International Center for Technology Assessment

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments on Docket # FDA-2008-N-0416. *Consideration of FDA-Regulated Products That May Contain Nanoscale Materials; Public Meeting*

Dear FDA Commissioner Andrew C. von Eschenbach:

The International Center for Technology Assessment (ICTA) provides the following comments on the Food and Drug Administration (FDA)'s second public meeting on nanotechnology, held September 8, 2008, and the associated call for comments and docket. 73 Fed. Reg. 46,022 (08-07-2008).

In summary, we view the FDA's meeting as little more than more process for the sake of process. The agency already held an "information gathering" public meeting, nearly two years ago in October 2006. Since that time, the agency has issued its Task Force report, which did not include any binding regulatory recommendations, and re-opened the OTC Sunscreen Monograph, again simply calling for information on nano-sunscreens. No nano-specific regulatory action has been taken or even planned. In the interim, the universe of nanomaterial products under the FDA's jurisdiction has continued to grow exponentially, increasing human and environmental exposures and raising the stakes of continued delay. The public's right to know and choose whether or not to buy nanomaterials continues to be denied, without FDA mandating the labeling of products. The window to address nanotechnology in a concrete manner before exposures cause foreseeable health and/or environmental problems continues to close. This new platform technology is not longer "emerging" but rather is here. The time for action was ripe at least two years ago and the FDA's failure to act grows more egregious as every day, month and year passes. Instead continued, repeated bureaucratic process and malaise – without actual regulatory action – increases the odds that nanotech will join the long line of new technologies upon which regulators and those charged with protecting the public health and environmental safety have fiddled while Rome burns. Like PCBs, asbestos, lead, CFCs, DDT, leaded gasoline, mercury, and other former "wonder" substances and technologies, some nanomaterial will undoubtedly have significant and unintended negative consequences on human health and the environment. Whether our policymakers

and regulators will wait until a catastrophe occurs or will adapt laws and regulations preemptively in an attempt to avoid such a disaster remains to be seen. FDA's continued delay, in the face of growing scientific evidence and public concern – as evidenced by the thousands of public comments filed with the October 2006 meeting and now again for this meeting – makes it more and more likely we will fall into the same destructive and reactive path of old mistakes. In doing so FDA is violating its fundamental duties of protecting the public health and environment and passing the buck to the next administration to solve these problems. As we have numerous times in the past, we strongly urge FDA to act to address nanomaterials in a serious manner as soon as possible. The agency has had both the legal impetus and blueprint for needed action in front of it for over two and a half years now – our May 2006 legal petition, described below.

BACKGROUND

The International Center for Technology Assessment

ICTA is a non-profit, non-partisan organization committed to providing the public with full assessments and analyses of technological impacts on society. ICTA is devoted to fully exploring the economic, ethical, social, environmental and political impacts that can result from the applications of technology or technological systems. ICTA works towards adequate oversight of nanotechnology through its Nanotechnology Project, *NanoAction*. ICTA is located at 660 Pennsylvania Ave., S.E., Suite 302, Washington, D.C. 20003, www.icta.org

ICTA's Legal Petition to FDA on Regulation of Nanomaterials in Consumer Products including Nano-Sunscreens

On May 16, 2006 ICTA and a coalition of seven other consumer, health and environmental groups[1] filed a *Petition Requesting FDA Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles* (CTA petition or petition), FDA docket number 2006P-0210.

The petition has two distinct halves, one dealing generally with nano-product regulation and one focusing specifically on nano-sunscreen regulation. Section one documents the existing body of scientific evidence studying nanomaterial risks stemming from their unpredictable toxicity and seemingly unlimited mobility. It requests FDA issue a formal opinion[2] on engineered nanoparticles in light of this evidence, amend its regulations to include nanotechnology definitions necessary for proper regulation, and enact comprehensive nano-product regulations, including nanomaterial-specific toxicity testing

