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FDA's Evolving Approach to Nanotechnology

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I. Introduction

Nanotechnology is a trillion dollar industry poised to revolutionize many types of FDA-regulated products, including foods, dietary supplements, human drugs, vaccines, biologics, medical devices, cosmetics, and veterinary products.[1] To date, industry has supported FDA's efforts to better understand nanotechnology's potential implications on certain FDA-regulated products. At the same time, legal practitioners and their clients are wary of the possibility that FDA's actions could inadvertently stigmatize an emerging technology that will provide innumerable societal benefits.

Fortunately, nanoscale materials are not completely foreign to FDA. The agency has been regulating products that interact with the human body at the nanoscale for several years. The first nanoscale pharmaceuticals were approved by FDA as early as 2003.[2] However, since the mid 2000's, some have questioned whether existing regulations are sufficient to deal with new, highly innovative FDA-regulated products that use nanoscale materials or employ nanotechnology in ever more purposeful ways uncontemplated in the past.[3] FDA's new draft guidance documents can be viewed as the next step in a long, thoughtful, and evolving response to these emerging concerns.

In August 2006, FDA formally entered into the debate about the sufficiency of its existing regulatory tools to deal with nanotechnology when it formed an internal Nanotechnology Task Force to survey the existing nanotechnology landscape and plan a course of deliberate FDA action. After almost a year of review and analysis, the task force issued a July 2007 report[4] which took the position that the existing regulatory framework was largely sufficient to manage FDA-regulated products employing nanotechnology, and that FDA would continue to deal with these products on a case-by-case basis. FDA also promised to issue written guidance documents to help industry by providing

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[1] Nanotechnology has been broadly described as working with materials at the nanoscale (one billionth of a meter) in order to take advantage of unique or novel properties of those materials due to their small size. The federal National Nanotechnology Initiative has defined "nanotechnology" as "science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers." National Nanotechnology Initiative, http://www.nano.gov/nanotech-101/what/definition (last visited October 9, 2012).

[2] Merck's aprepitant drug, Emend® was approved in March 2003. Mary C. Till, et al., *Nanotech Meets the FDA: A Success Story About the First Nanoparticulate Drugs Approved by the FDA*, 2 Nano L. Bus., 163-167 (2005).

[3] *See, e.g.*, Michael R. Taylor, Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs?, PEN 5 (2006), *available at* http://www.nanotechproject.org/process/assets/files/2705/110_pen5_fda.pdf. Although almost seven years old, Mr. Taylor's work still provides the best overview on the question of the efficacy of FDA's existing regulatory authority in the nano-realm.

[4] U.S. Food and Drug Admin., Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force (2007), *available at* hhttp://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf .

its current thinking regarding various nano-related issues. Following up on its 2007 promise, FDA issued its first draft nanotechnology guidance document in June 2011.[5] This first draft guidance document was followed by two more in April 2012.[6] While all three of FDA's draft guidance documents explicitly disclaim establishing binding legal authority, they may become "de facto" authority through industry adoption and use by FDA and, thus, merit close attention.

II. DRAFT NANO-CONSIDERATIONS GUIDANCE

In June 2011, FDA's Office of the Commissioner published "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (hereafter referred to as "Draft Nano-Considerations Guidance"). The document addresses the fundamental issue of how FDA determines when and whether a product that it regulates contains nanoscale materials or uses nanotechnology. This is a foundational issue upon which all of FDA's future policies about nanotechnology are based.

To the uninitiated, this may seem like a simple issue — certainly not one that should take four years to reduce to writing. However, developing a consensus on what actually constitutes "nanoscale materials" or "nanotechnology" has been anything but simple. In probably the best example, the International Standards Organization ("ISO") formed its first international group of scientists, industry representatives, and regulators devoted to nanotechnology in November 2005. It took ISO until October 2010 to issue its first document defining "nanoscale materials" and "nanotechnology."[7] Even with this herculean effort, ISO's definitions are still subject to debate. Thus, FDA's slow and deliberate thinking on this issue is in good company.

The Draft Nano-Considerations Guidance begins with a disclaimer that the document is not intended to provide a formal definition of "nanoscale materials" or "nanotechnology," but rather 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." However, while declining to establish a formal definition, the document essentially creates an informal definition which may become "de facto" authority through industry adoption and use by FDA.

