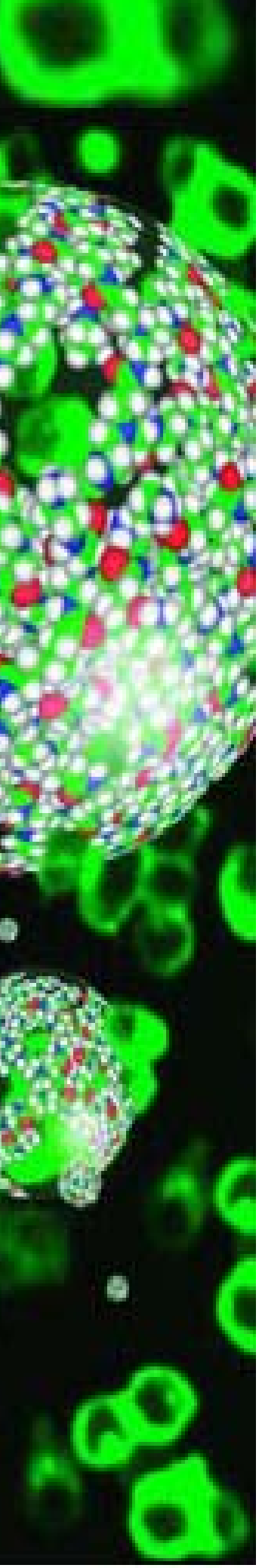

Nanotechnology

A Report of the

U.S. Food and Drug Administration

Nanotechnology Task Force

July 25, 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: July 23, 2007

TO: Deputy Commissioner for Policy
Associate Commissioner for Science

FROM: Commissioner of Food and Drugs

SUBJECT: Nanotechnology Task Force Report

Thank you for submitting to me the Nanotechnology Task Force Report. Nanotechnology holds great promise for the development of new treatments and diagnostics. However, as with other emerging technologies, it poses questions regarding the adequacy and application of our regulatory authorities. I commend you and the rest of the Nanotechnology Task Force on your efforts in developing this report and its recommendations to improve the FDA's scientific knowledge of nanotechnology and to address the regulatory challenges that may be presented by products that use nanotechnology. I appreciate the fact-finding efforts that the Task Force undertook, such as holding the October 2006 public meeting and soliciting public comment, to understand the issues and provide me with informed recommendations.

I endorse the report and its recommendations. This includes the recommendations to issue additional guidance to provide greater predictability of the pathways to market and for ensuring the protection of public health. Please move forward with these recommendations, pursuant to FDA's good guidance practice (GGP) process (21 CFR 0.115), as appropriate.

Andrew C. von Eschenbach, M.D.

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Executive Summary

As other emerging technologies have in the past, nanotechnology poses questions regarding the adequacy and application of regulatory authorities. The then Acting Commissioner of the Food and Drug Administration (FDA) initiated the Nanotechnology Task Force (Task Force) in 2006 to help assess these questions with respect to FDA's regulatory authorities, in light of the current state of the science for nanotechnology. This report offers the Task Force's initial findings and recommendations to the Commissioner.

The report includes:

- A synopsis of the state of the science for biological interactions of nanoscale materials;
- Analysis and recommendations for science issues; and
- Analysis and recommendations for regulatory policy issues.

The report addresses scientific issues as distinct from regulatory policy issues in recognition of the important role of the science in developing regulatory policies in this area, rapid growth of the field of nanotechnology, and the evolving state of scientific knowledge relating to this field. Rapid developments in the field mean that attention to the emerging science is needed to enable the agency to predict and prepare for the types of products FDA may see in the near future.

A general finding of the report is that nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies. However, these challenges may be magnified both because nanotechnology can be used in, or to make, any FDA-regulated product, and because, at this scale, properties of a material relevant to the safety and (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range. In addition, the emerging and uncertain nature of the science and potential for rapid development of applications for FDA-regulated products highlights the need for timely development of a transparent, consistent, and predictable regulatory pathway.

The Task Force's initial recommendations relating to scientific issues focus on improving scientific knowledge of nanotechnology to help ensure the agency's regulatory effectiveness, particularly with regard to products not subject to premarket authorization requirements. The report also addresses the need to evaluate whether the tools available to describe and evaluate nanoscale materials are sufficient, and the development of additional tools where necessary.

