GUIDANCE DOCUMENT

Guidance for Industry: Safety of Nanomaterials in Cosmetic Products

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Center for Food Safety and Applied Nutrition, Office of Cosmetics and Colors

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- Nanotechnology and Cosmetics (http://wcms-internet.fda.gov/nanotechnology-0)

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. The guidance document 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 safety considerations regarding the use of specific nanomaterials in cosmetic products with FDA. This guidance is not applicable to other products regulated by FDA, including over-the-counter and prescription drugs and medical devices.

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 our guidances means that something is suggested or recommended, but not required.

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. Such materials, due to their nanoscale size, can have chemical, physical, and biological properties that differ 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. 1). These new or altered properties may affect the performance, quality, safety, and/or effectiveness, if applicable, of a product that incorporates that nanomaterial.

In July of 2007, FDA issued a report prepared by its Nanotechnology Task Force ("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). Specifically, with respect to cosmetic products, the Task Force recommended that we 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 ongoing efforts to implement the Task Force recommendations (Ref. 2).

The Task Force also recommended 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 considered the information obtained at, and subsequent to, the public meeting in developing this guidance. We 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 regarding the safety of nanomaterials (Refs. 3, 4, 5, 6). This guidance also refers to other relevant reports, such as the Organization for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterials "Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials" (Ref. 7), the Scientific Committee on Consumer Safety (SCCS) "Guidance on the Safety Assessment of Nanomaterials in Cosmetics" (Ref. 8), and relevant ICCR reports, such as on the "Currently Available Methods for Characterization of Nanomaterials," and "Principles of Cosmetic Product Safety Assessment." (Refs. 9, 10).

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. In June 2014, FDA issued a guidance for industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (Ref. 1). As described in that guidance, at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask: (1) 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 (2) whether a material or end product is engineered to exhibit 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 (1,000 nm). We will 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 particular examination.

However, we do 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, we consider the characteristics of the finished product and the safety for its intended use. Our consideration of nanotechnology applications in cosmetic products in this document is consistent with the agency guidance (Ref. 1) and with the broader federal guidance on regulatory oversight of emerging technologies and nanotechnology.

III. Discussion

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

Section 301(a) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 331(a)) prohibits the marketing of adulterated or misbranded cosmetics[2] in interstate commerce. 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 (section 601 of the FD&C Act (21 U.S.C. 361)) or misbranded (section 602 of the FD&C Act (21 U.S.C. 362)).[3]

Cosmetic product manufacturers must ensure that the product is not misbranded or adulterated. The FD&C Act does not give us the authority to require that safety data be submitted to us or to approve a cosmetic product before it is marketed. Nevertheless, manufacturers or distributors are responsible for obtaining all data and information needed to substantiate the safety of their products before introducing them into the marketplace.

In the Federal Register of March 3, 1975 (40 FR 8912 at 8916), we 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 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."

We believe that these general principles are applicable to the safety substantiation of cosmetic products whether they contain nanomaterials or conventionally manufactured ingredients. In applying these principles, however, it may be important to give particular

consideration to the fact that a material at nanoscale may show changes in, or have novel, physicochemical properties, behaviors, and/or effects that could be different from a larger scale material with the same chemical composition (Refs. 2, 8).

For example, the small particle size of a nanomaterial has the potential to alter the distribution and bioavailability of that material compared to a larger scale material with the same chemical composition. The small size leads to increased surface area relative to the mass of the particle, which could result in increased biological interactions. In addition, the uptake, absorption, and biodistribution of the material may be altered, leading to potential systemic exposure (Refs. 5, 8).

In some cases, the traditional testing methods that have been used to determine the safety of cosmetic ingredients and finished products may not be fully applicable due to a nanomaterial's distinctive properties and behavior. Such distinctive physicochemical characteristics or biological interactions may affect the results or interpretation of results obtained from traditional toxicology testing, which form an integral part of safety substantiation. 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, we encourage you to meet with us to discuss the test methods and data that might help substantiate the product's safety, including short-term toxicity and long-term toxicity data, as appropriate. We encourage you to 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

We consider the current framework for safety assessment sufficiently robust and flexible to be appropriate for a variety of materials, including products containing nanomaterials. Just as the traditional safety assessment includes material characterization and toxicology considerations, safety evaluations of cosmetic products containing nanomaterials should also take these considerations into account. As noted in section III.A, nanomaterials may exhibit new or altered physicochemical properties that may affect biological interactions, which may raise questions about the safety of the product containing nanomaterials. Any such unique properties or biological effects of nanomaterials should be identified and appropriately addressed during safety evaluations.

With respect to nanomaterial characterization, safety should be assessed through fully describing the nanomaterial and evaluating a wide range of physical and chemical properties, as well as through the assessment of impurities, if present. The toxicology and absorption,

distribution, metabolism, and excretion considerations for nanomaterials in cosmetic products can be informed by addressing the routes of exposure, the uptake and absorption, and toxicity testing. In addition, any distinctive properties and biological behavior of nanomaterials should be considered in determining the suitability of traditional testing methods for toxicity testing of cosmetic products containing nanomaterials. As needed, traditional toxicity testing methods should 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 toxicological testing should include consideration of toxicity of both the ingredients and impurities; dosimetry for *in vitro* and *in vivo* toxicology studies, if needed; clinical testing, if warranted; and toxicokinetics and toxicodynamics. The overall package of data and information should substantiate the safety of the product under the intended conditions of use. These considerations are discussed in greater detail in sections III.B.1 and III.B.2 below.

