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 Thus, although FDA's overall regulatory approach to nanotechnology, including the Agency's 2011 draft guidance "*Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology,*" discussed in this response, applies to all FDA-regulated products,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).

For the reasons stated above, and having substantively answered your inquiries regarding particle size and testing methods in response to requests 1 and 3, we deny your request that the Agency issue a formal advisory opinion explaining FDA's position regarding engineered nanoparticles in products regulated by FDA.

> *3. Petitioners request that the Agency 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.*

Below we address each of the individual issues raised in this request separately.

> (a) That the Agency enact new regulations requiring that nanoparticles be treated as new substances

In your petition, you assert that the novel properties of engineered nanomaterials make them fundamentally different from existing materials with the same chemical composition, and that because of these differences, "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."[24] This request is, therefore, interrelated to your request for nano-specific testing requirements, which we address in detail in the next portion of our response. To the extent that this represents an independent request for enactment of regulations requiring that nanoparticles be treated as new substances, however, your petition does not persuade us that such action would be useful or appropriate at this time.

Your petition asserts that "the novel properties of engineered nanoparticles make them different, for all purposes relevant to FDA's statutory mandate."[25] Without further legal discussion of the authority for, or effects of, such action, your petition broadly endorses establishing regulations classifying any engineered nanoparticle in any FDA-regulated product as a "new substance."

FDA has recognized the potential for nanomaterials and products involving nanotechnology to exhibit differences from their conventional counterparts. For example, the Task Force Report stated that nanomaterials often have chemical, physical, or biological properties that are different from those of their larger counterparts.[26] The 2011 draft guidance indicates that the application of nanotechnology may result in product attributes that differ from those of conventionally manufactured products. Although FDA recognizes the potential for difference between nanomaterials and their larger-scale counterparts, and follows a regulatory policy that is designed

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[24] Petition at 22. Although you request that the agency enact new regulations to impose this requirement, you also request that FDA conclude that engineered nanoparticles must be "regulated as a separate class than bulk material counterparts" through an advisory opinion. Petition at 24. As we decline to reach your requested conclusion for the reasons explained, we also find it would not serve the public interest to issue an advisory opinion taking the position you request.

[25] Petition at 24.

[26] 2007 Task Force Report at 4.

to examine such differences, we decline to issue regulations as you requested. In assuming that "difference" in a material alone should have uniform regulatory significance, your request overlooks certain critical considerations. First, FDA's legal authorities are not uniform for the broad range of products it regulates under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act, and, thus, FDA's regulation must also vary and be consistent with those authorities. Second, because FDA's authority is over foods, drugs, devices, and other products as defined in relevant statutes, regulatory consequences of the application of nanotechnology are determined ultimately by evaluating the effects of nanotechnology, if any, on the safety or other statutorily relevant attributes of a particular regulated product as a whole, for its intended use.

To elaborate, FDA's legal authorities for different product types vary. For example, one major area of variation among the legal frameworks for different FDA-regulated product types is whether or not there is a mandatory evaluation by FDA prior to marketing. Some FDA-regulated products, such as cosmetics, are not subject to any mandatory pre-market review. In other cases, pre-market review is extensive and product-specific. For example, new drugs, new animal drugs, biological products, and most class III medical devices are subject to product-specific review and approval in the form of an NDA or abbreviated new drug application (ANDA), new animal drug application or abbreviated new animal drug application (NADA/ANADA), biologics license application (BLA), or pre-market approval application (PMA), respectively.[27] Food additives[28] and color additives are also subject to pre-market authorization,[29] and certain new dietary ingredients in dietary supplements are subject to pre-market notification requirements.[30] In other cases, safety and effectiveness data are systematically examined in other ways. For example, most OTC drug products do not require individual approved applications, but are marketed subject to OTC monograph regulations that establish the conditions under which products of a particular type (such as OTC sunscreen drug products) are considered to be generally recognized as safe and effective (GRAS/E), and these conditions are established based on the review of scientific data.[31]

In addition, the substantive standards required for Agency review of different types of products vary. For example, food additives are considered safe when there is a reasonable certainty of no harm from their intended use.[32] Drugs, by contrast, are evaluated not only on the basis of their risk profile but also their predicted benefit.[33] These differing legal standards demonstrate how different contexts could lead to different regulatory outcomes, even if two products present the same level of risk.

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[27] *See* FD&C Act sections 505, 512, and 515 (21 U.S.C. 355, 360b, and 360e); and Public Health Service Act Section 351 (42 U.S.C. Sec. 262).
[28] This includes food contact substances, such as food packaging.
[29] *See* FD&C Act sections 409 and 721 (21 U.S.C. 348 and 379e).
[30] *See* FD&C Act section 413 (21 U.S.C. 350b). Although not approvals, these notifications include information about safety.
[31] *See* 21 CFR part 330. The monograph proceeding for OTC sunscreen drug products is discussed in more detail in section III.B of this response.
[32] *See* FD&C Act section 409 (21 U.S.C. 348) and 21 CFR 170.3(i).
[33] *See* FD&C Act section 505 (21 U.S.C. 355) and 21 CFR 330.10(a)(4)(iii).

The 2007 Task Force Report recommended that FDA provide guidance to manufacturers about when the use of nanomaterials may require submission of additional data, change the product's regulatory status or pathway, or merit taking additional or special steps to address potential safety or product quality issues, particularly for products not subject to pre-market review requirements, and the Agency is following this approach. For example, the Foods draft guidance 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. And in another example, the Cosmetics draft guidance describes factors to consider in conducting safety assessments of cosmetic products, and recognizing that cosmetic products or ingredients (with the exception of color additives) are not subject to pre-market approval,[34] encourages manufacturers to consult with the Agency to discuss test methods and data necessary to substantiate the product's safety.

FDA has also reiterated its advice for consultation with the Agency in other guidances. Manufacturers of new dietary ingredients or of devices subject to the 510(k) pre-market notification requirements are encouraged to meet with the Agency to address questions related to the use of nanotechnology in these products (see draft guidances on new dietary ingredients[35] and 510(k) devices[36]). FDA also discussed the relevance of particle size in guidance documents addressing submissions of safety assessments for food additive petitions,[37] color additive petitions,[38] and food contact notifications.[39] FDA also issued instructions to relevant internal FDA reviewers regarding review of submissions on certain drug products that may involve nanotechnology.[40]

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[34] The FD&C Act prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce (21 U.S.C. 331(a)).

[35] Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, July 2011 (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm).

[36] Draft Guidance for Industry and FDA Staff - 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device, July 2011 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265274.htm).

[37] Guidance for Industry - Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions, March 2009 (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm124917.htm).

[38] Guidance for Industry - Color Additive Petitions. FDA Recommendations for Submission of Chemical And Technological Data On Color Additives For Food, Drugs Or Cosmetics, July 2009 (http://www.fda.gov/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm).

[39] Guidance for Industry - Preparation of Pre-market Submissions for Food Contact Substances: Chemistry Recommendations, December 2007 (http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm).

[40] Reporting Format for Nanotechnology-Related Information in CMC Review, FDA's Center for Drug Evaluation and Research, June 2010 (http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf); and Review of ONADE regulated products that contain nanomaterials or otherwise involve the use of nanotechnology, FDA's Center for Veterinary Medicine, August 2011

Going forward, we will consider issuing additional regulatory documents, as needed, to advise industry or establish requirements about the use of nanotechnology in FDA-regulated products. The Agency will continue to evaluate safety and effectiveness (as applicable under statutory provisions) of products using FDA's current review processes. We will also explore voluntary pre-market submissions as well as post-market surveillance options to consider issues related to products that, under current statutory provisions, are not subject to pre-market notice or approval.