The Task Force also assessed the agency's regulatory authorities to meet any unique challenges that may be presented by FDA-regulated products containing nanoscale materials. This assessment focused on such broad questions as whether FDA can identify products containing nanoscale materials, the scope of FDA's authorities to evaluate the safety and effectiveness of such products, whether FDA should require or permit products to be labeled as containing nanoscale materials, and whether the use of nanoscale materials in FDA-regulated products raises any issues under the National Environmental Policy Act.

The Task Force concluded that the agency's authorities are generally comprehensive for products subject to premarket authorization requirements, such as drugs, biological products, devices, and food and color additives, and that these authorities give FDA the ability to obtain detailed scientific information needed to review the safety and, as appropriate, effectiveness of products. For products not subject to premarket authorization requirements, such as dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS), manufacturers are generally not required to submit data to FDA prior to marketing, and the agency's oversight capacity is less comprehensive.

The Task Force has made various recommendations to address regulatory challenges that may be presented by products that use nanotechnology, especially regarding products not subject to premarket authorization requirements, taking into account the evolving state of the science in this area. A number of recommendations deal with requesting data and other information about effects of nanoscale materials on safety and, as appropriate, effectiveness of products. Other recommendations suggest that FDA provide guidance to manufacturers about when the use of nanoscale ingredients may 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 also recommends seeking public input on the adequacy of FDA's policies and procedures for products that combine drugs, biological products, and/or devices containing nanoscale materials to serve multiple uses, such as both a diagnostic and a therapeutic intended use. The Task Force also recommends encouraging manufacturers to communicate with the agency early in the development process for products using nanoscale materials, particularly with regard to such highly integrated combination products.

The guidances the Task Force is recommending would give affected manufacturers and other interested parties timely information about FDA's expectations, so as to foster predictability in the agency's regulatory processes, thereby enabling innovation and enhancing transparency, while protecting the public health.

Introduction

Nanoscale materials often have chemical, physical, 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. Because of these properties, nanoscale materials have great potential for use in a vast array of products. Of particular interest to the Food and Drug Administration (FDA, the agency), nanoscale materials may enable new developments in products to advance public health. Also because of some of their special properties, nanoscale materials may pose different safety issues than their larger or smaller (i.e., molecular) counterparts.

FDA is generally responsible for overseeing the safety and effectiveness of drugs and devices for humans and animals, and of biological products for humans. The agency is also generally responsible for overseeing the safety of foods (including food additives and dietary supplements), color additives, and cosmetics.[1] The agency conducts these oversight functions under a variety of laws and regulations, which establish the specific pre-market and/or post-market oversight mechanisms applicable to a particular class of products. Most of the laws and regulations under which FDA operates were written before the advent of nanotechnology. Most are general in nature by design, however, offering flexibility to accommodate products made with new technologies or containing new kinds of materials.

Research and development relating to nanotechnology applications promises the development of products having multiple, highly integrated functions. FDA will need to anticipate this shift in the nature of products received for review and authorization. For example, disease diagnosis, drug targeting, and non-invasive imaging elements are being combined in individual nanotechnology products.[2] A goal of this report is to assist in the development of a transparent, consistent, and predictable regulatory pathway for such products.

More broadly, this report is intended to outline ways in which FDA can both (1) enhance its knowledge of nanotechnology to support its oversight for products using such technology and (2) inform interested stakeholders of what information may need to be developed to support the marketing of FDA-regulated products that use nanoscale materials.

FDA is a member agency in the National Nanotechnology Initiative (NNI), a federal research and development program established to coordinate the multi-agency efforts in

[1] Among other requirements, the Federal Food, Drug, and Cosmetic Act requires that drugs and devices be safe, and the Public Health Service Act requires that biological products be safe. Among other requirements, the FFDCA states that food and cosmetics must not be adulterated. For convenience, in this report the term "safe" is used not only in reference to drugs, devices, and biological products but also in reference to foods and cosmetics as an approximate short-hand for "not adulterated." See 21 USC 342, 361, defining the term "adulterated" for foods and cosmetics. In addition to regulating their safety, the agency also regulates use claims made with regard to foods and cosmetics, including claims regarding the effects of these products. However, in keeping with the primary focus of the Task Force's mandate, this report addresses mainly issues relating to the safety of these products.

