Guidance for Industry

Safety of Nanomaterials in Cosmetic Products

Draft Guidance

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For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
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Safety of Nanomaterials in Cosmetic Products

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I. Introduction

This document provides guidance to industry and other stakeholders (e.g., academia, other regulatory groups) on FDA's current thinking on the safety assessment of nanomaterials in cosmetic products. It is intended to assist industry and other stakeholders in identifying the potential safety issues of nanomaterials in cosmetic products and developing a framework for evaluating them. This guidance also provides contact information for manufacturers and sponsors who wish to discuss with FDA safety considerations regarding the use of specific nanomaterials in cosmetic products.

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.

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

II. Background

Nanomaterials are used in a variety of FDA-regulated products because of their unique properties, imparting potential advantages to products considered for development. Nanotechnology, used to make nanomaterials, allows scientists to create, explore, and manipulate materials measured in nanometers (equal to one-billionth of a meter). Such materials can have chemical, physical, and biological properties that differ from those of their larger counterparts. Importantly, properties of a material might change in ways that could affect the performance, quality, safety, and/or effectiveness, if applicable, of a product that incorporates that specific nanomaterial.

FDA has not adopted a formal definition of "nanotechnology," "nanoscale," or related terms (Ref. 1). Although there are numerous definitions of "nanotechnology," the term is perhaps most commonly used to refer to the intentional manipulation, manufacture or selection of materials that have at least one dimension in the size range of approximately 1 to 100 nanometers. 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." Other factors such as function, shape, charge, the ratio of surface area to volume, and other physical or chemical properties have also been mentioned in various published definitions.[2]

[2] As discussed in the Task Force report, we believe it is appropriate to take into account the potential importance of material size and the evolving state of the science. However, while one definition for "nanotechnology," "nanoscale material," or a 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. As we learn more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform our judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in products we regulate.

In July of 2007, FDA issued a report prepared by its Nanotechnology Task Force. The Task Force report presented an assessment of scientific and regulatory considerations relating to the safety and effectiveness of FDA-regulated products containing nanomaterials and made recommendations in light of these considerations (Ref. 2).

The recommendations of the Task Force included proposals for FDA to provide assistance to manufacturers when the use of nanomaterials might require submission of additional data, change the product's regulatory status or pathway, or merit taking additional or special steps to address potential safety or product quality issues. The Task Force highlighted the need for FDA to evaluate the adequacy of current testing approaches to assess safety and other relevant characteristics of FDA-regulated products that use nanomaterials. Specifically, with respect to cosmetic products, the Task Force recommended that FDA issue guidance describing safety issues that manufacturers should consider to ensure that cosmetic products made with nanomaterials are safe and not adulterated. We are issuing this guidance as part of our effort to implement the Task Force recommendations (Ref. 2).

One of the other recommendations of the Task Force was that FDA request submission of data and other information addressing the effects of nanomaterials in those products that are not subject to premarket authorization, such as cosmetic products. On September 8, 2008, FDA held a public meeting to discuss such data and information, along with related scientific and regulatory issues concerning nanotechnology. FDA has considered the information obtained at, and subsequent to, the public meeting in developing this guidance. The agency has also considered information provided by the cosmetic industry to the International Cooperation on

Cosmetics Regulations (ICCR), publications and information regarding recent advances in nanotechnology, and other authoritative guidance/ reports for the safety of nanomaterials in preparing this guidance (Refs. 3, 4, 5, 6).

FDA recently issued draft guidance to industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (Ref. 1). As described in that guidance, 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. Once the guidance is finalized, the agency intends to apply these considerations broadly to all FDA-regulated products, including cosmetic products.

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. Rather, for nanotechnology-derived and conventionally-manufactured cosmetic products alike, FDA considers the characteristics of the finished product and the safety for its intended use. FDA's consideration of nanotechnology applications in cosmetic products in this document is consistent with the agency's draft guidance (Ref. 1) and with the broader federal guidance on regulatory oversight of emerging technologies (Ref. 7) and nanotechnology (Ref. 8).

