

Use of Nanoscale Materials in Commercial Sunscreen Products

Michael F. Cole, Lynn L. Bergeson, and Carla N. Hutton*

Abstract

The decision that the U.S. Food and Drug Administration (FDA) will make on the citizen petition filed by the International Center for Technology Assessment to require FDA to amend its requirements for products containing nanomaterials will be a watershed event in the history of the regulation of products utilizing nanoscale materials.¹ In this article, we will discuss the rise to prominence of nanoscale titanium dioxide and zinc oxide as ingredients of sunscreen formulations, and the reasons for the increase in use. We will review the concerns raised by public interest groups and others regarding potential public health and environmental risks attributed to the unique characteristics of the materials, and the actions taken to design and conduct studies to determine whether the nanoscale materials are suitable for use in sunscreens. We will then move to consider how FDA might utilize the data being developed to respond to the aforementioned petition, reviewing FDA's possible options. The article will conclude with a recommendation as to how FDA might accommodate the competing considerations involved.

I. Introduction

The last decade has seen great strides in the development of nanotechnology and its application to a wide variety of products. At the same time, debate is spirited about the possible risks associated with the use of nanoparticles to replace and/or supplement traditional macromaterials, and the

* Michael Cole is Of Counsel with Bergeson & Campbell, P.C. (B&C). He has a distinguished background in a wide range of matters arising under the Federal Food, Drug, and Cosmetic Act (FFDCA). His practice involves business and regulatory planning to expedite the approval of pharmaceuticals, medical devices, and diagnostic products. Prior to entering private practice, Mr. Cole served as a Johnson & Johnson General Attorney responsible for medical device regulation and as Vice President and General Counsel of the Health Industry Manufacturers Association. Lynn L. Bergeson is Managing Principal of B&C, a Washington, D.C. law firm focusing on conventional, nanoscale, and biobased industrial, agricultural, and specialty chemical product regulation and approval matters, environmental health and safety law, chemical product litigation, and associated business counseling and litigation issues. She is President of The Acta Group, L.L.C. (Acta) and Managing Director of The Acta Group EU, Ltd (Acta EU) with offices in Washington, D.C. and Manchester, UK, and President of B&C Consortia Management, L.L.C. (BCCM) with offices in Washington, D.C. Carla N. Hutton has previously coauthored articles concerning chemical testing issues. Her current work emphasizes global nanotechnology issues.

¹ International Center for Technology Assessment (Citizen Petition to FDA), *Petition Requesting FDA Amend Its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically*, Docket 2006P-0210 (MAY 16, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06p0210/06p0210.htm>.

need to regulate such new uses to minimize potential public health risks. In the main, the discussion has been theoretical, with some notable exceptions. Perhaps the most important one in terms of its possible near term effect on government regulation is the widespread incorporation of nanoparticle titanium dioxide and/or zinc oxide into a variety of sunscreen products, both in the U.S. and worldwide. The sunscreens have been promoted as applying clear, avoiding the traditional and uniquely unflattering chunky white color, particularly of zinc oxide. Proponents claim the sunscreens are very effective, particularly against ultra-violet (UV) light, since the small particles spread more evenly due to the particle size and offer better coverage with less sunscreen being applied—an economic advantage. Another advantage constantly touted is that the nanomaterials will not penetrate normal skin to reach viable skin cells, but will only reach the surface or outer layer of skin.

Opponents of the use of nanomaterials claim that sunscreens using nanotechnology are really no more effective than the traditional formulations, and therefore, should not be used if there will be any increased risk. The opponents point to a variety of such risks.² One claim that is made is that use of the nanomaterial can produce free radicals that can damage DNA. Other stakeholders worry that titanium dioxide is toxic to algae and water fleas, vital parts of the marine ecosystem. A 2009 Report circulated by Consumers Union contained information from Consumers Union and Friends of the Earth summarizing other major concerns:

[Engineered nanomaterials] have been shown to exhibit different fundamental physical, biological, and chemical properties than their larger counterparts. The report indicates that very few nanomaterials have been adequately tested, though the limited data that is available shows that their small size makes them more able to enter the lungs, pass through cell membranes, and possibly penetrate damaged or sun-burnt skin.