[2] See for example descriptions of research and development activities at: http://nint-innt.nrc-cnrc.gc.ca/research/index_e.html; http://www.jst.go.jp/kisoken/nano/en/VirlaboResearchY01.html ; http://nano.cancer.gov/resource_center/cancer_nanotechnology_brochure.pdf.

nanoscale science, engineering, and technology. The goals of the NNI are to: (1) maintain a world-class research and development program aimed at realizing the full potential of nanotechnology; (2) facilitate transfer of new technologies into products for economic growth, jobs, and other public benefit; (3) develop educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and, (4) support responsible development of nanotechnology. FDA centers are conducting nanoscale material research within programs that support their specific regulatory priorities. Participation in the NNI provides FDA and the other regulatory and research funding agencies the opportunity to define their research needs.

Task Force Mission

In August 2006, then Acting Commissioner of Food and Drugs, Andrew C. von Eschenbach, M.D., announced the formation of an internal FDA Nanotechnology Task Force. He charged the Task Force with determining regulatory approaches that would enable the continued development of innovative, safe, and effective FDA-regulated products that use nanoscale materials.[3] The Task Force was asked to identify and recommend ways to address any knowledge or policy gaps that exist to better enable the agency to evaluate safety aspects of FDA-regulated products that contain nanoscale materials. Specifically, the Task Force was directed to:

- Chair a public meeting to help FDA further its understanding of developments in nanoscale materials that pertain to FDA-regulated products, including new and emerging scientific issues such as those pertaining to biological interactions that may lead to either beneficial or adverse health effects;

- Assess the current state of scientific knowledge pertaining to nanoscale materials for purposes of carrying out FDA's mission;

- Evaluate the effectiveness of the agency's regulatory approaches and authorities to meet any unique challenge that may be presented by the use of nanoscale materials in FDA-regulated products;

- Explore opportunities to enable innovation using nanoscale materials to develop safe and effective drugs, biologics and devices, and to develop safe foods, feeds, and cosmetics;

- Continue to strengthen FDA's collaborative relationships with other federal agencies, including the agencies participating in the NNI such as the National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA), as well as with foreign government regulatory bodies, international organizations, healthcare professionals, industry, consumers, and other stakeholders, to gather information regarding nanoscale materials used or that could be used in FDA-regulated products;

- Consider appropriate vehicles for communicating with the public about the use of

[3] For additional information on the Task Force, including its membership, see http://www.fda.gov/nanotechnology/nano_tf.html.

nanoscale materials in FDA-regulated products; and

- Submit its initial findings and recommendations to the Commissioner within nine months of the public meeting.

As requested by the Commissioner, the Task Force opened a public docket and held a public meeting on October 10, 2006. The objectives of the meeting and the docket were to learn about:

- New nanoscale material products under development in the areas of foods (including food additives and dietary supplements), color additives, animal feeds, cosmetics, drugs and biologics, and medical devices;

- New or emerging scientific issues that should be brought to FDA's attention, including issues related to the safety of nanoscale materials; and

- Any other issues concerning the use of nanoscale materials in FDA-regulated products regarding which regulated industry, academia and the interested public wished to inform FDA.

Following the public meeting, the Task Force:

- Reviewed both the oral and written comments it received;

- Assessed the current state of nanotechnology-related science; and

- Evaluated the scope of the agency's current authorities to meet any unique challenges presented by the use of nanoscale materials in FDA-regulated products.

Definitions for Nanotechnology and Related Terms

Nanotechnology allows scientists to work on the scale of molecules to create, explore, and manipulate the biological and material worlds measured in nanometers, one-billionth of a meter. By way of comparison, a sheet of paper is about 100,000 nanometers thick; a human hair is about 80,000 nanometers wide.

FDA regulates a wide range of products, which may use a wide range of materials for varied purposes inside and outside the body. The Task Force has sought to apply a sufficiently comprehensive analytical approach to address the scientific and policy issues FDA must consider to protect and promote human and animal health in regulating products within its jurisdiction that use nanoscale materials. Accordingly, the Task Force has considered a broad array of available information on a wide range of products, materials, techniques, and technologies. The Task Force has not adopted a precise definition for "nanoscale materials," "nanotechnology," or related terms to define the scope of its work. The Task Force concluded that it would be most productive to take a broadly inclusive approach in identifying potentially relevant studies, data, and other information.

