes showing that the product, however it works, is safe. Instead, it is based at least in part on assumptions about what makes one compound "like" another. Zinc oxide and titanium oxide were judged sufficiently safe to be included in sunscreens because of their history of unchallenged use. Yet that history is relevant only to the extent those existing products are relevantly "like" the application of zinc in sunscreen. Variables like size and photoactivation are known to change the toxicity of these compounds but remain undefined in the monograph. While nothing has definitively shown that the sunscreen products are actually unsafe, this uncertainty indicates that the FDA's decision-making process may let such products through based on invalid analogies to other safe products.

¶ 50 Yet the application of the phase III clinical testing process to sunscreen is not a practicable alternative. The costs, both to the producer and to the consumer that would no longer have access to the product, are simply too great. Thus, the solution must be to improve the knowledge base such that the FDA can determine which products are relevantly similar and to thereby make a valid judgment about safety. This requires substantial research in developing a model for nanotoxicity. Given the billions of dollars pouring into research, diverting some of these funds to safety would seem prudent at the very least.

VIII. REGULATORY FRAMEWORK: DEVICES

¶ 51 FDA regulation of devices incorporates a number of different approaches, including demonstrations of safety and effectiveness equivalent to phase III clinical trials for drugs, pre-market notification, and light regulation requiring good manufacturing practices. These approaches are based on risk categories, with the riskiest devices regulated the most stringently. To the extent that nanotechnology-based products are placed in class III (the highest risk category), regulation will be just as successful as it is for new drugs. Devices with nanotechnology placed in lower categories run into some of the same challenges that face the monograph process: without an understanding of the mechanisms of nanotoxicity, it is impossible to determine what other products are adequately similar to make a safety determination by comparison.

[74] *Id.* at 50.

¶ 52 A device is defined as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body."[75]

¶ 53 The FDA divides devices into three classes. Class I is regulated very lightly, only requiring compliance with good manufacturing practices and notification if a device fails. Manufacturers of class II devices will sometimes be required to give pre-market notification through the 510(k) process discussed below. Class II products are also subject to performance standards as promulgated by the FDA. Class III devices require pre-market approval and clinical studies similar to those of the phase III trials for drugs.[76]

¶ 54 Like the monograph process, the device regime is partly a product of history and limited resources. After the 1976 amendments creating the new authority over devices, the FDA began the process of classifying current products. It finished the process in 1985. Performance standards for class II products are applied only selectively due the difficulty and cost of developing such standards.

¶ 55 New products which are similar to pre-1976 products that were placed in class I or II logically should be regulated by the same performance standards which apply to them. Thus the 510(k) process was born, in which a manufacturer submits notification of intent to market a device and argues that it is similar to a pre-1976 device and therefore should be regulated along with that category. If the manufacturer successfully persuades the agency to adopt its comparison, this method essentially boils down to FDA approval for marketing without significant further requirements since few performance standards were ever adopted.[77]

¶ 56 The comparison turns on a finding of "substantial equivalence," meaning that the nature and purposes (again often determined by labeling claims) of the product are similar to a pre-1976 product or another product which itself was deemed similar to a pre-1976 product. Two issues are of note in this determination. First, the FDA can, and increasingly will, demand some clinical data to support the finding of substantial equivalence. Thus a finding of substantial equivalence can turn on data showing a similar safety profile to an existing product.[78] Second, such a finding places the product within the same regulatory category as other similar devices, but if the device is categorized as a class II or III product, then it still may be subject to further regulation along with the category as a whole (for example if the FDA promulgates a performance standard).

---

[75] 21 U.S.C. § 321(h) (2006).

[76] *See* U.S. Food & Drug Administration, *Overview of Regulations*, http://www.fda.gov/cdrh/devadvice/overview.html (last visited Mar. 3, 2007).

[77] *Id.*

[78] *See* U.S. Food & Drug Administration, *Premarket Notification 510(k)*, http://www.fda.gov/cdrh/devadvice/314.html (last visited Mar. 3, 2007).

¶ 57 The case of interest for the purposes of this article is the determination of substantial equivalence. By its very nature, determination of equivalence requires an understanding of the relevant variables that make two products "equivalent." To the extent one product has nanotechnology it can only be determined "equivalent" to another product if the same particle is presented in the same form. If the particles are not presented in the same form, the FDA cannot validly find that a product is "substantially equivalent" without knowledge of whether the differences between the products alter the toxicity.

