August 15, 2011

SUBMITTED ELECTRONICALLY TO DOCKET FDA–2010–D–0530

The Nanotechnology Panel of the American Chemistry Council appreciates the opportunity to comment on the draft guidance *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*.[1] The Panel recognizes that FDA is already evaluating nanotechnology-enabled products and appreciates that FDA is taking measures to ensure that the benefits of nanotechnology can be realized and that any potential health or safety concerns can be anticipated and minimized. The Panel believes that FDA has taken the appropriate step of issuing guidance instead of a regulation. This choice sends a strong signal that FDA is open to ongoing input and discussion around the use of nanotechnology-enabled products. Following the structure of the draft guidance, the Panel offers the comments below to inform and enhance FDA's process for considering whether FDA-regulated products include nanomaterials or otherwise involve nanotechnology. The Panel recommends that FDA consider the following:

SCOPE

The Panel supports the FDA approach of reviewing products that contain nanomaterials or otherwise involve nanotechnology on a case-by-case basis using existing review processes. The Panel believes that it would be inappropriate, based on available information, to attempt to review nanomaterials or products that contain them as a broad class. We also believe that existing FDA review processes are adequate to address any potential safety, effectiveness, or public health impacts associated with the application of nanotechnology in FDA-regulated products.

DISCUSSION: Points to Consider

1. Engineered material or end product

In the draft guidance FDA states that incidental particles, background levels of nanomaterials, and materials that naturally occur in the nanoscale are not of interest to the Agency. FDA "is particularly interested in the *deliberate* manipulation and control of particle size to produce specific properties, because the emergence of these new properties or phenomena may warrant further evaluation." The Panel strongly supports this approach.

[1] As noticed in *Federal Register* Vol. 76, No. 114, June 14, 2011, page 34715.

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

The Panel recommends that FDA use a weight-based threshold of 10% nanomaterial content.[2] A 10% weight cut-off is consistent with economical and readily available detection capabilities and sensitivity of relevant analytical instrumentation. It will capture materials of the size range that have been the subject of nanotechnology discussions within various agencies and other groups (e.g., OECD Working Party on Manufactured Nanomaterials), while at the same time providing clarity for manufacturers of FDA-regulated products.

2. At least one dimension in the nanoscale range (approximately 1 nm to 100 nm)

FDA has focused on objects (particles) when referring to nanomaterials. The Panel believes that materials containing nanovoids (pores) or other nano features should not be considered nanomaterials (particles) for the purposes of this guidance document. The Panel recommends that FDA focus on materials that have the potential to release nano-objects.[3]

3. Exhibits properties or phenomena . . . that are attributable to its dimension(s)

FDA indicates that materials with dimension-dependent properties are of interest when it states that "[t]he properties and phenomena may be due to altered chemical, biological, or magnetic properties, altered electrical or optical activity, increased structural integrity, or other unique characteristics of nanoscale materials not normally observed in their larger counterparts." Certainly, physical and chemical properties may change as a particle becomes smaller. This relationship has long been known for some substances. Inferring biological properties is troublesome, however, for several reasons:

a. There is significant ongoing work in venues such as the International Organization for Standards (ISO), the OECD Working Party on Manufactured Nanomaterials, and the Minimum Information on Nanoparticle Characterization initiative examining the relationship between physical and biological properties. It would be inappropriate based on the state of science to conclude that changes in physical properties *per se* change biological properties;
b. Screening level assays may be adequate to identify priorities for further evaluation, but by themselves are insufficient at this time to demonstrate "true" hazards;[4] and
c. Biological properties such as toxicity may be *different* based purely on the metric used (e.g., mass), whereas the property may be *predictable* using a different metric (e.g., surface area).[5]

The Panel suggests that this element in the "Points to Consider" may be overly broad and not particularly helpful because <u>all</u> materials exhibit properties or phenomena that are attributable to their dimensions. What is of interest is whether a material possesses any unanticipated properties or phenomena at the nano-scale that may have relevance to safety, effectiveness, or public health. The Panel recommends that as this is an active area of scientific exploration, FDA should open a dialogue with the regulated community and other stakeholders on how to address the question of size and physical and/or biological properties.