In 2007 Consumer Reports (published by Consumers Union) tested sunscreens containing nanomaterials and found no correlation between their presence and sun protection. Consumer Reports testing found neither nanoscale zinc nor titanium oxides provide a clear and consistent performance advantage over other active ingredients. . . . Studies have raised red flags about the environmental impacts that may stem from the release of nanomaterials into broader ecosystems. Once released into the environment, many nanomaterials may persist and accumulate as pollutants in air, soil or water.³

Sunscreen products are popular consumer articles and people use them to try to avoid contracting skin cancer, so there is evidence that there is a real benefit, while the risks appear to be largely speculative at this point. Nevertheless, the theoretical concerns about the safety of nanomaterials of various configurations has led to calls such as in the report above for the discontinuation of use of such substances in sunscreens until extensive testing is conducted to determine whether the nano forms of materials have a similar safety profile to their macro counterparts. The most serious effort is a citizen petition submitted to FDA to halt the use of nanoscale substances until they are more adequately tested.⁴ The petition and other activities involving FDA will be discussed below. Such testing has been and is underway, but it is hardly conclusive. About the only point on which there is any agreement is that nanomaterials are safe for use on undamaged skin, but even that is

² Journal of Drugs in Dermatology, *Nanotechnology in cosmetics and sunscreens: an update* (Oct. 2009), http://findarticles.com/p/articles/mi_m0PDG/is_10_8/ai_n39372974/pg_2/?tag=content;col1 (last visited Mar. 12, 2012).

³ Consumers Union, *New Report From Public Interest Groups Warns of Risks From Nanomaterials in Sunscreens* (Aug. 19, 2009), http://www.consumersunion.org/pub/core_product_safety/014360.html (last visited Mar. 12, 2012).

⁴ See Citizen Petition to FDA, *supra* note 2.

contested by some.⁵ A *New York Times* article sheds more light on the debate and the participants, some taking unlikely positions. The article reported that a Friends of the Earth “Consumer Guide” posted in 2007 drives home the fact that some reported laboratory research suggests that the smaller particles could penetrate the body in ways the larger particles cannot. It also spotlights the fact that at this point FDA has announced no plans to inhibit the sales of such products by requiring more safety studies or labeling telling consumers which products contain new nanoscale ingredients, and goes on to say:

But the Environmental Working Group, while agreeing that the regulators have been more passive than a sunbather when it comes to requiring nanotechnology safety research in cosmetics, took a different view of the available evidence.

The 15 peer-reviewed studies on skin absorption showed no absorption of small-scale zinc and titanium sunscreen ingredients through healthy skin, the Environmental Working Group said. It noted that studies investigating absorption through damaged skin are not available, but added that such data is also missing “for nearly all of the 17 sunscreen chemicals approved for use in the U.S.”⁶

And some of those alternative ingredients, which Friends of the Earth ignored, troubled the Environmental Working Group. “In contrast to zinc and titanium, studies show that some traditional sunscreens like oxybenzone and octinoxate definitely absorb into healthy skin—in large amounts according to some studies.”—and act like estrogens in the body, raising risks for breast cancer, and showing effects like hormone-driven uterine damage in other studies,” it said.⁷

Even talk of the safety when used on intact skin complicates the issue, since proponents of use say warnings can suffice about use on damaged skin and additional testing is not needed prior to marketing when used on viable skin.

II. Testing Nanoscale Materials

Public interest groups, product manufacturers, academics, and various governmental agencies have begun conducting tests to try to ascertain the answers to the risk questions. Much of the test data from studies conducted by the proponents and opponents are contained in the aforementioned citizen petition, and perhaps not unexpectedly in such a highly charged atmosphere, the study results conflict on every score. Part of the fundamental lack of accord stems from the lack of agreement about what to test, and the circumstances under which the testing is being conducted. Initially, manufacturers made much of the fact that their product offerings contained nanoparticles, usually of zinc oxide or titanium dioxide. As concerns about safety spread, some manufacturers ceased using the materials. W.S. Badger Company, Inc., a New Hampshire firm that manufactures a variety of personal care products, including sunscreens, in describing on its website why it changed the components of its sunscreen products, states:

⁵ *Id.*

⁶ Barnaby J. Feder, *Nanoparticles in Your Sunscreen: Too Hot to Handle*, *N.Y. Times* (Aug. 14, 2007), available at <http://bits.blogs.nytimes.com/2007/08/14/nanoparticles-in-your-sunscreen-too-hot-to-handle/> (last visited Mar. 12, 2012).

⁷ See *id.* (In the article, the author, Barnaby J. Feder, concluded somewhat facetiously, “So who wins this argument? Perhaps the folks who make beach umbrellas.”).

Badger's sunscreens have become extremely popular in the past few years, largely because our only active ingredient is the mineral zinc oxide. Starting in March of 2011 all Badger sunscreens use only uncoated non-nano sized particles of zinc oxide (the same kind found in calamine lotion and diaper rash cream).⁸

Badger goes on to discuss the rationale for switching:

What is the zinc oxide nanoparticle controversy about anyway?