[1] The petitioning organizations were ICTA, Friends of the Earth (FoE), Greenpeace International, The Action Group on Erosion, Technology, and Concentration (ETC Group), Clean Production Action (CPA), The Center for Environmental Health (CEH), Our Bodies Ourselves, and The Silicon Valley Toxics Coalition (SVTC).
[2] See 21 C.F.R. § 10.85(a).

and mandatory nano-product labeling. These regulations should be retroactive in order to cover existing nano-products. In addition, section one requests that any current or future FDA actions on nanotechnology and nanomaterials comply with the National Environmental Policy Act (NEPA), 42 U.S.C. §§ 4321 *et seq.*, assess the human health and environmental impacts of its nano-related actions, and that FDA conduct a Programmatic Environmental Impact Statement (PEIS).

The petition's second half focuses on engineered nanoparticles of titanium dioxide and zinc oxide used in nano-sunscreens. Sunscreens are classified by FDA as human drugs, unlike many other personal care products, and consequently can be subject to more rigorous FDA regulation. Any new drug manufacturer must submit a premarket new drug application with evidence supporting the drug's safety and efficacy. [3] The commercial allure of nano-sunscreens is that they appear transparent or "cosmetically clear" because of the nanoparticles' fundamentally different properties. The engineered nanoparticles are also patented for their profitable novelty. Yet in the agency's first and only word on sunscreens, a 1999 regulation, FDA considered engineered nanoparticle ingredients in these sunscreens a mere reduction in size and not a new drug ingredient. This has permitted sunscreen manufacturers to sell nano-sunscreens based on the safety assessment of bulk material sunscreens.[4]

The petition asks FDA to reconsider its 1999 equivalency stance on nano-sunscreens, again pointing out that it is contrary to the universal scientific opinion regarding the fundamental differences and unique dangers of engineered nanoparticles. The petition requests the agency to instead classify nano-sunscreens as new drug products which require premarket review of health and safety evidence.[5] The zinc oxide and titanium dioxide nanoparticles used in nano-sunscreens have raised red flags for scientists because of: their ability to be inhaled; open questions regarding the ease of skin penetration and circulation throughout the body;[6] and studies that have shown them to be photoactive in some cases, producing free radicals and causing DNA damage to human skin cells.[7] The petition calls for regulations classifying nano-sunscreens as new drug products which

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[3] Id.; see 58 Fed. Reg. 28195; 21 U.S.C. § 321(g)(1).

[4] U.S. Food and Drug Administration, HHS, Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph, 64 Fed. Reg. 27666-27693, 27671 (1999). FDA used the term "micronized" and the agency has not clarified whether or not this term was meant to be inclusive of nanoparticles. See also Kulinowski & Colvin, *Environmental Implications of Engineered Nanomaterials*, 1 NANOTECHNOLOGY L. & BUS. 52, 53 (2004).

[5] See 21 U.S.C. §§ 321(p), 355(a).

[6] See, e.g., European Commission's Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP), *Statement on Zinc Oxide In Sunscreens*, adopted September 20, 2005 http://europa.eu.int/comm/health/ph_risk/committees/04_sccp/docs/sccp_o_00m.pdf (finding insufficient evidence presented for a finding of safety); see also The Royal Society and the Royal Academy of Engineering, *Nanoscience and nanotechnologies: Opportunities and uncertainties*, London, 2004 at 73.

[7] See, e.g., Hidaka 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); Dunford et al., *Chemical oxidation and DNA damage by inorganic sunscreen ingredients*, 418 FEBS LETTERS no. 1-2, pp. 87-90 (1997); Donaldson et al., *Free radical activity associated with the surface of particles: a unifying factor in determining biological activity?*, 88 TOXICOLOGY LETTERS 293-98 (1996).

require premarket review of health and safety evidence. Because nano-sunscreens are currently sold without such premarket testing or review by FDA, the petition asks FDA to declare that those products an imminent hazard to public health and to request that manufacturers cease production until FDA nanomaterial product regulations are developed and implemented.[8]

