American Chemistry Council | Nanotechnology Panel

July 24, 2012

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

SUBMITTED ELECTRONICALLY TO DOCKET FDA–2011–D–0489

Re: Draft Guidance for Industry: Safety of Nanomaterials in Cosmetic Products (FDA–2011–D–0489)

To Whom It May Concern:

The Nanotechnology Panel of the American Chemistry Council appreciates the opportunity to submit comments on the Food and Drug Administration's (FDA) draft guidance to industry titled "Guidance for Industry: Safety of Nanomaterials in Cosmetic Products."[1] The Panel appreciates that the FDA has described its current thinking on oversight of the use of nanomaterials in cosmetics. The Panel concurs with FDA on the benefits nanomaterials and nanotechnology can provide. The benefits are based on the properties of the materials, which includes size. The Panel notes that while the size of nanomaterials is a property of special focus, the concept of considering the relationship between physical properties (including size) and benefits is a long-standing practice.

The Panel appreciates FDA's wisdom in not publishing prematurely regulatory definitions for terminology related to nanomaterials and nanotechnology in cosmetics. Regulatory agencies in many countries and regions have struggled with regulatory definitions. Because definitions are often intended to provide focus on subjects of potential regulatory interest, it may be necessary to use different definitions in different regulatory contexts in order to provide sufficient focus on a given topic. Thus a single definition is not practical at this time. The Panel recommends that FDA consider providing a definition that makes clear whether a material that may be referred to as a "nanomaterial" is of regulatory interest in the context of cosmetic ingredient oversight. Drawing from the elements of a regulatory definition of manufactured nanomaterial developed by the International Council of Chemical Associations (ICCA),[2] as

[1] Noticed in the Federal Register of April 25, 2012 (Volume 77, number 80).
[2] International Council of Chemical Associations. ICCA Core Elements of a Regulatory Definition of Manufactured Nanomaterials. November 22, 2010. See www.icca-chem.org/en/Home/Policy/.

Members of the ACC Nanotechnology Panel are BASF Corporation, Bayer MaterialScience, Cabot Corporation, Cytec Industries, The Dow Chemical Company, DuPont, Evonik Degussa Corporation, Ferro Corporation, Lockheed Martin Corporation, Procter & Gamble, and 3M.

The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $720 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

well as some additional considerations that provide greater focus, the Panel submits that FDA should implement the following considerations in order to clarify the materials that would be affected:

- Solid, particulate substances
- Intentionally manufactured at the nano-scale
- Consisting of nano-objects as defined by the International Standards Organization (ISO),[3] but without the word "approximately" to describe the size range. As discussed below, the Panel believes that for regulatory purposes, the ambiguity introduced by "approximately" will be problematic. Any meaningful compliance or enforcement standard based on particle size depends on the ability to measure with known accuracy and precision, an issue addressed in subsequent paragraphs. The Panel therefore recommends setting a lower limit of 1 nm and an upper limit of 100 nm.
- A mass-based cutoff for ISO nanomaterial content (per the previous bullet) to provide increased clarity on what is in scope and to ensure focus on those materials that have been the subject of nanomaterial discussions.
- Consideration of aggregates and agglomerates of nanomaterials
- Exclusion of aggregates/agglomerates if they cannot be readily broken down into nano-objects.

The Panel has taken note of the recent *Science* article by Commissioner Hamburg[4] in which she described three areas of interest to FDA regarding nanomaterials:

1. Identifying Nanomaterials for Regulation

The Panel notes that the category of nanomaterials includes many materials: new materials for which it is clear that new information is likely to be needed to assess safety, legacy materials that were nanomaterials before the word had been coined, and modified forms of existing materials where the nanoform may be new but the chemical composition is not. Each of these scenarios may benefit from different review processes where for new materials a thorough data set may need to be generated, for legacy materials no additional information may be needed and for new nanoforms of existing materials the amount of data needed could be somewhere in between.

2. Evaluating Products Containing Nanomaterials

The Panel is a strong proponent of sound characterization of nanomaterials and this is discussed further below. The Panel also recognizes that the science and technology of characterizing nanomaterials is still developing in both the physical and biological fields. Thus, all of the test results suggested in the guidance may not be reasonably or practically obtainable in every product. The Panel suggests that FDA may wish to identify tiers of tests based on whether or not methods are readily available and the applicability of the data to the use and exposure patterns of products.

3. Ensuring a Responsive Regulatory Framework

We appreciate that FDA clearly acknowledges that the generation of new information and data is likely to result over time in different conclusions in how FDA views nanomaterials in general as well as individual nanomaterials. The Panel also appreciates FDA's intent to be flexible in its approach to the application of its regulatory authorities, taking into account what it will be learning. To make FDA's regulatory

[3] International Organization for Standards. 2008. Nanotechnologies—Terminology and definitions for nano-objects—Nanoparticle, nanofibre and nanoplate. TS 27687:2008. The Panel notes that TS 27687 is currently under systematic review and that changes may be made in the future.
[4] Hamburg, M.A. 2012. FDA's Approach to Regulation of Products of Nanotechnology. Science 336:299-300.

processes as transparent as possible, the Panel requests that FDA be proactive in communicating to all stakeholders what it has learned and how that information will be applied in the regulatory decision-making process.