When a substance is so small that it is measured in nanometers (1 to 100 billionths of a meter) the surface area to volume ratio is so great that the properties of the substance may change. One comprehensive review of the scientific literature shows that particles of zinc oxide greater than 30nm do not exhibit characteristics any different than those of larger sized particles. Well intentioned groups such as Friends of the Earth and Consumer Reports popularize the nanoparticle controversy by highlighting the potential health risks caused by nanoparticles if they were to enter deeper tissues, the blood, or the lungs. Science overwhelmingly shows that particles of zinc oxide greater than 30nm, when applied to the skin, do not get absorbed into the body, do not enter the bloodstream, and are not a threat to human health. There are no studies showing that nanoparticles of zinc oxide can penetrate healthy human skin, whereas there are several studies showing that chemical sunscreen ingredients, which are molecular in size and thus significantly smaller than nanoparticles, are absorbed into the blood. The biggest concern with nanoparticles in cosmetics is the threat of inhalation with powders. This is not a concern when the powder is dispersed in a cream base. Even the Environmental Working Group recommends the use of nano sized mineral sunscreens over chemical sunscreens.⁹

Other companies were purported to have stopped promoting the use of nanomaterials entirely or ceased even mentioning that nanomaterials were incorporated into sunscreens, leaving prospective users with no way of knowing whether there are nanomaterials in the sunscreens they are buying. For example, Consumers Union reported that it tested eight sunscreens, all of which contained nanoparticles, but only one disclosed the incorporation of such nanoparticles.¹⁰ Some companies have taken to talking of micronized or microfine particles instead of mentioning nanotechnology. There is no agreement about the terms, although many use micronized to describe something between 100 and 2,500 nanometers. Where nanomaterials are mentioned, there is very little noted about the form of materials used, although it appears that metal oxides are used and described simply as nanoparticles. The titanium dioxide used is said generally to be a composite of rutile and anatase titanium dioxide. Fullerenes and quantum dots have been tested using titanium dioxide at the National Toxicology Program (NTP), but do not appear to be in use, given the expressed concern, again largely theoretical, of the increased risk of those forms penetrating the body. Inquiries to manufacturers to find out what form of nanomaterial they are using are routinely met with claims of confidential trade secrets being involved.

⁸ W.S. Badger Company Inc., *Zinc Oxide & Nanoparticles in Sunscreens*, http://www.badgerbalm.com/t-sunscreen_zinc_oxide_nanoparticles.aspx (last visited Mar. 12, 2012).

⁹ *Id.*

¹⁰ Letter from Michael Hansen, Ph.D., Senior Scientist, Consumers Union, to The Honorable Andrew C. von Eschenbach, M.D., Commissioner, U.S. FDA (Oct. 30, 2008), available at http://www.consumersunion.org/pub/core_product_safety/006254.html. See also Friends of the Earth Australia, Nanotechnology Project, *Companies deny consumers information on nano-ingredients in sunscreens, cosmetics*, available at <http://nano.foe.org.au/companies-deny-consumers-information-nano-ingredients-sunscreens-cosmetics> (last visited Mar. 12, 2012).

Given the controversy, the substantial commercial stakes, and the overarching concern of public interest groups, it is hardly surprising that there is continuing disagreement about the design, conduct, analysis, and even the relevance of work undertaken to demonstrate the nanoparticles of zinc oxide and titanium dioxide are safe when used in sunscreens. NTP has listed a number of impediments to conducting effective research on the subject:

Prioritizing and obtaining materials to evaluate are major challenges for the NTP. Specific nanomaterials with the highest exposure potentials are not well known, making it difficult to identify the most important materials to study. Obtaining materials is also an impediment. In many cases, information about the nanoscale material is proprietary. Consequently, the NTP may be unable to study those materials that pose the highest potential exposure to humans. In other cases, the material may be available, but not in sufficient quantities to allow an adequate hazard evaluation, particularly regarding long-term, repeated exposure studies.

Characterization of nanomaterials has proven to be more difficult than anticipated for several reasons. First, a standard nomenclature has not been developed. Second, biologists, physicists, and materials scientists working in this area often do not communicate effectively. In addition, an analytical infrastructure to allow characterization is not consistently available or well-located. The high degree of variability in size and surface chemistry of nanoscale materials and in the coatings, crystal structure, shape, and composition used in preparing these materials increase both their complexity and the multiple permutations that must be considered in their evaluation. Adequate methods to detect nanomaterials in cells and tissues also need further development.¹¹

Various FDA components have announced testing designed to address many of the problems NTP cited related to the use of nanomaterial in sunscreens and otherwise, presumably in part to be able to respond to the aforementioned petition and other issues that will come up as nanoscale material is used in more regulated products. The Center for Drug Evaluation and Research (CDER) is investigating particle size determination in marketed sunscreens with titanium dioxide and zinc oxide nanoparticles, and is developing *in vitro* assays to assess toxicity of selected nanoparticles in collaboration with the Center for Devices and Radiological Health (CDRH).¹² The Center for Food Safety and Applied Nutrition (CFSAN) is collaborating with FDA's National Center for Toxicological Research (NCTR), NTP, and Rice University in evaluating the effects of varying nano-size on the penetration of quantum dots through human and pig skin; evaluating the penetration of titanium dioxide and zinc oxide nanoparticles through human skin; and evaluating the photocytotoxicity of titanium dioxide nanoparticles using human skin fibroblasts. NCTR lists other collaborative studies.¹³ It is evaluating the effect of size and coating on dermal penetration of quantum dots in skin of hairless mice (collaboration with NTP and Rice University) and evaluating the toxicology of nanoscale titanium dioxide and zinc oxide (size and coating); dermal penetration *in vitro* and in mice and pigs; pharmacokinetics (PK) and toxicogenomics in mice; phototoxicity *in vitro* and mice; and photocarcinogenicity in mice (collaboration with NTP, CFSAN, and Rice University). The unit at

