

**CITIZEN PETITION TO THE UNITED STATES
FOOD AND DRUG ADMINISTRATION**

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

THE INTERNATIONAL CENTER FOR)
TECHNOLOGY ASSESSMENT,)
660 Pennsylvania, Ave., S.E., Suite 302)
Washington, DC 20003)
)
et al.,) Docket Number _____
Petitioners,)
)
Filed With:)
)
ANDREW C. VON ESCHENBACH)
in his official capacity as,)
Acting Commissioner)
Food and Drug Administration)
5630 Fishers Lane, Room 1061)
Rockville, MD 20852)

**PETITION REQUESTING FDA AMEND ITS REGULATIONS FOR PRODUCTS
COMPOSED OF ENGINEERED NANOPARTICLES GENERALLY AND SUNSCREEN
DRUG PRODUCTS COMPOSED OF ENGINEERED NANOPARTICLES
SPECIFICALLY**

Nanotechnology and consumer products containing engineered nanoparticles have arrived and represent the crest of a wave of nanomaterial products spanning many technologies. Numerous consumer products composed of engineered nanoparticles, like nano-cosmetics and nano-sunscreens, are now widely available. Engineered nanoparticles have fundamentally different properties from their bulk material counterparts—properties that also create unique

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human health and environmental risks—which necessitate new health and safety testing paradigms. Yet policymakers have failed to address the risks of nanomaterials with concrete regulatory initiatives.

The Food and Drug Administration (“FDA”) regulates numerous nanomaterial products, including sunscreens and cosmetics that contain engineered nanoparticles. Yet the agency has taken no regulatory steps to formally recognize the inherent differences of nanomaterials and begin to address their associated new risks to human health and the environment. Accordingly, pursuant to the Right to Petition Government Clause contained in the First Amendment of the United States Constitution,¹ the Administrative Procedure Act,² and FDA’s implementing regulations,³ the undersigned submit this citizen petition for rulemaking and collateral relief pursuant to the Federal Food, Drug and Cosmetic Act (“FFDCA” or “Act”) requesting that the

¹U.S. Const., amend. I. (“Congress shall make no law … abridging … the right of the people … to petition Government for a redress of grievances.”). The right to petition for redress of grievances is among the most precious of the liberties safeguarded by the Bill of Rights. United Mine Workers of Am., Dist. 12 v. Illinois State Bar Ass’n, 389 U.S. 217, 222 (1967). It shares the “preferred place” accorded in our system of government to the First Amendment freedoms, and has a sanctity and a sanction not permitting dubious intrusions. Thomas v. Collins, 323 U.S. 516, 530 (1945). “Any attempt to restrict those First Amendment liberties must be justified by clear public interest, threatened not doubtful or remotely, but by clear and present danger.” Id. The Supreme Court has recognized that the right to petition is logically implicit in, and fundamental to, the very idea of a republican form of government. United States v. Cruikshank, 92 U.S. (2 Otto) 542, 552 (1875).

²5 U.S.C. § 553(e) (2005) (“Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule.”).

³21 C.F.R. § 10.30(a), (b) (authorizing any person to request that the FDA Commissioner “issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action”); see also § 10.20 (submission of documents to FDA, including petitions); id § 10.85(a) (delineating that a party may request an advisory opinion from the commissioner on a matter of general applicability).

Commissioner of Food and Drugs take regulatory action regarding products composed of engineered nanoparticles.

ACTIONS REQUESTED

Petitioners request that the Commissioner undertake the following actions with regard to all nanomaterial products:

- 1) Amend FDA regulations to include nanotechnology definitions necessary to properly regulate nanomaterial products, including the terms “nanotechnology,” “nanomaterial,” and “engineered nanoparticle.”
- 2) Issue a formal advisory opinion explaining FDA’s position regarding engineered nanoparticles in products regulated by FDA.
- 3) Enact new regulations directed at FDA oversight of nanomaterial products establishing and requiring, *inter alia*, that: nanoparticles be treated as new substances; nanomaterials be subjected to nano-specific paradigms of health and safety testing; and that nanomaterial products be labeled to delineate all nanoparticle ingredients.
- 4) Any currently existing or future regulatory FDA programs for nanomaterial products must comply with the requirements of the National Environmental Policy Act (NEPA), including, *inter alia*, that FDA conduct a Programmatic Environmental Impact Statement (PEIS) reviewing the impacts of nanomaterial products on human health and the environment.

Petitioners request that the Commissioner undertake the following actions with regard to nanomaterial sunscreen drug products:

- 5) Reopen the Administrative Record of the Final Over-the-Counter (“OTC”) Sunscreen Drug Product Monograph for the purpose of considering and analyzing information on engineered nanoparticles of zinc oxide and titanium dioxide currently used in sunscreens.
- 6) Amend the OTC Sunscreen Drug Monograph to address engineered nanoparticles, instructing that sunscreen products containing engineered nanoparticles are not covered under the Monograph and instead are “new drugs” for which manufacturers must complete a New Drug Application in accordance with 21 U.S.C. § 355.
- 7) Declare all currently available sunscreen drug products containing engineered nanoparticles of zinc oxide and titanium dioxide as an imminent hazard to public health and order entities using the nanoparticles in sunscreens regulated by FDA to cease manufacture until FDA’s Sunscreen Drug Monograph is finalized and broader FDA nanotechnology regulations are developed and implemented.

8) Request a recall from manufacturers of all publically available sunscreen drug products containing engineered nanoparticles of titanium dioxide and/or zinc oxide until the manufacturers of such products complete new drug applications, those applications are approved by the agency, and the manufacturers otherwise comply with FDA's relevant nanomaterial product testing regulations.

PETITIONERS

Petitioner, **The International Center for Technology Assessment (“CTA”)**, is located at 660 Pennsylvania Ave., S.E., Suite 302, Washington, DC 20003. Formed in 1994, CTA seeks to assist the public and policy makers in better understanding how technology affects society. CTA is a non-profit organization devoted to analyzing the economic, environmental, ethical, political, and social impacts that can result from the application of technology or technological systems.

Petitioner, **Friends of the Earth (“FOE”)**, is located at 1717 Massachusetts Avenue, NW, Suite 600, Washington, DC 20036. FOE is a non-profit organization that seeks to create a more healthy, just world. FOE is the U.S. voice of Friends of the Earth International, the world's largest federation of democratically elected grassroots environmental groups, located in 70 countries.

Petitioner, **Greenpeace**, is located at 702 H Street, N.W. Suite 300, Washington, D.C. 20001. Greenpeace was founded in 1971 and has 250,000 members in the U.S. and 2.5 million worldwide. Greenpeace is an independent campaigning organization that uses peaceful direct action and creative communication to expose global environmental problems and promote solutions that are essential to a green and peaceful future.

Petitioner, **The Action Group on Erosion, Technology and Concentration (“ETC Group”)**, is an international civil society organization headquartered in Canada, with offices in the USA and Mexico. ETC Group is dedicated to the conservation and sustainable advancement of cultural and ecological diversity and human rights. To this end, ETC Group supports socially responsible developments in technologies useful to the poor and marginalized, and it addresses governance issues affecting the international community. ETC Group also monitors the ownership and control of technologies and the consolidation of corporate power.

Petitioner, **Clean Production Action (“CPA”)**, is a non-profit organization based in New York State. CPA partners with environmental organizations, public health advocates, labor unions, and progressive businesses to develop and build technical and policy support for clean production policies that promote the use of products that are safer and cleaner across their life cycle.

Petitioner, **Center for Environmental Health (“CEH”)**, is located at 528 61st Street, Suite A, Oakland, CA 94609. Founded in 1996, CEH is a non-profit organization dedicated to protecting the public from environmental and consumer health hazards. CEH is committed to environmental justice, reducing the use of toxic chemicals and practices, supporting communities in their quest for a safer environment, and corporate accountability.

Petitioner, **Our Bodies Ourselves**, also called the **Boston Women’s Health Book Collective**, is a non-profit 501(c) 3 organization founded in 1970 and based in Boston, MA. A leading voice

on women and health both nationally and internationally, the organization brings a consumer and evidence-based perspective to policy advocacy, to educational outreach to women and men of all ages, and to challenging unethical corporate practices. The organization works in the public interest, frequently collaborates with other organizations, and is committed to providing accurate health and medical information in lay language.

Petitioner, **Silicon Valley Toxics Coalition** (“SVTC”), is located at 760 North First Street, San Jose CA, 95112. SVTC is a diverse grassroots coalition that engages in research, advocacy, and organizing around the environmental and human health problems caused by the rapid growth of the high-tech electronics industry. SVTC is interested in incorporating a precautionary approach and the appropriate regulatory structure to emerging technologies, such as nanotechnology, that have the potential for tremendous good as well as devastating harm to human health and the environment.

STATEMENT OF GROUNDS

I. FDA REGULATION OF PRODUCTS CONTAINING ENGINEERED NANOPARTICLES

A. Background: FDA’s Stance on Nanotechnology

The FDA currently defines “nanotechnology” informally on its website as

research and technology or development of products regulated by FDA that involve all of the following:

1. the existence of materials or products at the atomic, molecular or macromolecular levels, where at least one dimension that affects the functional behavior of the drug/device product is in the length scale range of approximately 1-100 nanometers;
2. the creation and use of structures, devices and systems that have novel

properties and functions because of their small size; and,

3. the ability to control or manipulate the product on the atomic scale.⁴

FDA notes that it regulates a “wide range of products, including foods, cosmetics, drugs, devices, and veterinary products, some of which may utilize nanotechnology or contain nanomaterials.”⁵

However, this is not necessarily a new development according to FDA because FDA has “traditionally regulated many products with particulate materials in this size range.”⁶ Moreover, FDA “believes that the existing battery of pharmacotoxicity tests is probably adequate for most nanotechnology products” that it regulates and that “[p]article size is not an issue.”⁷ FDA reiterated this stance as recently as January 2006.⁸ Elsewhere, FDA has said that its existing requirements for products “may be adequate for most nanotechnology products that we will regulate.”⁹ FDA’s “approach to nanotechnology is no different than its approach to any other technology . . .”¹⁰ However, FDA has “only limited authority over some potentially high risk

⁴FDA, Nanotechnology, at <http://www.fda.gov/nanotechnology/>.

⁵Id.

⁶FDA, Regulation of Nanotechnology Products, at <http://www.fda.gov/nanotechnology/regulation.html>.

⁷Id.

⁸Rick Weiss, *Stricter Nanotechnology Laws Are Urged*, WASH. POST (January 11, 2006), at A02.

⁹FDA, FDA and Nanotechnology Products, Frequently Asked Questions, at <http://www.fda.gov/nanotechnology/faqs.html>.

¹⁰Jennifer Kuzma, Ed., *The Nanotechnology-biology Interface: Exploring Models for Oversight*, Workshop Report, p. 21 (paraphrasing Norris Alderson, Associate Commissioner of Science at FDA) (September 15, 2005), Huber H. Humphrey Institute of Public Affairs, University of Minnesota, available at http://www.hhh.umn.edu/img/assets/9685/nanotech_jan06.pdf.

products, e.g. cosmetics,” and has “comparably few resources available to assess the risks of these products. . . . Few resources currently exist to assess the risks that would derive to the general population from the wide-scale deployment of nanotechnology products.”¹¹

B. Integrating Nanotechnology into FDA Product Regulation

1. Amend FDA regulations to include necessary nanotechnology definitions

FDA should formally amend its regulations to include nanotechnology definitions.¹² FDA’s mission begins with the “promot[ion] [of] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner.”¹³ With respect to drugs, FDA is charged with insuring that they are “safe and effective.”¹⁴ Establishing the appropriate nomenclature for nanotechnology is a necessary prerequisite to enforcing, amending, and enacting appropriate agency regulation of nanotechnology products; regulators, the regulated industry, and the public must share a vocabulary. Formalizing FDA’s nano-terminology will eliminate the problem of particle size references that are imprecise and/or ambiguous, like “micronized” or “fines.”¹⁵ Finally, formalizing nano-terminology will help foster interagency collaboration between FDA and other

¹¹FDA, FDA and Nanotechnology Products, Frequently Asked Questions, at <http://www.fda.gov/nanotechnology/faqs.html>.

¹²FDA notes that the definition of “nanotechnology” on its website is not a formal definition. www.fda.gov/nanotechnology/faqs.html.

¹³21 U.S.C. § 393(b)(1).

¹⁴Id. § 393(b)(2)(B).

¹⁵See Section II(B)(2) *infra* (discussing the ambiguous use of “micronized” in FDA’s 1999 Monograph for Sunscreen Drug Products, 64 Fed. Reg. 27666-27693, 27671).

science-based agencies, and will also help fulfill FDA's statutory mandate of fostering interagency collaboration.¹⁶

In addition to its own informal definition, FDA can gain insight from other agencies' nano-lexicon: the National Nanotechnology Initiative (NNI), the federal research and development program established to coordinate the multi-agency efforts in nanoscale science, engineering, and technology, in which FDA participates;¹⁷ and the U.S. Patent Office, which has defined a Patent Classification Class, Class 977, for Nanotechnology patents.¹⁸ Congress has

¹⁶See 21 U.S.C. § 393(c).

¹⁷NNI defines "nanotechnology" as

the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale.

National Nanotechnology Initiative, Factsheet: What Is Nanotechnology?, <http://www.nano.gov/html/facts/whatIsNano.html>. FDA participates in the NNI as a member of the Nanoscale Science, Engineering and Technology Subcommittee of the National Science and Technology Council. Id.

¹⁸Patent Class 977, Nanotechnology, Section I - Class Definition, reads:

- i. Nanostructure and chemical compositions of nanostructure;
- ii. Device that include at least one nanostructure;
- iii. Mathematical algorithms, e.g., computer software, etc., specifically adapted for modeling configurations or properties of nanostructure;
- iv. Methods or apparatus for making, detecting, analyzing, or treating nanostructure; and
- v. Specified particular uses of nanostructure.

As used above, the term "nanostructure" is defined to mean an atomic, molecular, or macromolecular structure that:

- (a) Has at least one physical dimension of approximately 1-100 nanometers; and
- (b) Possesses a special property, provides a special function, or produces a special

defined nanotechnology in the 2004 Nanotechnology Research and Development Act.¹⁹ Several national and international organizations are currently developing standard definitions for terms in nanomaterial science, including the International Association of Nanotechnology's Nomenclature and Terminology Subcommittee and the American National Standards Institute Nanotechnology Standards Panel (ANSI-NSP).²⁰ FDA's decision should correlate and be informed by these existing and developing national and international standards.

The following key definitions are used throughout this document.

Nanoscale

Having one or more dimension of the order of 100 nanometer (nm) or less.²¹

Nanoscience

The study of phenomena and manipulation of materials at atomic, molecular, and

effect that is uniquely attributable to the structure's nanoscale physical size.

Patent office Classification Definitions, Class 977, Nanotechnology, (November 2005), available at <http://www.uspto.gov/web/patents/classification/uspc977/defs977.htm#C977S000000>.

¹⁹15 U.S.C. 7501 et seq.; Id. § 7509 (definitions); see note 41 infra and accompanying text.

²⁰Oberdorster et al., *Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy*, 2 PARTICLE AND FIBRE TOXICOLOGY 8, at 1.0 (2005); see also The Institute of Occupational Medicine, *Nanoparticles: An occupational hygiene review*, research report 274, at 9 (2004), available at <http://www.hse.gov.uk/research/rrpdf/rr274.pdf>.

²¹European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), *Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies*, at 9 (adopted September 28-29, 2005) (hereafter SCENIHR opinion on existing methodologies) (citing the British Standards Institution, Publicly Available Specification on the Vocabulary for Nanoparticles (BSI 2005)). A nanometer is one billionth of a meter; a human hair is roughly 80,000 nanometers wide, a sheet of paper is about 100,000 nm thick, and a red blood cell is approximately 7,000 nanometers wide. J. Clarence Davies, *Managing the Effects of Nanotechnology*, Report for the Woodrow Wilson International Center for Scholars (2005), at 7, available at <http://www.wilsoncenter.org/events/docs/Effectsnanotechfinal.pdf>.

macromolecular scales, where properties differ significantly from those at a larger scale.²²

Nanotechnology

The design, characterization, production and application of structures, devices and systems by manipulating shape and size at the nanoscale.²³

Nanoparticle

A particle with at least one dimension smaller than 100 nm including engineered nanoparticles, ambient ultrafine particles (UFPs), and biological nanoparticles.²⁴

Engineered/Manufactured Nanoparticle

A particle of less than 100 nm engineered or manufactured by humans on the nanoscale with specific physicochemical composition and structure to exploit properties and functions associated with its dimensions and exhibits new or enhanced size-dependent properties compared with larger particles of the same material.²⁵

Nanomaterial

Any material that either contains a certain proportion of nanoparticles or consists exclusively of them.²⁶

Petitioners request that FDA amend its regulations at 21 C.F.R. § 3.2, or elsewhere where it deems appropriate, to include these necessary definitions.

2. Issue an advisory opinion recognizing the inherent differences of engineered nanoparticles from bulk material counterparts in products regulated by FDA

Any interested party may request an advisory opinion from the Commissioner on a matter of general applicability.²⁷ Petitioners request, as part of this citizen petition, that the

²²Id.