The Panel appreciates FDA's policy of maintaining an open door for regulated entities to meet with the agency to resolve questions and gain alignment on safety evaluations for all products and ingredients under its jurisdiction. It is particularly appropriate that the draft cosmetics guidance document continues to encourage these types of conversations considering the use of nanomaterials in cosmetic applications. The Panel trusts the FDA has the resources to engage in these types of conversations in a timely manner.

Manufacturers of cosmetic products are responsible for their products. This is appropriate for many reasons. The manufacturer is the most familiar with the ingredients, the ingredients' properties, and use and exposure patterns associated with the product. Manufacturers consider these factors in the product development process and evaluate safety before products enter the marketplace. Put simply, unsafe products will not be tolerated by customers, and cosmetics manufacturers go to great lengths to evaluate both safety and performance. It is appropriate to put manufacturers on the front lines of safety assurance, backed by FDA's regulatory authorities.

The Panel supports the approach described in FDA's June 2011 draft guidance "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" [5] and how that guidance relates to the draft cosmetics guidance. Notably, the June 2011 guidance makes clear that products containing nanotechnology are neither benign nor harmful because of the use of this technology. The characteristics of a product itself should be the basis of evaluation. To support this position, the Panel notes that some ingredients used safely in cosmetic products for decades were nanomaterials long before word had been coined. The Panel notes that FDA intends to consider products containing particles up to 1 micron (1000 nm) as if they may contain nanomaterials. It is understood that this approach will appropriately include some aggregates and agglomerates. However, the Panel questions how FDA will distinguish between nanomaterials and non-nanomaterials when considering particles this large. Also, what differences does FDA intend to implement in its practices based on the distinction between nano and non-nano forms of substances? The Panel recommends that FDA provide additional clarity on these points.

The Panel appreciates that FDA intends to be available to discuss safety assessments of nanomaterials to be used in cosmetics, and we concur that some nanomaterials may have characteristics that require modifications to existing assessment practices. However, the Panel recommends that FDA take into account the available information for those ingredients already in commerce that supports a conclusion of safety. FDA should take advantage of this growing body of evidence and experience. The Panel noted FDA's willingness to work with cosmetic manufacturers when there is a need for clarity but is concerned it may result in an unnecessary drain on FDA resources and set unwarranted expectations for industry to request meetings with FDA every time a nanomaterial is used in a cosmetic product.

The Panel strongly supports the need for thorough characterization of nanomaterials and appreciates that FDA has referred to the work of the Working Party on Manufactured Nanomaterials (WPMN) of the Organization for Economic Co-operation and Development (OECD) as a source of information. It is also recognized that the processes used in the manufacture and processing of nanomaterials into cosmetic products can affect the performance of products. The Panel appreciates FDA's interest in learning more about these factors, which can often be the basis of a manufacturer's competitive advantage. However, if

[5] June 2011. Accessed July 17, 2012 at www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

it is deemed necessary for a manufacturer to share business sensitive manufacturing and processing information with FDA, FDA should be clear that it will not share that information with anyone who does not have a need to have it. This will include almost anyone outside of FDA and even many people within FDA. The Panel recognizes that there may be benefits to limited sharing within FDA and other Federal agencies and the Panel does not object to this, as long as the terms under which sharing will occur are clear and continue protections of confidential business information.

The Panel recognizes the need for and the value of the considerations listed in the draft guidance's section "Toxicology Considerations" (page 12) and that there may be needs to modify existing toxicology tests to account for the properties of some nanomaterials. The Panel appreciates that the intent of the listed tests is to provide guidance as to the type of methods available to generate information relevant to risk assessment. However, the Panel disagrees with the use of the types of tests described in the section as a minimum set of tests that should be conducted on all nanomaterials used in cosmetics. FDA has wisely acknowledged that each application of nanomaterials in cosmetics will have to be evaluated based on its own merits and use. A minimum data set undermines that scientific approach and could result in unnecessary testing or a false reliance on that list as sufficient demonstration of safety. As mentioned above, we recommend that FDA make clear that there can be a reasonable reliance on existing information when its applicability can be demonstrated.