¹¹ Dept. of Health and Human Svcs., National Toxicology Program (NTP), Frequently Asked Questions (FAQs), <http://ntp.niehs.nih.gov/?objectid=30302D16-F1F6-975E-7B315D93D4A1246F> (last visited Mar. 12, 2012).

¹² NAKISSA SADRIEH, PH.D., FDA CONSIDERATIONS FOR REGULATION OF NANOMATERIAL CONTAINING PRODUCTS (2006), available at [www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-31-FDA-Nano%20Sadrieh%20nanotech%20presentation%20\(2\).pdf](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-31-FDA-Nano%20Sadrieh%20nanotech%20presentation%20(2).pdf).

¹³ *Id.* See also FDA, Existing Public Private Partnerships: Public-Private Partnership Program Descriptions, <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm> (last visited Mar. 12, 2012).

Rice University is the Center for Biological and Environmental Nanotechnology (CBEN).¹⁴ In addition to the aforementioned work, CBEN lists the characterization of nanoscale oxides of titanium and zinc from five selected commercial products for size, crystallinity (titanium dioxide anatase or rutile), morphology/aggregation state, elemental composition, surface coatings and surface area, and generation of reactive oxygen species (ROS).

Another government collaboration occurred where, recognizing that extensive cross-sector and multi-disciplinary efforts are needed to understand and develop nanotechnology-based platforms and tools for cancer research, as well as diagnostic and therapeutic applications, FDA, the National Cancer Institute (NCI), and the National Institute for Standards and Technology (NIST) embarked upon a partnership that leverages each party's core expertise and resources to facilitate nanotechnology.¹⁵

This effort was an expansion of what FDA terms an already robust collaboration with NCI under the auspices of the Interagency Oncology Task Force (IOTF), started in 2003. The nanotechnology subcommittee under the IOTF, with a mission to foster greater understanding of the biomedical applications of nanotechnology, maintains this collaboration in nanotechnology. These joint activities include active participation with the staff at the Nanotechnology Characterization Laboratory (NCL) of the NCI.¹⁶ Other activities include:

- Co-development of characterization assay cascades associated with *NCI's NCL*.
- FDA staff on the standardization of approaches for evaluating nanoscale particles submitted to the NCL.
- FDA providing scientific and regulatory input and guidance to the investigators and partners within the *NCI's Alliance for Nanotechnology in Cancer*.¹⁷

Another of the collaborative efforts FDA is engaged in is collaboration with the Houston-based *Alliance for NanoHealth (ANH)* and its eight member institutions to help speed development of safe and effective medical products in the emerging field of nanotechnology. Under a Memorandum of Understanding, the FDA/ANH Nanotechnology Initiative will work to expand knowledge of how nanoparticles behave and affect biological systems, and to facilitate the development of tests and processes that might mitigate the risks associated with nanoengineered products. All outcomes from this public-private partnership will be placed in the public domain for the benefit of all stakeholders.

The eight academic institutions include Baylor College of Medicine, the University of Texas M.D. Anderson Cancer Center, Rice University, the University of Houston, the University of Texas Health Science Center at Houston, Texas A & M Health Science Center, the University of Texas Medical Branch at Galveston, and the Methodist Hospital Research Institute.¹⁸

¹⁴ See Rice University, Center for Biological and Environmental Nanotechnology, <http://cben.rice.edu/showhome.aspx> (last visited Mar. 12, 2012).

¹⁵ FDA, FDA Collaborations With NCI and NIST on Nanotechnology, <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm231125.htm> (last visited Mar. 12, 2012).

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ FDA, News Release, FDA and Eight Academic and Research Institutions to Collaborate Under Nanotechnology Initiative (Mar. 10, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149541.htm>.