The ICTA legal petition is the first U.S. legal action filed on the potential human health and environmental risks of nanotechnology,[9] and provides the agency with both a blueprint for its possible regulatory amendments and a legal impetus to take that action. Since the filing of the petition, FDA has undertaken numerous actions illustrating that it is indeed aware of the complex issues surrounding its oversight of nanomaterials, including creating an internal Task Force to prepare a report and recommendations, holding its first-ever Public Meeting on nanotechnology in 2006 and now holding this second meeting in 2008. In FDA's interim procedural response to the ICTA petition the agency pointed to these actions, as well as FDA's plans to amend the OTC Sunscreen Drug Monograph, as evidence of a good faith effort to respond to the issues raised in the ICTA petition.[10] Unfortunately FDA has not answered the petition in any substantive manner nor offered any other regulatory solution.

Note: The following ICTA comments should not be in any way interpreted to supersede, affect, or alter the legal status or legal positions of the ICTA Petition filed with FDA on May 16, 2006. Rather, ICTA respectfully submits the following comments and enclosed materials to: update and/or supplement our legal petition with relevant evidence; provide the agency with up-to-date information relevant to the nanomaterial oversight and assessment questions the agency is now addressing; reiterate our petition's arguments; and otherwise comment on the proposed sunscreen rule.

Comments

I. Reiteration of the Petition's Calls With Regard to the Oversight of Nanomaterials in Consumer Products under FDA's Jurisdiction

First and foremost, these comments reiterate the 2006 legal petition's positions with regards to nanotechnology and nanomaterial oversight. The eighty-page petition included over 250 citations and a voluminous supporting record and will not be repeated here. The scope of the legal petition is summarized above. From the *Actions Requested* of the petition:

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

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[8] 21 C.F.R. §§ 2.5(a) (imminent hazard), 7.45(a) (recall).

[9] See, e.g., Keay Davidson, *FDA urged to limit nanoparticle use in cosmetics and sunscreens*, San Francisco Chronicle, May 17, 2006.

[10] FDA 180-day Response to ICTA, Letter of Randle Lutter, Associate Commissioner for Policy and Planning, November 9, 2006.

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.

The explanation and support for each of these actions is laid out in the ICTA petition, the accompanying footnotes, and concurrently submitted administrative record. ICTA applauds FDA for engaging with the public in 2006 to gather information. However, this action by the agency is meritorious only if it is not merely a formality for show: it becomes meaningless if the agency does not in short order follow it up regulation and oversight of nanomaterials. Instead FDA has waited over two years and followed up its "information gathering" meeting with yet another "information gathering" meeting. Our legal petition and its supporting documentation provide the legal impetus, scientific support, and oversight blueprint necessary for the agency to make these regulatory changes and properly fulfilling its statutory duties of protecting the public health and safety.

III. General Comments

A. Nanomaterials are New Substances with New Properties that Require New Safety Testing.

FDA seemingly recognizes the fundamentally different characteristics of nanoparticles in its informal adoption of the NNI definition of nanotechnology, which includes the requirement of "the creation and use of structures, devices and systems that have novel properties and functions because of their small size."[11] Yet FDA's existing testing methodologies are based on bulk material or larger particles, and the agency assumes that this battery of testing is "probably adequate" for testing the safety of manufactured nanoparticles.[12]

FDA must remedy this misinformed view. The agency's general conclusion is inaccurate, and is at loggerheads with the consensus view of the scientific community: "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."[13] For example, 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."[14] Similarly, the U.K. Royal Society and the Royal Academy of Engineering emphasized: "Free particles in the nanometre size range do raise health, environmental, and safety

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[11] National Nanotechnology Initiative, *Factsheet: What Is Nanotechnology?,* http://www.nano.gov/html/facts/whatIsNano.html.

[12] FDA, Regulation of Nanotechnology Products, at http://www.fda.gov/nanotechnology/regulation.html.

[13] The 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, at 30.