FDA indicates that it asks two (2) primary questions when determining when and whether an FDA-regulated product involves the application of nanotechnology:

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

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[5] U.S. FOOD AND DRUG ADMIN., CTR. FOR FOOD SAFETY AND APPLIED NUTRITION, DRAFT GUIDANCE FOR INDUSTRY: CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY, http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

[6] U.S. FOOD AND DRUG ADMIN., CTR. FOR FOOD SAFETY AND APPLIED NUTRITION, DRAFT GUIDANCE FOR INDUSTRY: SAFETY OF NANOMATERIALS IN COSMETIC PRODUCTS, http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm300886.htm; U.S. FOOD AND DRUG ADMIN., CTR. FOR FOOD SAFETY AND APPLIED NUTRITION, DRAFT GUIDANCE FOR INDUSTRY: 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, http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm300661.htm.

[7] ISO, TECHNICAL SPECIFICATION ON NANOTECHNOLOGIES — VOCABULARY — PART 1: CORE TERMS, NO. ISO/TS 80004-1:2010 ("Nanotechnology - The application of scientific knowledge to manipulate and control matter in the nanoscale in order to make use of size- and structure-dependent properties and phenomena, as distinct from those associated with individual atoms or molecules or with bulk materials." "Nanomaterial - Material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale.").

2. Whether any 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 fall outside the nanoscale range, up to one micrometer.

FDA makes it clear that these two (2) questions not only apply to newly-created products, but also to existing FDA-regulated products which have undergone manufacturing changes involving the use of nanotechnology. Thus, practitioners should be sure to raise this issue with clients working in the area.

Understandably, FDA has carefully selected its words. "Engineered material or end product" means those products specifically created to use nanoscale materials or applications, not those that incidentally use nanomaterials, existing nanoparticles, or materials already naturally existing on the nanoscale such as microorganisms or proteins. Regarding novel or unique "properties," FDA defines these as "dimension-dependent properties or phenomena" used to enhance a product's effectiveness. Examples include improved drug performance, pathogen detection, food packaging, and delivery of food nutrients.

Regarding its focus on materials up to 1000 nm in dimension, FDA recognizes that the technical definition of "nanoscale" ends at the upper size range of 100 nm, but concludes that this should not be a hard and fast limit for FDA's purposes. FDA reasons that regulated products may conceivably exhibit unique/novel phenomena attributable to the use of nanotechnology even if their smallest components are larger that 100 nm. Accordingly, in the absence of a suitable "bright line" test, FDA believes it is prudent to examine products on a case-by-case basis to determine whether they involve the use of nanotechnology as long as those products contain components up to 1000 nm in size and exhibit size-dependent phenomena. Practitioners, however, should understand that many substances used in FDA-regulated products for decades have properties or qualities attributable to their small size, and that this is not unique to nanoscale materials. Often, these materials are specifically selected for use because of their special properties. Additionally, many of these materials may be smaller than 1000 nm in one or more dimensions. Accordingly, the factors FDA proposes have far-reaching consequences and capture numerous substances that many would not consider to be nanoscale materials.

Further, whether a property is somehow "special" or "unique" is a subjective determination and lies in the eye of the beholder. Some may consider a property "special" or "unique," while others may view it as expected or ordinary. Simply put, the second prong of FDA's analysis does not provide a consistently reliable basis for issuing guidance documents or related regulatory activities. However, practitioners should be aware of FDA's informal definitions because their clients may erroneously assume the materials with which they work are not nanoscale and/or do not involve the use of nanotechnology while FDA believes the opposite.

III. Draft CFSAN Guidance

In April 2012, FDA's Center for Food Safety and Applied Nutrition ("CFSAN") published its "Draft Guidance for Industry: 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" (hereafter referred to as "CFSAN Draft Guidance"). Although the term "nanotechnology" does not appear in the title, it is the document's primary focus.

CFSAN notes at the outset that it has already received some food contact notifications including food contact substances in nanometer range. However, none have been for food additives or color additives, or Generally Recognized as Safe ("GRAS")[8] affirmation petitions or notices.

Of some solace to companies working with nanotechnology, the CFSAN Draft Guidance states that "[t]he 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." Rather, FDA evaluates products employing nanotechnology on a case-by-case basis looking at the intended use of the finished product. Thus, CFSAN has taken great pains to assure the public that FDA does not lump all regulated-products employing nanotechnology into the same boat. They are not "intrinsically benign or harmful" and must be looked at individually and in context.

The CFSAN Draft Guidance applies to food ingredients, color food additives, and food contact substances. While equally applicable to newly created products, the document primarily addresses existing additives, colors, and food contact substances which have undergone manufacturing changes employing the use of nanoscale components and/or nanotechnology. The document recommends early consultation with CFSAN in cases of doubt or uncertainty when working with nanoscale materials or nanotechnology in the context of FDA-regulated products. Early informal consultation with FDA is often helpful, but industry and practitioners should be careful that these informal discussions do not somehow change into a "de facto" pre-market approval process that does not otherwise currently exist.