In addition to the various collaborations, FDA has been working to expand its ability to research regulated products. FDA has created a Nanotechnology Core Facility on the NCTR and Office of Regulatory Affairs/Arkansas Regional Laboratory (ORA/ARL) campus that provides NCTR and ORA scientists with the tools and expertise to characterize and determine the toxicity of nanotechnology-based, potentially FDA-regulated nanomaterials. This Core Facility is jointly funded by the FDA and the National Institute of Environmental Health Sciences (NIEHS)/NTP providing FDA regulatory scientists and study scientists with the tools to properly conduct toxicity studies on nanotechnology-based materials and products. The NCTR/ORA Nanotechnology Core Facility is also providing support to FDA by providing materials characterization, the use of external techniques to probe into the internal structure and properties of a material, analytical support, and electron microscopy support for a broad range of nanomaterial studies. Nanotechnology research will aid in the development of guidelines for the safe and effective use of these materials in drug products, devices, foods, cosmetics, and dietary components. By continuing nanomaterials research, FDA hopes to have a better understanding of the consequences of human exposure to nanoscale materials. The Nanotechnology Core Facility was able to hire key scientific personnel and purchase and install equipment during the 2011 fiscal year. These new additions will ensure a scientific core for nanotechnology research at FDA.¹⁹

FDA has listed on its website a selected group of the publications its staff has helped to prepare.²⁰ Only one of the publications, an article written by Dr. Nakissa Sadrieh as the lead author, on its face appears to relate directly to sunscreens.

Finally, NTP has been actively considering the nanoparticle/sunscreen issue. It discusses on its website its program objectives, which are to evaluate nanoscale titanium dioxide and zinc oxide due to their presence in cosmetics. NTP intends to study:

- Characterization of size, crystallinity, and coating of these metal oxides in representative commercial sunscreens;
- Evaluation of photoactivation of titanium dioxide in *in vitro*, *ex vivo*, and *in vivo* models;
- Dermal penetration of titanium dioxide in *in vivo* and *in vitro* models;
- Phototoxicology of titanium dioxide in mice; and
- Photocarcinogenicity of titanium dioxide in mice.²¹
- No abstract or study report is listed on the site.

In addition to FDA and related organizations described above, other agencies at the federal and state level are considering nanoscale materials, including in sunscreen. For example, the U.S. Environmental Protection Agency (EPA) published case studies on the use of nanoscale titanium dioxide as an active ingredient in topical sunscreen, as well as an agent for removing arsenic from drinking

¹⁹ FDA, Nanotechnology Toxicity Studies Support, <http://www.accessdata.fda.gov/FDA/track/track-proj?program=nctr&id=NCTR-OSC-Nanotechnology-Toxicity-Studies-Support> (last visited Mar. 12, 2012).

²⁰ See FDA, FDA Nanotechnology Regulatory Science Research Categories: Selected FDA Publications Related to Applications of Nanotechnology, available at <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm196697.htm>.

²¹ NTP, Nanotoxicology Safety Initiative Projects, <http://ntp.niehs.nih.gov/?objectid=303069A0-F1F6-975E-72D33ECBD3E11363> (The reference also discusses many other aspects of the NTP program.) (last visited Mar. 12, 2012).

water.²² According to EPA, it organized the case studies around a comprehensive environmental assessment framework, combining a product life-cycle perspective with the risk assessment paradigm. EPA intends the case studies to help identify what may need to be known to conduct a comprehensive environmental assessment of the potential risks related to nanoscale titanium dioxide. In developing the case studies, EPA first released them in draft for public review and comment, and then held a workshop to identify and prioritize research questions related to nanoscale titanium dioxide. EPA finally conducted an independent external peer review of the draft case studies document.

At the state level, the California Department of Toxic Substances Control (DTSC) has been active, initiating two data call-ins (DCI) for nanomaterials. The first, in January 2009, concerned carbon nanotubes.²³ The second, initiated on December 21, 2010, concerned nanoscale titanium dioxide, as well as several other nanoscale metals and oxides and quantum dots.²⁴ DTSC notes that nanoscale titanium dioxide is used widely, including in cosmetics and consumer products. DTSC requested information no later than December 21, 2011. Prior to its DCI for nanoscale titanium dioxide, on March 8, 2010, DTSC and EPA participated in a conference call hosted by BASF, Evonik, Dupont, and Pennsylvania Bio Nano Systems, LLC. According to the DTSC website, the call was intended to educate DTSC and EPA staff on specific aspects of titanium dioxide and organic sunscreens, including a description of the manufacture and post-manufacture processing of titanium dioxide; the characterization of titanium dioxide; the general uses of titanium dioxide; and the specific uses of titanium dioxide in sunscreens.²⁵

DTSC is currently in the process of developing Safer Consumer Products Regulations that focus on chemicals and chemical ingredients in consumer products.²⁶ While there had been a contemplated exemption for nanomaterials in the prior draft regulations, the most recent draft does not mention nanomaterials or offer any specific exemption for nanomaterials. Under the Safer Consumer Products Regulations, DTSC will develop a list of chemicals of concern. To the extent that any nanomaterials have not yet been identified by regulatory agencies on the lists from which DTSC will derive its chemicals of concern list, it would appear that nanomaterials will not, at least initially, be subject to these requirements.