[14] European 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 6 (adopted September 28-29, 2005) (emphasis added); id. at 34.

concerns and their toxicology *cannot be inferred* from that of particles of the same chemical at a larger size."[15] And finally, 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.*[16]

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, the biological activity of nanoparticles is likely to depend on physicochemical characteristics that are not routinely considered in toxicity screening studies.[17] There are many more factors affecting the toxicological potential of nanoscale materials, up to at least sixteen in fact, including: size, surface area, surface charge, solubility, shape or physical dimensions, surface coatings, chemical composition, and aggregation potential- a "**far cry from the two or three usually measured.**"[18] Unless we perform thorough investigations of all variables, we have no idea about the toxicity or safety of various products. Size is one of many factors, but is crucial: The relevance of the nano-size is that unlike larger particles, we cannot predict the toxicity of nanomaterials from the known properties of larger substances.

In short, FDA is wrong that existing tests are "probably adequate." Current testing is not totally useless, but rather that it is badly insufficient alone, because it does not take into account new parameters necessary. FDA's established methods of safety assessments must be significantly modified in order to address the special characteristics of engineered nanoparticles.

The European Union's relevant regulatory and scientific advisory groups recently issued (September 2007) a report*, Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009: First Implementation Report 2005-2007*, (EU Report) summarizing the general findings of the EU's primary consultative body for nanotechnology risk

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[15] See, e.g., The Royal Society and the Royal Academy of Engineering, *Nanoscience and nanotechnologies: Opportunities and uncertainties*, London, 2004, at 49 (emphasis added).

[16] 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 34 (emphasis added).

[17] European 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 6 (adopted September 28-29, 2005), at 32; Nuala Moran, *Nanomedicine lacks recognition in Europe*, 24 NATURE BIOTECHNOLOGY, No. 2 (February 2006).

[18] Andrew Maynard, *Nanotechnology: The Next Big Thing, or Much Ado about Nothing?*, at 7 Annals of Occupational Hygiene, 7 September 2006.

assessment – the Scientific Committee on Emerging and Newly Identified Risks (and the much longer 2006 SCENIHR report, see above).[19] The 2007 EU report states:

> According to the SCENIR, although the existing toxicological and ecotoxicological methods are appropriate to assess many of the hazards associated with nanoparticles, they may not be sufficient to address all the hazards. **Because of uncertainties, the current risk assessment procedures require modification for nanoparticles.** Knowledge gaps have been confirmed in areas such as nanoparticle characterization, detection and measurement; their fate and persistence in humans and the environment; and all aspects of the associated toxicology and ecotoxicology. These should be addressed to allow satisfactory risk assessments for humans and ecosystems.[20]

Upon the EC's request, SCENIHR carried out further analysis of current risk assessment methodology, and established a further opinion on risk assessment in relation to nanotechnologies, June 21, 2007. The SCENIHR again concluded that, "while the current methodologies are generally likely to be able to identify hazards associated with the use of nanoparticles, **modifications of the existing guidance will be necessary."**[21]

As to cosmetics, the EC invited the Scientific Committee on Consumer Products (SCCP) to review and if appropriate amend its Notes of Guidance for the testing of ingredients and to evaluate the safety of cosmetic ingredients in the form of nanoparticles.[22] The SCCP approved an opinion for public consultation on 19 June 2007,[23] concluding that it is "**necessary to review the safety of the nanomaterials presently used in sunscreens in the light of recent information; and stressing the possible influence of physiologically abnormal skin and mechanical action on skin penetration."**[24]

In fact, nanotoxicology is an emerging field in its own right, underscoring the differences of nanomaterial toxicity. In an agenda-setting 2006 article in Nature, fourteen international nanotechnology scientists put forth nanotechnology's five "grand challenges," which included the urgent need to develop methods for assessing nano-toxicity.[25] Two recently published articles suggest new paradigms of predictive toxicology for engineered nanoparticle testing.[26] FDA should develop a basic screening

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[19] Commission of the European Communities, Communication From the Commission to the Council, The European Parliament, and the European Economic And Social Committee, *Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009: First Implementation Report 2005-2007,* September 6, 2007, at ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/com_2007_0505_f_en.pdf

[20] EU Report at 9.