The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, 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. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products.[4]

Organization of this Report

This report provides the Task Force's initial findings and recommendations. The report is divided into three sections. The first section discusses scientific knowledge of the potential effects of nanoscale materials relevant to FDA's regulation of products. The second section assesses scientific issues relating to FDA's regulation of products using nanoscale materials. The third section assesses the agency's regulatory authorities as these authorities relate to FDA-regulated products using nanoscale materials. The report takes into account comments submitted to relevant public dockets and made at the public meeting, and then presents recommendations to the Commissioner for actions the agency can take in furtherance of its mission to protect and promote the public health.

[4] The Task Force notes that the use of the terms "nanoscale materials," "nanoscale particles", and "nanotechnology" in this report does not reflect a Task Force position as to how these or related terms should be used or defined for regulatory purposes, including for purposes of any information requests or guidance recommended in this report.

State of the Science of Nanotechnology Relevant to FDA

The science and applications of nanotechnology are developing at a very rapid pace. In 1990, approximately 1,000 scientific publications on nanotechnology were published and approximately 200 patent applications (worldwide) were filed.[5] By 2002, the number of publications had risen to over 22,000 with over 1,900 patent applications. This exponential increase in scientific publications and patents is the result of increased discovery and investment in nanotechnology that will likely result in substantial and continual changes in products falling under the regulatory authority of the FDA.

Numerous reviews have been published focusing on the state of knowledge of behavior, interaction with biological systems (both for advantageous and toxicity outcomes), and potential environmental disposition of nanoscale materials. Government bodies have published some of these,[6] as have private entities focusing on the risk associated with nanoscale materials,[7] and still others can be found in the peer-reviewed public literature.[8] Often these reports stress the need for research on: characterization of materials in the nanoscale range; methods for identifying hazards; understanding biological response to nanoscale materials; and characterizing nanoscale material exposure and transport (in humans and the environment).

Identifying precisely what qualifies as a nanoscale material is difficult and currently a subject of substantial discussion in the scientific, regulatory, and standards communities. As a result, developing a comprehensive description of products that are currently produced with nanotechnology, or may be produced with this technology in the future, would be difficult at best, and likely infeasible. Instead this report considers examples based on what is currently known about use of this technology.

Perhaps of greatest relevance to products regulated by FDA is what the current study of structures in the nanoscale range is teaching about biological interactions.

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[5] Heinze, T. 2004. Nanoscience and nanotechnology in Europe: Analysis of publications and patent applications including comparisons with the United States. *Nanotechnology Law & Business* **1**(4): 10.

[6] Australian Safety and Compensation Council. A Review of the Potential Occupational Health & Safety Implications of Nanotechnology. July 2006. ISBN 0 642 32609 6; Borm,P.J.A.,et al. 2006. The potential risks of nanomaterials: a review carried out for ECETOC. *Particle and Fiber Toxicology* **3:** 11. National Nanotechnology Initiative (NNI). 2006. Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. Available at www.nano.gov.

[7] Davies, J.C. 2006. Managing the effects of Nanotechnology. Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano; ICF International. 2006. Characterizing the environmental, health, and safety implications of nanotechnology: Where should the federal government go from here? ICF international, Fairfax, VA. Available at www.icfi.com; Maynard, A.D. 2006. Davies, J.C. 2006. Nanotechnology: A research strategy for addressing risk. Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano; Taylor, M.R. 2006. Regulating the products of nanotechnology: Does the FDA have the tools it needs? Woodrow Wilson Institute for Scholars. Available at www.wilsoncenter.org/nano .

[8] Chan, V.S.W. 2006. Nanomedicine: An Unresolved Regulatory Issue. *Regulatory Toxicology and Pharmacology*, **46** (3): 218-224; Davis, J.M. 2007. How to assess the risks of nanotechnology: Learning from past experience. *J. Nanoscience and Nanotechnology*, **7** 1-8.; Oberdörster, G., et al. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ. Health Perspect*. **113**: 823-829.