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 larger scale material with the same chemical composition. As stated earlier, 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 FDA 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 (Ref. 2, 8). Therefore, thorough characterization of nanomaterials can form an integral part of the safety assessment. This would include proper identification of the chemical composition as well as impurities, structure, and configuration of the nanomaterial(s) used in the cosmetic product. In addition, characterization of the nanomaterial(s) as present in the raw material, formulation, test media, and in the relevant biological environment for toxicological testing should be considered to help determine potential biological interactions and effects (Ref. 8). In addition, stability of the nanomaterial under testing conditions and in a formulation under intended conditions of use should be determined.

a. Physicochemical Properties

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

- the nanomaterial name,

- the Chemical Abstracts Service (CAS) number,
- the structural formula,
- the elemental and molecular 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 (Refs. 7, 11, 12, 15). Proper characterization should include, as appropriate:

- 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.

Although a wide range of analytical techniques are available for measurement of physicochemical properties of materials (Refs. 8, 9, 16), many of these methods have not been validated for the evaluation of nanomaterials in cosmetic products. Therefore, appropriate analytical methods suitable for the specific nanomaterial and the cosmetic product formulation should be chosen, and results obtained from such tests appropriately

interpreted and reported for adequate characterization of the material.

b. Impurities

As with any cosmetic ingredient, a change in the starting material used to prepare a formulation will likely result in altered composition of the final product, which may result in different impurities. Variables such as altered purity or changes in the starting material should be considered. A manufacturer should assess the identity 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 in cosmetic products.

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. In determining what toxicological testing may be appropriate, manufacturers should consider each ingredient's chemical structure and composition, and physicochemical 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 for its intended use. Manufacturers should address both short-term and long-term toxicity of nanomaterials (Ref. 8), and consider the need to evaluate the possibility of ingredient-ingredient interactions or ingredient-packaging interactions.

Where traditional toxicity test methods are used, manufacturers should consider the applicability of the test methods and, as needed, modify them with respect to such factors as appropriate solvents and dosing formulations, solubility, agglomeration and aggregation of particles, and stability conditions associated with the cosmetic product containing nanomaterials (Refs. 2, 17, 18). For example, whether a nanomaterial is soluble, insoluble, or partially-soluble may affect the suitability of a traditional toxicity test method. Some traditional *in vivo* test methods may be suitable for only soluble nanomaterials (Ref. 17). Some traditional *in vitro* and *in vivo* test methods may need to be adjusted for testing insoluble or partially-soluble nanomaterials (Refs. 7, 18). These considerations are important because nanoparticles tend to stick to each other to form larger agglomerates/aggregates that

may be insoluble. Therefore, in a dosing or test medium, nanomaterials may be present as a nano-dispersion rather than in solution (Refs. 7, 18). Agglomeration and aggregation of particles is another factor that may affect the suitability of traditional toxicity testing methods, and manufacturers should ensure that testing appropriately reflects the range of free particles and any aggregates or aggolomerates found in the cosmetic product formulation. Toxicological testing may need to be conducted separately on the free nanoparticles and the agglomerated/aggregated nanoparticles because they will likely have different chemical and biological properties. Due to their high surface energy, nanomaterials may also interact with the testing medium or bind to different substances, including proteins, in the test medium, resulting in an altered biological activity (Refs. 8, 19, 20, 21). Thus, manufacturers should consider and make necessary adjustments to traditional toxicity testing methods, taking into account the specific characteristics of the nanomaterial as it is intended to be used in the cosmetic product. In instances where traditional toxicity testing methods cannot be satisfactorily modified, FDA recommends developing new methods to adequately assess the toxicity of the nanomaterial in the cosmetic product and ensure the product is safe.

It is also important to mention that the dose metrics currently used for toxicological testing of conventionally manufactured chemicals (measured and expressed in mass, volume or number of particles such as mg/kg, or mg/L) may not be appropriate for nanomaterials because of their large surface area per particle mass or volume (Refs. 5, 8). In addition to weight/volume metrics, evaluations of the safety of nanomaterials should also consider alternative metrics, such as weight/volume concentration, particle number concentration and surface area, until suitable parameters for dose metrics become available.

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. Additionally, systemic absorption can result from dermal, inhalation, ocular and oral exposures (Refs. 22, 23). Therefore, for nanomaterials, the dose to the primary exposure organs as well as the dose to any 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 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. 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. 24).