[21] Id.

[22] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_nano_en.pdf

[23] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_099.pdf

[24] EU Report at 9.

[25] Maynard et al., *Safe Handling of Nanotechnology*, NATURE November 16, 2006.

[26] Andre Nel et al., *Toxic Potential of Materials at the Nanolevel*, 311 SCIENCE 622 (2006); Oberdorster 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).

framework to guide its testing, such as the tiered approach that would start with non-cellular tests to establish particle reactivity, followed by in vitro and in vivo tests for exposure pathways that are relevant to a chemical's anticipated use patterns and lifecycle.[27]

All nanomaterials' characteristics–including hazardous traits–must be learned anew by direct experimentation and cannot be inferred from existing testing completed on larger particles. This is a fundamental paradigm shift that scientists recognize and that should be similarly recognized and initiated by FDA. ICTA calls on FDA to do just this, among other things, in its legal petition and again here.

Until such time, nanomaterials should be considered new substances for regulatory purposes, as the U.K. Royal Society and Royal Academy of Engineering recommended:

> "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 . . . ."[28]

B. FDA Nanotech Task Force Report (July 25, 2007)

The September 2008 public meeting began with the FDA announcing the Task Force report and spending the morning going through its findings. Unfortunately, the report is not new or news; the FDA released the report to the public over a year ago, in July 2007! Moreover the Task Force report falls far short of what is necessary, as outlined below.

The FDA report correctly concludes that the agency needs new safety assessment tools, characterization methods, new detection/inspection tools, staff expertise, and much research to assess health effects.[29] It properly recognizes that nanomaterials can present fundamental different properties, uncertainties, and new challenges (e.g., to knowledge of risk and way that testing is performed.)[30] Unfortunately, the report fails to recommend

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[27] Id.

[28] The Royal Society and the Royal Academy of Engineering, *Nanoscience and nanotechnologies: Opportunities and uncertainties*, London, 2004.

[29] See, e.g., FDA Task Force Report at 14, 17-18.

[30] See, e.g., FDA Task Force Report at 4, 11, 12, 13 ("There may be a fundamental difference in the kind of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way testing is performed."), 15 ("Also as discussed above, there may be general differences in properties relevant to evaluation of safety and effectiveness (as applicable) of products using nanoscale materials compared to products using other materials."), 17 ("[B]ecause many of these tests were developed for molecular forms of materials, and nanoscale materials may behave differently, the ability of these tests to support decisions about biological effects or further testing requirements need to be evaluated."), 18 ("Currently, ability to detect nanoscale materials in the body or in products regulated by FDA is limited and … may require substantial effort."), 18 ("[M]aterials in the nanoscale range may present particular challenges, for example relating to tests that assess product stability or development of potentially hazardous byproducts."), 18 ("Standard approaches for handling materials for testing will also need to be evaluated and may need to be modified . . . ."), 20 ("As discussed in the

oversight actions necessary to account for these new and fundamentally different properties, uncertainties, and challenges.

The report notes FDA's authority to call for nano-specific safety data for premarket review products or amend/propose regulations (drugs, devices, food additives.) It calls such authority "generally comprehensive."[31] It notes that for drug products such as sunscreens FDA can "require manufacturers to provide the necessary scientific information to support regulatory decisions."[32] Unfortunately —across the board for products over which it claims adequate premarket authority, for human drugs, animal drugs, devices, food additives, color additives, etc. —the report fails to recommend any such action.