¶ 58 The agency's ability to demand clinical data mitigates somewhat this problematic situation. The clinical data could be used to demonstrate that the toxic profile of a device is consistent with the profile of another product. In application, even this process presents two challenges. First, the FDA must demand data specifically addressing the toxic potential of the nanotechnology. Clinical data showing that one device is as strong or as durable as another device in no way helps demonstrate its use of nanotechnology is safe. Second, such clinical data begins to look like the pre-market approval of a class III product or a phase III trial, imposing potentially crippling costs on small start-ups. Thus the ability to demand clinical data does not get around the basic problem: either judgments are made on a comparative basis and are therefore invalid without better understanding of nanotoxicity, or the agency demands costly clinical data that can cripple a start-up. Both of the challenges can be obviated by the development of a knowledge base giving the FDA the tools it needs to determine which characteristics of two products make them relevantly similar.

¶ 59 The following case example illustrates the 510(k) process and the comparative analysis made without sufficient attention to the unique toxicity of nanotechnology.

A. Case Example: NanOss

¶ 60 NanOss is a synthetic bone material used to replace damaged or removed bone, as well as an alternative to metallic medical devices and the use of donor bones.[79] Based on calcium and phosphate, the same basic building material of natural bones, NanOss follows a line of earlier products seeking to repair or replace damaged bone. NanOss is unique in utilizing a new approach to reduce the size of the calcium and phosphate crystals to the nano scale (forty to sixty nanometers).[80] When formed into a single solid, the crystals form structures that allow natural cells to grow in and around them, eventually recreating natural bone. The patient thus ends up with a bone just as strong as the original. This load bearing ability is unique among synthetic bone replacements.[81]

¶ 61 NanOss was approved by the FDA for marketing as a class II device in February 2005 after submission of a 510(k) application. The FDA found the device to be "substantially equivalent" to other calcium/phosphate bone void fillers, and therefore

[79] Angstron Medicia, *Technology*, http://www.angstrommedica.com/technology/default.htm (last visited June 9, 2007).

[80] Andrew S. Baluch, *Angstrom Medica: Securing FDA Approval and Commercializing a Nanomedical Device*, 2 NANOTECH. L. & BUS. J. 168 (2005).

[81] *Id.*

allowed current marketing subject to future regulation along with the category of bone filler products.[82]

¶ 62 The substantial equivalence determination was based on comparison to five other class II products. None of these products utilizes nanotechnology to the degree that NanOss does. Indeed, its use of nanotechnology is precisely what grants NanOss its unique strength.

¶ 63 Despite NanOss's distinctiveness and the unique toxicity associated with nanoparticles, the FDA found it equivalent to products without nanotechnology. In fact, Angstrom Medica, the company producing NanOss, noted that its regulatory strategy explicitly turned on the FDA's treatment of calcium phosphate as the same regardless of its particle size: "in the eyes of the FDA, it is just calcium phosphate and, therefore, falls under the category of a Class II device."[83] Angstrom pointed this out as a necessary part of its business strategy since it could not afford the clinical trials of a Class III product.[84]

¶ 64 NanOss may well be completely safe. In many of its applications, the nanoparticles have already been formed into a large solid. In vitro and animal in vivo testing could also supply information indicating safety. The problem, demonstrated by Angstrom's very strategy, is that the product is considered similar to regular calcium phosphate when the FDA has insufficient knowledge about nanotoxicity to be sure of such a claim. Even animal testing would only be effective if it specifically looked for nanotoxicity. If the tests were only checking for acceptance of the implant, structural integrity, and durability, for example, it is unlikely that free radical damage to surrounding cells would be noticed. Furthermore, implants such as NanOss expose the patient to very long term exposure, raising the potential that low levels of damage could build up slowly over time.

¶ 65 The purpose here is not to argue that NanOss is in fact dangerous, but rather to point out that the approval process is flawed if it is truly based on a finding of substantial equivalence with existing products. The very rationale of the "substantial equivalence" finding is that products with a long history of use are presumably safe, and new products substantially like those products are likely to have the same safety profile. Yet nanotechnology has no such history, and its toxic profile is unknown, making such analogies inherently invalid. If the FDA requests safety testing information, it could ameliorate this problem. Again, however, such testing must be for toxicity. It is further unclear, then, what justifies the less extensive testing of a Class II device as opposed to the more extensive testing of a Class III. Without an adequate knowledge base about the toxic potential of nanoparticles, the FDA is not in a position to guess which nano-based products carry a high risk of harm and which do not and therefore belong in Class II.

¶ 66 Angstrom Medica points out the countervailing problem: Class III classification would kill the project entirely. Stuck between stifling innovation and allowing products

[82] Memorandum from Federal Drug Administration 501(k) Approving Application K050025 for Angstrom Medica (Feb. 3, 2005), *available at* http://www.fda.gov/cdrh/pdf5/K050025.pdf.

