DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 20 2012

Andrew Kimbrell
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660 Pennsylvania Ave., S.E., Suite 302
Washington, D.C. 20003

Re: FDMS Docket No. FDA-2006-P-0213-0003 (previously 2006P-0210/CP1)

Dear Mr. Kimbrell:

This letter responds to your citizen petition (petition) received by the Food and Drug Administration (FDA or the Agency) on May 16, 2006, as supplemented on June 21, 2006, which was submitted on behalf of the International Center for Technology Assessment (ICTA); Friends of the Earth; Greenpeace; Action Group on Erosion, Technology and Concentration; Clean Production Action; the Center for Environmental Health; Our Bodies Ourselves; and the Silicon Valley Toxics Coalition (the petitioners).

The petition makes eight requests for FDA action.

With regard to "all nanomaterial products,"[1] you request that FDA:

1. Amend FDA regulations to include nanotechnology definitions necessary to properly regulate nanomaterial products, including definitions of 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 that would establish and require, *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.

[1] In 2006, when the present citizen petition was filed, FDA's regulatory oversight extended to foods (including dietary supplements), food and color additives, cosmetics, drugs for human and animal use, devices for human and animal use, and biological products for human use. In 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), Pub L. No. 111-31, 123 Stat. 1776, charging FDA with oversight of tobacco products. Your 2006 petition does not mention tobacco. Thus, although FDA's overall regulatory approach to nanotechnology, including the Agency's 2011 draft guidance "*Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology,*" discussed in this response, applies to all FDA-regulated products, including tobacco products, this citizen petition response does not address the applicability of the petition requests to tobacco products.

4. Comply with the requirements of the National Environmental Policy Act (NEPA) with respect to any currently existing or future regulatory FDA programs for nanomaterial products, including, *inter alia*, that FDA conduct a Programmatic Environmental Impact Statement (PEIS) reviewing the impacts of nanomaterial products on human health and the environment.[2]

With regard to "nanomaterial sunscreen drug products," you request that FDA:

5. Reopen the administrative record of the Final Over-the-Counter ("OTC") Sunscreen Drug 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 (NDA) in accordance with 21 U.S.C. section 355.
7. Declare all currently available sunscreen drug products containing engineered nanoparticles of zinc oxide and titanium dioxide to be an imminent hazard to the 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 publicly 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.[3]

In a letter dated November 9, 2006, in accordance with Title 21 of the Code of Federal Regulations (CFR) 10.30(e)(2), FDA provided an interim response to your petition to inform you that the Agency was unable to reach a decision on your petition by that date because the petition raised complex issues requiring extensive review and analysis by Agency officials, and in relation to which the Agency was seeking public input. FDA also pointed out relevant ongoing Agency activities, and noted that the Agency would respond to your petition at a later date.

FDA has carefully reviewed your petition and has determined that it does not provide sufficient data and information to persuade FDA to take the specific actions you requested at this time (other than the reopening of the administrative record for the OTC Sunscreen Monograph). As described below, FDA has already undertaken many steps, and plans further actions, to help ensure the safe use of nanotechnology in FDA-regulated products, including OTC sunscreen drug products. As a matter of science and policy, FDA has determined that continuing its overall science-based, product-specific regulatory approach, including considering titanium dioxide and

[2] Petition at 3.
[3] Petition at 3-4.

zinc oxide nanomaterials[4] within the broader ongoing monograph proceeding for OTC sunscreen drug products, is the most appropriate course of action at this time. In continuing this overall approach, FDA will also meet its obligations under the National Environmental Policy Act (NEPA) by assessing on a case-by-case basis the impact to the environment of major actions taken in connection with FDA-regulated products containing nanomaterials.

Section I below provides background on FDA's actions regarding nanotechnology. Section II responds to your requests 1-4 related to nanotechnology applications in FDA-regulated products, and section III responds to your requests 5-8 related to nanotechnology applications in OTC sunscreen drug products.

I. BACKGROUND

Nanotechnology involves manipulation of materials on an atomic or molecular scale.[5] It is an emerging technology that has the potential to be used across the spectrum of FDA-regulated products, including medical products such as drugs, biological products, or medical devices (*e.g.*, to increase bioavailability of a drug), foods (*e.g.*, to improve food packaging), and cosmetics (*e.g.*, to change optical properties and feel on the skin). Over the past several years, FDA has taken multiple steps to ensure that its regulation of products within its jurisdiction that may involve application of nanotechnology is based on sound science, and is consistent with governing legal frameworks, which vary among product types.