As described above, both public interest groups and industry associations have been active in the consideration of nanoscale issues involving sunscreen. The Personal Care Products Association (formerly the Cosmetics, Toiletries and Fragrances Association (CTFA)) has submitted comments and testified at the FDA information gathering activities.²⁷ Global organizations have been involved

²² EPA, *Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen (Final)*, EPA/600/R-09/057F (2010), available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=230972>.

²³ DTSC, Carbon Nanotube Information Call-In, <http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/CNTcallin.cfm> (last visited Mar. 12, 2012).

²⁴ DTSC, Chemical Information Call-In - Nano Metals, Nano Metal Oxides, and Quantum Dots, <http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/nanometalcallin.cfm> (last visited Mar. 12, 2012).

²⁵ See DTSC, SPONSORED FORUMS: PUBLIC WORKSHOP ON STATE AND FEDERAL NANOMATERIAL ACTIVITIES, available at <http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/ArchivedSymposium.cfm>.

²⁶ DTSC, Safer Consumer Products Regulations, available at <http://dtsc.ca.gov/SCPRegulations.cfm>.

²⁷ See Citizen Petition to FDA, *supra* note 2 for the comments filed by CTFA to the petition.

as well.²⁸ The Organization for Economic Co-operation and Development (OECD) established a Working Party on Manufactured Nanomaterials (WPMN). In 2007, WPMN launched the Sponsorship Program on the Testing of Manufactured Nanomaterials. Under the Program, OECD member countries, as well as some non-member economies and other stakeholders, work together and fund the safety testing of specific manufactured nanomaterials, including titanium dioxide. The Nanotechnology Industries Association (NIA) is a key participant in the Sponsorship Program on the Testing of Manufactured Nanomaterials. The Ecotoxicology Test Protocols for Representative Nanomaterials in Support of the OECD Sponsorship Programme (PROSPeCT) Project is a public-private partnership between NIA, specific NIA member companies, several university laboratories, and the United Kingdom's Department for Environment, Food and Rural Affairs, Technology Strategy Board, and Engineering and Physical Sciences Research Council.²⁹ Through PROSPeCT, NIA is the lead sponsor for nanoscale zinc oxide, as well as the co-lead sponsor for nanoscale cerium oxide.

III. The Role of FDA in Regulating Sunscreen Products Containing Engineered Nanoparticles

As sunscreens containing nanoscale material became more and more popular with consumers, and as concerns about risk increased commensurately, questions arose about what role FDA should have in this new usage of material in regulated products. Sunscreens are not subject to premarket approval by FDA, and that seems to trouble nano-critics. The products must comply, however, with an Over-the-Counter (OTC) Monograph. In FDA's words, the OTC Monograph:

...tells what kind of ingredients may be used to treat certain diseases or conditions without a prescription, and the appropriate dose and instructions for use. OTC products that meet a monograph's requirements may be marketed without FDA review. OTC products that do not fit under an existing monograph must be approved under an application like the applications for prescription products.³⁰

With regard to nanoscale titanium dioxide and zinc oxide used in sunscreens, the questions raised were whether they met the description of the macro version of the materials in the Monograph, and whether the dosage and instructions would comply. FDA made no definitive pronouncements on the subject, and things came to a head when a group of public interest organizations submitted a citizen petition to FDA on May 16, 2006.³¹ The citizen petition is a vehicle provided for in the regulations put into effect by FDA whereby anyone can seek to compel or restrain agency action on a given subject.³² Pursuant to 21 C.F.R. Section 10.30(e)(2), the Commissioner is supposed to make a decision on each petition filed within 180 days, but there is an important caveat. The Commissioner may "provide a tentative response, indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency

²⁸ NIA was formed in 2005 by a group of companies from a variety of industry sectors, including healthcare, chemicals, automotive, materials processing, and consumer products. See its website at <http://www.nanotechia.org/about-nia> for more information (last visited Mar. 12, 2012).

²⁹ NIA, PROSPeCT, <http://www.nanotechia.org/prospect-project-20090101/prospectproject20090101> (last visited Mar. 12, 2012).

³⁰ FDA, Center for Drug Evaluation and Research, What are over-the-counter (OTC) drugs and how are they approved?, <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194951.htm> (last visited Mar. 12, 2012).

³¹ Citizen Petition to FDA, *supra* note 2.