Sunscreens are a primary example of the report's failings: its finding of nascent authority but disappointing failure to apply what would seem to be the logical necessary recommendations needed for adequate oversight. With regard to drugs, the report recognizes, as it must, that a drug such as a sunscreen is "new" under section 505 of the FFDCA if it is not generally recognized as safe and effective[33] and that new drugs require a new drug application (NDA) pursuant to 21 C.F.R. § 314.50.[34] The report notes that during FDA's review of an NDA the agency has the authority to call for additional data, including particle size data, if such data are needed for a class of drugs, such as sunscreens, FDA can recommend to applicants that such data be submitted in the application as well.[35] The report notes that "changes to a product to introduce nanoscale ingredients or processing would trigger change notification chemistry supplements and permit FDA to review and approve the revised formulation. Depending on the change, the product might be considered a new product for which a new approval is needed."[36]

Crucially, with regard to OTC Monograph Drugs, the report notes that FDA can "**require data and information to determine if these proposed additional ingredients contain nanoscale materials, and if so, require safety and effectiveness data directly related**

State of the Science section, the Task Force believes that nanoscale materials will present regulatory challenges that are similar to those posed by other new technologies that FDA has dealt with in the past, such as biotechnology products, but also some potentially new challenges."), 30 ("As discussed in the State of the Science section, although the science of nanotechnology is continuing to evolve, it is known that the size of a particle can affect its properties such that versions of the same substance with differing particle sizes can have different properties . . . . To appropriately assess the safety . . . it will be important in some cases for FDA or the manufacturer to take into account whether the product contains nanoscale materials."), 32 (Because nanoscale materials can behave differently than other versions of the same materials, it will be important for FDA to obtain relevant information about the characteristics of products containing nanoscale materials."), 32 ("[T]he presence of nanoscale materials may change the regulatory status/regulatory pathway of products.")

[31] FDA Task Force Report at ii.
[32] FDA Task Force Report at 14.
[33] FDA Task Force Report at 19 n. 28.
[34] FDA Task Force Report at 22.
[35] FDA Task Force Report at 22.
[36] FDA Task Force Report at 23.

to particle sized to determine whether the ingredient qualifies for inclusion in the monograph."[37] Given this report finding, one wonders why FDA's recent OTC Sunscreen Monograph proposed rule includes a *request* for data on nano-sunscreens rather than a *requirement* from the nano-sunscreen manufacturers that they provide the nano-specific health and safety data needed to assess the material. This is similar to the calls of the CTA petition (as well as that the products are recalled and not sold while the agency makes this determination).

Further, the report notes that even after the Monograph is final and covers active ingredients, FDA can take various actions "if the agency learns that a new version of a drug product marketed under an OTC Monograph raises a safety or effectiveness concern. A new version that might raise such concerns could be a drug product that contains a monograph ingredient whose particle size has been reduced to the nanoscale range."[38] Again importantly, the report notes that FDA has the authority to address the situation by, among other things, conducting a rulemaking "**to determine whether a nanoscale version of a monograph ingredient should be considered nonmonograph (i.e., not GRAS/E) and therefore require submission of data in an NDA to establish its safety and effectiveness.**"[39] Once again, this is similar to what the CTA legal petition calls for —an agency rulemaking determining the substances new for regulatory purposes and requiring of NDAs; yet the agency's actual action of merely "requesting" information in the proposed OTC Sunscreen rule falls far short of this urgently needed action.

The report recognizes the agency's inherent lack of authority in some cases, for example products where it has little or no premarket review (e.g., cosmetics).[40] However, the report again fails to recommend the need for legislative/regulatory changes. In addition, the report notes that cosmetics that meet the definition of a cosmetic but are intended to affect the structure or function of the body of a human will also be subject to regulation as a device or drug.[41] The FDA is aware of numerous nano-enhanced "cosmetics" that are so intended, for example, nano-infused cosmetics and personal care products listed in the Friends of the Earth product appendix to the 2006 report, "*Nanomaterials, Sunscreens and Cosmetics: Small Ingredients, Big Risks*,"[42] such as nano-zinc oxide and nano-titanium dioxide face creams, moisturizers, lip and cheek balms intended to, among other things protect from UV rays. Yet the report fails to recommend that these products be classified and regulated as new drug products as they should based on their purpose and the lack of being generally recognized as safe and effective.

