Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology Guidance for Industry

DRAFT GUIDANCE
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended for manufacturers, suppliers, importers and other stakeholders. The guidance describes FDA's current thinking on whether FDA-regulated products [2] contain nanomaterials or otherwise involve the application of nanotechnology.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE

This guidance document does not establish any regulatory definitions. Rather, it is intended to help industry and others identify when they should consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise with the application of nanotechnology in FDA-regulated products. Public input on the guidance may also inform the development of any regulatory definitions in the future, as needed.

Nor does this guidance document address the regulatory status of products that contain nanomaterials or otherwise involve the application of nanotechnology, which are currently addressed on a case-by-case basis using FDA's existing review processes.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful.

In the future, FDA may issue additional guidance documents to address considerations for specific products or classes of products, consistent with the "Principles for Regulation and Oversight of Emerging Technologies" released March 11, 2011 as well as the "Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials" released on June 9, 2011, that were issued jointly by the Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative. [3]

III. DISCUSSION

FDA has not to date established regulatory definitions of “nanotechnology,” “nanoscale” or related terms. [4] However, there are numerous definitions of “nanotechnology.” The term is perhaps most 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. For example, the National Nanotechnology Initiative Program defines nanotechnology as “the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications.” [5] Other factors such as function, shape, charge, the ratio of surface area to volume, or other physical or chemical properties have also been mentioned in various published definitions.

As a first step toward developing FDA’s framework for considering whether FDA-regulated products include nanomaterials or otherwise involve nanotechnology, the agency has developed the points discussed below. Based on FDA's current scientific and technical understanding of nanomaterials and their characteristics, FDA believes that evaluations of safety, effectiveness or public health impact of such products should consider the unique properties and behaviors that nanomaterials may exhibit.

These points to consider are intended to be broadly applicable to all FDA-regulated products, with the understanding that additional guidance may be articulated for specific product areas, as appropriate in the future.

A. Points to Consider

At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask:

1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or

2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.

These considerations apply not only to new products, but also may apply when manufacturing changes alter the dimensions, properties, or effects of an FDA-regulated product or any of its components. Additionally, they are subject to change in the future as new information becomes available, and to refinement in future product-specific guidance documents.

B. Rationale for Elements within the Points to Consider

1. Engineered material or end product

This term is used to distinguish between products that have been engineered to contain nanoscale materials or involve the application of nanotechnology from those products that contain incidental or background levels of nanomaterials or those that contain materials that naturally occur in the nanoscale range. 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. This is distinct from the more familiar use of biological or chemical substances that may naturally exist at small scales, including at the nanoscale, such as microorganisms or proteins.

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

A size range of approximately 1 nm to 100 nm is commonly used in various working definitions or descriptions proposed by the regulatory and scientific community. [6] In this size range, materials can exhibit new or altered physicochemical properties which enable novel applications. [7]

Accordingly, a range of approximately 1 nm to 100 nm should be applied as a first reference point in considering whether an FDA-regulated product contains nanomaterials or otherwise involves application of nanotechnology.

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

These terms are used because properties and phenomena of materials at the nanoscale enable applications that can the affect safety, effectiveness, performance, quality and, where applicable, public health impact of FDA-regulated products. For example, dimension-dependent properties or phenomena may be used for functional effects such as increased bioavailability, decreased dosage, or increased potency of a drug product [8], decreased toxicity of a drug product [9], better detection of pathogens [10], enhanced protection offered by improved food packaging materials [11], or improved delivery of a functional ingredient or a nutrient in food [12]. The 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. [13] These changes may raise questions about the safety, effectiveness, performance, quality or public health impact of the products. In addition, considerations such as routes of exposure, dosage, and behavior in various biological systems (including specific tissues and organs) are critical for evaluating the wide array of products under FDA's jurisdiction.

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

Materials or end products can also exhibit properties or phenomena attributable to a dimension(s) above the approximate 100 nm range. A reduction in size can lead to properties that are clearly different from those of the conventionally-scaled material although the material or end product itself may not necessarily be within the nanoscale range. Structures such as agglomerates and aggregates are of interest in this context [14] as are coated, functionalized, or hierarchically assembled structures [15]. To account for such materials, some definitions of nanomaterial have applied the 100 nm upper dimension to the *internal* structure [16]. In the absence of a bright line as to where an upper limit should be set, the agency considers that an upper bound of one micrometer (i.e., 1,000 nm) would serve as a reasonable parameter for screening materials with dimensions beyond the nanoscale range for further examination to determine whether these materials exhibit properties or phenomena attributable to their dimension(s) and relevant to nanotechnology. [17] The agency believes that the one micrometer upper limit in the second point to consider serves both to (1) exclude macro-scaled materials that may have properties attributable to their dimension(s) but are not likely relevant to nanotechnology; and (2) include those materials (such as aggregates, agglomerates, or coated, functionalized, or hierarchically assembled structures) with dimension(s) above 100 nm that may exhibit dimension-dependent properties or phenomena relevant to nanotechnology and distinct from those of macro-scaled materials.