[83] Baluch, *supra* note 81, at 173.

[84] *Id.*

onto the market it believes to be safe, but cannot be sure, the FDA is erring on the side of approval. The real solution to this, however, lies in developing a knowledge base so that the "substantial equivalence" determination can be made based on known properties of nanotechnology rather than on guesses.

IX. REGULATORY FRAMEWORK: FOOD

¶ 67 Foods are another area of application for nanotechnology. For now at least, the major focus is on packaging: everything from smart packages that change color when food goes bad, to plastics made impermeable, to oxygen making the "holy grail" of a plastic beer bottle possible.[85]

¶ 68 Foods are regulated primarily for adulteration, which occurs when a product contains an additive which has not been approved as safe by the FDA.[86] An additive is any substance which reasonably can be expected to get into or affect food.[87] Thus, FDA regulatory authority covers food packaging where the packaging residue could enter the food. The burden is on the manufacturer to demonstrate that an additive is safe, though as of 1997 the manufacturer need not seek formal approval from the FDA.[88]

¶ 69 One major exception to the definition of "additive" are those substances "generally recognized among experts qualified by scientific training and experience to evaluate its safety . . . to be safe" (also known by the acronym GRAS).[89] Since other additives must be demonstrated to be safe, nanotechnology should not pose a problem to the regulatory framework. But if a larger version of a compound is GRAS, and the FDA follows a similar path it has in other areas, it might allow the nanoparticulate version of the compound as GRAS without an independent demonstration of safety. This would be a mistake, as has already been discussed extensively above, due to the lack of understanding of the mechanisms by which nanoparticles become toxic.

A. Case Example: Nanocor

¶ 70 Nanocor uses a natural volcanic clay that breaks into one nanometer sheets as an additive to plastics.[90] This process can produce greater thermal and gas barrier properties among other benefits. The technique allows manufacturers to create, for example, a plastic beer bottle that stays colder, keeps beer fresher, and is lighter than a typical plastic bottle.[91] The benefits to a manufacturer could be a substantial reduction in shipping weight and reduced storage costs.

---

[85] Azonano.com, *Food Packaging Using Nanotechnology Methods: An Overview of "Smart Packaging" and "Active Packaging,"* http://www.azonano.com/details.asp?ArticleID=1317 (last visited June 10, 2007).

[86] 21 U.S.C. § 342(a)(2) (2007).

[87] 21 U.S.C. § 321(s) (2007).

[88] 21 U.S.C. § 348 (2007).

[89] 21 U.S.C. § 321(s) (2007).

[90] *See* Nanocor, http://www.nanocor.com/ (last visited June 10, 2007).

[91] Azonano.com, *Nanotechnology and Food Packaging*, http://www.azonano.com/details.asp?ArticleID=857 (last visited June 10, 2007).

¶ 71 This is but one of many potential applications to food. It is likely that this use of nanotechnology poses little risk since the particles are contained within the packaging material. Nevertheless, this is precisely the kind of new technology that cannot be GRAS because of its unknown qualities. A GRAS finding would contain the same reasoning by analogy flaw that is present in the monograph process and the "substantial equivalence" determination discussed above: without an understanding of the underlying toxicology, reasoning by analogy cannot be valid since the characteristics that make two products relevantly alike are unknown. As a result, unless the product is the same in every way as a product that is GRAS, the FDA cannot confidently declare the new product GRAS since the way in which it is dissimilar may radically change its toxicology. The FDA should therefore follow a regulatory strategy akin to that for drugs, which avoids invalid analogical reasoning, and requires demonstrations of safety from each individual product until a sufficient knowledge base has been formed to label some nanoparticles GRAS.

X. REGULATORY FRAMEWORK: COSMETICS

¶ 72 Cosmetics are very lightly regulated. While they cannot be misbranded or adulterated, the FDA does not have pre-market approval authority, meaning that only cosmetics shown to be unsafe can be pulled from the market through enforcement actions.[92] This renders discussion of the treatment of nanotechnology a relatively moot point except to note that nanotechnology is already showing up in cosmetic products. For example, Zelens is marketing an entire line of creams based on the use of buckyballs (the sixty carbon soccer balls).[93] It attempts to take advantage of the antioxidant properties of these nanoparticles. Of course, it does not mention that these caused brain damage in fish at high doses. Thus cosmetics have been, and will continue to be, a domain in which potentially unsafe products can reach consumers.