III. Discussion

A. General Framework for Assessing the Safety of Nanomaterials in Cosmetic Products

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) prohibits the marketing of adulterated or misbranded cosmetics[3] in interstate commerce (21 U.S.C. 331(a)). The FD&C Act does not subject cosmetics or cosmetic ingredients (with the exception of color additives) to FDA premarket approval in order to be marketed legally in the United States. Except for color additives and those ingredients that are prohibited or restricted from use in cosmetics by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic provided that the use of the ingredient does not otherwise cause the cosmetic to be adulterated (sec. 601 of the FD&C Act (21 U.S.C. 361)) or misbranded (sec. 602 of the FD&C Act (21 U.S.C. 362)).[4]

It is the responsibility of the manufacturer of a cosmetic product to ensure that the product is not misbranded or adulterated. Although the FD&C Act does not require the approval of FDA prior to marketing a cosmetic product, manufacturers or distributors should have obtained all data and information needed to substantiate the safety of the product before marketing.

In the Federal Register of March 3, 1975 (40 FR 8912 at 8916), FDA advised that "the safety of a product can be adequately substantiated through (a) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to

[3] The FD&C Act defines cosmetics by their intended use as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap" (sec. 201(i) of the FD&C Act).

[4] The name of each ingredient must be declared on the label of the cosmetic product, as required by 21 CFR 701.3.

the particular cosmetic, and (b) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information. Although satisfactory toxicological data may exist for each ingredient of a cosmetic product, it will still be necessary to conduct some toxicological testing with the complete formulation to assure adequately the safety of the finished cosmetic."

At the nanoscale, properties of materials might change resulting in changes to the product's performance, quality, safety, and/or effectiveness (Ref. 2). Nanomaterials may have chemical, physical, or biological properties that are different from their larger counterparts. The use of nanomaterials may alter the bioavailability of the cosmetic formulation (Ref. 5). In some of these cases, the traditional safety tests that have been used to determine the safety of cosmetic ingredients and finished products may not be fully applicable. As noted in the 2007 FDA Nanotechnology Task Force report, there may be a higher degree of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way that testing is performed. In Section III.B of this document, we highlight key scientific considerations relevant to the assessment of the safety of nanomaterials used in cosmetic products.

If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an already marketed ingredient, FDA encourages you to meet with us to discuss the test methods and data needed to substantiate the product's safety, including short-term toxicity and other long-term toxicity data as appropriate. Individuals outside the Federal Government may request a private meeting with a representative of FDA to discuss a matter, and FDA will

make reasonable efforts to accommodate such requests (21 CFR 10.65(c)). We encourage you to take advantage of this provision and contact us to discuss any aspect of the safety assessment of cosmetic ingredients or finished products.

B. Points to Consider in Assessing the Safety of Nanomaterials in Cosmetic Products

FDA believes that the current general framework for safety assessment which includes hazard identification, dose-response assessment, exposure assessment, and risk characterization is generally robust and flexible enough to be considered appropriate for nanomaterials, even though they can have properties that may be different from conventional ones. However, standard safety tests may need to be modified or new methods developed to address (1) the key 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 safety assessment for cosmetic products using nanomaterials should address the physico-chemical characteristics of the nanomaterials, impurities, if present, and the potential product and ingredient exposure levels to help determine what other testing may be needed. The safety assessment should include consideration of the toxicity of both the ingredients and their impurities; dosimetry for in vitro and in vivo toxicology studies, if needed; and clinical testing, if warranted. The safety assessment should also address the issues of toxicokinetics and toxicodynamics. The overall package of data and information should substantiate the safety of the product under the intended conditions of use.

1. Nanomaterial Characterization

Nanomaterials vary widely in composition, morphology, and other characteristics and cannot be considered a uniform group of substances. These substances may have physical, chemical, or

biological properties that are different from those of their larger counterparts. Such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Ref. 6).

As discussed in the Task Force report, studies indicate that various attributes of a particular nanoscale material, including increased surface-area-to-volume ratio, morphology, surface features, and charge, can affect the distribution of that material in the body and that material's interaction with biological systems. For example, there are data indicating that both liposomes and nanoemulsions can increase transdermal and topical delivery of substances (Ref. 9, 10). They can modify the bioavailability and toxicological behavior of dispersed ingredients, and may create safety concerns (Ref. 2). Depending on the use, application, and exposure potential of each nanomaterial, appropriate physico-chemical parameters should be evaluated.

a. Physico-Chemical Properties

As with any cosmetic ingredient, the nanomaterial should be fully described:

- the nanomaterial name,
- the Chemical Abstracts Service (CAS) number,
- the structural formula,
- the elemental composition including:
    - the degree of purity, and
    - any known impurities or additives.