As with the Draft Nano-Considerations Guidance document that it incorporates by reference, the CFSAN Draft Guidance defines the term "nanometer range" as 1 nm to 1000 nm. However, the document purports to provide no formal definition of "nanotechnology" or "nanoscale" because in CFSAN's estimation any definition "may offer meaningful guidance in one context, [but] that definition may be too narrow or broad to be of use in another." CFSAN indicates, however, that at some point FDA may find it "productive" to adopt formal definitions of "nanotechnology" and "nanoscale" for use with certain products, but provides no insight regarding why, when, or how this might occur.

After summarizing FDA's general regulatory authority applicable to nanoscale materials (FFDCA,[9] FDAMA,[10] 1960 Color Additives Amendments),[11] the CFSAN Draft Guidance then provides an overview of CFSAN's methods for assessing the safety of food substances and how they relate to nanoscale materials and nanotechnology.

CFSAN notes that initial FDA submissions generally include providing "the manufacturing process as part of the information describing the identity of food substances," CAS or ECN numbers, chemical formula, and physical and chemical properties, amongst other data. Though not explicitly stated, the implication is that the use of nanoscale components should be disclosed to FDA in initial submissions for purposes of conducting CFSAN safety assessments.

Moving beyond information submissions, the CFSAN Draft Guidance notes that new types of testing may be required to evaluate the safety of food substances employing nanoscale materials or nanotechnology undergoing safety assessments. CFSAN states

[8] *See* Federal Food, Drug, and Cosmetic Act, §§ 201(s), 409, 21 U.S.C. §§ 321, 348 (2006).

[9] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (2006).

[10] Food and Drug Administration Modernization Act, 21 U.S.C. § 301 et seq. (2006).

[11] Color Additives Amendments of 1960, 21 U.S.C. § 301 et seq. (2006).

that the use of nanotechnology may "warrant additional or different evaluation during a safety assessment of a food substance." The document does not, however, recommend what type of new testing might be needed and when, and the final version of the document could be improved by including this type of information.

Regarding the disclosure of particle size in FDA submissions, CFSAN notes that prior FDA guidance documents for food additives,[12] color additives,[13] and food contact substances[14] "discuss the relevance of particle size in submitting safety assessments for food additive petitions, color additive petitions, and food contact notifications." Accordingly, CFSAN refers readers to those documents for clarification regarding when the disclosure of the size and use of nanoscale components is appropriate.

Finally, the most impactful portion of the document is somewhat buried in the text. CFSAN states that "[a]t this time, we are not aware of any food ingredient or [food contact substances] intentionally engineered on the nanometer scale for which there are generally available safety data sufficient to serve as the foundation for a determination that the use of a food ingredient or [food contact substance] is GRAS." Practitioners can decide the implications of this language for themselves, but it appears that using nanoscale components or materials in previously determined GRAS food ingredients or food contact substances will require new safety determinations and industry cannot rely on prior GRAS determinations. If true, this should provide a flurry of activity for consulting and law firms in this area.

IV. Draft Cosmetics Guidance

In April 2012, FDA's Center for Food Safety and Applied Nutrition published its "Draft Guidance for Industry: Safety of Nanomaterials in Cosmetic Products" ("Draft Nano-Cosmetics Guidance"). The guidance document was designed to "assist industry and other stakeholders in identifying the potential safety issues of nanomaterials in cosmetic products and developing a framework for evaluating them."

As with FDA's other two draft nanotechnology guidance documents, the Draft Nano-Cosmetics Guidance does not establish legally enforceable responsibilities. Nonetheless, FDA's guidance documents are often considered authoritative by the general public, industry, and other stakeholders.

Again, FDA should be commended for its intent to "not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful." FDA states that the characteristics of each individual finished product and its intended use should determine whether the use of a particular material in a cosmetic is warranted. These requirements are already in place for cosmetics, and cosmetics employing nanoscale materials or nanotechnology are not unique in this regard.

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[12] U.S. Food and Drug Admin., CFSAN, Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions (2009), http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/UCM124917.htm.

[13] U.S. Food and Drug Admin., CFSAN, Guidance for Industry: Color Additive Petitions. FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices (2009), http://www.fda.gov/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm.

[14] U.S. Food and Drug Admin., CFSAN, Guidance for Industry: Preparation for Premarket Submissions for Food Contact Substances: Chemistry Recommendations (2009), http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm.