Therefore, we decline, at this time, to issue new regulations requiring that nanoparticles be treated as new substances.

> (b) That the Agency enact new regulations requiring that nanomaterials be subjected to nano-specific paradigms of health and safety testing

Your petition states that "there must be proactive toxicology and environmental research to anticipate and characterize potential risks" associated with nanomaterials. In this regard, you suggested that predictive toxicology could be used as a "toxicity screening strategy" that involves three key elements: physicochemical characterization, *in vitro* assays (cellular and noncellular), and *in vivo* studies.[41]

We agree with you on the need for adequate safety assessments using appropriate testing approaches. However, we do not believe that FDA must adopt regulations in order to apply existing, new, or modified safety or toxicity testing methodologies in our safety evaluations of products containing nanomaterials or otherwise involving the use of nanotechnology. We consider the current framework for safety assessment sufficiently robust and flexible to be appropriate for a variety of materials, including nanomaterials. Moreover, mandatory protocols for the determination of safety and toxicity of products would not provide the needed flexibility to determine, on a case-by-case basis, the specific tests (whether traditional, modified, or new) that may be needed to assess the safety of a product involving the use of nanotechnology, for its intended use. For both of these reasons, we conclude that the regulations you requested are unnecessary.

As explained above, FDA currently evaluates products involving the application of nanotechnology under existing regulatory frameworks. Regardless of whether products contain nanomaterials, FDA asks relevant questions to understand any uncertainties that may exist concerning product safety to ensure that the product meets statutory and regulatory requirements for safety.

We will provide guidance to industry on safety assessments, as appropriate. Both the Foods draft guidance and the Cosmetics draft guidance address the use of nanotechnology and factors to consider in safety assessments of such products. The Cosmetics draft guidance, in particular,

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(http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/PoliciesProceduresManual/UCM270271.pdf).

[41] Petition at 25.

points out that questions about the applicability of traditional safety testing methods to cosmetic products that involve nanotechnology still exist and, therefore, the Agency recommends that testing methods and data needed should be evaluated in light of the properties or functions of nanomaterials used in cosmetic products.

You also assert that nanomaterial characteristics and effects must be learned anew and that "the existing scientific . . . paradigms for assessing health effects are inapposite to engineered nanoparticles because of their intrinsic fundamental differences."[42] We disagree with your categorical rejection of the utility and value of traditional testing approaches.

The 2007 Task Force Report specifically addressed the issue of adequacy of testing approaches. As explained in that report, testing methods for different types of products may need to be evaluated to determine whether and how they can be applied to nanotechnology products. The Task Force recommended a staged approach to determine whether current testing methods are adequate to support risk management decisions, and where they are not, to collect data and update testing procedures.[43]

FDA is investing in an FDA-wide nanotechnology regulatory science program to further enhance FDA's scientific capabilities, including developing necessary data and tools to identify and measure dimension-dependent properties and assess their impact on safety and effectiveness.[44] FDA also conducts research to support its regulatory needs in specific product areas (see the description in section III.C of certain Agency research related to titanium dioxide nanomaterials in sunscreen formulations). A list of selected FDA publications related to nanotechnology regulatory science research is available on our website.[45]

For all of these reasons, we decline to issue new regulations requiring that nanomaterials be subjected to nano-specific paradigms of health and safety testing.

> (c) That the Agency enact new regulations requiring that nanomaterial products be labeled to delineate all nanoparticle ingredients

You request that FDA regulations be amended to specifically require that all "nanomaterial products" be "labeled as including nanomaterials and to describe what type of nanoparticle is included in the product."[46] You contend that absent such specific labeling, the use of the same

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[42] Petition at 23.

[43] 2007 Task Force Report at 17. The report noted the need for tools and data to understand physicochemical characterization, biodistribution, pharmacokinetics, and toxicity/biocompatibility of nanomaterials, in order to understand how they will interact with biological systems under varying conditions, such as routes of exposure, dosage, and behavior in specific tissues and organs.

[44] FDA Nanotechnology Regulatory Science Research Plan (http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm).

[45] Selected FDA Publications Related to Applications of Nanotechnology (*See* http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm)

[46] Petition at 26. Given your proposed definitions, this request apparently would include special labeling of any product containing particles (including biological nanoparticles and engineered nanoparticles alike) with at least one dimension less than 100 nm present in a "certain" proportion. Under this scenario, special labeling would be

ingredient name for "nanomaterial consumer product ingredients" and for their "bulk material counterparts" would be "false and misleading." You also suggest that such labeling would assist consumers, in part by helping avoid unwarranted negative perceptions of nanotechnology.[47]

Your petition does not provide sufficient support for the conclusion that the categorical labeling requirements you request are necessary or appropriate for all "nanomaterial" products. Labeling of FDA-regulated products is governed by multiple statutory and regulatory provisions. Among these provisions, the FD&C Act requires that labeling of foods, cosmetics, devices, and drugs (including biologics) be truthful and not misleading.[48] To be non-misleading, among other things, labeling must include material information, including with respect to consequences which may result from the use of the product under the conditions of use prescribed in the labeling or under customary or usual conditions of use.[49] The risk information contained in prescription drug labeling is an example of material information. Information about the characteristics of a food (e.g., its nutritional or functional properties) can be material information, which may also influence the naming of that food. If labeling is false or misleading in any particular, the product is "misbranded" and it is unlawful to market such a product.[50]

The legal requirements governing the labeling of all FDA-regulated products apply with equal force to those involving the use of nanotechnology. Thus, where the use of nanomaterials results in, for example, characteristics of the product or consequences with respect to conditions of its use that constitute material information, such information is required to be declared in the labeling of that product.

At this time, however, given the emerging variety of potential applications of nanotechnology across various FDA-regulated products and the current state of scientific understanding of the effects of nanotechnology on safety and effectiveness of a product, FDA cannot make a categorical determination that "delineat[ing] all nanoparticle ingredients" in labeling, as you request, is necessary for all nanotechnology products to ensure that their labeling is not false or misleading. Rather, FDA will need to determine on a case-by-case basis whether the specific use of nanotechnology in a product produces effects that warrant special labeling requirements to ensure that the labeling of that product provides material information and is truthful and not misleading. How best to convey such information (such as through a new or modified naming of the product or ingredient or other statements on the label or labeling of the product) would need to be determined in the context of the specific product and its intended use, and in light of

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required without regard to whether the presence of such small scale particles was the result of deliberate manipulation and control to produce specific properties, and without distinction between products containing such "engineered" nanomaterials and those with naturally occurring or incidental levels of nanomaterials. For example, conventional products that contain substances that exist naturally at small scales, such as microorganisms or proteins, would be subject to special labeling requirements. You offer no explanation why including special labeling of the type you request would be necessary for products whose original or commonly-used form includes materials that may naturally exist at small scales, including the range of 1 to 100 nm.

[47] Petition at 27-28.

[48] *See* FD&C Act sections 403(a), 502(a), 602(a).

[49] *See* FD&C Act section 201(n).

[50] *See* FD&C Act sections 403(a), 502(a), 301(a-c).

governing statutory provisions.[51] For this reason, issuing regulations as you request would not be appropriate at this time.