²³See id.

²⁴Oberdorster, supra note 20, at 1.0.

²⁵Id.

²⁶Swiss Re, *Nanotechnology: Small Matter, Many Unknowns*, (2004) at 11, available at [http://www.swissre.com/INTERNET/pwsfilpr.nsf/vwFilebyIDKEYLu/ULUR-5YNGET/\\$FILE/PUBL04_Nanotech_en.pdf](http://www.swissre.com/INTERNET/pwsfilpr.nsf/vwFilebyIDKEYLu/ULUR-5YNGET/$FILE/PUBL04_Nanotech_en.pdf) (hereafter Swiss Re Report).

²⁷21 C.F.R. § 10.85(a). An advisory opinion “represents the formal position of the FDA on a matter and . . . obligates the agency to follow it until it is amended or revoked.” Id. §

Commissioner issue an advisory opinion on the inherent and fundamental differences of engineered nanoparticles from bulk substances of the same material.

This issue is one of broad applicability, properly the topic of a formal Commissioner advisory opinion.²⁸ Regulation of engineered nanoparticles is not limited to a particular product or ingredient. Quite the contrary, nanotechnology research and development are surging to unprecedented heights.²⁹ The global market is expected to reach at least \$1 trillion US by 2015.³⁰ Thousands of tons of nanomaterials are already being produced each year.³¹ Products containing nanotechnology have been and continue to enter the market at a steady pace: several hundred

10.85(e).

²⁸Id. § 10.85(a)(iv) (noting that the request may be denied if it covers only a particular product or ingredient or label and does not raise a policy issue of broad applicability).

²⁹Globally nanotechnology research and development is estimated at around \$9 billion, with \$1 trillion in global spending estimated by 2015. External Review Draft *Nanotechnology White Paper* (hereafter EPA White Paper), Prepared for the U.S. Environmental Protection Agency by members of the Nanotechnology Workgroup, a group of EPA's Science Policy Council. Science Policy Council, U.S. Environmental Protection Agency, Washington, DC 20460, December 2, 2005, available at <http://www.epa.gov/osa/nanotech.htm>. Investments in federally funded nanotechnology-related activities coordinated through the National Nanotechnology Initiative were approximately \$1 billion in 2005. Id. at 11. About \$2 billion in annual research and development investment is currently being spent by non-federal sectors such as states, academia, and private industry. Id. at 12. Some overviews of research on nanotechnology can be found at the President's Council of Advisors on Science and Technology (PCAST), *The National Nanotechnology Initiative at Five Years: Assessment and Recommendations of the National Nanotechnology Advisory Panel*, May 2005, available at www.ostp.gov/PCAST/pcast.html ; National Nanotechnology Initiative, www.nano.gov ; Center for Biological and Environmental Nanotechnology, Rice University, www.cohesion.rice.edu/centersandinst/cben/index.cfm.

³⁰EPA White Paper, supra note 29, at 13.

³¹See The Royal Society and the Royal Academy of Engineering, *Nanoscience and nanotechnologies: Opportunities and uncertainties*, London, July 2004, pp. 26-27, available at <http://www.nanotec.org.uk/finalReport.htm> (hereafter Royal Society Report).

products that contain unregulated and unlabeled engineered nanoparticles are on the market today,³² including paints, coatings for eyeglasses and cars, sunscreens, sporting goods, cosmetics, stain-resistant clothing, and light emitting diodes used in computers, cell phones, and digital cameras.³³ Many of these products are intended for human consumption, either directly or indirectly, through lotions, sunscreens, and cosmetics that are absorbed by the skin.³⁴

Nanoparticles are currently being used in products regulated by FDA, as FDA has noted: “Several FDA regulated products [that] employ nanotechnology,” including “cosmetic products claim[ing] to contain nanoparticles to increase the stability or modify the release of ingredients” and “nanotechnology-related claims made for certain sunscreens.”³⁵ FDA has stated that it

³²See, e.g., H. Shand and K.J. Wetter, *Shrinking Science: An Introduction to Nanotechnology*, Chapter 5, STATE OF THE WORLD 2006, The Worldwatch Institute (Norton & Co. 2006) (counting more than 720 products containing nanoscale particles that are commercially available and “thousands more in the pipeline”); but cf. THE WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS, PROJECT ON EMERGING NANOTECHNOLOGIES, *Nanotechnology Consumer Products Inventory*, available at <http://www.nanotechproject.org/consumerproducts> (Database includes 212 self-identified nanomaterial consumer products). However, the Wilson Center staff acknowledges that this number is a conservative estimate and that the actual numbers are likely much higher. Rick Weiss, *For Now Nanotechnology Means Little More than Better Golf Ball*, WASH. POST., at A03 (March 10, 2006). Determining the number of commercially available products is a difficult task, as there is as of yet no regulatory requirement that products containing nanoscale materials be labeled as such. See Petition Request 3 (New Nanomaterial Product Regulations including Mandatory Labeling).

³³Id.; see also, e.g., Rick Weiss, *For Now, Consumer Nanotech Concentrates on the Little Things*, WASH. POST. (March 10, 2006), at A03; Garry Kranz, *Buyer Beware: Product List highlights both nanotech and nano-marketing*, Small Times (March 16, 2006), available at http://www.smalltimes.com/print_doc.cfm?doc_id=11050; Applications/Products, National Nanotechnology Initiative, <http://www.nano.gov/html/facts/appsprod.html>.

³⁴Kranz, *supra* note 33.

³⁵FDA and Nanotechnology Products, Frequently Asked Questions, at www.fda.gov/nanotechnology/faqs.html.

believes that the existing battery of pharmacotoxicity tests is *probably adequate* for most nanotechnology products that we regulate. *Particle size is not an issue.* As new toxicological risks that derive from new materials and/or new conformations of existing materials are identified, new tests will be required.³⁶

Petitioners respectfully disagree with the agency's above conclusions, regarding FDA's regulation of products containing engineered nanoparticles, that: 1) particle size at the nanoscale is not "an issue"; and 2) that existing health and safety tests, created for and utilized on bulk material counterparts of nanomaterials, are "probably adequate" to assess the health and safety effects of nanomaterials regulated by FDA. Petitioners request a formal advisory opinion on this matter in order to clarify whether it is indeed the position of the Commissioner. Petitioners submit the following evidence to be considered by the Commissioner in his formal opinion on FDA regulation of products containing engineered nanoparticles.

(a) "Nano" means fundamentally different properties

The size of engineered nanoparticles is critical because "nano" does not simply mean smaller; it means fundamentally different. Making materials smaller does not simply lead to an increase in compactness or refinement of the structure or properties of the material; rather, materials engineered to the nano-scale exhibit numerous different fundamental properties – electrical, optical, magnetic, toxicity, chemical or photoreactive, persistence, bio-accumulation, explosiveness – to list but a few.³⁷ FDA recognizes these characteristics in its informal definition

³⁶FDA Regulation of Nanotechnology Products, U.S. Food and Drug Administration, at <http://www.fda.gov/nanotechnology/regulation.html> (emphases added). Although this statement appears on the FDA Nanotechnology website, it is not the topic of a previous advisory opinion or FDA regulation and therefore an appropriate topic for this request. See 21 C.F.R. § 10.85(a)(iii).

³⁷See, e.g., Ernie Hood, *Nanotechnology: Looking as We Leap*, 112 ENVTL. HEALTH PERSP. A741 (2004) (citing Kristen Kulinowski, Executive Director for Education and Policy at Rice University Center for Biological and Environmental Nanotechnology).

of nanotechnology, defined in relevant part as “the creation and use of structures, devices and systems *that have novel properties and functions because of their small size.*”³⁸ The nanotechnology definitions of the NNI and the U.S. Patent Office recognize that nanoparticles are “unique phenomena enabl[ing] novel applications,”³⁹ and “possess[] a special property, provide[] a special function, or produce[] a special effect that is uniquely attributable to the structure’s nanoscale physical size.”⁴⁰ Congress too, recognized this basic fact, in passing the 2004 Nanotechnology Research and Development Act, 15 U.S.C. § 7501 *et seq.*, defining nanotechnology as

the science and technology that will enable one to understand, measure, manipulate, and manufacture at the atomic, molecular, and supramolecular levels, aimed at creating materials, devices, and systems with fundamentally new molecular organization, properties, and functions.⁴¹

There are two main reasons why nanoparticles differ significantly from larger particles of the same materials. First, reduction in size to the nanoscale level results in an enormous increase of surface to volume ratio, so a greater proportion of atoms are found at the surface compared to inside, giving nanoparticles a much greater surface area per unit mass compared to larger particles.⁴² Because growth and catalytic chemical reactions occur at the particle surface, a given

³⁸See note 4 *supra* and accompanying text (emphasis added).

³⁹See notes 17-18 *supra*.

⁴⁰See note 18 *supra*.

⁴¹15 U.S.C. § 7509(2).

⁴²See, e.g., Andre Nel *et al.*, *Toxic Potential of Materials at the Nanolevel*, 311 SCIENCE 622-27, 622, 623 Fig. 1 (2006) (showing the inverse relationship between particle size and the number of surface expressed molecules). “In the size range < 100 nm, the number of surface molecules (expressed as a % of the molecules in the particle) is inversely related to particle size.

mass of nanoparticles will have an increased potential for biological interaction and be much more reactive than the same mass made up of larger particles, thus enhancing intrinsic toxicity.⁴³ Second, any particle smaller than about 50 nanometers (nm) is no longer subject to the laws of classical physics but rather of quantum physics, affecting, *inter alia*, the optical, electrical, and magnetic behavior of materials.⁴⁴

For these reasons, knowledge of the properties of a substance when in bulk cannot predict how that substance will behave at the nanoscale: substances change colors at various nano-levels (e.g., gold);⁴⁵ substances that were stable as bulk materials can become reactive when engineered to nanoparticle level (e.g., aluminum); substances can become highly elastic, stretching to 50 times their original length without breaking (e.g., copper);⁴⁶ substances that were insulators can become conductors.⁴⁷ Zinc oxide and titanium dioxide, two metal oxides discussed in this petition infra and used in sunscreen drug products regulated by FDA, become transparent at the

For instance, in a particle of 30 nm size, about 10% of its molecules are expressed on the surface, whereas at 10 and 3 nm size the ratios increase to 20% and 50%, respectively. Because the number of atoms or molecules on the surface of the particle may determine the material reactivity, this is key to defining the chemical and biological properties of nanoparticles.” *Id.* at 623 (Fig. 1).

⁴³*Id.*; see, e.g., SCENIHR opinion on existing methodologies, supra note 21 at 22; Warheit, D.D., *Nanoparticles: Health impacts?*, 7 MATERIALS TODAY 32-35 (2004).

⁴⁴Swiss Re Report, supra note 26, at 12.

⁴⁵See, e.g., Kenneth Chang, *Tiny Is Beautiful: Translating ‘Nano’ Into Practical*, NEW YORK TIMES (February 22, 2005).

⁴⁶Shand & Wetter, supra note 32, at 80.

⁴⁷In fact, the properties of the same substance can also change within the nanometer realm, depending on nanoparticle size, shape, and the presence or absence of a surface coating.

nanoscale and are able to absorb and reflect UV light.

(b) These new properties create new risks that cannot be inferred from bulk material counterparts or the testing of them

Regulators, the public, and industry cannot rely on the existing knowledge of conventional chemicals to predict the properties and risks of nanomaterials: Just as the size and physics properties of engineered nanoparticles give them unusual properties of strength and reactivity, those properties also give them unpredicted risks, like increased toxicity, due to modifications of physicochemical properties and extreme mobility, causing increased uptake and interaction with biological tissues.⁴⁸ Those same features that make engineered nanomaterials unique—small size, high surface area to volume ratio, high reactivity—can have negative consequences for human health.⁴⁹ “The combination of effects can generate adverse biological effects in living cells that would not otherwise be possible with the same material in larger form.”⁵⁰

First, central to these health risk concerns is that the human species has evolved mechanisms of protection against environmental agents; size is an important factor in the efficacy of these mechanisms. The exposure to engineered nanoparticles, having characteristics not previously encountered, presents new challenges to the normal defense mechanisms of, *inter alia*, the body’s immune and inflammatory response systems. Unlike larger particles, engineered

⁴⁸See, e.g., Nel, *supra* note 42, at 622.

⁴⁹Id. at 622 (“[T]heir properties differ substantially from those bulk materials of the same composition, allowing them to perform exceptional feats of conductivity, reactivity, and optical sensitivity. Possible undesirable results of these capabilities are harmful interactions with biological systems and the environment, with the potential to generate toxicity.”)

⁵⁰Id.

nanoparticles have the unique ability to move from one area of the body to another, be absorbed by organs and tissues, and penetrate into cells;⁵¹ research has highlighted movement from the lungs to the blood stream, the GI tract to other organs, and the nose via olfactory nerves into the brain.⁵² When inhaled, they reach all regions of the respiratory tract, and can move out of it via different pathways and mechanisms; when in contact with the skin, there is evidence of penetration of the dermis and subsequent translocation via the lymph nodes; when ingested, systematic uptake can occur; when in the blood circulatory system, they can distribute through the body, and be taken up into the liver, spleen, bone marrow, heart, and other organs.⁵³

Second, the change in the physicochemical and structural properties of engineered nanoparticles can also be responsible for a number of material interactions that could lead to toxicological effects. There is a dependent relationship between size and surface area and nanoparticle toxicity; as particles are engineered smaller on the nano-level, they are more likely to be toxic.⁵⁴ Once inside cells, they can interfere with cell signaling, cause structural damage,

⁵¹See, e.g., Oberdorster, *supra* note 20, at 3.0 & Figure 1. Once inside cells, engineered nanoparticles can bind to cellular structures and move through the cytoplasm. See, e.g., Karen Florini *et al.*, *Nanotechnology: Getting It Right the First Time*, NANOTECHNOLOGY LAW & BUSINESS (Feb/March 2006), at 41-42.

⁵²*Id.*; see notes 187-200 and accompanying text *infra*.

⁵³Oberdorster *et al.*, *Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles*, 113 ENVIRONMENTAL HEALTH PERSPECTIVES 823, 837 (2005) (hereafter Oberdorster II). Engineered nanoparticles are likely more available for efficient translocation processes than natural ambient nanoparticles because of their uniform size. *Id.*

⁵⁴See generally Tran *et al.*, *A Scoping Study to Identify Hazard Data Needs For Addressing The Risks Presented By Nanoparticles and Nanotubes*, INSTITUTE OF OCCUPATIONAL MEDICINE Research Report (December 2005), at 21.

and cause harmful damage to DNA.⁵⁵ Many relatively inert and stable chemicals, such as carbon, pose toxic risk in their nano-scale form.⁵⁶

(c) Nanoparticle safety testing requires new paradigms of toxicology testing

FDA states that “the existing battery of pharmacotoxicity tests is *probably adequate* for most nanotechnology products that we regulate.”⁵⁷ Yet such tests are based on and completed regarding bulk material states of many recently engineered nanoparticles. As noted by numerous studies on the risks of nanotechnology, “Experts are *overwhelmingly* of the opinion that the adverse effects of nanoparticles cannot be reliably predicted or derived from the known toxicity of the bulk material.”⁵⁸ Again, as the European Commission’s Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded: “Experts are of the *unanimous* opinion that the adverse effects of nanoparticles cannot be predicted (or derived) from the known toxicity of material of macroscopic size, which obey the laws of classical physics.”⁵⁹

⁵⁵Oberdorster *supra* note 20; Tran, *supra* note 54.

⁵⁶Nel, *supra* note 42 at 622 (“Thus, as particle size shrinks, there is a tendency for pulmonary toxicity to increase, even if the same material is relatively inert in bulkier form (e.g. carbon black and TiO₂).”).

⁵⁷See note 36 *supra* and accompanying text.

⁵⁸The Allianz Group and the Organisation for Economic Co-operation and Development (OECD), *Small Sizes that Matter: Opportunities and risks of Nanotechnologies*, (June 3, 2005) at § 6.4, p. 30, available at http://www.allianz.com/Az_Cnt/az/_any/cma/contents/796000/saObj_796424_allianz_study_Nanotechnology_engl.pdf (emphasis added); Dreher, K., *Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles*, 77 TOXICOLOGICAL SCIENCES 3-5 (2004).

⁵⁹SCENIHR opinion on existing methodologies, *supra* note 21, at 6 (emphasis added), 34 (existing regulatory tests are inadequate because they do not anticipate the significance of the

The world's oldest scientific organization, the U.K. Royal Society and the Royal Academy of Engineering also repeatedly emphasized that safety testing of nanoparticles should not be inferred from larger particles of the bulk material: "Free particles in the nanometre size range do raise health, environmental, and safety concerns and their toxicology *cannot be inferred* from that of particles of the same chemical at a larger size."⁶⁰ The British Institute for Occupational Medicine similarly concluded:

Because of their size and the ways they are used, they [engineered nanomaterials] have specific physical-chemical properties and therefore may behave differently from their parent materials when released and interact differently with living systems. *It is accepted, therefore, that it is not possible to infer the safety of nanomaterials by using information derived from the bulk parent material.*⁶¹

Toxicology normally correlates health risks with the mass to which an individual is exposed, resulting in an accumulated mass as an internal dose/exposure. However for nanoparticles, "the concentration number and resulting total surface area predominately influence their interactions with biological systems, and are more reasonable parameters for doses of exposure."⁶² Moreover, pharmacokinetics and the pharmacodynamics of nanoparticles are

new nanoparticle physicochemical parameters in play, and as a result "safety evaluations of nanoparticles and nanostructures cannot rely on toxicological and ecotoxicological profile of bulk material that has been historically determined.").