In light of the current state of the science, an understanding of the interactions of nanoscale materials with biological systems is probably best gained through case-by-case analysis of specific types of nanoscale materials and of variations in their characteristics. However, recent reviews have developed initial approaches for more general description of the kinds of interactions that might be expected with biological systems.[9] Generalized approaches to organizing information for risk assessment and risk management of nanoscale materials have also been developed that provide insight for how biological interactions of nanoscale materials might be understood.[10]

Generalizable Knowledge of Biological Interactions

Generalizable principles are being derived from studies of specific types of nanoscale materials. For instance, studies in some laboratories have determined that surface area per unit of volume or mass can be a better measure than mass for assessing relative toxicity across particle size and material variations.[11] This tells us, for example, that the suitability of mass-based dose measurements should be evaluated before drawing conclusions about potency of a drug effect or about toxic response. However, it is important to recognize that in some cases surface area has been shown to be a much less important determinant of biological interaction than surface modification (for example, binding different chemical groups to the surface of a particle) for those particular types of particles in which this has been examined systematically.[12] This indicates that one should pay particular attention to the composition and surface characteristics of nanoscale materials that may come in contact with biological systems.

In some cases, features of materials such as charge or the position of the surface modification have been found to affect toxicity.[13] For example, positively charged nanoscale lipid vesicles (nanovesicles) induced cerebral edema, but neutral nanovesicles and

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[9] Tsuji JS et al. Research strategies for safety evaluation of nanomaterials, part IV: risk assessment of nanoparticles. *Toxicol Sci* 2006 **89**(1): 42-50; Oberdörster, G., et al., Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. *Part Fibre Toxicol* **2**: 8 2005.
http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf
http://www.nanotec.org.uk/finalReport.htm

[10] Morgan, K. Development of a Preliminary Framework for Informing the Risk Analysis and Risk Management of Nanoparticles. *Risk Analysis*, **25**(6): 1621-1635 2005.

[11] Warheit DB, et al. Pulmonary Bioassay Studies with Nanoscale and Fine-Quartz Particles in Rats: Toxicity is Not Dependent upon Particle Size but on Surface Characteristics. Toxicological Sciences 2007 95(1):270-280.; Warheit DB, et al. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations: Impact of surface treatments on particle toxicity. *Toxicological Sciences* **88**(2): 514-524 2005.

[12] Hoshino A, et al. Physicochemical properties and cellular toxicity of nanocrystal quantum dots depend on their surface modification. *Nano Letters* **4**(11): 2163-2169 NOV 2004; Warheit DB, et al. Pulmonary Bioassay Studies with Nanoscale and Fine-Quartz Particles in Rats: Toxicity is Not Dependent upon Particle Size but on Surface Characteristics. *Toxicological Sciences* 2007 **95**(1):270-280.; Warheit DB, et al. Comparative pulmonary toxicity inhalation and instillation studies with different TiO2 particle formulations: Impact of surface treatments on particle toxicity. *Toxicological Sciences* **88** (2): 514-524 2005.

[13] It is important to note with respect to the development of general knowledge that many of the studies published in the literature have been conducted with nanoscale materials that are either poorly characterized, or not characterized. Therefore, in many cases the quality and applicability of the findings reported may be inadequate.

low concentrations of negatively charged nanovesicles did not.[14] Studies have also shown that modifying the surface of nanoscale materials with surfactants or biocompatible polymers (e.g., polyethylene glycol, PEG) reduced the toxicity *in vitro*[15] and altered the half-life and tissue deposition *in vivo*.[16] Such findings are relevant to drug delivery for example, for understanding the potential distribution of nanoscale materials in the body, and for evaluating toxicity and biocompatibility. However, these findings are material-specific and, we are not aware of methods or models that would extend these findings to provide a better understanding of broad classes of materials.

There is also well-developed literature on biological interactions of naturally occurring particles or particles released from industrial processes that include particles in the nanoscale range, such as combustion-related particulate matter, silica dust, and biological particles. These data sets may provide valuable information for understanding generalizable properties of nanoscale particles. However, because of the great significance of surface modification to the properties of nanoscale particles that has been shown in some cases, the value of these existing data that deal with widely variable nanoscale particle subtypes may be limited to understanding of basic issues such as biological filtering and dose metrics.