Under existing statutory and regulatory provisions, manufacturers are able to voluntarily include information about the use of nanomaterials or nanotechnology in the labeling of products where such information presented in the context of the entire label or labeling is not false or misleading in any particular, and does not violate other labeling requirements. For example, manufacturers may voluntarily label their products as containing nanomaterials or as not containing nanomaterials, as the case may be, in a manner that is truthful and non-misleading.

For all of these reasons, we deny your request to enact new regulations requiring that nanomaterial products be labeled to delineate all nanoparticle ingredients.

> *4. Petitioners request that FDA comply with the requirements of the National Environmental Policy Act 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.*

In your petition, you state that in order to comply with NEPA, FDA should conduct a PEIS regarding nanomaterial products. This request appears to encompass several different scenarios, which we address in turn below.

FDA actions with regard to applications and petitions are subject to the requirements of NEPA. Specifically, NEPA requires Federal agencies to consider the environmental consequences of "major federal actions significantly affecting the quality of the human environment." The Council for Environmental Quality (CEQ) has issued regulations implementing NEPA that apply to all agencies of the Federal government and are codified in 40 CFR Parts 1500–1508. The CEQ regulations provide for the evaluation of the environmental effects of a major federal action in an environmental impact statement, an environmental assessment, or a claim of categorical exclusion.[52] In consultation with CEQ, FDA has promulgated its own regulations for implementing NEPA. These regulations, which describe industry obligations and the processes applicable to FDA for evaluating the potential environmental impacts of its actions, can be found at 21 CFR Part 25.

In your petition you request that, if FDA grants the petition and enacts new regulations, or amends existing regulations, FDA conduct a PEIS if the regulations would significantly affect the quality of the human environment.[53] Because FDA is not at this time issuing new regulations

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[51] For example, established names for drugs and devices are subject to particular statutory provisions that are not applicable to foods, and would therefore require consideration in determining how to best convey any material information about a drug or device. *See* FD&C Act sections 502(e) and 508.

[52] *See* 40 CFR sections 1508.4, 1508.9, 1508.11.

[53] Petition at 34.

or amending existing regulations with regard to nanomaterial products, FDA denies this request at this time.

FDA's 2011 draft guidance had not been issued at the time you submitted your petition. To the extent that your petition implicitly requests that FDA conduct a PEIS of the 2011 draft guidance,[54] it is FDA's position that the draft guidance does not constitute a major federal action under NEPA because it maintains the substantive status quo and takes no overt action. As previously discussed, FDA will continue to regulate nanotechnology products under existing authorities and ensure that the specific legal standards applicable to each type of product under its jurisdiction are met. The 2011 draft guidance "does not bind [the Agency's] decisionmaking authority," and, therefore, is not the kind of "irreversible action that is necessary to require preparation of an EIS."[55] The 2011 draft guidance maintains the regulatory status quo in that FDA-regulated products containing nanomaterials continue to be addressed on a case-by-case basis using FDA's existing review processes.[56]

As a result, FDA's NEPA obligations are not triggered in conjunction with the 2011 draft guidance, and FDA therefore denies your request that the Agency complete a PEIS of its policy regarding FDA-regulated products containing nanomaterials, under its 2011 draft guidance.

In addition, you request that, if FDA declines to enact or amend its regulations, but continues to act pursuant to an Agency "de facto" nanomaterial regulatory policy, that it conduct a PEIS of this "de facto" policy.[57] In making this request, you do not specify what you believe constitutes such a "de facto" nanomaterial regulatory policy, although elsewhere in your petition you contend, essentially, that the Agency has declined to regulate nanotechnology products, as a class, differently from other products.[58] Declining to act would not trigger the need to prepare a PEIS under NEPA.[59]

In sum, FDA concludes that it meets its NEPA obligations under its existing regulatory framework. Therefore, we decline your requests regarding NEPA.

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[54] Petition at 34 ("If FDA grants this petition and … 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").

[55] *See* Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d. 166, 174-175 (D.D.C. 2000).

[56] 2011 draft guidance at section II (http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm).

[57] Petition at 35.

[58] *See id.* at 6-7.

[59] *See* Alliance for Bio-Integrity, 116 F. Supp. 2d at 174-175 (quoting Defenders of Wildlife v. Andrus, 627 F.2d 1238, 1243 (D.C. Cir. 1980)) ("NEPA applies only to Agency actions, 'even if inaction has environmental consequences").

III. NANOTECHNOLOGY APPLICATIONS IN OVER-THE-COUNTER SUNSCREEN DRUG PRODUCTS

This section of our response addresses your concerns and requested actions relating to the safety and regulatory status of OTC sunscreen drug products containing titanium dioxide or zinc oxide nanomaterials as active ingredients. The petition describes a number of asserted harms that you state might occur if these ingredients penetrate through the skin and then are distributed throughout the body.[60]

As we explain, we are considering the safety of titanium dioxide and zinc oxide nanomaterials as part of our ongoing proceeding to develop a regulatory monograph for OTC sunscreen drug products (the OTC sunscreen review or OTC review), and we have reopened the administrative record of the review as you requested, to include your petition as well as to solicit and admit any other relevant information. As a matter of science and policy, we conclude that the most appropriate course at this time is to continue our consideration of titanium dioxide and zinc oxide nanomaterials within the broader OTC sunscreen review, and, thus, we are denying your request to amend that monograph at this time. Neither your petition and its supporting material nor the additional data and information we have reviewed to date are sufficient to persuade us to take categorical action at this time to remove from the market sunscreens containing titanium dioxide or zinc oxide nanomaterials, as you request.

A. Regulatory Framework

OTC sunscreen drug products are intended to help prevent sunburn, early skin aging, and skin cancer caused by ultraviolet (UV) radiation from the sun (solar radiation), and they are regulated as drugs under the FD&C Act.[61] When used as directed along with other sun protection measures, OTC sunscreen drug products can decrease the risk of these types of skin damage caused by exposure to solar radiation, and they are routinely used for this purpose by millions of consumers in the United States.[62] OTC sunscreens are applied topically, and their protective action results from the ability of sunscreen active ingredients to absorb, reflect, or scatter UV radiation. Because their therapeutic action takes place in the outer layers of the skin, OTC sunscreen drug products need not, and are not meant to, penetrate into or beyond the deeper layers of the skin.

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[60] *See, e.g.,* Petition at 50 (potential damage to DNA in living cells); *id.* at 56-57 ("extreme mobility" of nanoparticles permits access to blood cells, vasculature, heart, bone marrow, muscles, liver, and spleen as well as crossing of the blood-brain and placental barriers); *id.* at 58-59 (detailing potential for damage due to chemical reactivity and/or damage to phagocytes); and *id.* at 62-63 (potential damage within cells penetrated by nanoparticle ingredients).

[61] The FD&C Act defines drugs, in part, as articles intended to be used in "the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals," FD&C Act, section 201(g)(1). Cosmetic products such as moisturizers, lip balms, or makeup that are labeled with sunscreen drug claims are also regulated as drugs. *See* 21 CFR 700.35.

[62] Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use. Final Rule. 76 FR 35620 at 35630-34 (June 17, 2011).