A thorough understanding of the details of the manufacturing process will help identify residual additives and impurities, as well as certain other physical and chemical properties.

A wide range of physical and chemical properties should be evaluated to help determine if a substance produced with nanotechnology is safe for the proposed use. Proper characterization should include:

- measurement of particle size and distribution,
- aggregation and agglomeration characteristics,
- surface chemistry, including:
    - zeta potential/surface charge, surface coating,
    - functionalization, and
    - catalytic activity
- morphology including:
    - shape,
    - surface area,
    - surface topology, and
    - crystallinity
- solubility,
- density,
- stability, and
- porosity (Ref. 11).

The long-term stability of the nanomaterial in a formulation under intended conditions of use should be considered as well. Nanomaterials may agglomerate and interact with other ingredients of the formulation (Refs. 12, 13).

b. Impurities

As with any cosmetic ingredient, a change in the starting material used to prepare a formulation will likely result in different impurities in the final product. Variables such as altered purity, altered concentration of the starting materials, or changes in its identity should be considered. A manufacturer should assess the quality and quantity of impurities and how they may affect the overall safety of the end product.

It is also important to understand how the nanomaterial is manufactured. Nanoscale impurities may arise from the manufacturing process. Changes in the manufacturing process, including use of different solvents, time/temperature conditions and changes to the starting chemicals (*e.g.,* alternative starting materials, different purity levels or different concentrations of the chemicals used in the process) may change the types and/or quantities of impurities in the final product. Additional agents, such as dispersing agents and surface modifiers, are often used in the manufacture of nanomaterials. These additional agents and impurities should be considered in the safety substantiation for nanomaterials.

2. Toxicology Considerations

The appropriateness of toxicological testing depends on the intended use, exposure levels, and degree of concern for potential toxicity of an ingredient or formulation. For nanomaterials, manufacturers should consider modifying traditional toxicity testing with respect to such factors as appropriate solvents and dosing formulations, methods to prevent agglomeration of particles, purity and stability conditions, and other variables (Ref. 2). In instances where traditional toxicity testing methods cannot be satisfactorily modified, FDA recommends developing new methods to address particular safety issues. The design of safety testing should consider each ingredient's chemical structure and physico-chemical properties, purity/impurities,

agglomeration and size distribution, stability, conditions of exposure, uptake and absorption, bioavailability, toxicity, and any other qualities that may affect the safety of the product according to its intended use. The testing methods used should address the issues of both short-term and long-term toxicity of nanomaterials. The method of safety testing may also warrant further evaluation for possible ingredient-ingredient interactions or ingredient-packaging interactions.

a. Routes of Exposure

The safety of an ingredient is based in part on the potential for exposure and the relevant routes of exposure that are determined by its intended use and its application. Although most cosmetic products are applied directly to the skin, some products may be applied by spray presenting the possibility of inhalation exposure. Additionally, some cosmetic products are applied in an area where there is the possibility of oral exposure. Evidence suggests that in addition to direct exposure to tissues locally via dermal, inhalation, and oral routes, nanomaterials may also become systemically absorbed, creating exposure to other tissues and organs (Refs. 14, 15). Therefore, for nanomaterials, the dose of the intake organ as well as the dose in secondary target organs should be considered in developing or modifying toxicological testing methods and for evaluating the test data (Ref. 5).

b. Uptake and Absorption

As stated above, some nanomaterials have unique physicochemical properties that may alter the potential toxicity of a compound (e.g. reduction in particle size could increase the ability for the compound or its constituents to be absorbed). Therefore, the safety assessment should address whether there will be an increase in uptake, absorption, transport into cells, and transport across barriers (e.g. blood-brain barrier) or altered bioavailability or biological half-life. The

manufacturer should consider if there are any specific toxicity issues related to the changes in structure or activity. For example, there may be an increase in the dose delivered to sensitive tissues due to the increased ability of the nanomaterial to pass through the blood-brain barrier (Ref. 16).