⁶⁰Royal Society Report, supra note 31, at 49 (emphasis added); id. at 77 ("regulatory bodies [] will need to be aware of the potential for nanoparticles and nanotubes to present hazards not present in materials at the larger scale."). As one renowned scientist explained, "although the toxicology of the base material may be well defined, the toxicology of the nanosize form of the substance may be dramatically different from its parent form. As a result, new toxicology data on the nanosize form of the substance is likely to result in a different hazard assessment for the [nanoparticles]."; Oberdorster II, supra note 53, at 835.

⁶¹Tran, supra note 54, at 34 (emphasis added).

⁶²SCENIHR opinion on existing methodologies, supra note 21, at 32.

different: “there are specific issues to address in toxicology, which existing schemes don’t do.”⁶³

For example, the biological activity of nanoparticles is likely to depend on physicochemical characteristics that are not routinely considered in toxicity screening studies.⁶⁴

In December 2005, U.S. EPA published a Draft White Paper⁶⁵ on Nanotechnology, in which that agency repeatedly emphasized the inherent differences of engineered nanoparticles and the dangers posed by them:

It is important to note that nanomaterials have large surface areas per unit of volume, and *novel electrical and magnetic properties relative to conventional chemicals*. Some of the special properties that make nanomaterials useful are also properties that may cause some nanomaterials to pose hazards to humans and the environment . . . It will be *necessary to consider these unique properties* and their potential impacts on fate, exposure, and toxicity *in developing risk assessments* for nanomaterials.⁶⁶

According to the EPA, these new nano-scale properties cause health and safety concerns that may be absent from a given material in bulk form, including increased toxicity:

[I]t is generally believed that nanoparticles can have toxicological properties that differ from their bulk material. A number of studies have demonstrated that nanoparticle toxicity is complex and multifactorial, potentially being regulated by a variety of physicochemical properties such as size, chemical composition, and shape, as well as surface properties such as charge, area and reactivity. As the size of particles decreases, a resulting larger surface-to-volume ratio per unit weight for nanoparticles correlates with increased toxicity as compared with bulk

⁶³Nuala Moran, *Nanomedicine lacks recognition in Europe*, 24 NATURE BIOTECHNOLOGY, No. 2 (February 2006) (quoting Rogerio Gaspar, Professor of Pharmacology at Coimbra University, Portugal).

⁶⁴Id.

⁶⁵EPA White Paper, supra note 29.

⁶⁶EPA White Paper, supra note 29, at 33 (emphases added).

*material toxicity.*⁶⁷

(d) Engineered nanoparticles must be considered a new class of materials for purposes of regulation

As a result of these crucial differences and new dangers, engineered nanoparticles should be considered entirely new materials and placed in a regulatory class of their own, especially with regard to testing for health and safety effects.⁶⁸ All nanomaterials' characteristics—including hazardous traits—must be learned anew by direct experimentation and cannot be inferred from

⁶⁷Id. at 69 (emphases added). The EPA White Paper similarly addressed the clear limitation of attempting to extrapolate the toxicity of engineered nanoparticles from current particle toxicological databases, noting that several researchers have demonstrated that, for example, “graphite is not an appropriate safety reference standard for carbon nanotubes, since carbon nanotubes displayed very different mass-based dose-response relationships and lung histopathology when directly compared to graphite.” Id. at 52.

⁶⁸See pp. 14-18 and accompanying footnotes supra. FDA notes that it has traditionally regulated natural particles of the same size. See note 6 supra. The fact that humans have always been exposed to some nanoparticles in nature or created accidentally by man does not negate the potential harm from intentionally created engineered nanoparticles that are new to humans, and need full safety reviews before use. It is only recently that scientists have developed techniques for synthesizing and characterizing many new materials with at least one dimension on the nanoscale, including nanoparticles, nanolayers, and nanotubes. The rapidly developing field of nanotechnology is a new source for human exposures to nanoparticles, and by new and different exposure routes: inhalation, ingestion, dermal, and injection. Nature produces some nanoparticles, like salt nanocrystals found in ocean air or carbon nanoparticles emitted from fire and there may be no intrinsic risk associated with the nanoscale per se. The assessment of risks associated with the nanoscale are largely concerned with increased exposure levels, of both humans and the environment, now that engineered nanostructures are being manufactured and generated in greater and greater quantities, in the new materials that are being so generated, and the potentially new routes/scenarios by which exposure may occur with the current and anticipated applications. Also, there are some obvious and major differences between unintentional and intentional nanoparticles, with the latter being uniform, with precisely engineered characteristics and a monodispersed size, and the former being more physically and chemically variable and polydispersed. Particle morphology also differs, with natural ultrafine particles often a branched structure and engineered nanoparticles manufactured to be a spherical form (tubes, wires, rings, and planes are also manufactured).

existing testing completed on larger particles.⁶⁹ The existing scientific and regulatory paradigms for assessing health effects are inapposite to engineered nanoparticles because of their intrinsic fundamental differences.

The U.K. Royal Society and the Royal Academy of Engineering's 2004 report⁷⁰ concluded that engineered nanoparticles should be treated as new chemicals/new substances: "Substances made using nanotechnology should be considered new chemicals and undergo extra safety checks before they hit the market to ensure they do not pose a threat to human health. . . . We recommend that chemicals produced in the form of nanoparticles and nanotubes be treated as new chemicals"⁷¹

⁶⁹The European Commission's Health and Consumer Protection Directorate-General report also discussed the impacts of engineered nanoparticles in the next 3-5 years and concluded that "the adverse effects of nanoparticles *cannot be predicted (or derived) from the known toxicity of bulk material.*" European Commission, *Nanotechnologies: A Preliminary Risk Analysis on The Basis of a Workshop Organized in Brussels on 1-2 March 2004 by the Health and Consumer Protection Directorate General of the European Commission*, p. 11 (2004) (emphasis added).

⁷⁰The Royal Society Report, *supra* note 31. The Royal Society defined "nanoscience" to be "the study of phenomena and manipulation of materials at atomic, molecular, and macromolecular scales, *where properties differ significantly from those at a larger scale.*" *Id.* at 5, 79.

⁷¹*Id.* at 6 (summary and recommendations), 43, 73, & 83; see also id. at 76 ("Regulators need to consider the new or enhanced properties that nanoparticles may have compared with larger particles of the same chemical. These may affect, but not be limited to: toxicity; chemical or photoreactivity; persistence; bio-accumulation; explosion"); *id.* at 73 ("Based on the evidence that some chemicals have different properties when in their nanoparticulate form, safety assessments based on the testing of a larger form of a chemical cannot be used to infer the safety of nanoparticulate forms of the same chemical (as outlined in section 8.3.2). Therefore, we recommend that ingredients in the form of nanoparticles undergo a full safety assessment by the relevant scientific advisory body before they are permitted for use in products."); Allianz Group, *supra* note 58, at § 6.4, p. 30 ("The same reason that makes nanoparticles technologically interesting leads to the fact that they represent a new category of [potentially] toxic substances."); Innovest, *Nanotechnology: Non-traditional methods for valuation of nanotechnology producers*;

Engineered nanoparticles present new and unique health and safety risks from larger particles of the same substance, and testing of those larger particles cannot adequately account for the fundamental differences of engineered nanoparticles. The science of toxicology with bulk substances centers on the composition of that substance; however, on the nanoscale, the particle size and surface chemistry are proving to be the most important features. This is a fundamental paradigm shift that scientists recognize and that should be similarly recognized by regulators like FDA. FDA should issue an advisory opinion concluding that: 1) engineered nanoparticles are fundamentally different substances; 2) that present wholly unique health risks; 3) which requires them to be regulated as a separate class than bulk material counterparts.

3. New regulations for nanomaterial products

The novel properties of engineered nanoparticles make them different, for all purposes relevant to FDA's statutory mandate, from existing materials with the same chemical composition. To properly assess the risks of engineered nanoparticles, established methods of chemical safety assessments have to be modified to address the special characteristics of engineered nanoparticles. The main difference from the assessment of bulk materials is the fact that additional parameters like size, shape, and surface properties will come into play.⁷²

introducing the Innovest Nanotechnology Index for the value investor, August 29, 2005, available at http://www.innovestgroup.com/pdfs/Nanotechnology_Report.pdf (“It is widely recognized that particles at the nanoscale do not adhere to the principles of classical physics. This suggests the existence of a particle with fundamentally new characteristics that need to be screened as new chemicals.”).

⁷²Oberdorster, *supra* note 20 (“There is a strong likelihood that biological activity of nanoparticles will depend on physicochemical parameters not routinely considered in toxicity screening studies. Physicochemical properties that may be important in understanding the toxic effects of test materials include particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, and

Regulations must simultaneously remain flexible and interactive because the health and safety implications of engineered nanomaterials are still being studied. Petitioners request that FDA recognize *ab initio* that, because of their inherent properties, engineered nanoparticles used in drug products regulated by FDA should be treated as new substances, i.e., drugs and devices, and enact regulations implementing such regulatory mandate accordingly.

The challenge in addressing these hazards will be to draw upon the existing structure-function relationships when possible, while discarding, altering, and supplementing that data by conducting studies that probe hazards that may be unique to nanomaterials. There must be proactive toxicology and environmental research to anticipate and characterize potential risks and safely design new classes of nanomaterials.

(a) New nano-specific health and safety testing methodologies

With regard to toxicity, a review of past studies published in *Science* suggests one strategy for screening engineered nanoparticles using “predictive toxicology,” which looks at subtle signs that cells in a culture are starting to defend themselves, indicating that the particles that they’ve been exposed to could be dangerous.⁷³ The goal would be to develop a series of toxicity assays. “The three key elements to a toxicity screening strategy should include physicochemical characterization of engineered nanoparticles, in vitro assays (cellular and noncellular) and in vivo studies.”⁷⁴ Because there is a “strong likelihood that biological activity will depend on physicochemical characteristics that are not usually considered in toxicity porosity.”).

⁷³Nel, supra note 42.

⁷⁴Id. at 626.

screening studies.”

any test paradigm must attempt to characterize the test material with respect to 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. This should be done at the time of [engineered nanomaterial] administration as well as at the conclusion, if possible.⁷⁵

However, even this method could overlook significant risks, because “it is also possible that new [engineered nanoparticle] properties may emerge that can lead to novel mechanisms of toxicity.”⁷⁶ Cellular assays should reflect portal-of-entry toxicity in lungs, skin, and mucus membranes; because the engineered nanoparticles can spread beyond the portal of entry, it will be important to assess systemic responses.⁷⁷

(b) Labeling: nanomaterial products cannot be labeled as the same material as their bulk material counterparts

FDA regulations covering nanomaterial products must include the requirement that such products be labeled as including nanomaterials and what type of nanoparticle is included in the product.⁷⁸ Under the FFDCA, a food or drug is deemed misbranded if its labeling is “false or

⁷⁵Id.

⁷⁶Id. at 623; See also Kevin Bullis, *Screening for Toxic Nanoparticles: Researchers suggest a strategy that could weed out dangerous nanoparticles*, TECHNOLOGY REVIEW-AN MIT ENTERPRISE, February 7, 2006, available at http://www.technologyreview.com/NanoTech-Devices/wtr_16296,303,p1.html (quoting Kevin Ausman, Executive Director of the Center for Biological and Environmental Nanotechnology at Rice University).

⁷⁷Nel, supra note 42, at 627.

⁷⁸See, e.g., 21 C.F.R. §§ 101.18 (misbranding of food), 201.6 (Drugs; misleading statements), 701.1 (cosmetics labeling misbranding).

misleading in any particular.”⁷⁹ Further, in accordance with Section 201(n), the FFDCA provides that:

If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also *the extent to which the labeling or advertising fails to reveal facts material in the light of such representations* or material with respect to consequences which may result from the use of the article to which labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary.⁸⁰

Because of the inherent differences of nanomaterials, product ingredient lists that refer to nanomaterial consumer product ingredients by the same name as a bulk material counterparts are false and misleading, a violation of the FFDCA. In order to comply with the statute, FDA must require nano-specific labeling of all nanomaterial products under its regulation, including all nanomaterial drugs, devices, foods, and cosmetics.

Furthermore, industry and consumers would be served by mandatory nanomaterial product labeling, a fact highlighted in April 2006 by a health-related recall of a nanomaterial product: German officials recalled a purportedly nanomaterial aerosol spray bathroom cleaner called “Magic Nano.”⁸¹ Seventy-seven people reported respiratory problems using the product,

⁷⁹See, e.g., 21 USC §§ 331 (a) (prohibiting the introduction into commerce of any food, drug, device, or cosmetic that is misbranded), 343(a) (Foods are misbranded if their labeling is “false or misleading in any particular”), 352(a) (Drugs and Devices are misbranded if their labeling is “false or misleading in any particular”), 362(a) (Cosmetics are misbranded if their labeling is “false or misleading in any particular”).

⁸⁰21 U.S.C. § 321(n)(emphasis added).

⁸¹Rick Weiss, *Nanotech Product Recalled In Germany*, WASH. POST. April 4, 2006, at A2.

with six people hospitalized.⁸² It is unclear whether the product actually includes engineered nanoparticles as an ingredient, and if so what type of nanoparticles, or alternatively, if the manufacturer was merely using the word “nano” for high tech appeal.⁸³ In either case, a safety recall causes consumer apprehension of nanomaterial products. Proper regulations requiring the labeling of nanomaterial products would inform consumers, allow them to make educated decisions, and eliminate the possibility of a possibly unwarranted public perception backlash.

C. Any currently existing or future regulatory FDA programs for nanomaterial products must comply with the requirements of the National Environmental Policy Act (NEPA), including, *inter alia*, that FDA conduct a Programmatic Environmental Impact Statement (PEIS) reviewing the impacts of nanomaterial products on human health and the environment

If FDA is currently acting pursuant to, or later decides to adopt or amend, a regulatory program to govern the regulation of nanomaterial products, as requested in Section B *supra*, then pursuant to NEPA, FDA is required to conduct a programmatic environmental impact statement (“PEIS”).

I. NEPA

The National Environmental Policy Act (“NEPA”) is the “basic national charter for protection for the environment.”⁸⁴ NEPA is intended to “promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of

⁸²Id.

⁸³Id.

⁸⁴40 C.F.R. § 1500.1.

man.”⁸⁵ Agency NEPA duties are not “inherently flexible.”⁸⁶ Recognizing the effects of new technologies on the environment, Congress explicitly states in NEPA that “new and expanding technological advances” are activities that could threaten the environment.⁸⁷ Thus, in order to understand and control the effects of new technologies like nanotechnology, Congress requires federal agencies to consider the environmental effects of new technology by complying with the requirements of NEPA.

2. The environmental impacts of engineered nanoparticles

Nanomaterials can enter the natural and human-built environments in numerous ways over their lifecycle, including during manufacturing or transportation, during use of products, or during disposal of products. In addition, some nanomaterials will be introduced deliberately for environmental remediation purposes. Sunscreens, cosmetics, and other consumer personal care products under FDA’s regulation will enter the environment as they are disposed of after use (with residual sunscreen in containers), washed off in showers, or directly dispersed from skin into oceans, rivers, lakes, ponds, community and private pools, and so on.⁸⁸

⁸⁵42 U.S.C. § 4321.

⁸⁶Calvert Cliffs Coordinating Comm. Inc. v. U.S. Atomic Energy Comm’n, 449 F.2d 1109 (D.C. Cir. 1971). In fact, “[c]onsideration of administrative difficulty, delay or economic cost will not suffice to strip the section of its fundamental importance.” Id.

⁸⁷42 U.S.C. § 4331(a). In the legislative history, Congress expressed its concern with “[a] growing technological power * * * far outstripping man’s capacity to understand and ability to control its impact on the environment.” Found. on Economic Trends v. Heckler, 756 F.2d 143, 147 (D.C. Cir. 1985) quoting S. Rep. No. 91-296 (1969).

⁸⁸Royal Society Report, supra note 31 at 46 (“Any widespread use of nanoparticles in products such as medicines (if the particles are excreted from the body rather than biodegraded) and cosmetics (that are washed off) will present a diffuse source of nanoparticles to the environment, for example through the sewage system. Whether this presents a risk to the

Once in the environment, engineered nanoparticles constitute a completely new class of non-biodegradable pollutants. The same unique mobility and toxicity concerns that apply to human health risks apply to environmental risks, including: possibly toxic interactions with ecosystems; the ability to persist and reach places that larger particles cannot;⁸⁹ and a high surface area that binds with or adsorbs pollutants, which could then be transported over longer distances/periods of time.⁹⁰ Even simply detecting engineered nanomaterials in the environment is a new challenge created by their unique physical and chemical characteristics.⁹¹ Once detected, to remove them from water or air requires new filtering techniques.