Most current sunscreen drug products are marketed under the ongoing OTC sunscreen review.[63] The purpose of that proceeding is to establish an FDA regulation (final monograph) that specifies active ingredients, labeling requirements, and other permitted conditions for OTC sunscreen drug products. OTC drug products whose active ingredients are listed in an applicable final monograph and that otherwise comply with the monograph and other applicable regulations are considered to be "generally recognized as safe and effective" (GRAS/E) and may be marketed without pre-market approval in the form of an NDA or an ANDA, as the statute would otherwise require.[64] As a matter of enforcement policy, FDA also exercises enforcement discretion with regard to the interim marketing of OTC drug products, without approved applications, while an applicable monograph review proceeding is ongoing, subject to certain conditions.[65]

The standards for establishing that an active ingredient is safe and effective for its intended OTC drug use are explained in FDA's procedural regulations for OTC drug reviews.[66] With respect to safety,[67] the regulation provides that:

> Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.[68]

The regulation also identifies broad categories of data that FDA may request and consider as evidence that an active ingredient of an OTC drug is generally recognized as safe; these include human and animal studies, pertinent marketing experience, documented reports of adverse effects, and medical and scientific literature.[69] The regulation does not prescribe specific tests and methods that FDA considers "adequate" and "reasonably applicable" to show that a given

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[63] A few OTC sunscreen drug products are marketed under approved NDAs or ANDAs.

[64] GRAS/E status is a critical (though not the only) requirement for establishing that a given drug product is not a "new drug" as defined in the FD&C Act, 21 USC 321(p). Section 505(a) (21 USC 355(a)) prohibits the marketing of new drugs without an approved NDA or ANDA.

[65] FDA's interim enforcement policy for OTC sunscreens is described in section III.B.1; *see also* Compliance Policy Guide, § 450.200 Drugs - General Provisions and Administrative Procedures for Recognition as Safe and Effective.

[66] *See generally* 21 CFR part 330.

[67] Because your petition is specifically focused on the safety, not the effectiveness, of nanoparticle forms of the active ingredients in OTC sunscreens, the parallel standard for proof of effectiveness is not addressed in this response. We note, however, that the effectiveness of individual sunscreen drug products, including products containing zinc oxide or titanium dioxide nanomaterials, is assured by performance testing of the end product formulation (i.e., sun protection factor (SPF) and broad spectrum testing), as established by regulation.

[68] 21 CFR 330.10(a)(4)(i).

[69] 21 CFR 330.10(a)(2).

active ingredient is safe for its intended use.[70] Rather, FDA has discretion to exercise scientific judgment to determine what testing or other data are adequate to demonstrate that the GRAS/E standard is satisfied for the drug under the relevant conditions of use.[71]

B. Ongoing FDA Actions Related to OTC Sunscreen Drug Products

1. FDA's Review of OTC Sunscreen Drug Products

The process for establishing a final OTC sunscreen monograph has been long and complex,[72] largely because, in addition to reviewing the safety and effectiveness of sunscreen active ingredients, we have needed to consider and resolve a number of important legal, scientific, and technical issues.[73] Because there is no final monograph in effect, the marketing of most OTC sunscreen drug products is currently subject to the enforcement policy set forth in a draft guidance document published in June 2011 (Sunscreen draft guidance).[74] Under this policy, FDA does not intend to object to the marketing without an approved NDA or ANDA of an OTC sunscreen product that is formulated, labeled, and tested as described in the Sunscreen draft guidance.[75]

FDA initially called for safety and efficacy data on OTC sunscreen drug products in 1972.[76] A panel of medical experts (the Panel) then reviewed the data submissions, and FDA published the Panel's report and recommended monograph text as an advance notice of proposed rulemaking (Panel Report) in 1978.[77] The Panel's draft monograph contained a list of active ingredients that

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[70] This is an example of the existing regulatory frameworks within which FDA can obtain necessary safety data, making your request for nano-specific testing regulations unnecessary. *See* Section II.

[71] "Conditions of use" is a collective term for an OTC drug product's active ingredient, dosage strength, dosage form, indications, warnings, and directions for use.

[72] This discussion does not cover every regulatory action associated with OTC sunscreen drug products. For a complete list of all such actions, please refer to our website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm072134.htm.

[73] This has resulted in numerous extensions of comment periods, reopening of the rulemaking record, and public meetings needed to establish efficacy measures and testing procedures.

[74] Guidance for Industry: Enforcement Policy – OTC Sunscreen Drug Products Marketed without an Approved Application; Draft Guidance (June, 2011) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf).

[75] Sunscreen draft guidance at 5-11. Such products also must comply with generally applicable requirements for OTC drugs such as the "Drug Facts" labeling format (21 CFR 201.66), as well as general requirements for all drugs, such as current Good Manufacturing Practice (cGMP), 21 CFR Parts 210-211, and drug establishment registration and drug listing requirements, 21 CFR Part 207. Consistent with FDA's general enforcement approach to drugs that are the subject of ongoing monograph reviews, this enforcement discretion policy does not apply if the failure to pursue regulatory action poses a potential health hazard to the consumer. Sunscreen draft guidance at 5; *see also* CPG 450.200. Thus, FDA may pursue individual enforcement actions, as appropriate. However, as discussed further in this response, current evidence does not indicate a public health hazard from sunscreens containing titanium dioxide or zinc oxide nanomaterials, generally.

[76] Over-the-Counter Topical Analgesic, Including Antirheumatic, Otic, Burn, Sunburn Treatment and Prevention Products; Request for Data and Information, 37 FR 26456 (December 12, 1972).

[77] Sunscreen Products for Over-the-Counter Human Use; Establishment of a Monograph; Notice of Proposed Rulemaking, 43 FR 38206 (August 25, 1978) (Panel Report).

the Panel found to be GRAS/E for sunscreen use when used under the conditions recommended in the Panel Report.[78] The list included titanium dioxide but not zinc oxide, which the Panel classified as an inactive ingredient in sunscreen drug products. However, the same Panel reviewed zinc oxide for use as an active ingredient in OTC skin protectant drugs and found it to be safe for topical use in that context.[79]

On May 3, 1993, having reviewed the Panel Report and related public comments, we published a proposed rule known as a tentative final monograph.[80] As in the Panel Report, FDA included titanium dioxide, but not zinc oxide, in the tentative final monograph's list of GRAS/E active ingredients. In the tentative final monograph preamble, FDA stated that it was denying a commenter's request to classify zinc oxide as a GRAS/E active sunscreen ingredient – despite its long history of use in OTC sunscreens – because there was insufficient evidence in the OTC review record to establish its effectiveness.[81] We later received additional efficacy data and, in 1998, amended the tentative final monograph to include zinc oxide as a monograph active ingredient.[82] In the accompanying preamble, FDA specifically noted that it had reviewed products containing "fine particle size" zinc oxide and found them to be safe and effective.[83] The reported particle size range of the ingredient(s) in question was 10-70 nm (with an average of 30 nm).[84]

In 1999, we published a final sunscreen monograph (the 1999 final monograph) listing both titanium dioxide and zinc oxide as active ingredients.[85] Although the text of the final monograph makes no reference to particle size, the accompanying preamble stated that FDA had reviewed data on sunscreen drug products containing "micronized" titanium dioxide and found them to be safe and effective.[86] It further stated that:

> [t]he Agency is aware that sunscreen manufacturers are using micronized titanium dioxide to create high SPF products that are transparent and esthetically pleasing on the skin. The Agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed by the Panel. . . . Based on data and information presented at the

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[78] Panel Report, 43 FR 38219.
[79] Skin Protectant Drug Products for Over-the-Counter Human Use – Establishment of a Monograph; Notice of Public Rulemaking, 43 FR 34628 (August 4, 1978).
[80] Sunscreen Products for Over-the-Counter Human Use; Tentative Final Monograph; Proposed Rule, 58 FR 28194 (May 12, 1993).
[81] Tentative final monograph, 58 FR 28194 at 28213.
[82] 63 FR 56584 (October 22, 1998) (Tentative final monograph amendment).
[83] Tentative final monograph amendment at 56585.
[84] *Id.*
[85] Sunscreen Products for Over-the-Counter Human Use; Final Monograph, 64 FR 27666 (May 21, 1999) (1999 final monograph). Although indefinitely stayed as discussed above, the text of the 1999 final monograph appears at 21 CFR part 343.
[86] 1999 final monograph, 64 FR 27671 (Comment 19). Your petition states in connection with this discussion that "it is unclear whether the Agency intended 'micronized' to encompass engineered nanoparticles or not," and asks us to clarify this point. Petition at 48 and 52. Although the submission to FDA described the products as containing "micronized" titanium dioxide, it did not contain further information on the ingredient's particle size.