IV. CONCLUSION

There is a critical need to learn more about the potential role and importance of dimensions in the characteristics exhibited by engineered nanomaterials that may be used in producing products regulated by FDA. Premarket review, when required, offers an opportunity to better understand the properties and behavior of products that contain engineered nanomaterials or otherwise involve application of nanotechnology. And where products applying nanotechnology are not subject to premarket review, the agency urges manufacturers to consult with the agency early in the product development process. In this way, any questions related to the regulatory status, safety, effectiveness, or public health impact of these products can be appropriately and adequately addressed.

Footnotes

1. The points to consider presented in this guidance have been prepared by the U.S. Food and Drug Administration's Nanotechnology Task Force (Task Force). The Task Force, formed in August 2006, was charged with determining regulatory approaches that would enable the continued development of innovative, safe, and effective FDA-regulated products that use nanoscale materials.
2. The use of the word "products" in this guidance document is meant to include products, materials, ingredients and other substances regulated by FDA.
3. http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf; http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf
4. In the 2007 Report, the FDA Nanotechnology Task Force stated: "The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, while one definition for "nanotechnology," "nanoscale material," or related term or concept may offer meaningful guidance in one context, that definition may be too narrow or broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products" (Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007, page 6-7; available online at: http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm).
5. National Nanotechnology Initiative Website, http://www.nano.gov/nanotech-101/what.
6. For example, a size range of approximately 1 nm to 100 nm is used in definitions, working definitions, or descriptions published by the National Nanotechnology Initiative; Environmental Protection Agency; European Scientific Committee on Consumer Products; European Commission; Health Canada; International Standards Organization; Organization for Economic Cooperation and Development's Working Party on Nanotechnology and Working Party on Manufactured Nanomaterials; National Cancer Institute; and American National Standards Institute.
7. National Nanotechnology Initiative Website, http://www.nano.gov/nanotech-101/what; Powers KW, Brown SC, Krishna VB, et al. Research Strategies for Safety Evaluation of Nanomaterials. Part VI. Characterization of Nanoscale Particles for Toxicological Evaluation. Toxicological Sciences 90: 296–303, 2006.
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12. IOM (Institute of Medicine). Nanotechnology in food products: Workshop Summary. Washington, DC: The National Academies Press, 2009; Chen L, Remondetto GE, Subirade M. Food protein-based materials as nutraceutical delivery systems. Trends in Food Science & Technology 17:272-283, 2006.
13. Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007; available online at: http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm).
14. Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010; available online at: http://ec.europa.eu/dgs/jrc/downloads/jrc_reference_report_201007_nanomaterials.pdf.
15. Scientific Basis for the Definition of the Term "Nanomaterial", Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010; available online at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_030.pdf.
16. ISO Technical Specification on Nanotechnologies – Vocabulary – Part 1: Core terms (ISO/TS 80004-1:2010); European Commission draft recommendation on the definition of the term "nanomaterial" (October, 2010).
17. Including materials of interest with dimension(s) beyond 100 nm is consistent with the recent conclusions presented by the Joint Research Centre and the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission: "In order to base a nanomaterials definition for regulatory purposes on size alone, the upper nanoscale limit should ideally be high enough to capture all types of materials that would need particular attention for regulation due to their nanoscale size. Upper limits which are often used in existing definitions, for example 100 nm, may require the introduction of one or more qualifiers based on structural features or properties other than size, in order to capture structures of concern (for example agglomerates or aggregates) with a size larger than 100 nm in the regulation" (Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010); "The upper size limit for one or more external dimensions of 100 nm is complicated by the potential exclusion of aggregates, agglomerates and multicomponent assemblies that would have external sizes greater than this" (Scientific Basis for the Definition of the Term "Nanomaterial", Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010); "An upper limit of 100 nm is commonly used by general consensus but there is no scientific evidence to qualify the appropriateness of this value (Stated as SCENIHR conclusions in the EC draft recommendation on the definition of term "nanomaterial", October 2010; available online at: http://ec.europa.eu/environment/consultations/pdf/recommendation_nano.pdf). In addition, ISO "acknowledged that health and safety considerations associated with intentionally produced and incidental nano-objects do not abruptly end at dimensions of 100 nm" (ISO/TS 80004-1:2010).