FDA does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology to be either inherently benign or harmful. FDA will continue to regulate nanotechnology products under its existing statutory authorities in accordance with the specific legal standards applicable to each type of product under its jurisdiction. FDA believes that this regulatory policy allows for tailored approaches that adhere to applicable legal frameworks, and reflect the characteristics of specific products or product classes and evolving technology and scientific understanding. FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science.

The following overview briefly describes the Agency's activities relating to nanotechnology in general; more specific information regarding sunscreens in particular is provided in section III.

A. Task Force Report

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[4] In this document, we use the term "nanomaterial" generally, including in response to your requests in reference to "nanoparticles", "nanoscale particles", or other such terms referring to particles at a small scale, and we use the term "nanotechnology products" to refer to products that contain nanomaterials or otherwise involve the application of nanotechnology.

[5] For example, the U.S. National Nanotechnology Initiative (NNI) describes nanotechnology as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers (nm), where unique phenomena enable novel applications" (http://www.nano.gov/nanotech-101/what).

In 2006, FDA formed the Nanotechnology Task Force (Task Force) to help assess questions regarding the adequacy and application of FDA's regulatory authorities in light of the state of the science for nanotechnology at that time. The Task Force published its recommendations in 2007.[6] The Task Force's scientific recommendations focused on promotion of, and participation in, regulatory science research and other efforts to increase scientific understanding and to facilitate assessment of data needs for regulated products and the development of adequate testing methods. On regulatory policy issues, the Task Force concluded that the Agency's authorities are generally comprehensive for products subject to pre-market authorization requirements, and that these authorities give FDA the ability to obtain detailed scientific information needed to review the safety and, as appropriate, effectiveness of products. The Task Force further noted that for products not subject to pre-market authorization requirements manufacturers are generally not required to submit data to FDA prior to marketing.

FDA has pursued, and continues to pursue, additional scientific information on which to base its decision making. As recommended by the Task Force, FDA held a public meeting in 2008 to gather information to assist the Agency in further implementing the recommendations contained in the 2007 Task Force Report relating to the development of Agency guidances (2008 Public Meeting).[7] FDA also requested available data and information on the effects of nanoscale materials on quality, safety, and, where relevant, effectiveness of products subject to FDA oversight. In 2010, FDA convened a public workshop to obtain information on the safety and effectiveness of medical devices utilizing nanotechnology.[8] FDA presented its nanotechnology regulatory science program to the FDA Science Board Advisory Committee in August 2010[9] and updated the Committee in May 2011.[10] In August 2011, FDA published "Advancing Regulatory Science at FDA—a Strategic Plan," which encompasses nanotechnology.[11]

B. Draft Guidances

On June 14, 2011, FDA published a *Federal Register* notice announcing the availability of a Draft Guidance for Industry entitled, "*Considering Whether an FDA-Regulated Product Involves*

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[6] Nanotechnology – A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007 (2007 Task Force Report) (http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm).

[7] Consideration of FDA-Regulated Products that May Contain Nanoscale Materials; Public Meeting. 73 FR 46022; August 7, 2008 (http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForce/ucm129416.htm).

[8] Public Workshop - Medical Devices and Nanotechnology: Manufacturing, Characterization, and Biocompatibility Considerations, September 23, 2010 (http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm222591.htm).

[9] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/ucm198503.htm.

[10] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/ucm241888.htm.

[11] Strategic Plan for Regulatory Science. Advancing Regulatory Science at FDA: A Strategic Plan, August 2011 (http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm).

the Application of Nanotechnology" (the 2011 draft guidance), to present its thinking on considerations related to nanotechnology, and asked for public comment, including input from the scientific, regulatory, and broader community.[12] The draft guidance, which applies broadly to all FDA-regulated products, indicates that based on the Agency's current scientific and technical understanding of nanomaterials and their characteristics, evaluations of safety or effectiveness of FDA-regulated products that include nanomaterials or otherwise involve the application of nanotechnology should consider the unique properties and behaviors that nanomaterials may exhibit. The draft guidance identified two points based on dimensions and properties that should be considered when determining whether FDA-regulated products involve the application of nanotechnology and, therefore, merit further examination. (See also section II of this response).