> September 19 and 20, 1996 public meeting on the photobiology and photochemistry of sunscreens, the Agency is not aware of any evidence at this time that demonstrates a safety concern from the use of micronized titanium dioxide in sunscreen products.[87]

The effective date for complying with the 1999 final monograph was later extended and then stayed indefinitely to provide time to resolve various outstanding issues, none of which required FDA to revisit the list of active ingredients included in the final monograph.[88] Accordingly, under the OTC sunscreen enforcement policy, FDA has not objected and does not currently object to the marketing of products containing the active ingredients titanium dioxide or zinc oxide, regardless of particle size, without approved NDAs.

On August 28, 2007, after considering the information and comments from the 2006 Public Meeting, FDA published a *Federal Register* notice (proposed final monograph amendment) addressing several OTC sunscreen issues (the 2007 Sunscreen Notice).[89] As part of that notice, and expressly acknowledging your petition, we stated:

> FDA addressed issues concerning micronized sunscreen ingredients in the final monograph. The final monograph stated that FDA did not consider micronized titanium dioxide to be a new ingredient but rather a specific grade of the same active ingredient. The final monograph also stated that FDA was aware of concerns about potential risks associated with increased dermal penetration of such small particles. However, the final monograph explained that, based on the safety data submitted to FDA before publication of the final monograph, FDA was not aware of any evidence at that time demonstrating a safety concern from the use of micronized titanium dioxide in sunscreen products.
>
> FDA recognizes that more sunscreens containing small particle size titanium dioxide and zinc oxide ingredients enter the market each year. FDA is interested in receiving comments and data about these sunscreen ingredients and products that contain these ingredients, their safety and effectiveness, and how they should be regulated. FDA received a citizen petition shortly before publication of this document that, among other things, raises these issues. FDA is currently evaluating the citizen petition, which is filed as CP17 in the OTC sunscreen docket. FDA encourages other parties to submit additional data or information on

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[87] *Id; see also id.* at 27672 (noting that micronized titanium dioxide met current United States Pharmacopeia (USP) monograph specifications except for containing more associated water, which FDA would work with USP to amend).

[88] *See* Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph; Extension of Effective Date; Reopening of Administrative Record. 65 FR 36319 (June 8, 2000) (notice of initial extension); Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph; Partial Stay; Final Rule, 66 FR 67485 (December 31, 2001) (notice of indefinite stay). FDA issued the stay to provide additional time to address other issues, such as the formulation, labeling, and testing of finished sunscreen drug products.

[89] Sunscreen Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph, 72 FR 49070 (August 27, 2007). This call for data did not specify a closing date, and thus is still open.

> the safety and effectiveness of sunscreen ingredients formulated in particle sizes as small as a few nanometers.[90]

Thus, as your petition requested, the 2007 Sunscreen Notice reopened the OTC monograph sunscreen docket and invited interested parties to submit comments and data about the safety, efficacy, and regulatory status of sunscreen drug products containing small particle size titanium dioxide and zinc oxide.

As part of its ongoing nanotechnology activities, FDA convened two public meetings, in 2006 and in 2008. Both meetings were preceded by public notices that included calls for data on the use of nanotechnology in drug products, and the 2008 meeting notice specifically invited data relevant to the safety and efficacy of "over-the-counter drugs, including sunscreens." The safety and effectiveness of nanomaterial active ingredients in sunscreen drug products were specifically addressed at these meetings, and pertinent information and comments (including information presented by petitioner ICTA) were included in the record of the OTC sunscreen review as well as the pertinent public meeting records.

2. FDA's Preliminary Assessment of Potential Hazards Relating to Use of OTC Sunscreen Drug Products Containing Titanium Dioxide or Zinc Oxide Nanomaterials

In accordance with its ongoing oversight of all marketed drugs, and as part of the ongoing OTC Drug Review for sunscreens, FDA has reviewed not only the information addressing sunscreens containing titanium dioxide and zinc oxide nanomaterials provided in your petition,[91] but also relevant information from other available sources, including its own research. As explained in detail in our responses to your requests 7 & 8 below, we have reviewed scientific data available to date on nanomaterials in OTC sunscreens, and the evidence does not suggest that use of sunscreens containing titanium dioxide or zinc oxide nanomaterials presents a public health hazard.[92] However, there is not currently an effective final monograph setting forth all of the GRAS/E conditions for OTC sunscreens. The determination of monograph conditions for sunscreens will be based in part on our evaluation of additional data submitted in response to a forthcoming call for data regarding the safety of sunscreen active ingredients.[93] Given the absence of evidence to date demonstrating a significant potential risk, and the demonstrated health benefits of regular sunscreen use,[94] we believe that the products at issue can and should

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[90] 2007 Sunscreen Notice at 49110.

[91] Your petition states that it did not attempt to provide "all the relevant information regarding sunscreens made of engineered nanoparticles of zinc oxide and titanium oxide," choosing instead to rely on the request to reopen the administrative record to supply that information. Petition at 49.

[92] We use this term to encompass generally your contentions that sunscreens containing titanium dioxide or zinc oxide nanomaterials pose an immediate harm that merits action to remove them from the market, even during the pendency of the OTC drug review proceeding.

[93] *See* 77 FR 7949 (February 13, 2012); *See also* 76 FR 35619 at 35621-22 (June 17, 2011) (noting that issues regarding safety of sunscreen active ingredients, raised in comments received on 2007 proposed rule, would be addressed in a future rulemaking).

[94] Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use. Final Rule. 76 FR 35620 at 35630-34 (June 17, 2011).

remain available for use by the public while FDA completes its consideration of these products under the OTC Drug Review.

C. FDA Response to Specific Requests on OTC Sunscreen Drug Products

1. FDA's response to requests 5 through 8

> *5. Petitioners request that the Agency 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.*

This request has been granted. Your petition (together with related attachments, supplemental information, and public comments) has been included in the record of the ongoing OTC sunscreen review. As detailed in section III.B.1, in 2007 we also published a notice in which we requested data and information and reopened the record of the OTC sunscreen review proceeding for the purpose of obtaining additional information on nanoparticulate zinc oxide and titanium dioxide used as active sunscreen ingredients from any interested parties.[95] The calls for data that we issued in connection with the 2006 and 2008 Public Meetings also considered the OTC sunscreen issues raised in your petition, and pertinent information from those meetings has been entered into the OTC sunscreen review record for Agency consideration.

Therefore, your request that the Agency reopen the administrative record for the OTC sunscreen monograph has already been granted through previous Agency actions.

