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E-ALERT | Food & Drug

July 1, 2014

FDA ISSUES FINAL GUIDANCE ON THE AGENCY'S GENERAL APPROACH TO NANOTECHNOLOGY AND THE USE OF NANOTECHNOLOGY IN MANUFACTURING OF FOOD SUBSTANCES AND COSMETIC PRODUCTS

On June 24, 2014, the Food and Drug Administration (FDA) released three final guidance documents addressing the agency's general approach to nanotechnology and its use by the food and cosmetics industries, as well as a draft guidance on the use of nanomaterials in food for animals:

- "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (General Guidance), available here, explains FDA's current thinking on when nanotechnology applies to FDA-regulated products.
- "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), available here, describes the factors that food ingredients and food contact substance (FCS) manufacturers should consider in determining when a significant manufacturing change affects the substance's identity, safety, or regulatory status.
- "Safety of Nanomaterials in Cosmetic Products" (Cosmetics Guidance), available here, provides a framework to assist industry in identifying and evaluating the potential safety issues relating to nanomaterials in cosmetic products.
- "Use of Nanomaterials in Food for Animals" (Animal Food Draft Guidance), available here, outlines the FDA's current thinking on the safety of nanomaterials in animal feed and pet food products.

These guidance documents reflect FDA's understanding of nanomaterials as an emerging technology of major importance with the potential to be used in novel ways across the entire spectrum of FDA-regulated products. The documents suggest that FDA plans to approach nanotechnology-related issues cautiously, through an evolving regulatory structure that adapts to manufacturers' changing uses of this technology. FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. The guidance documents provide a framework for factors FDA will consider in evaluating a product's safety.

Rather than categorizing all products involving the use of nanotechnology as intrinsically either benign or harmful, FDA will consider on a case-by-case basis the characteristics of the finished product and the potential safety concerns for its intended use. FDA cautions manufacturers against assuming that a product containing nanomaterials is safe simply because larger particles of the same material have been established as safe. The agency encourages manufacturers to establish the safety of nanomaterials based on data relevant to the nanoscale version of the material and to consult the agency early and regularly with questions related to proper substantiation of product safety.

General Approach to Nanotechnology

In its General Guidance, FDA explained that in determining whether an FDA-regulated product involves the application of nanotechnology, it will consider:

- Whether a material or end product is engineered to have at least one external dimension or an internal or surface structure in the nanoscale range (approximately 1 nm to 100 nm); and
- Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, attributable to its dimension(s), even if these dimensions fall outside the nanoscale range (up to one micrometer (1,000 nm)).

An affirmative finding on either of these points may suggest that the nanomaterial merits particular industry or FDA attention to identify and address the product's potential implications for safety, effectiveness, public health impact, or regulatory status. Technical assessments will be specific to each product, taking into account the effects of nanomaterials in the context of the product and its intended use. These considerations apply to new products as well as changes to an FDA-regulated product's manufacturing process that alter its dimensions, properties, effects, or constituent parts.

- **Engineered material or end product**: The term "engineered" is employed to distinguish deliberate product dimension manipulation that may produce specific properties and thus warrant further evaluation. The guidance does not apply to products containing materials that naturally exist in the nanoscale range or are incidentally included in conventionally-manufactured products.
- **At least one dimension in the nanoscale range**: FDA notes that the regulatory and scientific community "commonly use" the size range of approximately 1 nm to 100 nm for nanomaterials and that materials in that size range may exhibit new or altered physicochemical properties enabling novel applications. This measurement is intended to apply to both individual nanoscale particles and aggregates or agglomerates thereof.
- **Properties or phenomena attributable to dimensions**: While size alone can suggest a nanomaterial has properties meriting further examination, FDA is more concerned with specific dimension-dependent properties impacting product safety, effectiveness, performance, quality, public health impact, or regulatory status. The agency is especially focused on functional effects, such as improved nutrient delivery or increased drug bioavailability that nanoscale materials might enable and that are not present when the same material is used at a larger size.
- **Dimensions up to 1,000 nm**: FDA finds that product properties relevant to safety, effectiveness, and performance evaluations can be attributable to particle sizes outside the nanoscale range. FDA has established a 1,000 nm upper limit as a reference point to identify materials or products with properties potentially relevant to a nanotechnology application. It may refine this upper limit for specific products or categories.

Nanotechnology and Food Substances

The Food Guidance establishes factors that manufacturers should consider when determining whether a manufacturing process change for a food or FCS (collectively, "food substance") already in the market affects its identity, safety, or regulatory status.[1] FDA notes that any intentional alterations of particle size distribution on the nanometer scale can alter a food substance's physical or chemical properties and thereby constitute a significant manufacturing change. Such a change may include an alteration in a starting material's identity or concentration, a catalyst, the source microorganism, or

[1] FDA recommends that manufacturers consult with it regarding significant manufacturing changes even if the manufacturer concludes that the change does not affect safety or regulatory status because any manufacturing change involving nanotechnology could affect safety.

food manufacturing or ingredient technology. The Food Guidance does not apply to conventionally manufactured food substances containing particles with size distributions in the nanometer range when those substances already have been determined to be Generally Recognized As Safe (GRAS) or approved in response to a food additive petition, color additive petition, or food contact notification (FCN).