The 2011 draft guidance reiterates that pre-market review, when required, offers an opportunity to better understand the properties and behavior of products that contain nanomaterials or otherwise involve application of nanotechnology. And, where products are not subject to pre-market review, the draft guidance urges manufacturers to consult with the Agency early in the product development process. In this way, manufacturers and FDA can appropriately and adequately address any questions related to the regulatory status, safety, or effectiveness of these products in a timely manner.

The Agency has also issued two product-specific draft guidances to industry to address questions related to the use of nanotechnology in cosmetic products and in food substances. The Draft Guidance for Industry entitled, "*Safety of Nanomaterials in Cosmetic Products*" (Cosmetics draft guidance)[13] describes FDA's current thinking on factors that need to be considered in conducting safety assessments of cosmetic products containing nanomaterials. The Draft Guidance for Industry entitled, "*Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives*" (Foods draft guidance)[14] describes factors that manufacturers should consider when determining whether a significant change in the manufacturing process for a food substance already in the market affects its safety, regulatory status, or both. This draft guidance addresses manufacturing changes involving emerging technologies, such as nanotechnology, as they relate to food substances.

II. FDA RESPONSE TO OVERARCHING REQUESTS

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[12] Draft Guidance for Industry; Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology; Availability. 76 FR 34715; June 14, 2011(http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0530-0001).

[13] http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm300886.htm

[14] http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm300661.htm

FDA addresses each of your enumerated requests 1 through 4 as follows.

> *1. Petitioners request that the Agency amend FDA regulations to include nanotechnology definitions necessary to properly regulate nanomaterial products, including the term "nanotechnology," "nanomaterial," and "engineered nanoparticle."*

In your petition, you request that FDA establish, by regulation, uniform, Agency-wide definitions for particular terms that you maintain are necessary for proper regulation of nanomaterial products. Although you indicate that FDA should be informed by existing and developing national and international standards in establishing the ultimate regulatory definitions, you suggest specific potential definitions including the following:

> Nanoscale -- Having one or more dimension of the order of 100 nanometer (nm) or less.
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> Nanotechnology -- the design, characterization, production and application of structures, devices and systems by manipulating shape and size at the nanoscale.
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> Nanoparticle -- A particle with at least one dimension smaller than 100 nm including engineered nanoparticles, ambient ultrafine particles (UFPs), and biological nanoparticles.
>
> 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.
>
> Nanomaterial -- Any material that either contains a certain proportion of nanoparticles or consists exclusively of them.[15]

You request the establishment of these definitions, by regulation, to further your remaining requests for additional regulation, which would apply where a product contains engineered nanoparticles or is a nanomaterial (that is, includes nanoparticles, whether engineered or not). The definitions you request rely primarily on size, specifically size below 100 nm, as a necessary condition for being considered "nano," and therefore, for being within the scope of the additional requests for particular regulatory actions in the remainder of your petition.

No specific statutory provision requires FDA to establish definitions for nanotechnology or related terms, or to establish other particular provisions for products falling within those proposed definitions, by regulation or otherwise. Thus, the Agency has broad discretion to

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[15] Petition at 10-11.

determine whether to promulgate regulations with respect to these issues.[16] For the reasons that follow, your petition does not persuade us to establish such regulations at this time.

The term *nanotechnology* is commonly used to refer to the engineering (i.e., deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range of approximately 1 to 100 nanometers. Although nanomaterials are most commonly distinguished on the basis of particle size, materials can exhibit novel properties or phenomena at dimensions above the approximate 100 nm range.[17] Several definitions adopted or being considered by regulatory agencies or other organizations, therefore, also make reference to physical and chemical properties in addition to particle size.[18] For purposes of effective oversight and regulation, however, the critical issue is whether any such new or altered properties and phenomena of nanomaterials create or alter the risks and benefits of a specific application of the material and its intended use.[19]

The 2011 draft guidance noted that, based on our current scientific and technical understanding of nanomaterials and their characteristics, evaluations of safety and, as applicable, effectiveness of such products should consider the unique properties and behaviors that nanomaterials may exhibit. As explained in greater detail in the draft guidance, whether the material or end product is strictly within the nanoscale range (of approximately 1 to 100 nm) or falls outside this range, the deliberate manipulation of small particles for properties that are not observed in conventionally scaled materials may warrant additional evaluation. For this reason, FDA explained that it is taking an inclusive approach to identifying products of interest in the context of nanotechnology. To ensure their consideration in developing final guidance, FDA requested comments on the draft guidance by August 15, 2011. We are currently reviewing comments received and will take them into account as we develop final guidance on this topic.