XI. CONCLUSION

¶ 73 Unlike the fantastical concerns that nanotechnology would create self-replicating robots that would reduce the world to "grey goo,"[94] the challenges that this kind of radical innovation poses to regulatory systems are quite real. Accepted methods of determining safety, short of actual clinical trials, falter under the pressure of unknown toxicological profiles of novel compounds. What is both particularly intriguing and particularly dangerous about nanotechnology is its superficial relationship to well known substances. Carbon would seem a well-understood and largely innocuous substance being the common thing of diamonds and pencils. Yet at the nano scale it takes on properties that are revolutionizing materials and simultaneously presenting some potentially toxic profiles. Any part of the regulatory system that relies on identifying relevant characteristics of a material to determine safety without full testing becomes invalid when faced with such radically unexpected properties.

---

[92] U.S. Food and Drug Administration, *FDA Authority over Cosmetics*, http://www.cfsan.fda.gov/~dms/cos-206.html (last visited June 10, 2007).

[93] Chemical & Engineering News, *Fullerene for the Face*, http://pubs.acs.org/cen/science/84/8413sci3.html (last visited Sept. 10, 2007).

[94] Robert F. Service, *Is Nanotechnology Dangerous?*, 290 SCI. 1526, 1526 (2000).

¶ 74 The failure of reasoning by analogy when the characteristics that make products relevantly similar are unknown undermines the monograph process, the "substantial equivalence" determination for devices, and GRAS determinations for food products and packaging. The monograph process has approved nanoparticulate-based formulations for sunscreen without adequate consideration of the unique toxicology of nanoparticles. It did so because the nanoparticulate forms of zinc and titanium oxide were not considered significantly different from their macroparticulate cousins. While nanotoxicity is insufficiently understood to claim that sunscreens with these nanoparticles are dangerous, it is precisely this ignorance that undermines the validity of the FDA reasoning behind allowing the product on the market: larger forms of zinc oxide are safe, but it is simply not known whether zinc oxide nanoparticles are safe.

¶ 75 Likewise, "substantial equivalence" determinations used in permitting marketing of devices are undermined by the lack of understanding of nanotoxicity. NanOss was approved based largely on comparisons to products which do not contain nanoparticles. Instead, substantial equivalence appeared to rest on chemical similarity. Analogies based on chemical similarity fail because nanoparticulate forms of an otherwise harmless compound can be highly toxic.

¶ 76 Finally, GRAS determinations, like "substantial equivalence" and the monograph process, require an understanding of nanotoxicity in order to determine which characteristics make two products relevantly similar. Unless a product containing nanotechnology is the same in every way as a product recognized as safe, its toxicity remains unknown since the determinates of nanotoxicity are unknown.

¶ 77 Thus the validity of decisions concerning nanotechnology in these areas is undermined to the extent they rely on any reasoning by analogy. The only way to avoid such reasoning is to follow a regulatory strategy similar to the one used for new drugs. By requiring demonstrations of safety from each individual product, no analogy is needed: the data demonstrates that a particular product is safe without any need to understand how or why it is safe (outside of experimental design issues).

¶ 78 Yet safety determinations by analogy are crucial to sustaining continuing innovation in the marketplace. They represent a far more cost effective way to monitor product safety than full clinical testing, which is only possible for those products expected to bring in hundreds of millions of dollars to well-capitalized firms. As noted above, it was the stated goal of Angstrom Medica to avoid clinical trials for its NanOss product since such trials would be prohibitively expensive to pursue. Thus instead of abandoning reasoning by analogy, it must be bolstered by improved knowledge to be made effective again. Once the characteristics relevant to nanotoxicity are understood, reasoning by analogy can proceed just as it does for many other types of products.

¶ 79 To do this, large investments in research to understanding the mechanisms of toxicity must be made. The Federal government has already allocated $1 billion to nanotechnology research, yet only four percent of this funding is allocated to create an

understanding of safety.[95] Since such knowledge is a kind of "commons" that is valuable to all and available to all once produced, private actors have little incentive to create such a knowledge base unilaterally. Thus it falls on the shoulders of the government to direct the public funds towards production of a public good: understanding the health and safety of a new technology that is revolutionizing our world. Other models of funding are certainly possible, yet whatever the source of funding, the regulatory response of the FDA to innovations such as nanotechnology requires a solid foundation of toxicological knowledge for effective functioning. Only armed with such understanding can the FDA maintain the flexibility and responsiveness it needs to support a new market and protect consumers.

[95] Robert F. Service, *Calls Rise for More Research on Toxicology of Nanomaterials: Environmentalists and Industry Insiders Alike Urge Major Investments to Maintain the Emerging Technology's Spotless Safety Record*, 310 SCI. 1609, 1609 (2005).