> *6. Petitioners request that the Agency 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.*

This request is denied at this time. As noted in our response to request 5, we have granted your request to reopen the administrative record of the OTC Sunscreen Monograph proceeding, not only to admit the information that you submitted, but also to obtain and consider other additional information regarding sunscreens containing titanium dioxide and zinc oxide nanomaterials.[96]

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[95] 2007 Sunscreen Notice, *supra* note 89.

[96] In addition to arguing that nanoparticle zinc oxide and titanium dioxide are inherently unsafe for use in OTC sunscreens, the petition maintains that the "fundamental and potentially dangerous differences between engineered nanoparticles and larger particles of the same bulk materials" cause sunscreens containing nanoscale zinc oxide or titanium dioxide to be novel substances and therefore "new drugs" within the meaning of 21 USC 321(p) and 355(a). Petition at 54. You further argue that "this decision on new drug status is also one separate from the Monograph, which the Agency could make in another form like an advisory opinion, separate rule, or interpretive/guidance document." Petition at 54-55. We decline at this time to declare categorically that titanium dioxide and zinc oxide nanomaterials cannot be included in the sunscreen monograph based on their asserted "fundamental" differences from the larger particles of the same ingredients used in historically marketed sunscreen

We will continue to monitor and/or participate in relevant ongoing research. We will also take further rulemaking action, as needed, to formalize the regulatory requirements for OTC sunscreen drug products, either by amending the monograph or other means. You are invited to continue to participate in opportunities for public comment, including by contributing additional data to the record.[97]

In sum, in light of the ongoing OTC sunscreen monograph proceedings, we decline at this time to amend the OTC monograph to exclude sunscreen drug products containing engineered nanoparticles, as you requested.

> *7. Petitioners request that the Agency 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. Petitioners request that the Agency 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.*

Both your seventh and eighth requests ask FDA to take action to remove from the market all sunscreen drug products that contain titanium dioxide or zinc oxide nanomaterials until certain conditions are satisfied, although these requests call for using different regulatory mechanisms to achieve these goals, and propose different sets of conditions for returning the products to the market. However, both requests are premised on the notion that use of these sunscreens presents a current public health hazard.

These two requests are denied. First, we decline to initiate broad, categorical actions to remove these products from the market as requested because, as we explain below, in our judgment, the evidence presented in your petition does not indicate a public health hazard from these products that would justify such action.[98] Nor does any other information currently available to the Agency, including that obtained from the Agency's own research, justify such action. Indeed,

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drug products. As detailed in section II above, FDA declines, at this time, to issue new regulations requiring that all nanoparticles be treated as new substances. Rather, we will determine on a case-by-case basis whether and how specific nanotechnology applications alter a drug product's regulatory status. As described above, we have requested data in the past on the safety and regulatory status of sunscreens containing zinc oxide or titanium dioxide nanomaterials as part of the ongoing OTC sunscreen review, and we intend to issue a further data request regarding sunscreen active ingredients. The arguments and evidence in your petition have also been made part of the OTC review record. Therefore, we have concluded that the issues raised in your petition can be adequately and most efficiently considered in the framework of the ongoing monograph proceeding.

[97] *See* 77 FR 7949 (February 13, 2012).

[98] Our denial of your request for categorical actions to remove certain sunscreens from the market at this time does not suggest that the agency will not take individual enforcement actions if merited. *See* our discussion of our current enforcement policy above, in section III.B.1 and *supra* note 75.

the public health benefits of regular sunscreen use are well-established.[99] Second, neither of the specific mechanisms you suggest is available or appropriate to achieve the end result you seem to desire: the market removal of OTC sunscreens that lack individual approved NDAs or ANDAs.

a. FDA's Evaluation of Potential Hazards Relating to Use of OTC Sunscreen Drug Products Containing Titanium Dioxide or Zinc Oxide Nanomaterials

OTC sunscreens are labeled and intended for topical administration, and their route of exposure is primarily dermal. [100] For this reason, a primary consideration for assessing whether use of sunscreens, including those containing titanium dioxide or zinc oxide nanomaterials, presents a public health hazard, is to determine whether those materials, when incorporated into sunscreens, penetrate into or beyond the stratum corneum (the non-living outer surface of the skin) into the dermis (inner levels of the skin) or beyond to other body systems.

i. FDA's Review of Available Scientific Literature

FDA experts have reviewed the published scientific literature and other available information on the dermal penetration of titanium dioxide and zinc oxide nanomaterials used as active ingredients in sunscreen drug products, including all of the pertinent articles cited in your petition. Neither the materials provided in your petition, nor other scientific literature we have reviewed to date, currently indicates that topical use of sunscreens containing titanium dioxide or zinc oxide nanomaterials presents a public health hazard.

FDA identified and reviewed 17 published studies and four review articles on dermal penetration of titanium dioxide nanomaterials in sunscreens.[101] With a single exception, all of these studies

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[99] Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use. Final Rule. 76 FR 35620 at 35630-34 (June 17, 2011).

[100] Some OTC sunscreen drug products are available in a spray dosage form and thus may potentially be unintentionally inhaled during application to the skin. At present, there is insufficient data on spray sunscreen products to establish final monograph conditions for these products. Accordingly, we have requested additional data on the safety and effectiveness of sunscreens in spray dosage form, including sunscreens containing titanium dioxide or zinc oxide as active ingredients. *See* 76 FR 35669 (June 17, 2011). Data submitted in response to that notice will be evaluated and taken into consideration as we determine final monograph conditions for these ingredients.

[101] Sadrieh, N, et al., 2010. Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO2 particles. Toxicol. Sci, 115: 156-166; Senzui, M, et al. 2010. Study on penetration of titanium dioxide (TiO2) nanoparticles into intact and damaged skin in vitro. The Journal of Toxicological Sciences, 35: 107-113; Durand, L et al., 2009. In vitro evaluation of the cutaneous penetration of sprayable sunscreen emulsions with high concentrations of UV filters. Int J Cosmet Sci, 31: 279–292; Wu, et al. 2008. Toxicity and penetration of TiO2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. Toxicology Letter, 191: 1-8; Jonaitis, et al. 2010. Concerns regarding nano-sized titanium dioxide dermal penetration and toxicity study, Letter to the Editor re: Wu, et al. Toxicology Letter, 192(2): 268; van der Merwe, D., et al. 2009. Nanocrystalline titanium dioxide and magnesium oxide in vitro dermal absorption in human skin. Cutaneous and Ocular Toxicology, 28(2): 78–82; Kiss, B., et al. 2008. Investigation of micronized titanium dioxide penetration in human skin xenografts and its effect on cellular functions of human skin-derived cells. Experimental Dermatology, 17: 659–667; Mavon, A., et al. 2007. In vitro Percutaneous Absorption and in vivo Stratum Corneum Distribution of an Organic and a Mineral Sunscreen. Skin Pharmacol Physiol, 20:10-20; University of Leipzig-NANODERM. Quality of Skin as a Barrier to ultra-fine Particles, available on-line (http://www.uni-leipzig.de/~nanoderm/ Downloads/Nanoderm_Final_Report.pdf); Gamer, A., et al., 2006. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicology in Vitro, 20: 301-307; Popov, A., et al.

indicate that titanium dioxide nanomaterial does not penetrate intact skin. The one study in which the authors did postulate a concern concluded, based on animal models, "that nanosize titanium dioxide may pose a health risk to humans after dermal exposure over a [sic] relatively long time."[102] Other researchers, however, subsequently questioned the design and conclusion of this study on methodological grounds.[103] The tentative conclusion from FDA's review of literature available to date is that some titanium dioxide can be detected down to the dermis, but there is minimal evidence of the further penetration down to the capillary beds that would be necessary for systemic delivery to the organs where it could potentially have deleterious effects.[104] In sum, currently available literature indicates that insoluble nanomaterials of titanium dioxide used in sunscreens do not penetrate into or through human skin to produce adverse health effects when applied topically.