Few studies of the environmental impacts of engineered nanoparticles exist or are available in the public domain.⁹² These research lapses leave many risks unknown. For example, engineered nanoparticles of iron have been investigated as part of environmental remediation technology. Field tests have shown that the engineered nanoparticles remain active in soil and

environment will depend on the toxicity of nanoparticles to organisms, *about which almost nothing is known*, and the quantities that are discharged.”) (emphasis added); see also EPA White Paper, supra note 29, at 46-47 (Table 4).

⁸⁹E.g., EPA White Paper, supra note 29 at 36-37 (“There are limited data on the fate and transport of nanoparticles, but existing data show that their behavior can be very different from much larger particles of the same material. Nanoparticles generally will be retained in the water column due to diffusion and dispersion.”).

⁹⁰Id. at 37, 40.

⁹¹Royal Society Report, supra note 31, at 42.

⁹²This is due to the relative paucity of federal funding of that research as compared to funding for nanotechnology commercial applications. See, e.g., International Center for Technology Assessment Congressional Letter on NNI 2006 Budget, available at http://www.icta.org/doc/nano%20approp%20letter_Feb_2006.pdf (Noting that, of the NNI’s \$1 billion dollar budget, only 4% is dedicated to health and environmental implications of nanotechnology).

water for several weeks and that they can travel in groundwater as far as twenty meters. However, the impact that the high surface reactivity of engineered nanoparticles used for remediation might have on plants, animals, microorganisms and ecosystem processes is unknown. As a consequence, the Royal Society has recommended that the release of free manufactured nanoparticles into the environment for remediation be prohibited until more research is completed.⁹³ More generally, the Royal Society also recommended that

until more is known about their environmental impact we are keen that the release of nanoparticles and nanotubes in the environment be avoided as far as possible. Specifically we recommend as a precautionary measure that factories and research laboratories treat manufactured nanoparticles and nanotubes as hazardous, and seek to reduce or remove them from waste streams.⁹⁴

Of the few available studies, the most well-known is a study of the effects of carbon₆₀ fullerenes (or buckyballs) on fish (largemouth bass).⁹⁵ Fullerenes are found in many commercial nanomaterial products, including several cosmetics.⁹⁶ Significant lipid peroxidation was found in the fish brains after exposure, demonstrating the toxic effects of these engineered nanoparticles on aquatic and possibly other organisms.⁹⁷ The fullerenes also caused all the water fleas in the

⁹³Royal Society Report, supra note 31, at 80.

⁹⁴Id. at 46.

⁹⁵Oberdorster, *Manufactured Nanomaterials (Fullerenes, C60) Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass*, 112 ENVIRONMENTAL HEALTH PERSPECTIVES 10 (2004) (hereafter Oberdorster III).

⁹⁶Bethany Halford, *Fullerene For The Face: Cosmetics containing C60 nanoparticles are entering the market, even if their safety is unclear*, Chemical and Engineering News, March 27, 2006, available at <http://pubs.acs.org/cen/science/84/8413sci3.html>.

⁹⁷Oberdorster III, supra note 95.

study to die off⁹⁸ and the water to become clear due to nanoparticle interference with bacterial growth.⁹⁹

Another study on fullerenes showed that they clump together in water to form soluble nanoparticles and persist up to 15 weeks, raising concerns of water as a vector for nanoparticle movement through the environment.¹⁰⁰ The 2005 study also found that, even in very low concentrations, fullerenes are toxic to soil bacteria, raising concerns about how they interact with natural ecosystems.¹⁰¹

Engineered nanoparticles of aluminum oxide have also raised red flags, as they were found to slow the growth of roots in at least five species of plants: corn, cucumber, cabbage, carrot and soybean.¹⁰² Seedlings can interact with the nanoparticles and stunt their growth.¹⁰³ Such nanoparticles are commonly used in coatings and sunscreens.¹⁰⁴

⁹⁸Rick Weiss, *Nanoparticles Toxic in Aquatic Habitat, Study Says*, WASH. POST (March 29, 2004) at A2.

⁹⁹Id.

¹⁰⁰Press Release Rice University's Center for Biological and Environmental Nanotechnology, *CBEN: Buckyball aggregates are soluble, antibacterial*, (June 22, 2005), available at http://www.eurekalert.org/pub_releases/2005-06/ru-cba062205.php.

¹⁰¹Id.; see J.D. Fortner et al., *C60 in Water: Nanocrystal Formulation and Microbial Response*, 39 ENVTL. SCI. & TECH. 4307, 4307-16 (2005).

¹⁰²*Study Show Nanoparticles Could Damage Plant Life*, SCIENCE DAILY (November 22, 2005), available at <http://www.sciencedaily.com/releases/2005/11/051122210910.htm>.

¹⁰³Id.

¹⁰⁴See THE WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS, PROJECT ON EMERGING NANOTECHNOLOGIES, *Nanotechnology Consumer Products Inventory*, available at <http://www.nanotechproject.org/consumerproducts> (hereafter Wilson Center Consumer Products Database).

3. FDA's NEPA responsibilities

According to FDA's NEPA regulations,

- (a) All of FDA's policies and programs will be planned, developed, and implemented to achieve the policies declared by NEPA and required by CEQ's regulations to ensure responsible stewardship of the environment for present and future generations.
- (b) Assessment of environmental factors continues throughout planning and is integrated with other program planning *at the earliest possible time* to ensure that planning and decisions reflect environmental values, to avoid delays later in the process, and to avoid potential conflicts.¹⁰⁵

To accomplish NEPA's purposes, all federal agencies are required to prepare a "detailed statement"—known as an Environmental Impact Statement (EIS)—regarding all "major federal actions significantly affecting the quality of the human environment . . ."¹⁰⁶ To determine whether an EIS is required, federal agencies must prepare an Environmental Assessment (EA), that provides sufficient evidence and analysis to support the agency's determination on whether a proposed action will significantly affect the environment.¹⁰⁷ In addition to environmental concerns, the proposed action's possible direct, indirect, and cumulative impacts on public health must be reviewed if they are linked to its environmental impacts.¹⁰⁸

¹⁰⁵21 C.F.R. § 25.10(a)-(b) (emphasis added).

¹⁰⁶42 U.S.C. § 4332 (C). The EIS must describe (1) the "environmental impact of the proposed action," (2) any "adverse environmental effects which cannot be avoided should the proposal be implemented," (3) "alternatives to the proposed action," (4) "the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity," and (5) any "irreversible or irretrievable commitment of resources which would be involved in the proposed action should it be implemented." Id.

¹⁰⁷40 C.F.R. §§ 1501.4(b), 1508.9. FDA NEPA regulations require an EA for the issuance, amendment, and enforcement of FDA regulations, unless categorically excluded. 21 C.F.R. § 25.20(g).

¹⁰⁸40 C.F.R. § 1508.8(b); Baltimore Gas & Elec. Co. v. NRDC, 462 U.S. 87, 106 (1983)(explaining that "NEPA requires an EIS to disclose the significant health, socioeconomic,

Beyond just assessing the impacts of particular project-related actions, FDA is also required to assess the broader impacts of its programmatic actions and to consider alternative program approaches. A programmatic EIS (PEIS) is called for under the CEQ NEPA regulations, which define a “Federal action” broadly to include, in pertinent part, when there is:

Adoption of programs, such as a group of concerted actions to implement a specific policy or plan; systematic or connected agency decisions allocating agency resources to implement a specific statutory program or executive directive.¹⁰⁹

If FDA grants this petition and enacts new regulations, or amends existing regulations with an aim at regulating nanomaterial products, or adopts an official policy in another form, such programmatic regulatory action would necessitate a PEIS if the action “significantly affects the quality of the human environment.”¹¹⁰ Moreover, an agency “program” or “proposal” that exists

and cumulative consequences of the environmental impact of a proposed action”).

¹⁰⁹40 C.F.R. § 1508.18(b)(3) (defining “Federal action”). CEQ’s “Question 24a” is instructive here as it addresses programmatic compliance on the topic of: “When are EISs required on policies, plans or programs?” It provides:

An EIS must be prepared if an agency proposes to implement a specific policy, to adopt a plan for a group of related actions, or to implement a specific statutory program or executive directive. In addition, the adoption of official policy in the form of rules, regulations, and interpretations pursuant to . . . formal documents establishing governmental or agency policy which will substantially alter agency programs, could require an EIS It should be noted that a proposal may exist in fact as well as by agency declaration that one exists.

46 Fed. Reg. 18026, 18033 (Forty Most Asked Questions Concerning CEQ’s NEPA Regulations) (Question and Answer 24(a)).

¹¹⁰21 C.F.R. § 25.22(b).

in fact, but is not necessarily expressly declared by the agency, also requires a PEIS.¹¹¹

Accordingly, if FDA declines to enact or amend its regulations, but instead continues acting pursuant to a “de facto” nanomaterial regulatory policy, such concerted action would also necessitate a PEIS.

4. FDA regulatory action or program regarding nanomaterials and nanotechnology is “significant” and requires a PEIS

CEQ’s implementing regulations list factors to determine whether a Federal action, such as FDA’s regulatory approach to nanotechnology and nanomaterials, is “significant,” which include:

- the degree to which the proposed action affects public health or safety
- the degree to which the effects on the quality of the human environment are likely to be highly controversial
- the degree to which the possible effects on the human environment are highly uncertain or involve unique or unknown risks
- [t]he degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration.¹¹²

In this case, all the above factors are present. First, given the unprecedented environmental and human health risks of nanomaterials,¹¹³ FDA regulatory actions or programs greatly affect public

¹¹¹See 40 C.F.R. § 1508.23 (Defining “Proposal” to include that a “proposal may exist in fact as well as by agency declaration that one exists”).

¹¹²40 C.F.R. § 1508.27(b)(2),(4),(5),(6) & (9). The Supreme Court has held that CEQ’s NEPA implementing regulations are entitled to substantial deference by the courts. Id. at 358; Marsh v. Oregon Natural Resources Council, 490 U.S. 360, 372 (1989). FDA has expressly adopted CEQ’s “significantly” definition in its own NEPA regulations. 21 C.F.R. § 25.5(a)(19).

¹¹³See pp. 29-32 supra and accompanying footnotes (summarizing human health and environmental risks).

health and safety. The petition discusses the significant risks engineered nanoparticles pose to public health and safety in Section I(B)(2) supra and again in Section II(D)(1)(a) infra. This section includes a discussion of the known environmental impacts and unknown environmental risks from the presence of engineered nanoparticles in the environment. Many of the consumer products being released into the environment are under FDA's regulatory umbrella, with the highest consumer and environmental exposures to nanomaterials arguably coming from sunscreens, cosmetics, and other lotions.

Second, FDA's current stance is that it regulates (or declines to regulate) nanomaterial products based on the safety assessment of the same material in bulk form.¹¹⁴ This false premise is at odds with all scientific studies on nanomaterials and their fundamentally unique properties and risks.¹¹⁵ Thus the agency's regulatory stance, if not corrected, is highly controversial at best and grossly negligent at worst.¹¹⁶

Third, due to the paucity of research funding on the environmental and health impacts of nanomaterials,¹¹⁷ the possible effects on the human environment are highly uncertain;¹¹⁸ given the fundamental differences of engineered nanoparticles from bulk materials, those risks are also

¹¹⁴Cite FDA website (stating that, with regard to nanomaterials, “particle size is not an issue” and that existing testing is “probably adequate”).

¹¹⁵See Section I(B)(2).

¹¹⁶See pp. 19-22 supra and accompanying footnotes (discussing scientific consensus findings on the unique properties and dangers of nanoparticles).

¹¹⁷See note 89-92 supra.

¹¹⁸EPA White Paper, supra note 29, at 35 (“The fundamental properties concerning the environmental fate of nanomaterials are not well understood [], as there are few available studies on the environmental fate of nanomaterials.) (footnote omitted).

quite unique.¹¹⁹

Finally, no U.S. regulatory agency has enacted regulations governing the release and marketing of nanomaterials. However, FDA has acknowledged that products containing nanomaterials that are currently available to consumers¹²⁰ fall under its regulation (including cosmetics and sunscreens).¹²¹ Accordingly, FDA's regulatory and/or policy stance on nanomaterial regulation is significant and precedential.

The "presence of one or more of these factors should result in an agency decision to prepare an EIS."¹²² In this case, at least four factors are present.¹²³ Accordingly, NEPA requires FDA to conduct a PEIS before enacting, adopting, or amending its regulations to create a regulatory program for nanomaterial product regulation, and before continuing to act under its regulatory program on nanomaterial product regulation.¹²⁴

D. Section I Conclusion and Agency Priorities

Now is the time for regulatory agencies like FDA to inform the public and establish

¹¹⁹See *id.* at 35-44 (discussing, *inter alia*, the different behavior of nanoparticles in water and soil, the inability to meaningfully predict the biodegradation, bioavailability, or bioaccumulation of nanomaterials, and the inability of existing methods to detect or track nanomaterials in the environment).

¹²⁰See note 104 *supra*.

¹²¹See note 5 *supra*.

¹²²Public Service Co. of Colo. v. Andrus, 825 F. Supp. 1483, 1495 (D. Idaho 1993); See Friends of the Earth, Inc. v. U.S. Army Corp of Eng'rs, 2000 U.S. Dist. LEXIS 11755 (D.D.C. 2000).

¹²³See 40 C.F.R. § 1508.27(b)(2),(4),(5),(6) & (9).

¹²⁴Id. §§ 1502.4(b)(3), 1508.18(b)(1).

principles and procedures that will ensure the safety of nanotechnology for workers, consumers, and the environment. Because so many nanomaterial products fall under FDA regulation,¹²⁵ FDA's regulations likely should prioritize risk assessment, focusing on establishing which materials should be tested first, and how to perform this testing. Products that are already on the market or near commercialization, that are produced in large quantities as free rather than fixed nanoparticles,¹²⁶ and that have the potential of substantial amounts of exposure to humans and the environment should presumably be given high priority. Nano-sunscreens, sunscreens made with an active ingredient of engineered nanoparticles, are widely available, use "free" engineered nanoparticles, and are placed directly on human skin, repeatedly and in large quantities by the general populace. Moreover, sunscreens are classified and regulated as human drugs, for which FDA regulation is more rigorous than other consumer products, requiring premarket approval and a determination of safety and efficacy. Thus, nano-sunscreens should be a regulatory priority for FDA and are the focus of the second half of this petition.

II. FDA'S REGULATION OF SUNSCREEN DRUG PRODUCTS THAT INCLUDE ZINC OXIDE AND TITANIUM DIOXIDE ENGINEERED NANO-PARTICLES

A. Sunscreens and Engineered Nanoparticles of Zinc Oxide and Titanium Dioxide

¹²⁵See notes 5 (FDA statement) & 104 (Wilson Center Consumer Product Database) supra.

¹²⁶"Fixed" engineered nanoparticles are immobilized within a solid matrix and cannot freely move or disperse within the human body or the environment. Hence, there is likely to be lower human exposure from fixed engineered nanoparticles than "free" particles. An example of fixed engineered nanoparticles in a consumer product would be those used in tennis racquets reinforced with carbon nanotubes. Conversely, nanoparticles used in liquids like sunscreens are "free."

Sunscreens fall within section 201(g) of the FDCA, to be regulated by FDA as a “drug,” which is defined in relevant part as

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, (C) articles (other than food) intended to affect the structure or function of the body of man, or (D) articles intended for use as a component of any articles specified in (A), (B), or (C) above.¹²⁷

Beach products like sunscreens are considered by FDA to be drugs because they purport to protect the skin against harm from the sun and because consumers equate the products with the mitigation of the harmful effects of the sun.¹²⁸ Zinc oxide and titanium dioxide have long been used in physical sunscreens, with one of their major limiting factors to an image-conscious user being their tendency to appear white when applied to the skin, due to excessive scattering of light from the particles contained within the sunscreen formulations. Recently however, companies have created, produced, and marketed “cosmetically clear” or transparent sunscreens and UV-resistant cosmetics with an active ingredient of engineered particles of zinc oxide and titanium dioxide of the nanometer size, including:

- U.S. company Rosacea Care’s “Rosacea Care Sunscreen ‘30,’” with the “primary ingredient” being “ZinClear,” which is “the most advanced form of zinc oxide,” and uses “zinc oxide particles so small as to be invisible - smaller in fact than the wavelength of light. These tiny particles in ZinClear protect the skin but do not scatter the light and thus leave no

¹²⁷21 U.S.C. § 321(g)(1); 21 C.F.R. Parts 200 through 499 (FDA’s drug regulations). FDA’s drug regulation is more rigorous than its regulations for most other consumer products. Drugs must be pre-approved by FDA, during which time their safety and efficacy need to be established; drugs and drug manufacturing facilities must be registered with FDA; product-related injuries must be reported to FDA; and current Good Manufacturing Procedures (GMPs) must be followed during drug manufacture.