In assessing a food substance's safety, FDA will consider its identity and technical effect, any self-limiting use levels, dietary exposure, safety studies and manufacturing processes that include the use of nanotechnology. The manufacturing process is particularly important to a safety assessment because it can affect impurity and contaminant levels in the food substance as well as the migration, absorption, and distribution of particles in the body. Safety assessments should be based on data relevant to the nanoscale version of the food substance. Data on traditionally-manufactured food substances may only be relevant on a case-by-case basis. Nano-engineered foods may have different properties than those manufactured via traditional means, and may require additional or different testing to establish their safety.

A significant change to the manufacturing process for a food substance already on the market, including through the use of nanotechnology, may require a new regulatory submission to clearly establish the safety of the food substance even if the original substance fell within the scope of a food additive regulation or effective FCN, or had been determined to be GRAS. Where a food substance does not clearly comply with an existing regulation, FDA recommends manufacturers take "appropriate steps" to ensure their use of the food substance satisfies all regulatory requirements:

- **Food substances subject to a food additive or color additive regulation, or food contact substances with an effective FCN:** Manufacturers should determine how the identity of the food substance has changed, conduct a safety assessment on the altered food substance, consider whether the applicable food additive or color additive regulation or FCN authorizes use of the altered food substance, and consult with and, if needed, make a regulatory submission to FDA regarding the impact of the manufacturing change.
- **GRAS food substances**: Manufacturers should follow the same steps described above, except that for food substances that are the subject of a GRAS regulation, manufacturers should consider whether the food substance remains within the scope of the GRAS regulation, and, if not, should make an appropriate regulatory submission following agency consultation. For foods subject to a GRAS determination, but not a GRAS regulation, manufacturers should consider whether the food substance is significantly different from that described in the previous GRAS determination, whether the manufacturing changes are so novel as to preclude general recognition, or the substance is no longer food grade as a result of impurities introduced by the manufacturing process change.[2] The manufacturer should make a regulatory submission as appropriate.

Nanotechnology and Cosmetic Products

In the Cosmetics Guidance, FDA describes the issues manufacturers should consider in assessing the safety of cosmetic products made with nanomaterials. As they do for cosmetics made through conventional manufacturing processes, manufacturers should, prior to marketing, substantiate the safety of cosmetic products made with nanomaterials. Safety can be substantiated through reliance on already existing toxicological test data for individual ingredients and similar product formulations, plus additional toxicological and other tests appropriate in light of existing data. Because

[2] FDA believes that nanotechnology applications to food substances will generally raise enough questions about the sufficiency of technical evidence and establishment of consensus among experts regarding product safety to warrant formal FDA premarket review rather than a GRAS determination.

nanomaterials may exhibit different physicochemical properties, behavior, and effects than larger-scale particles, traditional cosmetic product safety testing methods may not be fully applicable, and additional tests may be required. Tests should be adjusted as necessary to address the nanomaterial's key chemical and physical properties, which may affect its toxicity profile and the properties' effects on the formulation's function. Manufacturers should meet with the agency to establish proper testing methods for nanomaterial cosmetics to substantiate the product's safety.

Nanomaterial characterization forms an integral part of the cosmetics' safety assessment. Important factors include the proper identification of the nanomaterial's chemical composition,[3] its stability under intended conditions of use, and its impurities, structure, and configuration. FDA recommends that toxicological testing take into account the characterization of the nanomaterials as present in the raw material, formulation, test media, and relevant biological environment to determine their potential biological interactions and effects.

Manufacturers should assess both short- and long-term nanomaterial toxicity, including possible ingredient-ingredient and ingredient-packaging interactions. Manufacturers may need to adjust traditional toxicity test methods based on factors such as solvent and dosing formulations, solubility, particle agglomeration and aggregation, and stability conditions associated with nanomaterial cosmetics. Because free nanoparticles may have different chemical and biological properties than agglomerated or aggregated ones, FDA suggests conducting separate tests on these different nanoparticle formulations. In developing toxicological testing methods, manufacturers should consider the dose to primary and secondary target organs and make adjustments to traditional methodology to take into account the specific characteristics of the relevant nanomaterial.[4]

Nanotechnology and Animal Food

In its Animal Food Guidance, FDA provides a framework to help industry and other stakeholders identify potential issues regarding the safety or regulatory status of animal food that either contains nanomaterial or has been made using nanotechnology. Animal feed and pet food manipulated through nanotechnology may have altered biodistribution, biocompatibility, or toxicity when compared to larger particles of the same material. Animal food manufacturers should demonstrate that the nanomaterial version of an animal food ingredient is safe for its intended use, even if the larger-scale ingredient has already been established as safe. FDA is unlikely to find that these nanomaterials are GRAS, which may warrant premarket ingredient review. Before seeking FDA approval for a new use of nanotechnology, manufacturers should assess the nanomaterial additive's identity and characterization, byproducts and impurities associated with manufacturing the nanomaterial, intended use, use level, labeling, valid analytical methods to determine nanomaterial levels, safety of use by both target animals and humans and potential adverse environmental impact of the nanomaterial, and develop a proposed food additive regulation.

[3] FDA states that proper characterization of a nanomaterial includes particle size and distribution measurement, aggregation and agglomeration characteristics, surface chemistry, morphology, solubility, density, stability, and porosity.

[4] FDA also encourages testing with both intact and impaired skin if the cosmetic will result in exposure through dermal absorption and suggests manufacturers develop appropriate impaired skin models for these types of studies, if not already available. Manufacturers should include in a safety assessment a toxicokinetic and toxicodynamic examination for different exposure routes.

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. If you have any questions concerning the material discussed in this client alert, please contact any of the following:

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