Finally, with regard to nano-product and ingredient labeling, also called for in the CTA legal petition, the report correctly notes that it requires all products not be misbranded, include false or misleading information, and that product labeling must include all "material" information.[43] The report correctly notes the agency's authority to require

[37] FDA Task Force Report at 23.
[38] Id.
[39] Id.
[40] FDA Task Force Report at ii, 15.
[41] FDA Task Force Report at 27 n. 38.
[42] http://www.foe.org/camps/comm/nanotech/nanocosmetics.pdf
[43] FDA Task Force Report at 34.

disclosure of such information in labeling if "**FDA determined that a particular use of a specific nanoscale material, or the use of nanoscale materials more generally, was a material fact for a category of products, FDA could amend its regulations to require, for example, that all members of that category of products include labeling regarding such use of nanoscale material.**"[44] Then, in the next paragraph, the report uses a wholly different (and erroneous) standard to recommend that labeling not be required at this time:

> Because the current science does not support a finding that classes of products with nanoscale ingredients necessarily present greater safety concerns than classes of products without nanoscale materials, the Task Force does not believe there is a basis for saying that, as a general matter, a product containing nanoscale materials must be labeled as such. There the Task Force is not recommending that the agency require such labeling at this time.[45]

Of course the legal labeling standard is "materiality," much broader and encompassing many more factors than the report's above-given labeling standard of "necessary greater safety concern." Materiality includes many factors. It easily includes, for example, concerns over new, fundamentally different product ingredients where many unknowns, including unintended and potentially harmful consequences exist. The report's conclusion is completely at odds with its own analysis on the labeling standard, given one paragraph above. Instead the agency should grant the CTA legal petition's request for labeling, in line with fulfilling its statutory duties, including requiring that products are not misbranded, misleading, and include material information in their labels. This conclusion applies to nano-sunscreens as well as all other nanomaterial consumer products under FDA's jurisdiction.

Nano-Medicines[46]

The report recognizes that the FDA does have authority to issue regulations and guidance on new drugs, biological products, and devices and to require that they receive marketing authorization on a product-by-product basis. We urge that the FDA require all nano drugs, biological products and devices to undergo review as new products, along with combination products that may combine nanomaterials as one feature of their design. The FDA should treat all of these products as "new" under section 505 of the FFDCA given that they have not been generally recognized as safe and effective. Manufacturers of these products should not be able to claim that the product works in a new and unique way and then expect FDA approval without new testing and submission of data as would be required for any other new drug, biologic, or device. FDA should promptly issue nano-specific drug, biologic and device guidance documents and

[44] FDA Task Force Report at 35.
[45] Id.
[46] Please refer also to the testimony provided by Jaydee Hanson, Policy Director for Human Genetics, International Center for Technology Assessment at the September 8, 2008 hearing.

regulations so that manufacturers and the public know what the FDA expects and can assess its adequacy.

Given that nearly a quarter of new generation biological drugs produce serious side effects that lead to safety warnings soon after they go on the market, the FDA should require nano-drugs, biologics, and devices to be marketed only if the manufacturer has in place a robust system for collecting data on all side effects from the nano scale drugs.

In general the report lacks necessary urgency and fails to address oversight flaws and gaps. In contrast to the FDA's Task Force Report, an October 2006 Woodrow Wilson International Center for Scholars Report of the *Project on Emerging Nanotechnologies* is worth noting. In contrast to the FDA's own report, the Wilson Center report, written by a former FDA Deputy Commissioner for Policy Michael Taylor, was critical of FDA's preparedness and the adequacy of FDA's existing oversight framework, concluding that FDA was not "nano ready" and needed to take immediate steps to address the first wave of nanomaterial consumer products.[47] Taylor highlighted the regulatory gaps that exist in FDA's authority as applied to nanomaterials, particularly in the areas of cosmetics and dietary supplements, and recommended that FDA request cosmetic companies submit safety substantiation data.[48] Taylor also recommended that FDA establish criteria for nanomaterials, including "new for legal and regulatory purposes" and "new for safety evaluation purposes."[49] Such important steps were missing from the Task Force report's recommendations. FDA should address these problems for nano-sunscreens through the OTC Sunscreen Monograph process, see ICTA legal petition requests # 5-8.