Nanomaterials can be divided into two groups: (1) soluble and/or biodegradable nanoparticles which disintegrate into their molecular components (e.g. liposomes and nanoemulsions) upon application to skin, and (2) insoluble and/or biopersistent nanoparticles (e.g. TiO_2, fullerenes, quantum dots). Risk assessment based on mass metrics may be adequate for the soluble nanoparticles; however, insoluble nanoparticles may require other metrics, such as the number of particles, and their surface area as well as their distribution (Ref. 5).

For exposure via dermal absorption, studies should be conducted for intact skin and impaired skin (e.g. sunburned, atopic, eczematous, psotiatic skin) to address the possibility of an increased rate of penetration and ability of the ingredient to become systemically absorbed. The passive transport of many nanomaterials may not occur through intact skin, but there is a substantially increased probability for entry of nanomaterials through skin with an impaired barrier layer (Ref. 17). A variety of techniques used to study and quantify skin penetration of chemicals are discussed in current literature (Refs. 18, 19).

The use of aerosolized cosmetic products can also result in exposure to nanomaterials via the respiratory tract. The deposition of nanomaterials in the respiratory system depends on their aerosol properties and interactions with respiratory epithelium. The soluble nanoparticles may

be dissolved, metabolized and transported to other organs and blood whereas the insoluble nanoparticles may be retained in the airways or swallowed by coughing. As discussed earlier, the physical characteristics, including surface properties of nanomaterials, are important factors that warrant careful attention, particularly for inhaled nanoscale particles. Studies have indicated that decreasing the size of particles increases the surface area, resulting in potential adverse effects not only in the respiratory system, but also in the heart and blood vessels, the central nervous system, and the immune system (Ref. 20).

Exposure via the oral route is generally limited to those products that are introduced into or applied near the mouth (e.g., mouthwash, lipsticks). Limited evidence suggests that the nanomaterials uptake and translocation towards circulation depends on the size, surface charge, and surface ligand modification of nanomaterials (Ref. 20). Studies have indicated that nanomaterials have limited uptake in the gastrointestinal tract, but the translocation through the intestinal barrier of the biodegradable and non-biodegradable nanomaterials can be substantially increased (Refs. 21, 22).

Therefore, FDA recommends that the safety assessment process for nanomaterials should include the issues of toxicokinetics and toxicodynamics with reference to different exposure routes.

c. Toxicity Testing

The initial step in the evaluation of the safety assessment of cosmetic products is to conduct toxicity testing based on a toxicological profile of the ingredients and their routes of exposures. There are several guidelines (Refs. 4, 23, 24) for conducting toxicity testing (tiered testing strategy) of chemicals that can be used as a starting point in evaluating toxicity of nanomaterial

ingredients. Consistent with the guidelines issued by the Cosmetic, Toiletry and Fragrance Association (CTFA) (Ref. 23) and Organization for Economic Co-operation and Development (OECD) (Ref. 3), FDA recommends, at a minimum, testing for acute toxicity, skin irritation, dermal photoirritation, skin sensitization, mutagenicity/genotoxicity, repeated dose (21-28 days) toxicity, and subchronic (90 days) toxicity (Ref. 24). FDA also recommends phototoxicity testing (Ref. 25) for cosmetic products and cosmetic ingredients as provided for drugs and drug ingredients. Results obtained from this basic test battery may indicate a need for additional testing.

As stated previously, in designing tests for use with nanomaterials in cosmetics products, manufacturers should consider modifying traditional toxicity testing with respect to such factors as appropriate solvents and dosing formulations, methods to prevent agglomeration of particles, purity and stability conditions, and other variables. New methods may also need to be developed if traditional tests cannot be modified satisfactorily. For example, the Ames test, recommended as a battery of genotoxicity testing for conventional chemicals, may not be suitable for poorly soluble nanomaterials used in cosmetic products, because the bacterial cell wall may create a possible barrier for many nanomaterials (Ref. 26).

Toxicity testing *in vivo* has long been considered indispensable for obtaining information on translocation, biodistribution, accumulation, and clearance (Ref. 27). While conducting *in vivo* toxicity testing for nanomaterials, careful attention should be paid to the issue of dosimetrics. The manufacturer should consider the surface area and number of particles, as well as mass concentration in the study design of *in vivo* toxicity testing. For *in vivo* studies via the dermal

route of administration, the test substance should be applied directly to the skin, and for the oral route of administration, the test substance should be given either by gavage or in the diet. Agglomeration or aggregation characteristics of nanomaterials in the topical vehicle, gavage or feed matrix are other important factors to assess prior to conducting these studies for safety assessment. Additionally, the potential for nanomaterials to penetrate through the skin or be absorbed through the gut, becoming available for biodistribution, is another factor to assess while estimating the risks associated with the exposure of nanomaterials.