³² 21 C.F.R. § 10.30.

priorities, or a need for additional information.”³³ Initially, FDA did respond to the petition on November 9, 2006, stating only that it was unable to reach a decision because of the complex issues raised and expressing the need for extensive internal review and public input. That has been the only public response to petitioners.³⁴

The petition made a number of general requests regarding the regulation of nanotechnology, and then zeroed in on sunscreens, the consumer product where the use was greatest. Petitioners stated that nanomaterials had fundamentally different properties from their bulk macro counterparts, and novel properties that created unique health risks, necessitating a new paradigm. ICTA and the others asked that the Monograph be reopened for additional comment, and that FDA come to the conclusion that the OTC Sunscreen Monograph did not cover engineered nanoparticles. If those particles were incorporated into a sunscreen, the resultant product would not be Monograph compliant, but would be a new drug, requiring approval of a New Drug Application (NDA) prior to marketing. Sunscreens already on the market should be recalled as imminent health hazards, and NDAs filed and approved before the products came back into distribution. Labeling with disclosure of ingredients would be put into effect.

If FDA did as requested, it could have enormous fallout. Hundreds of NDAs would have to be reviewed, recalls would need to be conducted, and there would be no conceptual basis for not extending the scope of the ruling to any regulated product incorporating engineered nanoparticles. As described earlier, another basic problem facing FDA in 2006 was the lack of any consensus regarding the safety of the materials, very little basis for judging the utility of tests done, and little FDA expertise to review any such studies; FDA set about trying to remedy that situation, while ignoring a substantive response to petitioners. It appointed an internal Task Force, organized a large public meeting on October 10, 2006, to obtain the views of the public and the regulated industry, and then had the Task Force prepare a report summarizing where FDA stood.³⁵ In the Executive Summary of the ensuing report, issued July 25, 2007, the Task Force set forth the basic FDA position at that time:

A general finding of the report is that nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies. However, these challenges may be magnified 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 (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range. In addition, the emerging and uncertain nature of the science and potential for rapid development of applications for FDA-regulated products highlights the need for timely development of a transparent, consistent, and predictable regulatory pathway.

The Task Force’s initial recommendations relating to scientific issues focus on improving scientific knowledge of nanotechnology to help ensure the agency’s regulatory effectiveness, particularly with regard to products not subject to premarket authorization requirements. The report also addresses the need to evaluate whether the tools available to describe and evaluate nanoscale materials are sufficient, and the development of additional tools where necessary.

³³ *Id.* at § 10.30(e)(2)(iii). Over the years, this proviso has afforded FDA the opportunity to delay controversial decisions for years.

³⁴ See *infra* note 39, at paragraph 73.

³⁵ See FDA, Nanotechnology Task Force, <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForce/default.htm> (last visited Mar. 12, 2012).

The Task Force also assessed the agency's regulatory authorities to meet any unique challenges that may be presented by FDA-regulated products containing nanoscale materials. This assessment focused on such broad questions as whether FDA can identify products containing nanoscale materials, the scope of FDA's authorities to evaluate the safety and effectiveness of such products, whether FDA should require or permit products to be labeled as containing nanoscale materials, and whether the use of nanoscale materials in FDA-regulated products raises any issues under the National Environmental Policy Act.³⁶

Two additional public meetings have been convened and FDA has continued to work on the above mentioned implementation plan. FDA issued guidance documents in 2011.³⁷ Conspicuously absent, however, was any substantive response to the ICTA citizen petition. Five and a half years after the petition was filed, the petitioners raised the ante. They filed suit to compel FDA to respond.³⁸ In the complaint, plaintiffs renewed the call for the nanoscale material to be treated as a new substance, and for FDA to require specific nano-tox-testing and/or labeling.³⁹ The parties have agreed to give FDA an extension to April 23, 2012, to answer or take other action, apparently based on the FDA representation that it is working in good faith to respond to the citizen petition on or before that date.

IV. FDA's Response to the Petition

It is not known how FDA will respond on or after April 23, 2012. FDA could grant the petitioners' request, ruling that the nanoscale materials used in sunscreens, namely titanium dioxide and zinc oxide, are new drugs that cannot be marketed until an NDA is filed, reviewed, and approved. It seems unlikely that FDA would take that course of action, however. If it believed that the substances were all new and unique, it could have acted on the petition long ago, presumably within the six months after it was filed. As has been discussed earlier, however, there does not appear to be convincing and generally accepted data showing that the materials are new or dangerous. While there are claims of risk, there has been scant discussion of the injury profile that might result, and there are not a substantial number of reports of even conjectural injuries from use—and there is a demonstrable benefit from use, even though that is contested.

There is also a real and practical problem—acting favorably on the petition would be a major drain on resources in a time of budget cuts and belt tightening, and a drain on funds and on people needed for many other priority tasks at FDA. There would also be the specter of a very substantial number of reviews conducted by a staff, admittedly not yet trained to deal with all the issues and nuances that might be presented. On many levels, therefore, granting the petitioners' demands seems unlikely.

FDA certainly would have an equally hard time ignoring the points raised in the petition. The existing test data are equivocal, with much of it being done on substances that do not appear in commercial products. There are no long-term safety data that are generally accepted and, as allud-

³⁶ FDA, EXECUTIVE REPORT, NANOTECHNOLOGY TASK FORCE REPORT 2007, available at <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm#execsummary>.