Nanomaterials used in cosmetic products can be divided into two groups: (1) soluble and/or biodegradable nanoparticles, which disintegrate into their molecular components (e.g. some liposomes and nanoemulsions) upon application to skin and thus may not raise safety questions, and (2) insoluble, sufficiently stable and/or biopersistent nanoparticles (e.g. titanium dioxide (TiO_2), fullerenes, and quantum dots). Some insoluble, partially-soluble or sufficiently stable nanomaterials, particularly those in the lower nanoscale range and with certain surface characteristics, may be able to cross biological membrane barriers (Ref. 25) and may have harmful effects due to the potential interaction with organs and cellular compartments. Thus, when there is evidence of systemic exposure to nanomaterials, manufacturers should consider including absorption, distribution, metabolism, and excretion (ADME) parameters in safety assessments of the nanomaterial in the cosmetic product (Ref. 8).

For exposure via dermal absorption, studies should be conducted with both intact skin and impaired skin (e.g. sunburned, atopic, eczematous, psoriatic, or systematically damaged 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 an increased probability for entry of nanomaterials through skin with an impaired barrier layer (Refs. 26, 27). A variety of techniques used to study and quantify skin penetration of chemicals are discussed in the literature (Refs. 28, 29). We recognize that there are limitations to using impaired skin models for conducting dermal absorption studies as there is currently no standard or established method(s). We encourage manufacturers to develop appropriate impaired skin models for dermal absorption studies.

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 either retained in the airways and result in pulmonary effects or swallowed by coughing and cleared. 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 and increasing the surface area can result 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. 30).

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 uptake of nanomaterials and systemic absorption depends on their size, surface charge, and surface ligand modification (Ref. 30). Additional studies have indicated that nanomaterials have limited uptake in the gastrointestinal tract, but the translocation to certain regions of the intestinal barrier can be substantially increased (Refs. 31, 32).

Therefore, we recommend that the safety assessment process for nanomaterials 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 exposure. There are several guidelines (Refs. 4, 33, 34) 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. 33) and the Organization for Economic Co-operation and Development (OECD) (Ref. 3), we recommend, at a minimum, testing for acute toxicity, skin irritation, ocular irritation, dermal photoirritation, skin sensitization, mutagenicity/ genotoxicity, repeated dose (21-28 days) toxicity, and subchronic (90 days) toxicity (Ref. 34). We also recommend phototoxicity testing (Ref. 35) for a cosmetic product that is intended to be used on sun-exposed skin. Results obtained from this basic test battery may indicate a need for additional testing. Where available, other relevant data, such as toxicological data on individual ingredients that are similar in composition to the nanomaterial or data on a larger scale material with the same chemical composition as the nanomaterial, can also be considered.

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, 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 part of a battery of genotoxicity testing for conventional chemicals, may not be suitable for insoluble or partially-soluble nanomaterials used in cosmetic products because the bacterial cell wall may create a possible barrier for many nanomaterials (Ref. 36).

Toxicity testing *in vivo* has long been considered indispensable for obtaining information on translocation, biodistribution, accumulation, and clearance (Ref. 37). As mentioned earlier, while conducting *in vivo* toxicity testing for nanomaterials, careful attention should be paid to the issue of dose metrics (mass, volume or number of particles). 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 and becoming available for biodistribution, should be addressed while estimating the risks associated with the exposure to 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 Directive 2003/15/EC of the European Parliament and of the Council (Ref. 36) instituted a ban on animal testing of cosmetic products in 2004 and a ban on certain animal tests with validated alternatives in March 2009. We recommend 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. 37). 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 EpiskinTM and Epiderm TM 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 recommended tests covering the endpoints of gene mutation, and structural and numerical aberrations. While conducting genotoxicty tests, the nanomaterial's specific properties should be taken into account to understand the mechanism of nanomaterials' genotoxic effects (Ref. 36).

Finally, we note that *in vivo* studies may be more suitable for nanomaterials with limited solubility properties (Ref. 8).

C. Summary of Recommendations

In summary, nanomaterials can have chemical, physical, and biological properties that differ from those of larger scale particles with the same chemical composition, and the use of nanomaterials in cosmetic products may raise questions about the safety of the product for its intended use. As with any cosmetic product that has new or altered properties, data needs and testing methods should be evaluated to address any 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. We recommend that the safety assessment for cosmetic products using nanomaterials should address several important factors, including:

- the physicochemical characteristics,
- agglomeration and size distribution of nanomaterials under the conditions of toxicity testing and as expected in the final product,
- impurities,
- potential routes of exposure to the nanomaterials,
- potential for aggregation and agglomeration of nanoparticles in the final product,
- dosimetry for *in vitro* and *in vivo* toxicology studies, and
- *in vitro* and *in vivo* toxicological data on nanomaterial ingredients and their impurities, dermal penetration, potential inhalation, irritation (skin and eye) and sensitization studies, mutagenicity/genotoxicity studies.

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

The safety of a cosmetic product should be evaluated by analyzing the physicochemical properties and the relevant toxicological endpoints of each ingredient in relation to the expected exposure 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, we encourage 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 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.cosm

(mailto:industry.cosmetics@fda.gov)etics@fda.gov. (mailto:tics@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 June 3rd , 2014 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 June 23rd , 2014.

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[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.

[2] 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" (section 201(i) of the FD&C Act).

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

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