C. Principles for the Oversight of Nanotechnologies and Nanomaterials

Adequate Oversight and Effective Oversight Requires Much More: In general, in addition to granting ICTA's legal petition, FDA should act in accordance with the eight fundamental principles necessary for adequate and effective oversight and assessment of the emerging field of nanotechnology:

I. **A Precautionary Foundation**: Product manufacturers and distributors must bear the burden of proof to demonstrate the safety of their products: if no independent health and safety data review, then no market approval.

II. **Mandatory Nano-specific Regulations**: Nanomaterials should be classified as new substances and subject to nano-specific oversight. Voluntary initiatives are not sufficient.

[47] Michael Taylor, *Regulating the Products of Nanotechnology: Does FDA Have the Tools It Needs?*, Woodrow Wilson International Center. for Scholars, Project on Emerging Nanotechnologies, October 5, 2006.
[48] Id.
[49] Id.

III. **Health and Safety of the Public and Workers**: The prevention of exposure to nanomaterials that have not been proven safe must be undertaken to protect the public and workers.

IV. **Environmental Protection**: A full lifecycle analysis of environmental impacts must be completed prior to commercialization.

V. **Transparency**: All nano-products must be labeled and safety data made publicly available.

VI. **Public Participation**: There must be open, meaningful, and full public participation at every level.

VII. **Inclusion of Broader Impacts**: Nanotechnology's wide-ranging effects, including ethical and social impacts, must be considered.

VIII. **Manufacturer Liability**: Nano-industries must be accountable for liabilities incurred from their products.

This summary comes from *Principles for the Oversight of Nanotechnologies and Nanomaterials*, a collaborative declaration on urgently needed oversight principles for nanomaterials released in August 2007. [50] The complete document, now endorsed by

[50] The initial endorsing organizations were:
Acción Ecológica (Ecuador)
African Centre for Biosafety
American Federation of Labor and Congress of Industrial Organizations (U.S.)
Bakery, Confectionery, Tobacco Workers and Grain Millers International Union
Beyond Pesticides (U.S.)
Biological Farmers of Australia
Center for Biological Diversity (U.S.)
Center for Community Action and Environmental Justice (U.S.)
Center for Food Safety (U.S.)
Center for Environmental Health (U.S.)
Center for Genetics and Society (U.S.)
Center for the Study of Responsive Law (U.S.)
Clean Production Action (Canada)
Ecological Club Eremurus (Russia)
EcoNexus (United Kingdom)
Edmonds Institute (U.S.)
Environmental Research Foundation (U.S.)
Essential Action (U.S.)
ETC Group (Canada)
Forum for Biotechnology and Food Security (India)
Friends of the Earth Australia
Friends of the Earth Europe
Friends of the Earth United States
GeneEthics (Australia)
Greenpeace (U.S.)
Health and Environment Alliance (Belgium)
India Institute for Critical Action-Centre in Movement

over sixty organizations from six continents, is available at numerous endorsing organizations websites, including www.icta.org and www.foe.org

For any further information on these comments, please contact the undersigned.

Submitted by,

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Institute for Agriculture and Trade Policy (U.S.)
Institute for Sustainable Development (Ethiopia)
International Center for Technology Assessment (U.S.)
International Society of Doctors for the Environment (Austria)
International Trade Union Confederation
International Union of Food, Agricultural, Hotel, Restaurant, Catering, Tobacco and Allied Workers' Associations
Loka Institute (U.S.)
National Toxics Network (Australia)
Public Employees for Environmental Responsibility (U.S.)
Science and Environmental Health Network (U.S.)
Silicon Valley Toxics Coalition (U.S.)
Tebtebba Foundation - Indigenous Peoples' International Centre for Policy Research and Education (Philippines)
The Soils Association (United Kingdom)
Third World Network (China)
United Steelworkers (U.S.)
Vivagora (France)