¹²⁸See, e.g., 58 Fed. Reg. 28195.

white marks on the skin.”¹²⁹

- U.S. company Keys Soap’s “Solar Rx SPF 30+ Nano-Zinc Oxide Sunblock.”¹³⁰ Keys Soap states that its “cosmetically clear nano zinc oxide is 10 times smaller than micronized zinc oxide,” composed of a “narrow particle size distribution” of approximately “20 nanometer particle[s].”¹³¹
- U.K company Boots, the largest suncare retailer and manufacturer in the U.K., and leading European technology company Oxonica Ltd. have patented a UV filter called Optisol™, the active component of Boots’ product available to consumers, “Soltan Facial Sun Defence Cream.”¹³² “Optisol is a milder, longer lasting and innovative new form of titanium dioxide.”¹³³
- U.S. company ColorScience’s “Sunforgettable SPF 30 Brush,” a “perfectly clear” sunscreen created using “hightech nanotechnology.” Its active ingredients are “12% micronized titanium dioxide and 12% micronized zinc oxide.”¹³⁴
- Australian company Cancer Council Australia’s “Sunscreen Plus Clear

¹²⁹Rosecea Care, Sunscreen ‘30’ Website, at <http://rosaceacare.com/products/sun.html>; see also Rosacea Care Sunscreen ‘30’, at http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1029

¹³⁰Wilson Ctr. Products Database, *supra* note 105, Keys Soap’s “Solar Rx SPF 30+ Nano-Zinc Oxide Sunblock,” at http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1044

¹³¹Keys Soap, Solar Rx SFF 30+ Nano-Zinc Oxide Sunsblock website, at <http://www.keys-soap.com/solarrx.html>

¹³²Wilson Ctr. Products Database, *supra* note 105, Boots and Oxonica Soltan Facial Sun Defence Cream, at http://www.nanotechproject.org/index.php?id=44&action=view&product_id=0292.

¹³³Oxonica’s Optisol UV Absorber is Now Available to Buy at Boots’ UK Stores Nationwide, Nano Tsunami website, April 26, 2005, at <http://www.voyle.net/Nano%20Products%202005/Products%202005-0037.htm>.

¹³⁴Wilson Ctr. Products Database, *supra* note 105, ColorScience’s “Sunforgettable SPF 30 Brush,” at http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1055.

Zinc SPF 30+,” a “a non-whitening, non-oily, moisturising sunscreen with invisible zinc.”¹³⁵

- U.S. company NuCelle Inc.’s “SunSense™ SPF 30+ Sunscreen,” made with “Z-Cote HP1® (micro-fine zinc oxide), a substance made with nanotechnology, is the very highest quality zinc compound available so no white residue forms on the skin. The nanotechnology in Z-Cote produces a high-purity nanocrystalline zinc oxide, which allows the sunscreen to go on clear.”¹³⁶
- Vanicream Sunscreen SPF 15, formulated with transparent nanoparticles of zinc oxide [Z-Cote HP1, 8%] and titanium dioxide [T-Cote 031, 3%]¹³⁷
- Sensitive Skin Sunscreen’s 25 SPF Moisturizing Sunscreen Lotion, containing Z-COTE® transparent zinc oxide (9% and T-COTE® microfine titanium dioxide (3%).¹³⁸

Several companies make the nanoparticles that are incorporated into these sunscreens:

- Australian company Advanced Nanotechnology Unlimited’s “ZinClear™ Nano Zinc Oxide for Cosmetic Clarity and Broad Spectrum UV Protection,” a generic active ingredient of the 25-30 nanometer size, patented by Advanced Nanotechnology Unlimited, and that can be found

¹³⁵Wilson Ctr. Products Database, supra note 105, The Cancer Council’s Sunscreen Plus Clear Zinc SPF 30+, at http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1016; The Cancer Council Australia website, Sun Protection Products, at <http://www.cancer.org.au/content.cfm?randid=429012>.

¹³⁶Wilson Ctr. Products Database, supra note 105, NuCelle Inc.’s SunSense™ SPF 30+ Sunscreen, http://www.nanotechproject.org/index.php?id=44&action=view&product_id=1035; NuCelle Website, SunSense SPF 30+ Sunscreen, at http://www.nucelle.com/nucelle_companion1a.htm.

¹³⁷Amazon, Vanicream Sunscreens SPF 15, at <http://www.amazon.com/exec/obidos/tg/detail/-/B0000Y3E7C/104-7832511-0587929?v=glance>.

¹³⁸SkinCare-MD, Sensitive Skin SPF 25 Moisturizing Sunscreen Lotion, at <http://skincare-md.com/index.cfm?event=ProductDetail&ProductID=72>.

in various nano-sunscreen products.¹³⁹

- U.S. company BASF, the “world’s leading chemical company,” manufactures “Z-COTE® microfine zinc oxide,” an “innovative form of microfine zinc oxide” that “unlike the old, pasty white zinc oxide, [Z-COTE] goes on clear” and is used in various sunscreen products, including the above listed NuCelle “SunSense” and Vanicream’s SPF 15¹⁴⁰
- Elementis Specialties manufacturers “NANOX® 200, “nanosized zinc oxide for sunscreens,” with an average particle size of 60 nanometers.¹⁴¹

This listing is not intended to be comprehensive but rather instructive; there are many more nano-sunscreens currently available. For example, the Australian government recently counted almost 600 sunscreens containing zinc oxide or titanium dioxide or both, of which 70% of the sunscreens with titanium dioxide and 30% of the sunscreens with zinc oxide used engineered nanoparticles of these substances.¹⁴²

B. FDA’s Regulation of Sunscreen Drug Products: The OTC Sunscreen Drug Product Monograph

¹³⁹Wilson Ctr. Products Database, supra note 105, Advanced Nanotechnology Unlimited’s ZinClear Nano Zinc Oxide, http://www.nanotechproject.org/index.php?id=44&action=view&product_id=0104; Advanced Nanotechnology Unlimited website, ZinClear™, at <http://www.advancednanotechnology.com/zinclear.php> and brochure, at http://www.advancednanotechnology.com/pdfs/zinclear/ZinClear_brochure.pdf.

¹⁴⁰BASF website, BASF Z-COTE. Microfine Zinc Oxide, <http://www.bASF.com/static/z-cote.html>; BASF news, BASF’s Z-COTE helps make NuCelle SunSense SPF 30+ sunscreen better, at <http://www.bASF.com/corporate/news2004/03012004.htm>.

¹⁴¹Elementis Specialties website, at <http://www.elementis-specialties.com/index.asp?fuseaction=Industries.prodDetailUpd&id=1641&bid=&aid=&sid=&mid=13>.

¹⁴²Australian Government, Therapeutic Goods Administration, *Safety of sunscreens containing nanoparticles of zinc oxide or titanium dioxide*, February 2006, available at www.tga.gov.au/npmeds/sunscreen-zotd.htm.

1. Procedural History of the OTC Sunscreen Drug Monograph

The OTC drug review is the FDA procedure for classifying OTC drugs as generally recognized as safe and effective and not misbranded.¹⁴³ The regulation that results of the review process, termed a “monograph,” establishes the safety and efficacy standards for marketing of non-prescription drug products not covered by new drug applications.¹⁴⁴

On August 25, 1978, FDA published an advance notice of a proposed rulemaking to establish a monograph for OTC sunscreen drug products that would, among other things, list the active ingredients to be generally recognized as safe and effective for use in these products. The agency’s proposed regulation, a tentative final monograph for OTC sunscreen drug products, was published on May 12, 1993.¹⁴⁵ On June 8, 1994, the agency proposed to amend the tentative final monograph to remove five sunscreen ingredients.¹⁴⁶ On April 5, 1994, the agency reopened the administrative record and announced a public meeting to discuss ultraviolet A (UVA) radiation claims and testing procedures.¹⁴⁷ On September 16, 1996, the agency amended the proposed rule to include avobenzone as a single ingredient and in combination with certain other sunscreen ingredients.¹⁴⁸ On October 22, 1998, the agency proposed to amend the tentative monograph to

¹⁴³See generally 21 C.F.R. § 330.10; id. § 330.10(a)(7)-(10).

¹⁴⁴43 Fed. Reg. 38206; see 330.10(a)(6).

¹⁴⁵58 Fed. Reg. 28194.

¹⁴⁶59 Fed. Reg. 29706.

¹⁴⁷59 Fed. Reg. 16042.

¹⁴⁸61 Fed. Reg. 48645.

include zinc oxide as a single ingredient and in combination with any proposed category I sunscreen active ingredient except avobenzone.¹⁴⁹

On May 21, 1999, the agency published the final monograph for OTC sunscreen drug products.¹⁵⁰ The monograph set a two year implementation period with a compliance date of May 21, 2001 for sunscreens and their labeling to comply or file a new drug application before introduction into interstate commerce.¹⁵¹ On June 8, 2000, the agency extended the effective date for all OTC sunscreen drug and cosmetic products regulated under the monograph until

¹⁴⁹63 Fed. Reg. 56584. See also 64 Fed. Reg. 27680. Both of the added active ingredients are UVA-absorbing, and the agency proposed indications for these ingredients such as “provides broad spectrum protection” and “provides protection from UVA rays that may contribute to skin damage and premature aging.” 61 Fed. Reg. 48655; 63 Fed. Reg. 56589; 65 Fed. Reg. 3620. The amendment nowhere mentions “nano” zinc oxide particles and it is unclear if such particles were even available or contemplated at the time.

¹⁵⁰64 Fed. Reg. 27666. The monograph included 16 active ingredients, required labeling for products that contain one or more of these active ingredients, a standardized test for measuring sun protection factor (SPF) values, and standard methods for measuring water resistant properties of sunscreens. The labeling and test methods covered products intended to provide UVB radiation protection. The monograph however did not address active ingredients, labeling, and test methods for products intended to provide UVA protection. The final rule also included related nonmonograph conditions addressing labeling for cosmetics products that contain sunscreen active ingredients for nontherapeutic, nonphysiologic uses (i.e., color additive or protect the color of product). See 310.545(a)(29), 700.35.

¹⁵¹64 Fed. Reg. 27667. On November 21, 1997, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA), which provided in part that the agency shall issue regulations for OTC sunscreen products no later than 18 months subsequent. 65 Fed. Reg. 36320. The FDAMA also prompted the FDA to identify those parts of the TFM for sunscreen products that could be finalized within the timeline set by the FDAMA. FDA was still working on developing testing standards and labeling for UVA radiation protection. Given these outstanding issues, the agency decided to finalize the UVB portions of the monograph to meet the FDAMA deadline, publishing the final monograph at 65 Fed. Reg. 27666. The monograph did not address active ingredients, labeling, and test methods for products intended to provide UVA protection. See 65 Fed. Reg. 36319

December 31, 2002.¹⁵² On December 31, 2001, the agency stayed the final monograph, 21 C.F.R. part 352, published at 64 Fed. Reg. 27666, until further notice.¹⁵³ The stay was taken because the agency will be again amending part 352, in order to develop a comprehensive monograph, addressing formulation, labeling, and testing requirements for both ultraviolet A (UVA) radiation protection and ultraviolet B (UVB) radiation protection. The Sun Protection Factor (SPF) of the Monograph measures only the efficacy of sunscreens with regard to UVB but not UVA radiation. However, there is mounting evidence that exposure to UVA may be a significant risk factor for premature aging of the skin and certain forms of skin cancer. Also, various short-term and long-term adverse effects may be relatively more sensitive to UVA than UVB-caused sunburns. The agency anticipated that the new effective date would not be before January 1, 2005.¹⁵⁴

On December 5, 2005 the agency announced a call for safety and effectiveness data for information on two proposed active sunscreen ingredients in order to determine their safety and

¹⁵²65 Fed. Reg. 36319.

¹⁵³66 Fed. Reg. 67485.

¹⁵⁴66 Fed. Reg. 67486; see also Sunscreens, Tanning Products, and Sun Safety, U.S. Food and Drug Administration, <http://www.cfsan.fda.gov/~dms/cos-220.html> (last visited on December 13, 2005). On June 4, 2003, the agency published a final rule for OTC skin protectant drug products and temporarily lifted the stay on the OTC sunscreen drug product monograph in order to make a technical amendment to part 352 (to include sunscreen-skin protectant combination products, and then returned the stay of part 352 until further notice. 68 fed reg 33362. On September 3, 2004, the agency also delayed the implementation date of the final rule establishing standardized format and content requirements for the labeling of OTC drug products regulated under the sunscreen monograph, as it would be impossible for manufacturers to comply until the monograph is final. 69 Fed. Reg. 53802.

efficacy for OTC use.¹⁵⁵

2. The 1999 OTC Sunscreen Drug Product Monograph and regulation of sunscreens with engineered nanoparticles

The 1999 Final OTC Sunscreen Drug Monograph, currently stayed, does not expressly address sunscreen drug products composed of engineered nanoparticles. However, FDA currently states that it is aware of both cosmetics and sunscreen products under its regulation that contain engineered nanoparticles.¹⁵⁶ The list of active sunscreen ingredients permitted under the Monograph includes Titanium Dioxide up to 25% concentration and Zinc Oxide up to 25% concentration. The Monograph does address “micronized” particles of titanium dioxide, albeit without defining that term:

the agency is aware that sunscreen manufacturers are using micronized titanium dioxide to create high SPF products that are transparent and esthetically pleasing to the skin. The agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of titanium dioxide originally reviewed by the Panel.¹⁵⁷

That is, since “fines” have been part of titanium dioxide powers for decades, “micronized” simply refers to “a refinement of particle size distribution.”¹⁵⁸ Finally, FDA noted that it was “not aware of any evidence at this time that demonstrates a safety concern from the use of

¹⁵⁵70 Fed. Reg. 72449. The two active ingredients are bisoctrizole, up to 10 percent as an active sunscreen ingredient and bemotrizinol, up to 10 percent as an active sunscreen ingredient. Id.

¹⁵⁶See FDA, Frequently Asked Questions on OTC Drugs, at http://www.fda.gov/cder/about/smallbiz/OTC_FAQ.htm.

¹⁵⁷U.S. Food and Drug Administration, HHS, Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph, 64 Fed. Reg. 27666-27693, 27671 (1999).

¹⁵⁸Id.

micronized titanium dioxide in sunscreen product.”¹⁵⁹ Thus, the 1999 Final Monograph addressed “micronized” particles and found them not to be new substances, separate from larger particles of the material. In doing so, the Final Monograph parallels FDA’s broader statement regarding nanotechnology regulation that “particle size is not an issue”¹⁶⁰ with regard to engineered nanoparticles and nanomaterials incorporating them. Petitioners have already addressed FDA’s erroneous and ill-advised interpretation of engineered nanoparticles generally—see petition section I(B)(2) supra—and now do so with regard to nano-sunscreens specifically.

C. Agency Actions Requested Regarding the OTC Sunscreen Drug Monograph

Petitioners request the agency to take three actions with regard to the currently-stayed OTC Monograph: 1) reopen its administrative record for the purpose of soliciting and reviewing all available safety and health information on engineered nanoparticles currently used as sunscreen ingredients; 2) amend the Monograph to address the fundamental differences between engineered nanoparticles—and the associated unique health and safety risks—and larger particles; and 3) require that all manufacturers of sunscreen drug products that contain engineered nanoparticles complete new drug applications pursuant to 21 U.S.C. § 321(p) and 355(a) rather than be accepted as safe for use under the Monograph based on safety testing completed on the particles’ bulk material counterparts.

1. Reopen the administrative record of the OTC Sunscreen Drug Monograph

The administrative record of a monograph may be reopened to consider new data and

¹⁵⁹Id.

¹⁶⁰See note 36 supra

information.¹⁶¹ In this case, the monograph is not yet final; the current regulation has been stayed while more research is done on UVB radiation and the agency can compose a comprehensive regulation covering both UVA and UVB radiation.¹⁶² Issues presented by engineered nanoparticles used in sunscreen products should also be addressed before the Monograph is finalized.

FDA stated in the 1999 Monograph that it was “not aware of any evidence at this time that demonstrates a safety concern from the use of micronized titanium dioxide in sunscreen products.”¹⁶³ It is unclear whether the agency intended “micronized” to encompass engineered nanoparticles or not.¹⁶⁴ Regardless of the agency’s 1999 intent, in the past seven years nanotechnology, nanomaterials, and their associated health and safety concerns have become of increasing concern. Products under FDA’s regulation containing engineered nanoparticles, including sunscreens, have come to market.¹⁶⁵ And the scientific community’s collective knowledge of the unique properties of engineered nanoparticles—and their corresponding hazards to human health and safety—has grown exponentially. Accordingly, in order to address this vital new research, petitioners request that FDA, in the course of amending the Final Sunscreen Drug Monograph through Federal Register Notice and Comment process, concurrently call for and

¹⁶¹ See 21 C.F.R. § 330.10(a)(12)(i). The Commissioner may publish a proposed amendment if the Commissioner finds general recognition of safety, effectiveness, and labeling under 21 C.F.R. § 330.10(a)(4).

¹⁶² See supra p. 43-46 and accompanying footnotes.

¹⁶³ See note 159 and accompanying text supra.

¹⁶⁴ See discussion pp. 51-53 infra on amending the Monograph.

¹⁶⁵ See, e.g., notes 32-35 supra and accompanying text.

review all available scientific data on the safety of zinc oxide and titanium dioxide engineered nanoparticles used in transparent sunscreens currently available to U.S. consumers. Only after reviewing this body of evidence should FDA proceed to amend and finalize the currrently-stayed Sunscreen Drug Monograph with regard to the safety of engineered titanium dioxide and zinc oxide nanoparticles used in sunscreens.