³⁷ See *supra* note 36. The principal guidance is discussed in Lynn L. Bergeson, *FDA's Regulation of Nanotechnology: Will the New Draft Guidance Help Industry?*, 8 *NANOTECHNOLOGY LAW & BUSINESS* 166 (2011).

³⁸ Complaint of Plaintiffs, *ICTA et al. v. Margaret A. Hamburg, M.D.*, CV 11 6592 (N.D. Cal.) (Dec. 21, 2011), available at <http://www.icta.org/nanotechnology/legal-actions-6/>.

³⁹ See *id.* (The complaint is a good summary of the objections that have developed and matured over the years to the use of engineered nanoscale materials in products such as sunscreens).

ed to above, there is no articulation of the type of injury that might be expected, or the severity of such injury. After over five years, however, FDA cannot credibly report that it has to study the issue further before doing anything regarding marketed products. What FDA needs to do is come up with a sensible means to sort out the many issues raised and reach a reasonable result. Sound information is needed on which to base a decision, and since FDA's activities have not been geared to accumulate that information in any meaningful way, it needs to start this process now. Companies wish to market sunscreens containing engineered nanoscale material. If they do not want to file NDAs, those companies should be tasked with providing the information needed to demonstrate safety and compliance with the OTC Monograph, and the opponents of that tack should have the opportunity to present their arguments in a formal setting, and not merely in speeches, articles, and web-postings.

V. Amendment of the Sunscreen Monograph

The most viable way to resolve the issues regarding the inclusion of engineered nanoscale materials in commercial sunscreen products would be for the FDA Commissioner to propose to amend the Sunscreen Monograph as provided in the regulations.⁴⁰ In its proposal, FDA would indicate that the amendment had a limited purpose: the consideration of data and views regarding whether and what types of engineered nanoscale titanium dioxide and zinc oxide are the equivalent of the forms of titanium dioxide and zinc oxide presently described in the Monograph;⁴¹ and therefore, considered to be Generally Recognized as Safe and Effective (GRAS).

In the proposal to amend, FDA would identify the kinds of data it regards as relevant to a demonstration that the engineered nanoscale materials are equivalent, and interested parties could then submit such information or comment as to the adequacy of the information being requested by FDA, within the 90-day period contained in the regulations.⁴² FDA should also ask interested persons to address in submissions the relevance of information and data on formulations and forms of engineered nanoscale material not used in commercial products, and other factors that might be deemed to limit the utility of the information submitted for consideration.

To address concerns about the possible risks associated with the use of engineered nanoscale material, FDA, in a companion notice, could articulate the types of injuries that might be attributed to any and all of the theoretical risks identified in various comments and publications, and companies, health care professionals, and others would be directed to report any such alleged nanotechnology-related injuries of which they become aware within a specified time after receipt, so that FDA can determine that there is no public health issue while the process of amending the Monograph proceeds in a timely fashion. A feature of any such notice would be that the submission of such alleged adverse reaction information would not be a concession that the engineered nanoscale material did in fact cause the injury. Interim labeling could be proposed to stipulate the disclosure of the presence of defined engineered nanoscale materials in any sunscreen products, and directing that the products not be used on damaged skin—specifying the types of damaged skin that would be relevant. This is reasonable, since it is the only circumstance where there is some agreement on the possible effect of the presence of engineered nanoscale materials.

After reviewing the comments and data submitted pursuant to the proposal, FDA would publish a final order to amend the Sunscreen Monograph. At that point, the engineered nanoscale material found to be equivalent to the titanium dioxide and zinc oxide listed in 21 C.F.R. Section 330.10

⁴⁰ 21 C.F.R. § 330.10(a)(12).

⁴¹ 21 C.F.R. §§ 352.10(p) (titanium dioxide), 352.10(r) (zinc oxide).

⁴² 21 C.F.R. § 330.10(a)(12).

would be regulated as are their equivalents, after the stay described in Section 330.10 is no longer effective. Any other necessary limitations and considerations could be detailed in the final order. Forms of engineered nanoscale materials found to be not equivalent could not be used after the stay and if those materials are presently used in marketed products, that marketing would be at the relevant manufacturer's assumed risk, since one consequence of the final order would be that such material is not GRAS, and it could not be legally marketed except by going through the new drug review process.

Finally, the petition submitted in May 2006 would be denied if the petitioners would not voluntarily withdraw it and FDA would seek to obtain agreement to dismiss the pending legal action without prejudice in light of the action it would be taking. The action on FDA's proposal to amend would result in a decision on the safety of the materials involved and their marketability—the ostensible purpose of the 2006 petition.

The process described above is a reasonable resolution of the situation involving sunscreens. It will give FDA the data it needs to make a supportable decision, give everyone the opportunity to comment formally on the record, and protect the public health in the interim.