Although not quite as abundant in the literature as titanium dioxide studies, there are numerous reports examining the dermal penetration of zinc oxide nanomaterials. FDA reviewers examined nine primary research articles covering a range of zinc oxide nanomaterial sizes, coatings, formulations, and model systems.[105] No significant penetration of zinc oxide nanomaterials was

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2005. Effect of size of TiO2 nanoparticles embedded into stratum corneum on ultraviolet-A and ultraviolet-B sun-blocking properties of the skin. J. Biomed. Opt., 10(6): 064037-1–064037-9; Menzel, F, et al. 2004.Investigations of percutaneous uptake of ultrafine TiO2 particles at the high energy ion nanoprobe LIPSION. Nucl. Instr. Meth. Phys. Res. B, 219-220: 82–86; Schulz, J, et al. 2002. Distribution of sunscreens on skin. Advanced Drug delivery Reviews, 54 (Suppl): S157-S163; Pflucker, F, et al. 2001. The Human Stratum corneum Layer: An Effective Barrier against Dermal uptake of Different Forms of topically Applied Micronised Titanium Dioxide. Skin Pharmacol Appl Skin Physiol, 14 Suppl 1: 92-97; Bennat, C. and Müller-Goymann C. 2000. Skin Penetration and Stabilization of formulations containing microfine titanium dioxide as a physical UV barrier. Int J Cosmet Sci, 22(4): 271-283; Pflucker, F, et al. 1999. The outermost stratum corneum layer is an effective barrier against dermal uptake of topically applied micronized titanium dioxide. Int J Cosmet Sci., 21(6):399-411; Lademann, J., et al. 1999. Penetration of Titanium Dioxide Microparticles in a Sunscreen Formulation into the Horny Layer and the Follicular Orifice. Skin Pharmacol Appl Skin Physiol, 12(5): 247-256; Dussert, et al. 1996. Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. Int J Cosmet Sci, 19(3): 119-129; Crosera, M, et al. 2009. Nanoparticle dermal absorption and toxicity: a review of the literature. Int Arch Occup Environ Health, 82(9): 1043-1055; Newman, M, et al. 2009. The safety of nanosized particles in titanium dioxide- and zinc oxide-based sunscreens. J Am Acad Dermatol, 61(4): 685-692; Australia Therapeutic Goods Administration Report, A review of the scientific literature on the safety of nanoparticulate titanium dioxide or zinc oxide in sunscreens, available on-line (http://www.tga.gov.au/pdf/review-sunscreens-060220.pdf); Nohynek, G, et al. 2008. Nanotechnology, cosmetics and the skin: is there a health risk? Skin Pharmacol Physiol, 21(3): 136-149.

[102] Wu et al, 2008, *id.* note 101.

[103] Jonaitis et al, 2010, *id.* note 101. After FDA's attempts to contact Dr. Wu were unsuccessful, FDA concluded that the Wu study was flawed and did not support the authors' conclusions.

[104] The only potentially viable pathway for penetration of the stratum corneum is via an empty hair follicle or glandular duct; however, even where this was seen, the amount deposited was small and did not penetrate to deeper skin structures. Senzui et al., 2010; Bennat and Müller-Goymann, 2000; Lademann et al., 1999, *id.* note 101.

[105] Cross, S, et al. 2007. Human skin penetration of sunscreen nanoparticles: in-vitro assessment of a novel micronized zinc oxide formulation. Skin Pharmacology and Physiology, 20: 148-154; Durand, L, et al. 2009. In vitro evaluation of the cutaneous penetration of sprayable sunscreen emulsions with high concentrations of UV filters. International Journal of Cosmetic Science, 31: 279-292; Dussert, A, et al. 1996. Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. Int J Cosmet Sci, 19: 119-129; Filipe, P, et al. 2009. Stratum corneum is an effective barrier to TiO_2 and ZnO nanoparticle percutaneous absorption. Skin Pharmacology and Physiology, 22: 266-275; Gamer, A, et al. 2006. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicology in Vitro, 20: 301-307;

observed in any of those studies. In the most definitive study to date, Monteiro-Riviere et al. examined two forms of zinc oxide nanomaterials found in commercial sunscreens using a porcine model. Sunscreen formulations were applied to unmodified skin and UVB sunburned skin. Both *in vitro* and *in vivo* models were utilized and dermal penetration was studied using microscopy and elemental detection techniques. Although UVB sunburn increased the penetration of the zinc oxide nanomaterials into the stratum corneum, the authors found minimal penetration of the nanomaterials into the epidermal and dermal layers of the skin.[106]

Other *in vitro* and *in vivo* studies have examined the permeability of zinc oxide nanomaterials in human skin. Transmission electron microscopy indicated that the zinc oxide nanoparticles remained at the surface of the skin or in the upper stratum corneum.[107] *In vivo* human studies also indicate that zinc oxide nanomaterials do not penetrate into viable skin.[108] In the only study where penetration through the dermis was observed, the zinc oxide nanoparticles were 10 nm in diameter and were formulated with the known penetration enhancers, ethanol and oleic acid.[109] The authors concluded that although the permeability enhancers allowed the nanoparticles to diffuse into the stratum corneum with greater ease, the particles did not penetrate significantly beyond the stratum corneum. In sum, currently available literature indicates that zinc oxide nanomaterials used in sunscreens do not penetrate into or through human skin to produce adverse health effects when applied topically.

ii. Relevant FDA Research on Sunscreens Containing Titanium Dioxide and Zinc Oxide Nanomaterials

To evaluate whether titanium dioxide nanomaterials in sunscreens penetrate the skin, FDA conducted a study to examine dermal penetration of formulated sunscreens containing three types of titanium dioxide nanomaterials (coated nanoparticles, uncoated nanoparticles, and "submicron" particles; particle size ranged from 20-500 nm). Following 4 weeks of topical application of sunscreens to minipigs, various tissues and organs were analyzed for the presence and levels of nanomaterials. No significant increases in titanium dioxide were seen in tissues and organs harvested (with the exception of the skin). Extensive analysis was performed on the skin. Titanium dioxide nanomaterials were found in the stratum corneum and upper follicular lumens. Although isolated nanomaterials were present in various locations in the dermis, the lack of pattern to their distribution indicated sample contamination rather than actual penetration of the particles. In addition, the few isolated particles that were identified in the dermis layer

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Gulson, B, et al. 2010. Small amounts of zinc from zinc oxide particles in sunscreens applied outdoors are absorbed through human skin. Toxicological Sciences, 118: 140-149; Kuo, T.R, et al. 2009. Chemical enhancer induced changes in the mechanisms of transdermal delivery of zinc oxide nanoparticles. Biomaterials, 30: 3002–3008; Lansdown, A, and Taylor, A. 1997. Zinc and titanium oxides: promising UV-absorbers but what influence do they have on intact skin? Int J Cosmet Sci, 19: 167-172; Monteiro-Riviere, N, et al. 2011. Safety evaluation of sunscreen formulations containing titanium dioxide and zinc oxide nanoparticles in UVB sunburned skin: an *in vitro* and *in vivo* study. Toxicological Sciences, 123(1): 264-280.