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[2] ISO Technical Specification on Nanotechnologies—Vocabulary—Part 1: Core terms. ISO/TS 80004-1:2010.
[3] Maier, M., Hannebauer, B., Holldorff, H., Albers, P. 2006. Does lung surfactant promote disaggregation of nanostructured titanium dioxide? Journal of Occupational and Environmental Medicine. 48:1314-1320.
[4] Puzyn T., Leszczynska D., and Leszczynski J. 2009. Toward the development of "nano-QSARs": advances and challenges. *Small*. 5(22):2494.
[5] National Institute of Occupational Health (NIOSH). 2011. *Current Intelligence Bulletin 33: Occupational Exposure to Titanium Dioxide.* Page vi: "In other words, all the rat tumor response data on inhalation of TiO2 (ultrafine and fine) fit on the same dose-response curve when dose is expressed as total particle surface area in the lungs."

4. Size range of up to one micrometer (1,000 nm)

The draft guidance makes clear that FDA takes a conservative screening approach followed by a case-by-case assessment. It also says that FDA focuses on dimension-dependent properties of materials, not just the fact that a material has a dimension at the nanoscale. The Panel appreciates FDA's recognition that size is not the lone characteristic that can influence a material's safety or performance. The Panel also supports FDA's position that it "does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful." Such a position is consistent with the recent guidance from the Executive Office of the President[6] (EOP) and will support a science- and risk-based approach to the assessment of nanomaterials. The Panel recommends that FDA continue to adhere to the principles outlined in the June 9 EOP memorandum as the Agency considers the development of additional guidance on nanomaterials.

The draft guidance indicates that the use of a material with at least one dimension between 1 and 100 nm is considered to be an application of nanotechnology. Moreover, FDA will consider materials that have external dimensions much greater than 100 nm, but may have internal structural dimensions in the 1 to 100 nm range. To ensure that effects attributable to these internal structural dimensions are considered in FDA's review processes, materials between 1 and 1,000 nm in external dimension are scrutinized closely for their relevance to nanotechnology. The Panel appreciates that FDA states clearly in the draft guidance that these dimensional considerations are not parts of a regulatory definition.

Clarification Needed

The draft guidance refers to the National Nanotechnology Initiative's definition of "nanotechnology" and lists several factors that have been mentioned in other definitions and that are appropriate for further consideration in a product evaluation. However, the draft guidance does not define the term "nanomaterials." It is our observation that the term "nanomaterial" almost always refers to insoluble or poorly soluble solids and does not apply to readily and fully soluble solids, liquids, liquid aerosols, liquid-liquid emulsions, and micelles/vesicles. The Panel recommends that FDA make a clear, definitive statement regarding whether or not it considers these examples as "applications of nanotechnology" in order to more clearly define the scope of materials and structures covered by the draft guidance. The Panel also recommends that FDA follow the work of ISO TC229 Joint Working Group 1 (Terminology and Nomenclature) to inform its thinking.

Conclusions

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. FDA has stated in the past that it has the authority to provide effective oversight of the use of nanotechnology in many of those products[7], and the draft guidance clarifies the thinking behind the application of that authority. It also articulates how FDA will seek and consider new information in order to inform its product reviews.

The Panel notes that the draft guidance does not address the processes used by FDA to review products, including those that may take advantage of nanotechnology, and this is appropriate given the scope of the draft guidance. However, the Panel identifies several cautions related to inferring biological properties of

[6] Memorandum for the Heads of Executive Departments and Agencies. June 9, 2011. *Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials.*
[7] U.S. Food and Drug Administration. 2007. *Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force*. July 25.

nanomaterials and would welcome an opportunity to discuss these and other issues related to FDA's review process with the Agency.

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 Jay West at Jay_West@americanchemistry.com or 202-249-6407.

Sincerely,

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ACC Nanotechnology Panel