Because cosmetics are not subject to premarket approval, the Draft Nano-Cosmetics Guidance again encourages industry to establish an early informal dialogue with FDA in advance of using nanomaterials in cosmetics to determine whether the development of new or additional data is necessary to substantiate a product's safety. Such nano-specific considerations include whether existing test methods and data are sufficient and whether new toxicity testing for the final product and/or its constituents is required. However, as with the CFSAN Draft Guidance, practitioners should make sure that these voluntary opportunities for dialogue are not construed as precursors to premarket regulatory approval or other implicit extensions of existing FDA authority. Practitioners and industry should also be aware that nanoscale versions of certain existing chemical substances have been used in cosmetic applications for many decades. Accordingly, developing new test data may not be warranted in every circumstance involving the use of nanoscale materials or nanotechnology in cosmetics, or merely because a cosmetic may incorporate nanoscale materials or the use of nanotechnology. The document could benefit from further explanation on this point.

The Draft Nano-Cosmetics Guidance also indicates that the physical characterization of nanoscale materials may present unique issues to cosmetic manufacturers and FDA. To this end, the document references several physical characteristics of import: particle size and distribution, aggregation and agglomeration characteristics, surface chemistry, morphology, solubility, density, stability, porosity, and impurities. However, it remains to be seen whether this list is warranted in all circumstances because the use of nanotechnology may pose no discernable safety issues in certain cosmetic uses. Additionally, the document does not provide any information regarding why the listed-characteristics are important to FDA or industry in the specific context of nanotechnology. In short, the document lacks any linkage between the cited nano-characteristics that industry should consider when evaluating the safety of cosmetics and why the industry should be potentially concerned about these characteristics. The draft guidance document would benefit from more development in this area.

Regarding toxicity testing, the Draft Nano-Cosmetics Guidance states that industry should develop new toxicology methods for use with cosmetics containing nanoscale materials "where traditional toxicity testing methods cannot be satisfactorily modified." The document, however, does not identify any such specific instances. As a result, industry is left to determine for itself the sufficiency of all of the various toxicity testing methods currently in use for their potential use with cosmetics incorporating nanoscale materials without substantive FDA input. When drafting the final version of the document, FDA should consider indicating which currently used toxicity testing methods are insufficient when used with nanoscale materials, and should also suggest changes to these methods where supported by the existing science.

The Draft Nano-Cosmetics Guidance further recommends determining whether any special nano-specific considerations affect the safety of cosmetics employing nanotechnology in the areas of routes of exposure, uptake, and absorption. Again, these concerns are not unique to cosmetics using nanotechnology. Exposure routes, uptake, and absorption should be considered by any cosmetic manufacturer making any type of cosmetic — not just those involving nanotechnology. FDA encourages industry to continue carefully examine these considerations and to apply any information in the existing literature and data that may be developed by individual companies should needs dictate. To this point, FDA provides citations to certain existing studies in some of these areas. However, a more thorough analysis would benefit the final version of

the document. Such a consolidated resource does not currently exist and would be invaluable to industry.

Additionally, the Draft Nano-Cosmetics Guidance explains and recommends the existing tiered testing strategy generally used with cosmetics for use with nano-cosmetics, consistent with Personal Care Products Council (formerly CTFA) and Organization for Economic Co-Operation and Development recommendations which include acute toxicity, skin irritation, dermal photoirritation, skin sensitization, mutagenicity/genotoxicity, repeated dose toxicity, subchronic toxicity, and phototoxicity testing. The document also explains how both *in vitro* and *in vivo* testing may be useful in certain instances with cosmetics utilizing nanoscale materials. FDA suggests that industry continue to use these tests, but recommends modifying them for use with nanoscale cosmetic ingredients, and developing new tests if existing tests prove insufficient. In the final version of the guidance, FDA should consider identifying appropriate modifications to existing test protocols for use with nanoscale materials, or at least identifying the information gaps that industry should attempt to fill when determining whether an existing test method is appropriate for use with nanoscale cosmetic ingredients.

Finally, the list of possible alternative test methods for use with nanoscale cosmetic ingredients provided in the Draft Nano-Cosmetics Guidance is helpful. However, a more detailed analysis by FDA of these methods and their possible modification for use with nanoscale materials would be very helpful if included in the final version of the document.

V. Conclusion

Although it has taken several years, FDA's three draft nanotechnology guidance documents begin to provide some critical thinking on how FDA intends to manage the challenges presented by the use of nanotechnology in FDA-regulated products. The documents provide a tentative first step that FDA will need to revisit as new submissions are made and the safety of products using nanotechnology is assessed. Practitioners should review these three documents with their clients working in this area to determine their impact on day-to-day activities. While the formal comment period for the three draft guidance documents is closed, FDA continues to accept comments. Industry and their counsel should strongly consider submitting comments to FDA on an ongoing basis until the documents are formalized.