This petition will not attempt to summarize all the relevant information regarding sunscreens made of engineered nanoparticles of zinc oxide and titanium oxide; reliance on the industry and interested scientific and public communities at large for such submissions is the very reason to reopen the administrative record. The public comment period would build the administrative record. However, petitioners submit the following as a starting point in the agency's analysis: The European Union, through the European Commission's¹⁶⁶ Scientific Committee on Cosmetic Products and Non-Food Products ("SCCNFP"), has been asked to review and, if appropriate, to amend its safety guidelines for the testing of cosmetic ingredients in the form of nanomaterials.¹⁶⁷ The SCCNFP is the scientific advisory body to the European

¹⁶⁶"The European Commission embodies and upholds the general interest of the Union and is the driving force in the Union's institutional system. Its four main roles are to propose legislation to Parliament and the Council, to administer and implement Community policies, to enforce Community law (jointly with the Court of Justice) and to negotiate international agreements, mainly those relating to trade and cooperation." See The European Commission, at http://europa.eu.int/comm/about_en.htm.

¹⁶⁷See SCCNFP, Risk Assessments, *Request for a scientific opinion: Safety of Nanomaterials in Cosmetic Products, available at* http://europa.eu.int/comm/health/ph_risk/committees/04_sccp/sccp_cons_02_en.htm. Parties had until August 31, 2005 to submit data to be considered. The EU's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has also been asked to deliver an opinion on "the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies." Id.; see note 21 supra and accompanying text.

Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers. Regarding zinc oxide, SCCNFP's previous guidance on its use does not specifically address engineered nanoparticles. In light of new findings on engineered nanoparticle safety, SCCNFP is reviewing this previous opinion. SCCNFP requested safety information on engineered nanoparticles of zinc oxide in order to determine whether the damage caused to DNA by microfine zinc oxide during tests on cell cultures (*in vitro*) would be seen in living animals (*in vivo*), and if zinc oxide could pass through the skin (a precursor to harm occurring).¹⁶⁸ SCCNFP found the evidence before it insufficient, ruled that "there is a lack of reliable data on the percutaneous absorption of microfine ZnO and the potential for absorption by inhalation," and required that the industry provide further safety information in order for it to properly assess its safe use as a UV filter in cosmetic products.¹⁶⁹ Then in 2005, SCCNFP issued a strongly worded update, a "Statement on Zinc oxide used in sunscreens," reiterating that an appropriate safety dossier on microfine ZnO itself, including possible pathways of cutaneous penetration and systemic exposure, is required. The requested safety dossier has not been provided. It is understood that microfine and ultrafine zinc oxide is widely used in sunscreen products on the European market. The safety to the consumer of this use remains to be assessed. The attention of the Commission and the Member States is drawn to this.¹⁷⁰

¹⁶⁸SCCNFP 2003 *opinion concerning zinc oxide*, (adopted June 24-25, 2003), [available at](http://europa.eu.int/comm/health/ph_risk/committees/2003/documents/out222_en.pdf) http://europa.eu.int/comm/health/ph_risk/committees/2003/documents/out222_en.pdf (31 page opinion).

¹⁶⁹Id.

¹⁷⁰SCCNFP 2005 *Statement on Zinc Oxide In Sunscreens*, adopted September 20, 2005 http://europa.eu.int/comm/health/ph_risk/committees/2005/documents/out222_en.pdf; [see also](#) Royal Society Report, [supra](#) note 31 at 73: "We recommend that industry submit the additional information on microfine zinc oxide that is required by the SCCNFP as soon as reasonably practicable so that the SCCNFP can deliver an opinion on its safety. The uncertainties about the safety of nanoparticles of zinc oxide are not just applicable to its use as a UV filter. . . . [U]ntil

FDA should similarly reopen the administrative record for this purpose, and request from manufacturers the data necessary in order for it to properly assess the safety of sunscreen drug products made of zinc oxide and titanium oxide engineered nanoparticles.¹⁷¹

2. Amend the Final OTC Sunscreen Drug Monograph

An interested party may petition the Commissioner to amend a monograph,¹⁷² and a citizen petition is a means to request an amendment or repeal of conditions covered by an existing proposed or final OTC drug monograph.¹⁷³ The 1999 monograph is inadequate and needs to be revised to: 1) provide a clear definition of engineered nanoparticles as relevant to sunscreen drug ingredients, parallel to FDA's broader regulatory nanotechnology definitions; 2)

the safety dossier is provided to the SCCNFP the uncertainties remain.”

¹⁷¹Regarding engineered nanoparticles of titanium dioxide, SCCNFP previously found titanium dioxide safe, “irrespective of particle size,” and recommended no restrictions on its use. European Commission’s Scientific Committee on Cosmetic Products and Non-Food Products, Opinion Concerning Titanium Dioxide, 24 Oct. 2000. However, the industry studies backing up the safety finding were not made available to the public. Several groups, including Swiss re-insurance giant Swiss Re, criticized the conclusion, noting that the Commission’s findings used sweeping generalizations on nanoparticles as well as relied on classified, non-public scientific studies provided by the nanotechnology industry. According to the Swiss Re report, “[t]his is remarkable, given that nanoparticles are distinguished from microparticles by several properties. *Were this not the case, there would be no sense in replacing the larger microparticles in a number of products by more expensive nanoparticles.*” Swiss Re report, *supra* note 26, at 36 (emphasis added). Moreover, the currently-under-review request to the SCCNFP includes the possibility that the Commission revise its titanium dioxide opinion in light of its findings regarding engineered nanoparticles: “In the light of the findings under (1), does the SCCP consider it is necessary to review existing opinions on nanosized Titanium dioxide and ZnO as cosmetic ingredients and if appropriate to identify which additional elements are required for the submission of a safety-file?” see SCCNFP, *supra* note 167.

¹⁷²See 21 C.F.R. § 330.10(a)(12).

¹⁷³See FDA, Frequently Asked Questions on OTC Drugs, at http://www.fda.gov/cder/about/smallbiz/OTC_FAQ.htm.

under those definitions, clarify that “micronized” and nano-scale engineered particles are not the same if that is the case; and 3) instruct that sunscreen drug products that contain engineered nanoparticles are new drugs, not properly regulated under the Monograph as an acceptable sunscreen ingredient; rather such sunscreens must be submitted for FDA approval separately, via a new drug application.

First, the Final Monograph, currently stayed, should expressly address engineered nanoparticles currently used in sunscreens. In order to do so, the Monograph must make reference to the agency’s definition of “engineered nanoparticles.” If FDA amends its general definitions section of its regulations to include such definitions, as proposed in this petition in pp. 7-11 supra, then the monograph likely need only reference those definitions and apply them to the products and ingredients at bar. The proposed definitions would recognize the sunscreens regulated by FDA with engineered nanoparticles of zinc oxide and titanium dioxide as nanomaterials.

Second, the Monograph does not address the use of engineered nanoparticles of titanium dioxide or zinc oxide in sunscreens, simply approving both substances for use without regard to the size of particles involved: The list of active sunscreen ingredients includes titanium dioxide up to 25% concentration and zinc oxide up to 25% concentration.¹⁷⁴ While not discussing nano-scale materials, as mentioned above, the 1999 FDA final rule on OTC sunscreen drugs did note that FDA does not find “micronized” titanium dioxide to be a new material or substance, despite comments that asserted it be considered a new ingredient with unresolved safety and efficacy

¹⁷⁴21 C.F.R. § 352.10(p), (r) (stayed).

issues.¹⁷⁵ “Micronized” was not defined; stated differently, FDA does not clarify whether the term is inclusive of nanoparticles.¹⁷⁶ If the FDA’s position in 1999 was that “micronized” does include nano-scale engineered particles and that the nano-scale reduction of particle size is not otherwise relevant, there is compelling evidence that this position no longer reflects the view of the scientific community (if it ever did), which is that nano-scale particles are not merely different grades of one material. Rather, nanoparticles are wholly different substances, with different fundamental properties, governed by a different realm of physics.¹⁷⁷ Even if no environmental or health concerns were associated with the use of engineered nanoparticles of titanium dioxide or zinc oxide in sunscreens, the fundamentally different properties of substances at the nano-scale make them not merely a refinement of particle size. The monograph errs in not considering engineered nanoparticles of substances as entirely different substances from the larger sized counterparts.

Third and finally, the Monograph as amended should include instruction that sunscreen drug products containing engineered nanoparticles as ingredients are new drugs for which the manufacturers of those drugs must file New Drug Applications. Because this decision on new drug status is one also separate from the Monograph, which the agency could make in another

¹⁷⁵64 FR 27666, 27671 and 21 C.F.R. § 352.

¹⁷⁶An ETC Group report cites a 2002 conversation with FDA employee John Lipnicki, the contact person for the 1999 monograph, regarding the meaning of “micronized.” According to the report, Mr. Lipnicki defines “micronized” as particles of a relatively homogenous size that is less than 250nm. ETC Group, *No Small Matter! Nanoparticles Penetrate Living Cells and Accumulate in Animal Organs*, p. 8 n. 17 (2002), available at <http://online.sfsu.edu/~rone/Nanotech/nosmallmatter.html>.

¹⁷⁷See advisory op discussion pp. 11-24 supra and accompanying footnotes.

form like an advisory opinion, separate rule, or interpretative/guidance document, this petition addresses it separately, directly below.

D. Other Agency Actions Requested Regarding Sunscreen Drug Products Containing Engineered Nanoparticles of Zinc Oxide and Titanium Dioxide

1. Require that manufacturers of drug products containing engineered nanoparticles file New Drug Applications

FDA drug regulation begins with a determination of whether a chemical is a new or existing substance. In light of all evidence discussed above regarding the fundamental and potentially dangerous differences between engineered nanoparticles and larger particles of the same bulk material, petitioners herein assert that sunscreens made from or using engineered nanoparticles of zinc oxide or titanium dioxide should be considered “new drugs” within the meaning of 21 U.S.C. § 321(p)¹⁷⁸ and 355(a),¹⁷⁹ and that the manufacturers of those drug products must complete a new drug application as required for all “new drugs” under 21 U.S.C. § 355 before FDA product approval.

¹⁷⁸Section 321(p) defines a “new drug” as

- (1) Any drug ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof ...; or
- (2) Any drug ... as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

¹⁷⁹21 C.F.R. § 355(a) (mandating that “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed [with the FDA] is effective with respect to such drug”).

(a) Engineered nanoparticles are categorically different, present new and unstudied risks, and must be assessed separately from any larger versions of the substance

A drug product must be considered a “new drug” if it is “not generally recognized” by scientific experts “as safe and effective.”¹⁸⁰ One new ingredient, such as engineered nanoparticles, is sufficient to cause a drug to be a “new drug.”¹⁸¹ That is, “[t]he newness of a drug may arise by reason (among other reasons) of: (1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be an active substance or . . . other component.”¹⁸² Thus, that a sunscreen drug product contains engineered nanoparticles which are considered “new” is sufficient for that product to be termed a “new drug” and mandate review if that new ingredient is not generally recognized as safe and effective.

In this case, petitioners have already explained in detail in Section I(B)(2) supra that: engineered nanoparticles are inherently different from bulk material counterparts, with fundamentally different properties and associated inherent health risks; they cannot be and are not generally recognized as safe and effective by experts under existing, inapposite testing methods; and that they must be categorically considered new substances by regulatory regimes, in the case of sunscreen drug products regulated by FDA, “new drugs.”¹⁸³ All nanomaterials’

¹⁸⁰See 21 U.S.C. § 321(p).

¹⁸¹21 CFR § 310.3(g) (“(g) New drug substance means *any substance* that when used in the *manufacture, processing, or packing* of a drug, causes that drug to be a new drug.”) (emphases added).

¹⁸²21 CFR § 310.3 (h).

¹⁸³See advisory opinion on engineered nanoparticles discussion pp 11-24 supra and accompanying footnotes.

characteristics—including hazardous traits—must be learned anew by nano-specific testing. And, as of yet, insufficient engineered nanoparticle health and safety testing has been done.¹⁸⁴ Without sufficient specific testing and resultant health and safety data, it is impossible to properly evaluate and determine whether the products comprised of these new substances are safe and effective.¹⁸⁵

The research that has been done raises serious concerns that nanomaterials pose significant health and safety, as well as environmental,¹⁸⁶ risks and impacts. Existing evidence supports the conclusion that new nanomaterials present new dangers that must be further studied and evaluated. One new property of engineered nanoparticles is their extreme mobility.¹⁸⁷ In contrast to larger particles, it has been shown that nanomaterials can enter the human body

¹⁸⁴See, e.g., Juliet Eilperin, *Nanotechnology's Big Question: Safety*, WASH. POST. (October 23, 2005), at A11; Rick Weiss, *Nanotechnology Regulation Needed, Critics Say*, WASH. POST. (December 5, 2005), at A8; Barnaby J. Feder, *As Uses Grow, Tiny Materials' Safety Is Hard to Pin Down*, NEW YORK TIMES (November 3, 2003) at C1; Keay Davidson, *Nanotechnology May Hold Risks, Scientists Warn New Approach Required to Test for Harmful Effects*, SAN FRANCISCO CHRON. (October 20, 2005), at A10.

¹⁸⁵Determining the safety is made more complicated by the fact that properties of nanoparticles of *the same substance* can change within the nanometer range, depending on nanoparticle size, shape, and the presence or absence of a surface coating. It may be impossible to affirm that titanium dioxide or zinc oxide nanoparticles are safe or unsafe without further qualifying the size and/or shape and/or surface features of the particles tested.

¹⁸⁶See Section I(C)(2) *supra*.

¹⁸⁷See generally David Rotman, *Measuring the Risks of Nanotechnology*, Technology Review, available at www.technologyreview.com/articles/03/04/impact0403.asp?PM=GO (Interview with Dr. Vicki Colvin, Director, The Center for Biological and Environmental Nanotechnology).

through several ports.¹⁸⁸ Engineered nanoparticles have “almost unrestricted access to the human body,”¹⁸⁹ because they can enter the blood stream through the lungs¹⁹⁰ and digestive tract,¹⁹¹ likely through the skin,¹⁹² and seem to enter the brain directly via olfactory nerves.¹⁹³ Once in the blood stream, engineered nanoparticles can “move practically unhindered through the entire body,” unlike larger particles that are trapped and removed by various bodily protective mechanisms.¹⁹⁴ While in the blood stream, nanoparticles have been observed entering blood cells themselves. Once in the body, they may enter the vasculature, heart, bone marrow, muscles, liver, and spleen.¹⁹⁵ During pregnancy, they would likely cross the placenta and enter the fetus.¹⁹⁶ Even the brain, one of the best protected of all human organs, guarded by the “blood-brain” barrier that prevents most substances in the blood from entering, has been repeatedly shown in

¹⁸⁸Hoet et al., *Nanoparticles-known and unknown health risks*, 2 JOURNAL OF NANOBIOTECHNOLOGY, 12 (December 2004). Depending on their size, engineered nanoparticles can enter the Alveolar surface of the lung (70 nm), cells, (50 nm), and the Central Nervous System (30 nm). This is the size of engineered nanoparticles of zinc oxide and titanium dioxide that are used in sunscreens.

¹⁸⁹Swiss Re report, *supra* note 26, at 7; see Oberdorster, *supra* note 20, at Figure 1 (Graph of confirmed and potential passageways).

¹⁹⁰Hoet, *supra* note 188, at 3.2

¹⁹¹*Id.* at 4.1.

¹⁹²*Id.* at 5.

¹⁹³*Id.* at 6.3.

¹⁹⁴Swiss Re report, *supra* note 26, at 7.

¹⁹⁵See, e.g., Nel, *supra* note 42, at 625.

¹⁹⁶Ben Wootliff, *British Scientist: Nanoparticles Might Move from Mom to Fetus*, Small Times 14 January 2004, available at www.smalltimes.com (Findings reported that gold nanoparticles can move across the placenta from mother to fetus).

animal studies to be breachable, where effects are unknown.¹⁹⁷ Nanoparticles are able to lodge in mitochondria.¹⁹⁸ In fact, “[i]t is likely that in the course of its entire evolution, *humankind has never been exposed to such a wide variety of substances that can penetrate the human body apparently unhindered.*”¹⁹⁹ Moreover, it is unknown how long the particles will remain in organs.²⁰⁰

This mobility creates possible new channels of human exposure, through which engineered nanoparticles may harm living tissue in at least two ways: through normal effects of chemical reactivity or by damaging phagocytes, scavenger cells that normally remove foreign substances. As to the latter, phagocytes can become overloaded by engineered nanoparticles and cease functioning, or retreat into deeper layers and so become unavailable to protect the body against foreign pathogens and invaders. Foreign particles entering the body thereafter are then able to do full reactive damage, and other invaders like bacteria may penetrate unhindered. As to the former, the surface reactivity of engineered nanoparticles give rise to “free radicals,” atoms containing unstable numbers of electrons, which then swap electrons with nearby atoms, creating further instabilities and setting off a domino effect. Some free radicals are beneficial, destroying

¹⁹⁷ Alex Kirby, *Tiny Particles Threaten Brain*, BBC News, 8 January 2004, available at <http://news.bbc.co.uk/1/hi/sci/tech/3379759.stm>; Rotman, supra note 187, at 2; Bharali et al., *Organically modified silica nanoparticles: A nonviral vector for in vivo gene delivery and expression in the brain*, 102 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 11539-44 (August 9, 2005).

