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FDA ISSUES DRAFT GUIDANCE ON THE USE OF NANOTECHNOLOGY IN MANUFACTURING OF FOOD SUBSTANCES AND COSMETIC PRODUCTS

On April 20, 2012, the Food and Drug Administration (FDA) released two draft guidance documents addressing the use of nanotechnology by the food and cosmetics industries. The first, entitled "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" (Food Guidance),[1] describes the factors manufacturers of food ingredients and food contact substances (FCSs) should consider when determining whether a significant change in a manufacturing process affects the identity, safety, or regulatory status of the food substance. The second guidance document, entitled "Safety of Nanomaterials in Cosmetics Products" (Cosmetics Guidance),[2] outlines FDA's current thinking on the safety assessment of nanomaterials in cosmetics products.[3]

These documents reflect that FDA is continuing its cautious, iterative approach to nanotechnology. They provide some basic guidance but do not reflect a particularly new or unexpected approach by the agency. FDA maintains its position that it will not categorize all products containing nanomaterials or otherwise involving the use of nanotechnology as inherently benign or harmful. Rather, the agency will assess the characteristics of the finished product and the safety of its intended use. FDA warns that the use of nanotechnology at any stage of manufacturing or packaging could trigger a duty to test and prove the safety of the nanotech particles, noting that evidence of the safety of larger particles of the same material is likely not sufficient to demonstrate its safety on the nanoscale. The burden of showing compliance and demonstrating safety remains squarely on the producer of the nanotech material. The Food Guidance and Cosmetics Guidance reflect the same set of principles regarding nanotechnology but apply them to the different regulatory regimes governing each product category.

NANOTECHNOLOGY AND FOOD SUBSTANCES

In its Food Guidance, FDA discusses how intentional alterations of particle size distribution on the nanometer scale might affect the identity, conditions of use, or purity of food substances already in use. FDA states that it considers food manufacturing processes that involve nanotechnology in the same manner as any other manufacturing technology, but notes that production of food substances with these extremely small particles may result in new properties not seen in traditionally manufactured food substances. As such, the Food Guidance addresses how the use of

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[1] *Available* here.

[2] *Available* here.

[3] On June 9, 2011, FDA released a draft guidance providing FDA's current view on whether products contain nanomaterials or otherwise involve the application of nanotechnology. FDA, "Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," 76 Fed. Reg. 34715 (June 14, 2011), *available* here. *See* Covington E-Alert, "FDA Issues Draft Guidance on the Application of Nanotechnology," (June 22, 2011), *available* here.

nanotechnology in manufacturing of food substances might impact safety and other regulatory assessments.

Food Substance Safety Assessments

FDA emphasizes that safety assessments should be based on data relevant to the version of the food substance intended for use. Thus, when a food substance is manufactured to include a particle size distribution in the nanometer range, safety assessments should be based on data relevant to the nanometer version of the food substance. In addition, where nano-engineered food substances have new properties, additional or different testing methods may be necessary to determine safety. FDA notes that particle size, surface area, aggregation/agglomeration, or shape may impact absorption, distribution, metabolism, and excretion and, thus, the potential safety of the food substance. As such, manufacturers may need to examine the effects of these types of property changes, including effects on bioavailability. FDA states that it is unaware of any food ingredient or FCS "intentionally engineered on the nanometer scale" for which there are safety data generally available sufficient to serve as the foundation for a determination that the use of that ingredient or FCS is generally recognized as safe (GRAS).[4]

Assessing the Impact of Manufacturing Process Changes

Significant changes in manufacturing processes, including the use of emerging technologies that affect the particle size distribution of a food substance, may impact the regulatory status of a food substance. Manufacturing processes using emerging technologies may alter the identity or intended use of a food substance, such that the substance no longer falls within the scope of a food additive regulation, Food Contact Notice (FCN), GRAS listing or affirmation, or GRAS notification. In such cases, a new regulatory submission would be required to establish the conditions under which the substance, as manufactured under the new process, is safe and lawful. In its guidance, FDA provides recommendations for assessing when such new regulatory submissions are required:[5]

- **Food Substances Subject to Food or Color Additive Regulation or GRAS Determination:** FDA recommends that manufacturers determine what changes have been made to the identity of the food substance as a result of the manufacturing process change, including the substance's physicochemical structure and properties, purity, and impurities. Taking this information into account, manufacturers should conduct a safety assessment for the use of the food substance (including characteristic properties such as physicochemical structure, purity, bioavailability, or toxicity). Finally, manufacturers should consider whether the use of the food substance is still authorized under a food/color additive regulation or GRAS affirmation/listing regulation or other GRAS determination (including consideration of the identity and conditions of use described in the administrative record for the relevant regulation). The agency notes that a food substance manufactured for the purpose of creating very small particle sizes with new functional properties is not likely to be covered by an existing FDA regulation or GRAS determination for a related substance manufactured without the use of such technology. If the food substance is not within the scope of the existing FDA regulation, a new regulatory submission to FDA will be required. FDA also emphasizes that many technologies are so new as to preclude a consensus among experts that the use of a food substance manufactured using that technology is safe, thus precluding a determination that the use of the substance is GRAS. Thus, FDA states that