There has been recent emphasis on the development of validated methods for *in vitro* testing of cosmetic products by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the European Center for the Validation of Alternative Methods (ECVAM). The seventh amendment to the EU Cosmetic Directive (2003/15/EC) (Ref. 28) instituted a ban on animal testing of cosmetic products in 2004 and a ban on certain animal tests with validated alternatives in March of 2009. FDA recommends validation of *in vitro* methods for safety testing of cosmetic products and ingredients and optimizing these models for nanomaterials, with particular attention being paid to the issues of cytotoxicity and precipitation of insoluble ingredients. Nanomaterials can settle, diffuse, and aggregate differentially according to their size, density, and surface chemistry (Ref. 29). Thus, the assessment of the agglomeration or aggregation of nanomaterials in the media used in the *in vitro* system should be addressed.

Alternative testing methods currently under consideration that can be optimized for a specific nanomaterial and might be useful to help determine ingredient safety include:

1. Reconstructed human skin such as Episkin™ and Epiderm ™ for skin irritation and corrosion testing;
2. Phototoxicity testing via 3T3 NRPT (3T3 fibroblasts neutral red uptake phototoxicity testing) applicable to ultra violet (UV) absorbing substances;
3. Human/pig skin in a diffusion cell for dermal absorption;
4. Bovine Corneal Opacity and Permeability (BCOP) and the Isolated Chicken Eye (ICE) for ocular irritation; and
5. Genotoxicity testing using a battery of three recommended tests: bacterial reverse mutation test, *in vitro* mammalian cell gene mutation test or *in vitro* mammalian chromosomal aberration test, and *in vitro* micronucleus test. While conducting genotoxicty the nanomaterial's specific properties should be taken into account to understand the mechanism of nanomaterials genotoxic effects (Ref. 26).

Finally, FDA notes that *in vivo* studies may be more suitable for nanoscale particles with limited solubility properties.

C. Summary of Recommendations

In summary, inclusion of nanomaterials in an FDA-regulated product or a change in the nanomaterials used might affect the quality, safety, effectiveness, and/or public health impact of the product. Therefore, as with any cosmetic product that has new or altered properties, data needs and testing methods should be evaluated accordingly to address the unique properties and function of the nanomaterials used in the cosmetic products as well as the questions that continue to remain about the applicability of traditional safety testing methods to products that involve nanotechnology. FDA recommends that the safety assessment for cosmetic products using nanomaterials should address several important factors such as:

- the physico-chemical characteristics,
- agglomeration and size distribution of nanomaterials at the toxicity testing conditions which should correspond to those of a final product,
- impurities,
- potential product exposure levels, and the potential for agglomeration of nanoparticles in the final product,
- dosimetry for *in vitro* and *in vivo* toxicology studies,
- *in vitro* and *in vivo* toxicological data on ingredients and their impurities, dermal penetration, irritation (skin and eye) and sensitization studies, mutagenicity/ genotoxicity studies, and
- clinical studies to test the ingredient, or finished product, in human volunteers under controlled conditions.

FDA expects that the science surrounding nanomaterials will continue to evolve and be used in the development of new testing methods.

In conclusion, the safety of a cosmetic product should be evaluated by analyzing the physico-chemical properties and the relevant toxicological endpoints of each ingredient in relation to the expected exposure levels resulting from the intended use of the finished product. If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an already marketed ingredient, FDA encourages you to meet with us to discuss the test methods and data needed to substantiate the product's safety, including short-term toxicity and other long-term toxicity data as appropriate. We welcome your contacting us with other questions relating to the use of nanomaterials in cosmetic products.

IV. How to Contact FDA About this Guidance

Contact the Office of Cosmetics and Colors at 240-402-1130 if you have questions or would like to meet with us. You may also contact FDA by email at industry.cosmetics@fda.gov.

V. References

We have placed these references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of April 16, 2012 FDA had verified the Web site addresses for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after April 16, 2012.

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