[106] Monteiro-Riviere et al, 2011, *id.* note 105.

[107] Cross et al., 2007; Dussert et al., 1997, *id.* note 105.

[108] Filipe et al., 2009, *id.* note 105. A second in vivo study examined zinc levels in blood and urine after zinc oxide nanoparticle sunscreen application but did not examine if the observed elevated zinc levels came from the nanoparticles or elemental zinc. Gulson et al, 2010, *id.* note 105.

[109] Kuo et al., 2009, *id.* note 105.

represented a tiny fraction of the total amount of applied titanium dioxide nanomaterials. The authors concluded that titanium dioxide nanomaterials in sunscreens lack significant dermal penetration.[110] In another FDA *in vitro* laboratory study, sunscreen formulations containing titanium dioxide or zinc oxide nanomaterials were found not to enhance the permeability of the skin barrier in either normal or sunburned skin models.[111] Overall, results from these studies indicate that titanium dioxide nanomaterials found in sunscreens do not cross the skin barrier in any significant amount.

In sum, the evidence available at this time does not suggest that use of sunscreens containing titanium dioxide or zinc oxide nanomaterials presents a public health hazard. Rather, the current weight of evidence suggests that, when used in sunscreens, neither titanium dioxide nor zinc oxide nanomaterials penetrate significantly beyond the outside layers of the skin.[112] Moreover, the public health benefits of regular sunscreen use are well-established.[113]

b. The specific actions you request are not appropriate or available

As already noted, your requests seek specific actions that are not available or appropriate to achieve the end result you seem to desire: the market removal of OTC sunscreens that lack individual approved NDAs or ANDAs. In request 7, although you state that FDA should "order entities using [engineered nanoparticles of zinc oxide and titanium dioxide] in sunscreens regulated by FDA to cease manufacture," you cite no legal provision authorizing such an order. In fact, with respect to drugs, the "imminent hazard" standard[114] that you refer to as the apparent basis for an order to cease manufacture is applicable only in the context of administrative

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[110] Sadrieh N, Wokovich AM, Gopee NV, Zheng J, Haines D, Parmiter D, Siitonen PH, Cozart CR, Patri AK, McNeil SE, Howard PC, Doub WH, Buhse LF. 2010. Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size titanium dioxide particles. Toxicol. Sci, 115: 156-166.

[111] Tyner, KM, Wokovich, AM, Godar, DE, Doub, WH, Sadrieh, N. 2011. The state of nano-sized titanium dioxide (TiO_2) may affect sunscreen performance. Int J Cosmet Sci, 33(3): 234-244.

[112] Your petition references a variety of specific potentially toxic effects, including intracellular damage due to the formation of free radicals, which you posit may result if zinc oxide or titanium dioxide nanomaterials in sunscreens migrate into skin cells or penetrate deeper into the body. *See, e.g.,* Petition at 17-19, 58-59, 62-63. The scientific literature cited in your petition is part of the OTC sunscreen record, and will be considered together with future pertinent data submissions in establishing final monograph conditions for sunscreens. However, based on currently available evidence, we do not believe that topical use of sunscreens containing titanium dioxide or zinc oxide nanomaterials poses a public health hazard meriting action to categorically remove these products from the market during the pendency of the monograph proceeding.

[113] Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use. Final Rule. 76 FR 35620 at 35630-34 (June 17, 2011).

[114] *See* 21 CFR 2.5.

proceedings to revoke *an approved NDA*,[115] not with regard to OTC monograph products, and in any case is not satisfied by currently available evidence.[116]

With respect to request 8, FDA lacks authority to *require* drug recalls, and the decision of whether to request a recall is within the agency's discretion.[117] Under FDA's policy on voluntary recalls, "a request by FDA that a firm recall a product is reserved for urgent situations," and the agency considers, among other things, whether "an agency action is necessary to protect the public health and welfare."[118] Based on our review of the scientific data currently available for OTC sunscreens containing titanium dioxide or zinc oxide nanomaterials, we do not agree that an FDA-requested recall is appropriate at this time.

In sum, your petition does not provide an adequate basis for FDA to take actions now to remove OTC sunscreens containing titanium dioxide and zinc oxide nanomaterials from the market. Indeed, as a matter of science and regulatory policy, FDA has determined that the most appropriate course of action at this time is to continue to examine the safety of sunscreens containing titanium dioxide and zinc oxide nanomaterials in the context of the OTC sunscreen review and FDA's ongoing nanotechnology activities. The decision whether to take or refrain from taking such an action falls squarely within the Agency's enforcement discretion. Moreover, such an action may not be requested in a citizen petition.[119]

Therefore, we deny your requests to declare all sunscreen drug products containing engineered nanomaterial forms of zinc oxide or titanium dioxide to be an imminent public health hazard and to order their manufacture to cease, and to seek recall of all such products.

IV. CONCLUSION

FDA understands the concerns raised in your petition, including the need for appropriate regulatory oversight of nanotechnology products, in general, and nanotechnology applications in

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[115] *See* 21 U.S.C. 355(e) (authority to withdraw approved application on safety grounds); 21 CFR 314.150(a)(1) (regulatory procedure for withdrawing an approved application following "imminent hazard" finding). Further, we note that the finding of "imminent hazard" is not the finding required to authorize withdrawal of an approved application, but rather is the standard under which, in the Secretary's discretion, an approval may be suspended during the pendency of a withdrawal proceeding. *See* section 505(e) ("if the Secretary . . . finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately").

[116] *See* 21 CFR 2.5(a) ("imminent hazard" finding requires at minimum "sufficient evidence to show that a product or practice . . . pos[es] a "significant threat of danger to public health").

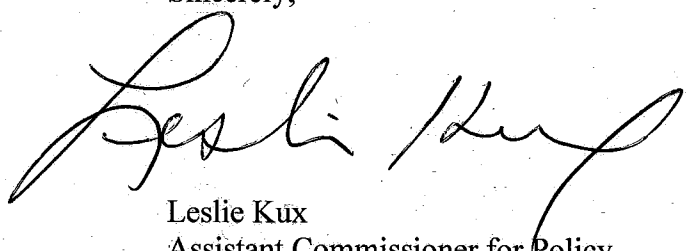
[117] *See* 21 CFR 7.45(a) (describing when FDA "may" request a firm to initiate a recall).

[118] *See* 21 CFR 7.40(b), 7.45(a)(3).

[119] Under 21 CFR 10.30, a person may petition the Agency to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of administrative action. FDA regulations at 21 CFR 10.3 define "administrative action" as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral." Similarly, under 21 CFR 10.30(k), citizen petitions may not be used with respect to "referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence."

sunscreens, in particular. As discussed above, FDA has granted your request to reopen the record for the OTC sunscreen monograph, and you are invited to participate in that ongoing public process. The data and information in your petition are not sufficient to support the other specific actions requested in your petition, however, and we are therefore denying these requests in accordance with 21 CFR 10.30(e)(3). Rather, as a matter of science and regulatory policy, the Agency concludes that the best course at this time is to continue to pursue its ongoing scientific research and regulatory approach for addressing the applications of nanotechnology in FDA-regulated products, including examination of the safety of sunscreens through the OTC drug review. FDA is performing, monitoring, and reviewing new studies and data as they become available, and depending on the results, any such information could influence FDA's assessment and future regulatory decisions regarding any FDA-regulated product involving the application of nanotechnology.

Sincerely,



Leslie Kux
Assistant Commissioner for Policy