[4] FDA notes that the guidance is not meant to call into question the regulatory status of conventionally manufactured food substances with incidental or background levels of nanomaterials that have already been determined to be GRAS or the subject of an approved petition or notification.

[5] FDA also provides, in Appendix 1 to the new guidance document, three examples of situations in which the agency reconsidered the regulatory status of the use of a food substance and concluded that a significant change in manufacturing process did not negatively impact safety.

premarket review and approval of such food substances on a case-by-case basis "may be warranted."

- **Food Contact Substances With Effective Food Contact Notifications (FCN):** FDA recommends that manufacturers determine what changes have been made to the identity of the FCS, and conduct a safety assessment of the FCS, taking into consideration any impact of the change in identity. Manufacturers should consider whether the substance remains within the scope of an effective FCN. Altering the manufacturing process of a notified FCS to produce components in the nanometer scale or increase the proportion of nanometer scale components can be a significant manufacturing change resulting in a substantive change to the specifications and/or identity of the FCS. Such changes may also result in changed levels of impurities. In such cases, FDA recommends submission of a new notification.

NANOTECHNOLOGY AND COSMETIC PRODUCTS

In its Cosmetics Guidance, FDA describes the safety issues that manufacturers should consider to ensure that cosmetic products made with nanomaterials are safe and not adulterated. The guidance states that the current framework for safety assessment (including hazard identification, dose-response assessment, exposure assessment, and risk characterization) is generally appropriate for nanomaterials. However, standard safety tests may need to be modified to address (1) the chemical and physical properties that may affect the toxicity profile of nanomaterials, and (2) the effects of those properties on the function of the cosmetic formulation. The Cosmetics Guidance highlights some scientific considerations relevant to the assessment of the safety of nanomaterials used in cosmetic products, including:

- **Nanomaterial Characterization.** Safety assessments for cosmetic products using nanomaterials should address the physico-chemical characteristics of the nanomaterials, including measurement of particle size and distribution, aggregation and agglomeration characteristics, surface chemistry, morphology, solubility, density, stability, and porosity. In addition, manufacturers should assess the quality and quantity of impurities and how they may affect the overall safety of the end product.
- **Toxicology Considerations.** When using nanomaterials, manufacturers should consider modifying traditional toxicity testing with respect to factors such as appropriate solvents and dosing formulations, methods to prevent agglomerations of particles, and purity and stability conditions. The design of testing should take into account each ingredient's chemical structure and properties, purity/impurities, agglomeration and size distribution, stability, conditions and routes of exposure, uptake and absorption, bioavailability, and any other qualities that may affect safety. Short-term and long-term toxicity should be assessed. FDA recommends validation of *in vitro* methods for safety testing of cosmetic products and ingredients and optimizing these models for nanomaterials, and suggests that particular attention should be paid to cytotoxicity and precipitation of insoluble ingredients. The Cosmetics Guidance lists a number of testing methods that the agency believes can be optimized for specific nanomaterial and might be useful to help determine ingredient safety. Nevertheless, where traditional toxicity testing methods cannot be adequately modified, the agency recommends developing new methods to address particular safety issues.

FDA emphasizes that data needs and testing methods should address the unique properties and function of the nanomaterials used in cosmetic products. Thus, safety assessments for cosmetic products using nanomaterials should address the following: (1) physico-chemical characteristics; (2) agglomeration and size distribution of nanomaterials at the toxicity testing conditions corresponding to those of a final product; (3) impurities; (4) product exposure levels; (5) dosimetry for *in vitro* and *in vivo* toxicology studies; (6) *in vitro* and *in vivo* toxicological data on ingredients and their impurities,

dermal penetration, irritation and sensitization studies, mutagenicity/genotoxicity studies; and (7) clinical studies to test the ingredient or finished product in human volunteers under controlled conditions.

FDA encourages those manufacturers who wish to use nanomaterial in a cosmetic product to meet with the agency to discuss the test methods and data needed to substantiate the product's safety.

Covington is closely tracking important developments in the regulation of emerging nanotechnologies across numerous industry sectors, and the firm is available to advise on the resulting implications for businesses engaged in this fast-developing area.

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