The Panel also appreciates FDA's recognition that there are many ways to measure dose. There is no agreement within the scientific community on whether a single dose metric is appropriate for all nanomaterials in all cases.[6] There is good evidence that surface area is also a reasonable way to express dose and predict biological effects, and volume or surface-area-to-volume ratios may be appropriate in some cases.[7] Given this uncertainly, the Panel suggests that as a default, dose should be expressed in mass units. Mass is almost universally used to express dose because it can be used for comparison of effects across a broad range of materials. In addition, the analytical techniques available for estimating mass are more refined and provide better precision and reproducibility than methods for counting particles, particularly in a product matrix. While there is not yet agreement on a universally accepted means to express dose for nanomaterials, the OECD WPMN concluded that the best practice at this time is to express dose in terms of mass and include other metrics for dose when appropriate.[8]

As particles get smaller there may be more interactions between the surface of particles and the body. Some have stated that this potentiality argues for reliance on particle number as the appropriate metric. The Panel does not fully agree, though we understand the reasoning. Particularly in formulated cosmetic products, particles are likely to be widely distributed in an organic matrix that will decrease contact to a fair degree because of dilution and/or because the particles are coated. Combined with the difficulty of measuring numbers of particles in formulations, a reliance on particle number would create impractical requirements that would make compliance and verification of compliance unnecessarily burdensome and could result in the generation of data with questionable value. Mass-based doses are more reliably measured, though the exposure and dose may still be overstated, resulting in conservative assessments.

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[6] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Risk assessment of products of nanotechnologies, 19 January 2009. Available at ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf.

[7] Sayes, C.M. and Warheit, D.B. 2009. Characterization of nanomaterials for toxicity assessment, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 1(6): 660-670. See also SCENIHR report cited at 6.

[8] OECD Environment, Health and Safety Publications Series on the Safety of Manufactured Nanomaterials: Guidance Manual for the Testing of Manufactured Nanomaterials: OECD's Sponsorship Programme; First Revision, June 2, 2010, ENV/JM/MONO(2009)20/REV.

The Panel appreciates the potential value of *in vitro* and *in silico* tests, and we concur with FDA's concerns that such tests may not be reliable for insoluble particles, as many of these tests were developed for liquid and soluble species. For example, and as noted in the draft guidance, the bacterial reverse mutation test may not be suitable for particles.

The Panel disagrees with the recommendation that dermal absorption studies should be conducted on both intact skin and impaired skin for the reason that reproducible models of compromised skin are not available. This makes their use inappropriate for regulatory safety studies. Regulatory safety studies should be performed under standardized conditions to ensure reproducibility and comparison of results across studies and among laboratories. Compromised skin models generally do not provide the kind of reproducible conditions necessary to meet those standards. Instead, studies on intact, healthy skin are recommended.[9]

The study cited in the draft guidance document as justification for studies in impaired skin is a good illustration of the limitations in applying compromised skin models for dermal penetration studies in regulated studies. The model of compromise used, mechanical disruption of the *stratum corneum* through abrasion, is extremely variable in terms of depth of injury and area affected and does not model the types of impaired skin stated as important to the FDA (i.e., sunburned, atopic, eczematous, psotiatic skin).

Finally, the inclusion of information from compromised skin models is not likely to alter the decisions made during the risk assessments. Differences in dermal penetration between intact and compromised skin are generally modest and within the degree of variability accounted for in the uncertainty factors addressing intra-species variability. A recent review shows limited differences in dermal permeability when compromised skin is compared to healthy skin.[10] The Panel notes that FDA scientists evaluating titania penetration in sunscreen formulations used whole animals with intact skin.[11]

The Panel appreciates the opportunity to comment on this draft guidance. Should FDA consider developing additional guidance, the Panel encourages the continued use of science- and risk-based approaches to ensure the responsible development of nanotechnology in a way that will maximize its benefits while managing any potential risks to human health and the environment. If you have any questions, please contact me at Jay_West@americanchemistry.com or 202-249-6407.

Sincerely,

Jay West
Senior Director, Chemical Products and Technology Division
ACC Nanotechnology Panel

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[9] See several OECD references: OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects. Available at www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788; OECD Guideline for the Testing of Chemicals (OECD TG 427), Skin absorption: *in vivo* method, adopted 13 April 2004; OECD Guideline for the Testing of Chemicals (OECD TG 428), Skin absorption: *in vitro* method, adopted 13 April 2004.

[10] Gatu and Maibach (2011). Modest but Increased Penetration through Damaged Skin: An Overview of the *in vivo* Human Model. Skin Pharmacol Physiol, 24: 2–9.

[11] Sadrieh, N, Wokovich, A. M., Gopee, N. V., Zheng, J., Haines, D., Parmiter, D., Siitonen, P. H., Cozart, C. R., Patri, A., McNeil, S. E., Howard, P. C., Doub, W. H., Buhse, L. F. Lack of Significant Dermal Penetration of Titanium Dioxide from Sunscreen Formulations Containing Nano- and Submicron-Size TiO_2 Particles. Toxicol. Sci. (2010) 115(1): 156-166.