¹⁹⁸ Nel, supra note 42, at 623.

¹⁹⁹ Swiss Re Report, supra note 26, at 40 (emphasis added).

²⁰⁰ Tran, supra note 54.

invaders; however, free radicals also cause inflammation and tissue damage, and may initiate tumor growth. *In vivo* studies on living cells have confirmed that nanoparticles produce free radicals which cause cellular damage that can be manifested in different ways, including genotoxicity²⁰¹ and altered rates of cell death (including apoptosis).²⁰² As summarized by one recent study, the possible pathophysiological outcomes of exposure to engineered nanoparticles supported by experimental evidence and clinical evidence include:²⁰³

- *Reactive oxygen species (ROS) generation,** leading to Protein, DNA and membrane injury,* oxidative stress†
- *Oxidative stress,** leading to Phase II enzyme induction, inflammation,† mitochondrial perturbation*
- *Mitochondrial perturbation,** leading to inner membrane damage,* permeability transition (PT) pore opening,* energy failure,* apoptosis,* apo-necrosis, cytotoxicity
- *Inflammation,** leading to tissue infiltration with inflammatory cells,† fibrosis,† granulomas,† atherogenesis,† acute phase protein expression (e.g., C-reactive protein)
- *Uptake by reticulo-endothelial system,** leading to asymptomatic sequestration and storage in liver,* spleen, lymph nodes,† possible organ enlargement and dysfunction
- *Protein denaturation, degradation,** leading to loss of enzyme activity,* auto-antigenicity
- *Nuclear uptake,** leading to DNA damage, nucleoprotein clumping,* autoantigens
- *Uptake in neuronal tissue,** leading to brain and peripheral nervous system injury

²⁰¹Rahman *et al.*, *Evidence that Ultrafine Titanium Dioxide Induces Micronuclei and Apoptosis in Syrian Hamster Embryo Fibroblasts*, ENVIRON HEALTH PERSPECT. 110(8); 797-800 (2002).

²⁰²*Id.*; Uchino *et al.*, *Quantitative determination of OH radical generation and its cytotoxicity induced by Titanium dioxide-UVA treatment*, 16 TOXICOLOGY IN VITRO 629-635 (2002).

²⁰³Nel, *supra* note 42 at Table 2. NM effects as the basis for pathophysiology and toxicity. Effects supported by limited experimental evidence are marked with asterisks; effects supported by limited clinical evidence are marked with daggers.

- *Perturbation of phagocytic function,* ‘particle overload,’ mediator release,* leading to chronic inflammation,† fibrosis,† granulomas,† interference in clearance of infectious agents†*
- *Endothelial dysfunction, effects on blood clotting,* leading to atherogenesis,* thrombosis,* stroke, myocardial infarction*
- *Generation of neoantigens, breakdown in immune tolerance, leading to autoimmunity, adjuvant effects*
- *Altered cell cycle regulation, leading to Proliferation, cell cycle arrest, senescence*
- *DNA damage, leading to mutagenesis, metaplasia, carcinogenesis*

Engineered nanoparticles of titanium dioxide and zinc oxide used in sunscreens, rubbed onto human skin, are no exception to the above health and safety concerns. The reason that such substances are prized by sunscreen manufacturers is precisely because they possess a fundamental property that larger particles of the bulk material lack: transparency. But, as discussed above, transparency is not the only change to engineered nanoparticles. Materials deposited on the outside of the skin are generally of the micrometer size and cannot normally pass through the skin. However, skin penetration is partially size-dependant,²⁰⁴ and research shows that engineered nanoparticles are small enough that they can slip beneath layers of outer skin and penetrate to the blood below. Particles below 20 nm can be taken up by the endothelium skin layers and those below 10-50 nm can enter cells through receptor mechanisms.²⁰⁵ As discussed in the EPA’s 2005 Draft White Paper,

Hart (2004) highlights physiological characteristics of the skin that may permit the absorption of nano-sized materials. In particular the review highlights a conceivable route for the absorption of nanoparticles as being through interstices formed by stacking and layering of the calloused cells of the top layer of skin (Hart, 2004). Movement through these interstices will subsequently lead to the

²⁰⁴Hoet, supra note 188.

²⁰⁵Kuzma, supra note 10.

skin beneath, from which substances can be absorbed into the blood stream. *Nanomaterials also have a greater risk of being absorbed through the skin than macro-sized particles.* Reports of toxicity to human epidermal keratinocytes in culture following exposure to carbon nanotubes have been made (Shvedova et al., 2003; Monteiro-Riviere et al, 2005).²⁰⁶

Studies have shown that titanium dioxide particles of up to one micron in diameter can get deep enough into the skin to be taken into the lymphatic system, while larger particles cannot.²⁰⁷

Several reports show penetration into the deeper parts of the stratum corneum and hair follicles, and a report of increased titanium in the epidermis and dermis following the application of sunscreens containing titanium dioxide.²⁰⁸ The implication is that smaller engineered nanoparticles particles can and will be assimilated into the body through the skin and interact with the immune system.²⁰⁹

Intact skin, when flexed, can permit particles of up to 1,000 nm in size to enter the dermis.²¹⁰ Moreover, broken skin is an ineffective barrier and enables particles up to 7,000 nm to reach living tissue,²¹¹ thus any of these sunscreens rubbed over shaving cuts, blemished skin or other opening can easily breach the skin. In fact, many nano-cosmetic products, including

²⁰⁶EPA White Paper, supra note 29, at 48-49 (emphasis added).

²⁰⁷Tinkle et al., *Skin as a Route of Exposure ans Sensitization in Chronic Beryllium Disease*, 111 ENVIRON. HEALTH PERSPECT. Vol 9, pp. 1202-08 (July 2003).

²⁰⁸Id. at 1202,1207 (citing Lademann et al., *Penetration of tianiun dioxide microparticles in a sunscreen formulation into the horny layer and the folliculer orifice*, 12 SKIN PHARMACOL APPL SKIN PHYSIOL 247-56 (1999)).

²⁰⁹Hoet, supra note 188 at 9 (citing Kreilgaard, *Influence of microemulsions on cutaneous drug delivery*, 54 ADV DRUG DELIV REV S77-S98 (2002)).

²¹⁰Tinkle, supra note 207.

²¹¹Oberdorster II, supra note 53.

sunscreens, are specially designed to be used on damaged skin, a fact ignored so far in the debate about whether nanoparticles can penetrate the skin. Still unanswered are questions of how other damaged skin conditions, such as sunburn or eczema, can affect the uptake of nanoparticles, a point noted by the Royal Society.²¹² Finally, many cosmetics products incorporate other ingredients that act as “penetration enhancers,”²¹³ which may alter the skin penetration analysis.

Once past the body’s defenses, if engineered nanoparticles of titanium dioxide or zinc oxide interact with DNA or RNA, serious damage to the substrates can ensue.²¹⁴ While both zinc oxide and titanium dioxide are generally considered inert in larger form, engineered nanoparticles of both substances can be highly photo-reactive in the presence of UV light, which is partially absorbed into the particle.²¹⁵ They can exert a “strong oxidizing power that attacks organic molecules”²¹⁶ and cause free radicals (unstable fragments of molecules that are highly reactive) in skin cells, damaging DNA.²¹⁷ Free radicals can have several damaging effects on

²¹²Royal Society Report, supra note 31, at 44.

²¹³See *Skin Deep: News about the safety of popular health & beauty brands*, Environmental Working Group, at www.ewg.org/reports/skindeep2/.

²¹⁴Hidaka et al., *In vitro photochemical damage to DNA, RNA and their bases by an inorganic sunscreen agent on exposure to UVA and UVB radiation*, 111 JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY 205-213 (1997).

²¹⁵Dunford et al., *Chemical oxidation and DNA damage by inorganic sunscreen ingredients*, 418 FEBS LETTERS no. 1-2, pp. 87-90 (1997); Hidaka, supra note 214.

²¹⁶GenomeWeb Daily News, *Argonne Nanotechnology Research May Yield New Sequencing Technology*, October 8, 2002, at <http://www.genomeweb.com/articles/view-article.asp?Article=2002108145653>.

²¹⁷Dunford, supra note 215; Hidaka, supra note 214.

cells with which they make contact, including DNA strand breaks and antioxidant depletion.²¹⁸

While normal-sized titanium dioxide has only a limited ability to cause DNA strain breakage, engineered nanoparticles of titanium dioxide are “capable of causing complete destruction of super-coiled DNA.”²¹⁹

These engineered nanoparticles should be considered entirely new substances and the sunscreens of which they are components should therefore be considered “new drugs,” for which manufacturers must complete new drug applications. Far from agreeing that they are “safe and effective,” experts have called for more information and further study of these nanoparticles, as a new class of materials, before engineered nanoparticles are approved. The Royal Society recommended that “chemicals in the form of nanoparticles or nanotubes be treated as new substances.”²²⁰ In particular, regarding the danger of nanoparticles and skin absorption, the Royal Society Report concluded that the issue of skin absorption leading to a higher resorption of nanomaterials should be explicitly addressed in order to assess their risk: “It is clear that nanoparticles have different properties to the same chemicals 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.*”²²¹ Specifically referencing the SCCNFP’s refusal to approve engineered nanoparticles of zinc oxide, the Royal Society recommended that “the

²¹⁸Donaldson et al., *Free radical activity associated with the surface of particles: a unifying factor in determining biological activity?*, 88 TOXICOLOGY LETTERS 293-98 (1996).

²¹⁹Id.

²²⁰Royal Society Report, *supra* note 31, at 71.

²²¹Id. at 43-44 (emphasis added).

industry submit the additional data on microfine zinc oxide that is required by the SCCNFP as soon as reasonably practicable so that the SCCNFP can deliver an opinion on its safety.”²²² That was in 2004, and as of late 2005, SCCNFP had not approved nanoparticulate zinc oxide for use in sunscreens, instead reiterating that “the safety to the consumer of this use [of ultrafine particles of zinc oxide in sunscreens currently on the market] remains to be assessed. The attention of the Commission and the Member States is drawn to this.”²²³

(b) Patents

The U.S. legal patent framework also strongly supports the conclusion that engineered nanoparticles generally—and engineered nanoparticles of titanium dioxide and zinc oxide specifically—are novel substances, for which manufacturers should be required to complete new drug applications. Many of the manufacturers of these nanomaterial products, regulated by FDA, have applied for and received patents for their products and/or the engineered nanoparticles in them, a legal and commercial reality that belies any claim that the engineered nanoparticles are not wholly unique substances which must be viewed as new substances.

Nano-sunscreens are new drugs because they make wholly new claims. By law, the issuance of a patent is a determination of novelty, and claims for novel disclosures are assigned one or more patent classifications. Taking advantage of quantum physics, nanotechnology companies have and are continuing to engineer materials that have entirely new properties never before identified in nature, and patenting them in the U.S and other countries. As noted above in Section I(B)(1) supra, in August of 2004, the United States Patent and Trademark Office

²²²Id.

²²³See note 170 *supra* and accompanying text.

(USPTO) created an art collection of Nanotechnology, Class 977, in response to the desire to gather in one place all published US Patents and US PreGrant Publications (US PGPUBs) that claim subject matter related to nanotechnology.²²⁴ In December of 2005, the USPTO revised the nanotechnology patent classification, replacing one comprehensive digest with 263 new subclasses for cross-referencing all nano-related patents. Class 977, which establishes the definitions and cross-references for these patents, has a two pronged definition of “nanostructures,” a necessary ingredient of all patents for which the class provides disclosures,²²⁵ to be an atomic, molecular, or macromolecular structure that both: 1) “has at least one physical dimension of approximately 1-100 nanometers,” and 2) “*possess[] a special property, provides a special function, or produces a special effect that is uniquely attributable to the structure’s nanoscale physical size.*”²²⁶ Thus, to be patentable under Class 977, a patent must not simply be a reduction in size of an existing element or particle; rather, that new size must alter the original substance creating a unique effect or property that is only possible at the nanoscale. The classification class notes on Class 977 are even more explicit, clarifying that

Special properties and functionalities should be interpreted broadly, and are defined as those properties and functionalities that are significant, distinctive,

²²⁴See supra note 18.

²²⁵The definition of nanotechnology as a class includes “nanostructures” and their chemical compositions, devices that include at least one nanostructure, mathematical algorithms for modeling configurations or properties of nanostructures, or specified uses of nanostructure. See note supra 17 and accompanying text (full definition); see also USPTO, Class 977, Nanotechnology, Class Definition, (November 2005), available at <http://www.uspto.gov/web/patents/classification/uspc977/defs977.htm#C977S000000>; supra note 18.

²²⁶See note 18 supra and accompanying text for full definition (emphasis added).

non-nominal, noteworthy, or unique as a result of the nanoscale dimension. In general, differences in properties and functionalities that constitute *mere differences of scale are insufficient* to warrant inclusion of the subject matter in Class 977.²²⁷

The President's Council of Advisors on Science and Technology (PCAST) reported in May 2005 that the Patent Office issued over 8,600 nanotechnology-related patents in 2003, an increase of 50% from 2000 (compared to about 4% for patents in all technology fields).²²⁸ Nanotechnology product patents were also issued in Japan, Germany, Canada, and France, among other nations.²²⁹ Some of these patents are for sunscreens containing engineered nanoparticles of titanium dioxide or zinc oxide or both. There is an existing trend in the sunscreen industry to develop and use sunscreen formulations containing zinc oxide of smaller and smaller particle size in efforts to reduce whiteness and improve transparency of sunscreen formulations. An enumerated search of currently-held patents discloses the following relevant patents:²³⁰

- U.S. Pat. 5,223,250 (Mitchell, 1993) a patent for a “substantially transparent sunblock comprised of micronized particles of zinc oxide;”
- U.S. Pat. 5,573,753 (Tapley, 1996), for a method of preparing sunscreens containing zinc oxide particles of 5 nm to 150 nm or milling nanoparticles of 5 to 150 nm of both zinc oxide and titanium dioxide, which is claimed to be substantially transparent to visible light while screening UV radiation;

²²⁷U.S. Patent Class 977, Nanotechnology, Classification Definitions, Note (3), available at <http://www.uspto.gov/web/patents/classification/uspc977/defs977.htm#C977S000000> (emphasis added); supra note 18.

²²⁸See PCAST report supra note 29.

²²⁹Id.

²³⁰See Petition Record.

- U.S. Pat. No. 5,531,985 (Mitchell, 1996) for a “visibly transparent UV sunblock compositions and cosmetic products containing the same,” which includes a dispersion of zinc oxide particles 10 nm to 100 micros in size;
- U.S. Pat. No. 5,587,148 (Mitchell, 1996) for “visibly transparent UV sunblock agents” comprised of substantially dispersed zinc oxide particles of a specific average particle size range less than about .2 micros;
- U.S. Pat. No. 5,498,406 (Nearn, 1996) for “titanium dioxide-based sunscreen compositions” having substantially uniform microfine TiO₂ having a particle size of less than about 100 nm;
- U.S. Pat. No. 6,187,824 (Swank, 1999) for a “zinc oxide sol and method of making,” with a mean particle size of less than 50 nm, that is characterized as clear and transparent; and
- U.S. Pat. No. 6,171,580 (Katsuyama, 2001) for an “ultraviolet-screening zinc oxide excellent in transparency and composition” in which zinc oxide particles with an average particle diameter of 50-100 nm “effectively exerts the above-described excellent characteristics; i.e. UV-screening effect and transparency and can be applied to a composition for external use such as make-up cosmetics or sunscreen cosmetics.”

More applications are pending: in August 2003, patent application number 20030161795 was filed, requesting a patent for a “substantially visibly transparent topical sunscreen formulation.”²³¹ The patent states that it is a topically applied sunscreen composition which by use of nano-sized particles of titanium dioxide and zinc oxide,²³² a physical UV screening agent in a dermatologically acceptable carrier, provides a dermatologically acceptable level of SPF and broad spectrum protection from both UVA and UVB radiation, without the need to include

²³¹U.S. Patent and Trademark Office, Patent Application Full Text and Image Database, Patent Application 20030161795.

²³²“A substantially visible clear and transparent topical sunscreen composition according to claim 1 wherein the physical UV screening agent is zinc oxide with up to 10% of one or more titanium dioxide or other physical UV screening agents.” Id.

chemical UV screening agents in the composition.²³³ The invention derives from the ability of the applicant to manufacture nano-sized zinc oxide particles with controlled size and distribution to a greater degree than previously achievable; the nano-sized zinc oxide particles in the sunscreen are substantially dispersed and have a mean particle size of less than 30 nm.