In sum, as a matter of science and policy, we conclude that it is not appropriate for FDA to adopt regulations establishing a definition of nanotechnology and related terms at this time. Therefore,

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[16] *Cf.* 21 USC 371 (authorizing, but not requiring, the Secretary to "promulgate regulations for the efficient enforcement of this Act").

[17] "Considerations on a Definition of Nanomaterial for Regulatory Purposes," Joint Research Centre, 2010; "Scientific Basis for the Definition of the Term "Nanomaterial," Scientific Committee on Emerging and Newly Identified Health Risks, 2010; European Commission recommendation on the definition of nanomaterial, October 18, 2011; International Standards Organization Technical Specification, Nanotechnologies – Vocabulary – Part 1: Core terms, ISO/TS 80004-1, 2010; and Policy Statement on Health Canada's Working Definition for Nanomaterial, 2011.

[18] Policy Statement on Health Canada's Working Definition for Nanomaterial, 2011; International Standards Organization Technical Specification, Nanotechnologies -- Vocabulary -- Part 1: Core terms, ISO/TS 80004-1, 2010; Australia National Industrial Chemicals Notification and Assessment Scheme's working definition of industrial nanomaterial, 2010; "Considerations on a Definition of Nanomaterial for Regulatory Purposes," Joint Research Centre, 2010; "Scientific Basis for the Definition of the Term "Nanomaterial," Scientific Committee on Emerging and Newly Identified Health Risks, 2010.

[19] *See generally* the 2011 draft guidance. *See also* "Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials," issued on June 9, 2011 (http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf).

we deny your request that the Agency amend its regulations to adopt definitions, including those for the terms "nanotechnology," "nanomaterial," and "engineered nanoparticle."

2. Petitioners request that the Agency issue a formal advisory opinion explaining FDA's position regarding engineered nanoparticles in products regulated by FDA.

Your petition requests that FDA issue a formal advisory opinion explaining FDA's position regarding engineered nanoparticles in products regulated by FDA. You express particular interest in determining whether it is FDA's current position 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."[20]

As noted above, FDA has chosen to proceed in accordance with the Agency's good guidance practices,[21] to provide its current thinking on nanotechnology while retaining sufficient flexibility to encompass evolving science and the varied statutory requirements for different products. Under the good guidance practice regulation, guidance documents are the appropriate means of communicating the Agency's official position on a policy issue to a wide audience for the first time, including on matters regarding product testing and evaluation and approval of submissions.[22] The development of guidance documents is informed by opportunity for public comment, including the opportunity for submission of relevant scientific and other factual information. Having recently solicited public comment on a draft guidance addressing nanotechnology, and being in the midst of considering comments received, FDA finds that it would not be appropriate or otherwise in the public interest to issue a formal advisory opinion on this matter.[23]

With regard to your requests for clarification, in the 2011 draft guidance FDA explained that the application of nanotechnology may result in product attributes that differ from those of conventionally manufactured products, and thus may merit examination. That draft guidance makes clear the Agency's current thinking that both particle size *and* properties attributable to size are important considerations for regulatory oversight. See also discussion in response to request 1 above.

As discussed in response to request 3 below, the Agency continues to review on a case-by-case basis the applicability and adequacy of testing methodologies in safety evaluations of products containing nanomaterials. The Agency will, as needed, provide guidance to manufacturers on specific data, information, or issues to be considered in adequate safety assessments of products that involve the application of nanotechnology. For example, both the Foods draft guidance and the Cosmetics draft guidance address the use of nanotechnology and related safety evaluations.

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[20] Petition at 14.
[21] *See* 21 CFR 10.115.
[22] *See* 21 CFR 10.115(e).
[23] *See* 21 CFR 10.85(a)(2)(v).