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–0490

Re: Draft Guidances for Industry: Assessing Effects of Significant Manufacturing Process Changes, Including Emerging Technologies on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances (FDA-2011-D-0490)

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American Chemistry Council appreciates the opportunity to submit comments on the Food and Drug Administration's (FDA) draft guidance to industry titled "Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of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."[1] The Panel appreciates that the FDA has described its current thinking on oversight of the use of nanomaterials in food substances. 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 premature regulatory definitions for terminology related to nanomaterials and nanotechnology in food substances. 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 food substance oversight. Drawing from the elements of a regulatory definition of manufactured

[1] Noticed in the Federal Register of April 25, 2012 (Volume 77, number 80).

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.

nanomaterial developed by the International Council of Chemical Associations (ICCA),[2] as 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. For new materials, a thorough data set may be needed. 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, which is discussed in more detail 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 draft 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

[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/.
[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.

The Panel appreciates FDA's clear acknowledgement that over time the generation of new information and data is likely to result in different conclusions in how the agency views specific nanomaterials and nanomaterials more generally. 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 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 supports the approach described in FDA's June 2011 draft guidance for industry "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology"[5] and how that guidance relates to the draft food substance guidance. Notably, the June 2011 draft guidance makes clear that products containing nanotechnology are not considered a *prioiri* to be either benign or 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 food products for decades, were nanomaterials long before word had been coined. The Panel also appreciates that FDA does not intend to bring into question existing ingredients for which some of the particle sizes extend into the nano-range. 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.

Clearly manufacturing processes are a focus of FDA with respect to food ingredients. FDA asks that changes in particle size be considered for potential impacts on good manufacturing practices and whether such changes could result in a conclusion of product adulteration. Unfortunately, this guidance is not sufficiently clear on when the agency will consider a change to be a significant manufacturing process change. For example, if the size of particles that start as 100 nm spheres are further reduced to 90 nm spheres, would the agency consider that a significant change? If not, what about 85 nm? If so, what is it about a 90 nm particle that leads to a conclusion of a significant change? For some aggregated/agglomerated materials the size of the primary particle may not change, but the density of the aggregate/agglomerate may change due to less space between primary particles. Is this significant? The Panel urges FDA to provide needed clarity on what does and does not constitute a significant manufacturing process change.

The Panel also requests clarification on another issue. In the draft guidance, FDA states, "To date, we have not, to our knowledge, received food or color additive petitions, or GRAS affirmation petitions or notices, for any uses of food ingredients with a particle size distribution fully in the nanometer range." (Page 14) While the Panel does not dispute that this is true, there are materials listed at 21 CFR Part 184[6] that may normally include fractions of their particle size distributions in the nanometer range and have included these fractions since their use began decades ago. Insoluble inorganic chemicals are the most likely to include such nanoscale fractions. If FDA's intent is only to consider materials for which all of the substance is in the nanoscale, this needs to be clarified.

[5] June 2011. Accessed July 17, 2012 at www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.
[6] Code of Federal Regulation Title 21. Chapter 21—Food and Drug Administration, Department of Health and Human Services. Subchapter B—Food for Human Consumption (Continued). Part 184—Direct Food Substances Affirmed as Generally Recognized as Safe.

Furthermore, the Panel suggests that an expansion of how FDA looks at the characterization of food substances as chemicals would be very helpful. Much of the draft guidance describes the authorities granted to FDA for the oversight of food substances and how those authorities are applicable to food substances that are nanomaterials. The Panel concurs. The draft guidance, beginning in Section III, discusses how for some materials a change in particle size can affect the performance and bioavailability of the material. Unlike the companion guidance document from FDA on nanomaterials in cosmetics, the draft food substance guidance does not address characterization in depth.

For some substances, particle size may be changed to take advantage of a limited change in performance. For example, a reduction in particle size of a somewhat soluble material may increase dissolution without changing any other property. Similarly, for an insoluble particle added to increase structure, a reduction in particle size may provide the same degree of increase but with relatively less additional mass. Following the examples provided in the Appendices of how FDA has viewed changes for other materials, it seems reasonable to conclude that in cases such as these, FDA will ultimately conclude that the particular allowances applied to the larger materials would apply to the smaller ones.

A characterization issue of particular interest to the Panel is how FDA views the relationship between "primary particles," aggregates, and agglomerates. The Panel recognizes that there terms are often used imprecisely and has concerns that imprecision could impact the quality of regulatory processes and decisions. The Panel recommends that FDA address this issue directly in future clarification of characterization.

The Panel supports FDA's ongoing practice of performing case-by-case risk-based reviews of the safety, effectiveness, and public health impacts of the diverse portfolio of products it regulates. The Panel appreciates that in the draft food guidance FDA invites the regulated community to meet with the agency frequently. The Panel believes those meetings would be more productive and efficient if the regulated entity better understands FDA's information needs and how that information will be used to evaluate the relationships among physical properties, performance and safety. With such clarity and understanding FDA and the regulated party could more rapidly conclude whether the nano-form of a material is equivalent to that described in existing authorizations or if the nano-form is a new food substance requiring a notification.

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