The patents and patent claims above belie any argument that engineered nanoparticles of zinc oxide and/or titanium dioxide do not create wholly new substances with their novel properties; specifically in the case of sunscreens, sunscreen drug products using the engineered nanoparticles are substantially different from other sunscreens without engineered nanoparticles of titanium dioxide and/or zinc oxide. If these substances were the same as their bulk material counterparts, they would not be patentable, as they would be unable to meet patent law standards for novelty. FDA's regulatory regime should recognize this legal reality and treat those sunscreens as new drugs for which manufacturers must complete new drug applications. Sunscreens comprised of engineered nanoparticles cannot be considered "safe and effective" based on the testing of bulk material counterparts; rather FDA must require safety information specifically addressing the new dangers presented by these new substances.

2. Declare engineered nanoparticles of zinc oxide and titanium dioxide to be an imminent hazard to human health

FDA should declare that sunscreen drug products containing engineered nanoparticles of titanium dioxide and zinc oxide are an imminent hazard to the public health. Pursuant to FDA regulation, an imminent hazard to public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected

²³³Id.

immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held.²³⁴

An imminent hazard “may be declared at any point in the chain of events which may ultimately result in harm to the public health,” and “the occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.”²³⁵

a. The public health situation should be corrected immediately to prevent injury

The skin is a primary route of potential exposure to toxicants, including novel engineered nanoparticles.²³⁶ Indeed, presently the “biggest concern [regarding nanotechnology] is that free nanoparticles or nanotubes could be inhaled, *absorbed through the skin*, or ingested.”²³⁷ Numerous companies have manufactured and currently market to consumers transparent sunscreens and UV-resistant cosmetics incorporating engineered nanoparticles of zinc oxide and titanium dioxide.²³⁸ These particles are “free” rather than “fixed.”²³⁹ Transparency is not the only change of the nanoparticles composed of those metal substances. While both zinc oxide and titanium dioxide are generally considered inert in larger form, engineered nanoparticles of both substances can be highly photo-reactive in the presence of UV light, which is partially absorbed

²³⁴21 C.F.R. § 2.5(a).

²³⁵21 C.F.R. § 2.5(a).

²³⁶Oberdorster, supra, note 20, at 4.2.2.2.

²³⁷Allianz Group, supra note 58, at 30 (emphasis added).

²³⁸See Section II(A) infra and accompanying footnotes.

²³⁹See note 126 supra.

into the particle.²⁴⁰ They can exert a “strong oxidizing power that attacks organic molecules”²⁴¹ and cause free radicals in skin cells, damaging DNA.²⁴² Free radicals can have several damaging effects on cells with which they make contact, including DNA strand breaks and antioxidant depletion.²⁴³ While normal-sized TiO₂ has only a limited ability to cause DNA strain breakage, engineered nanoparticles of TiO₂ are “capable of causing complete destruction of super-coiled DNA.”²⁴⁴ Oxidative stress as a common mechanism for cell damage induced by engineered nanoparticles is well documented in C₆₀ fullerenes,²⁴⁵ quantum dots, and carbon nanotubes,²⁴⁶ which have all been shown to induce free radical damage.²⁴⁷ Nanoparticles of various sizes and chemical compositions preferentially localize in mitochondria where they induce major structural damage and can contribute to oxidative stress.²⁴⁸

Specifically regarding nanoparticles of titanium dioxide, intratracheal instillation of titanium dioxide particles in rodents demonstrates that nanoparticles induce bigger inflammatory

²⁴⁰See note 215 supra.

²⁴¹See note 216 supra.

²⁴²See note 217 supra.

²⁴³Donaldson, supra note 218.

²⁴⁴Id.

²⁴⁵Fullerenes, sometimes called Buckyballs, have been found to cause brain damage to fish and be toxic to human liver cells. Oberdorster III, supra note 95.

²⁴⁶Carbon nanotubes are long carbon-based tubes that can be either single or multiwalled and have the potential to act as biopersistent fibers.

²⁴⁷Oberdorster, supra note 20, at 3.0; Green *et al.*, *Semiconductor Quantum Dots and free radical induced DNA nicking*, 1 CHEMICAL COMMUN. 121-123 (2005).

²⁴⁸Oberdorster, supra note 20, at 3.0

responses than larger particles of an equivalent mass dose.²⁴⁹ Regarding engineered nanoparticles of zinc oxide, SCCNFP has considered the safety of zinc oxide for use as a UV filter, and said twice that it requires more information from manufacturers to enable a proper safety evaluation.²⁵⁰ In doing so, SCCNFP highlighted evidence that “microfine” zinc oxide (200nm or smaller) has phototoxic effects on cultured mammalian cells and their DNA *in vitro*. In addition, the SCCNFP commented on the lack of reliable data²⁵¹ on the absorption of zinc oxide through the skin and noted that the potential for absorption by inhalation had not been considered.

Further careful studies of skin penetration by nanoparticles being used in sunscreens and the propensity of such particles to potentiate free radical damage are needed.²⁵² The Royal Society concluded that “insufficient evidence is available from relevant scientific advisory committee to provide a judgment about the likelihood of skin penetration by zinc oxide,”²⁵³ and recommended that

ingredients in the form of nanoparticles undergo a full safety assessment by the

²⁴⁹Obersdorster II, supra note 53.

²⁵⁰See notes 168-170 supra and accompanying text.

²⁵¹“Much of the information relating to the safety of these ingredients has been carried out by industry and is not published in open scientific literature.” The Allianz Group, supra note 58, at 31. Further research is currently underway to clarify the issue of skin penetration by engineered nanoparticles. See, e.g., The NANODERM research project funded by the European Commission, at http://www.uni-leipzig.de/~nanoderm/Brochure_NANODERM_WWW.pdf, is investigating the quality of skin as a barrier to nanoparticles.

²⁵²Existing studies of skin penetration have shown mixed results. See, e.g., Oberdorster II, supra note 53, at 833-836; Swiss Re report, supra note 26, at 18-19.

²⁵³Royal Society Report, supra note 31, at 80.

relevant scientific advisory body before they are permitted for use in products. Specifically: we recommend that industry submit the additional information on microfine zinc oxide that is required by the SCCNFP as soon as reasonably practicable so that it can deliver an opinion on its safety.²⁵⁴

In January 2004, nanosafety researchers from the University of Leuven, Belgium, published a study in *Nature* concluding that engineered nanoparticles require new toxicity tests: “We consider that producers of nanomaterials have a duty to provide relevant toxicity test results for any new material, according to prevailing international guidelines on risk assessment.”²⁵⁵

To prevent injury, FDA needs to specifically consider the new and unique risks posed by engineered nanoparticles of zinc oxide and titanium dioxide in sunscreen drug products already on the market, demand full health and safety dossiers on them, and test and regulate accordingly. While the FDA is researching these risks and reviewing this evidence, a moratorium on the manufacturer of nano-sunscreens must be imposed.

b. Sunscreens comprised of engineered nanoparticles should not be permitted to be manufactured and marketed while a hearing or other formal proceeding is being held

²⁵⁴Id. at 86, 83:

Nanoparticles of chemicals such as zinc oxide and iron oxide (should manufacturers wish to use in Europe) would await a safety assessment. In addition to taking into account our concerns about the potential for nanoparticles to penetrate damaged skin, the safety advisory committee should consider whether the tests introduced as alternatives to tests on animals are appropriate for the testing of the safety of nanoparticles. In the light of the regulatory gaps that we identify, we have also recommended that the EC (encouraged and supported by the UK Government and informed by its scientific advisory committees) review the adequacy of the current regulatory regime for the introduction of nanoparticles into all consumer products, not just cosmetics. We have recommended a similar regulatory review be performed about the use of nanoparticles in medicines and medical devices.

²⁵⁵Hoet, supra note 188, at 19.

The second requirement for FDA to declare an “imminent hazard to the public health” is that there be an ongoing “hearing” or “formal proceeding” in process.²⁵⁶ This requirement is also met: FDA is in the process of formally amending and finalizing the currently-stayed Sunscreen Drug Monograph to address UVA radiation.²⁵⁷ While the human skin is exposed to all UV wavebands of solar UV, the overwhelming majority of sunscreen products available provide protection primarily limited to shorter UVB rays (290-320 nm).²⁵⁸ However there is increasing evidence that longer wave-length UVA rays (320-400 nm) penetrate deeper and can also eventually cause cancer.²⁵⁹ New research has indicated that UVA rays are as harmful as UVB rays due to their similar ability to promote cancer and premature skin aging. DNA may be damaged by UVA as a result of free radical formation.²⁶⁰ Accordingly, FDA will amend the currently-stayed Sunscreen Drug Monograph to address UVA radiation.²⁶¹

Petitioners have requested in this petition that FDA reopen the administrative record of the Monograph to concurrently examine the body of evidence on engineered nanoparticles used

²⁵⁶21 C.F.R. § 2.5(a).

²⁵⁷66 Fed. Reg. 67485.

²⁵⁸Diffey *et al.*, *In vitro assessment of the broad-spectrum ultraviolet protection of sunscreen products*, 43 J AM ACAD DERMATOL 1024-35, 1025 (2000). The FDA’s sun protection factor (SPF) standard is directed at the efficacy of a sunscreen product in preventing UV-induced erythema, which is confined to wavelengths from 290-330 nm. *Id.* However SPF is not relevant to longer wavelength of UV exposure.

²⁵⁹Id.

²⁶⁰Wakefield *et al.*, *The effects of manganese doping on UVA absorption and free radical generation of micronised titanium dioxide and its consequences for photostability of UVA absorbing organic sunscreen components*, 3 PHOTOCHEM. PHOTOBIOLOGIC SCI. 648-652, 648 (2004).

²⁶¹66 Fed. Reg. 67485.

in ‘cosmetically clear’ sunscreens and their associated dangers, which include free radical formation. Many of these “cosmetically clear” nano-sunscreens using engineered nanoparticles of zinc oxide and titanium dioxide are being marketed as a blocker of UVA, as well as UVB, waves.²⁶² However, the current understanding of UVA light is insufficient, both in terms of whether these nano-scale sunscreens really block it and in terms of what the side effects are of having the nanoparticles absorb it. In any event, the use of engineered nanoparticles also raises issues of UVA radiation and, as discussed above, cancer causing free radical formation; the issues are interconnected. Accordingly, the ongoing finalization of FDA’s OTC Sunscreen Monograph, currently stayed, should be sufficient as a necessary ongoing “formal proceeding” currently being undertaken, and during which engineered nanoparticles of titanium dioxide and zinc oxide should not be marketed.

3. Recall

The Commissioner may request that a manufacturer recall a product if the following determinations have been made:

²⁶²See, e.g., supra note 133, Boots and Oxonica’s “Optisol” of their “Soltan Facial Sun Defence Cream,” which claims to “[i]n addition to protecting against UVB, the traditional focus of sun protection, Optisol offers enhanced protection against UVA light.” *Oxonica’s Optisol UV Absorber is Now Available to Buy at Boots’ UK Stores Nationwide*, Nano Tsunami website, April 26, 2005, at <http://www.voyle.net/Nano%20Products%202005/Products%202005-0037.htm> (stating that “Test data has shown that sunscreens formulated with Optisol can provide enhanced protection against both UVB and UVA”); supra note 131, Key’s Soap Solar Rx Nano-Zinc Oxide Sunblock, at <http://www.keys-soap.com/solarrx.html>, (“The narrow particle size distribution of the zinc oxide is more effective in providing broad-spectrum coverage from damaging UVA and UVB radiation.”); supra note 136, NuCelle Inc’s SunSense SFP 30+ Sunscreen, made with Z-Cote HP1®, at http://www.nucelle.com/nucelle_companion1a.htm (“SunSense provides excellent sun protection for all skin types . . . protecting against both UVA as well as UVB rays.”); supra note 140, BASF Z-Cote, at <http://www.bASF.com/corporate/news2004/03012004.htm> (“It protects even the most sensitive skin against both UVA and UVB rays.”).

- (1) That a product that has been distributed presents a risk of illness or injury or gross consumer deception.
- (2) That the firm has not initiated a recall of the product.
- (3) That an agency action is necessary to protect the public health and welfare.²⁶³

In this case, as discussed supra, all these factors are present. Sunscreens comprised of engineered nanoparticles are presented to the consumer based on the false assumption that such products are safe and effective based on scientific studies of bulk material counterparts of engineered nanoparticles. Further, as discussed in detail above, without further nano-specific safety research, such engineered particles represent a grave and untested “risk of illness or injury” to consumers because of their novel properties and the associated dangers. Finally, the recall is necessary to protect health and welfare, until proper study and testing of engineered nanoparticles can be completed and analyzed. Petitioners therefore request that the Commissioner request a recall of all sunscreen drug products containing engineered nanoparticles of zinc oxide or titanium dioxide until the manufacturers of such products complete new drug applications that are approved by the agency and otherwise comply with the agency’s relevant nanotechnology regulations.

ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. § 25.31(a), (c), this petition qualifies for a categorical exclusion from the requirement that an environmental assessment be submitted.²⁶⁴

²⁶³21 CFR § 7.45(a).

²⁶⁴This does not mean petitioners agree that an application for, and the potential approval of, a new drug application for a nanomaterial qualifies for a categorical exclusion.

ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following a review of this petition.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

CONCLUSION

It is the FDA's mission to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."²⁶⁵ FDA must protect the public health by ensuring that "human . . . drugs are safe and effective."²⁶⁶ "There is almost unanimous opinion among proponents and skeptics alike that the full potential of nanotechnology requires attention to safety issues."²⁶⁷ Regulatory agencies like FDA, with clear oversight mandates, can no longer postpone general safety evaluations of engineered nanomaterials. FDA must begin a comprehensive regulatory program aimed at fulfilling its mandate and protecting the public health from this growing and unregulated danger. In the process, FDA must comply with NEPA, examining all the environmental effects of its actions.

²⁶⁵21 U.S.C. § 393(b)(1).

²⁶⁶Id. at § 393(b)(2)(D).

²⁶⁷Nel, supra note 42, at 622.

Moreover, those engineered nanoparticles that are already in commercialization, are produced in large quantities as freely dispersible nanoparticles, and that have the potential for substantial exposures in humans and the environment should be given safety testing and regulatory priority. Nano-sunscreens are precisely that product: they are already on the U.S. market, in products regulated by FDA, and create widespread exposure to humans unaware of their potential dangers. Finally, because sunscreens are classified and regulated as human drugs, unlike other nano-personal care products like cosmetics, FDA has a different, higher statutory duty to ensure such products are safe, effective, and not misbranded. FDA can require manufacturers to prove the safety of these nano-sunscreen drug products. Thus sunscreens are the ideal avenue for the agency to assert its statutory authority and fulfill its statutory mandate to protect the public health from the dangers of currently unlabeled and unregulated nanomaterial products.

There is clear evidence that engineered nanoparticles of zinc oxide and titanium dioxide can induce free radical formation and damage human cells; what is unknown is the extent to which these particles can penetrate the dermis. In order to fulfill its mandate to protect the public health, FDA cannot permit this safety experiment to play out without regulatory oversight, with possibly tragic consequences.

WHEREFORE, for the reasons contained herein, petitioners respectfully request that the Commissioner:

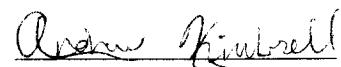
- 1) Amend FDA regulations to include nanotechnology definitions necessary to properly regulate nanotechnology issues, including the terms “nanotechnology,” “nanomaterial,” and “engineered nanoparticle.”

- 2) Issue a formal advisory opinion explaining FDA's position regarding engineered nanoparticles in products regulated by FDA.
- 3) Enact new regulations directed at FDA oversight of nanomaterial products establishing and requiring, *inter alia*, that: nanoparticles be treated as new substances; nanomaterials be subjected to nano-specific paradigms of health and safety testing; and that nanomaterial products be labeled to delineate all nanoparticle ingredients.
- 4) Any currently existing or future regulatory FDA programs for nanomaterial products must comply with the requirements of the National Environmental Policy Act (NEPA), including, *inter alia*, that FDA conduct a Programmatic Environmental Impact Statement (PEIS) reviewing the impacts of nanomaterial products on human health and the environment.
- 5) Reopen the Administrative Record of the Final Over-the-Counter ("OTC") Sunscreen Drug Product Monograph for the purpose of considering and analyzing information on engineered nanoparticles of zinc oxide and titanium dioxide currently used in sunscreens.
- 6) Amend the OTC Sunscreen Drug Monograph to address engineered nanoparticles, instructing that sunscreen products containing engineered nanoparticles are not covered under the Monograph and instead are "new drugs" for which manufacturers must complete a New Drug Application in accordance with 21 U.S.C. § 355.
- 7) Declare all currently available sunscreen drug products containing engineered nanoparticles of zinc oxide and titanium dioxide as an imminent hazard to public health and order entities using the nanoparticles in sunscreens regulated by FDA to cease manufacture until FDA's Sunscreen Drug Monograph is finalized and broader FDA nanotechnology regulations are developed and implemented.
- 8) Request a recall from manufacturers of all publically available sunscreen drug products containing engineered nanoparticles of titanium dioxide and/or zinc oxide until the manufacturers of such products complete new drug applications, those applications are approved by the agency, and the manufacturers otherwise comply with FDA's relevant nanomaterial product testing regulations.

In accordance with FDA regulations, petitioners request that FDA provide an answer to this petition within 180 days.²⁶⁸

²⁶⁸21 C.F.R. § 10.30(e)(2).

Respectfully submitted,



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