Predictability of Biological Interactions

At a first level of approximation, understanding simple particle movement into or from one compartment to another in the body involves consideration of various absorption and transport mechanisms that either passively keep particles from entering some areas of the body depending on how large they are, or actively move the particles. An understanding of these mechanisms can help predict what movement might occur for particular nanoscale particles. Accordingly, the significance of size to biological interaction may be relatively straightforward to predict and assess in many cases where changing particle size can be expected to affect absorption and transport mechanisms.

Furthermore, if a specific kind of surface reactivity is known for a material, then it might be expected that the reactivity per unit of mass would increase with decreasing particle size because specific surface area would increase. It could also, therefore, be predicted that important biological effects could arise when the surface area is substantially increased with the same mass of exposure. The argument has been made, for example, that generation of reactive oxygen species for some particles may increase as particle size decreases and surface area increases, leading to increased inflammatory response in lung tissue.[17] The particle size range or particle concentrations at which such an increase in reactivity could cause adverse effects would depend on adaptive responses of the affected biologic system, however, and, therefore, would be difficult to predict in the absence of test data.

In addition, biological interaction may be focused such that only a specific particle size range will have biological effects. For example, there may be an upper size limit for dermal

[14] Lockman PR, et al. Nanoparticle surface charges alter blood-brain barrier integrity and permeability, *J. Drug Target.* **12**(9-10): 635-641 (2004).
[15] Derfus AM, et al. Probing the cytotoxicity of semiconductor quantum dots, *Nano Lett.* **4**(1):11-18 (2004).
[16] Ballou B, et al. Noninvasive imaging of quantum dots in mice, *Bioconjugate Chem.* **15**(1): 79-86 (2004).
[17] Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. *Toxicol Appl Pharmacol* 2001, **175**:191-199.

absorption of any specific type of particle, though that limit may vary based on other factors as well (e.g., particle charge or chemical properties, conditions of dermal exposure). A compound that previously was excluded from exposure to internal tissues might then produce effects, beneficial or adverse, due to the exposure of internal tissues when particle size decreased below the threshold for exclusion. These effects could be based on somewhat simple physical interaction, such as the filtering capacity of phagocytic cells, transport effects of capillary structures, or adhesion to proteins or other molecules in biological fluids.[18] In some cases, these interactions may be predictable, for example, based on knowledge of the size of materials that can pass through capillary walls. In others, data could be developed that would allow better prediction of biological interaction, for example regarding size-dependent dermal absorption as is being developed by FDA in collaboration with the National Toxicology Program.[19]

Biological interactions influenced by the particular chemistry and physical configuration of the nanoscale material might also occur in ways that are unpredictable without specific test data for the material. For example, similar to how charge and functional group locations on a molecule will affect interactions with chemicals in the body, characteristics such as a particle's shape and the location of changes in its surface may affect the interactions of nanoscale materials with chemicals in the body.

The available information does not suggest that all materials with nanoscale dimensions will be hazardous. Furthermore, if all nanoscale materials are compared to all non-nanoscale materials, whether larger or smaller, it is not apparent that the nanoscale materials as a group would have more inherent hazard. However, consideration of the basic science of how materials interact with biological systems does indicate that a material's properties can change when size is increased or decreased into, or varied within, the nanoscale range.

Science Issues

Introduction

Virtually any product category regulated by FDA might currently or in the future involve uses of nanotechnology somewhere in the manufacturing process. A somewhat smaller set of products can be expected to retain nanoscale structures in the finished product, such as systemically bioavailable nanoscale drugs or nanoscale particles or nanoscale structures in solid objects that may release nanoscale materials through use. As discussed above, the biological interactions of regulated products using nanoscale materials are of particular importance to FDA. This section addresses scientific issues relevant to FDA. They relate to:

- Understanding of interactions of nanoscale materials with biological systems; and

[18] Lynch I. 2007. Are there generic mechanisms governing interactions between nanoparticles and cells? Epitope mapping the outer layer of the proteinBmaterial interface. *Physica A: Statistical and Theoretical Physics* **373**: 511-520.

[19] Description of the NTP's Nanotechnology Safety Initiative at**:** http://ntp.niehs.nih.gov/go/20837.

- Adequacy of testing approaches for assessing safety, effectiveness, and quality of products containing nanoscale materials.

We will address both issues below, taking into account relevant comments submitted to the public docket for the FDA Nanotechnology Task Force's October 2006 public meeting and to the docket opened in response to a petition submitted by the International Center for Technology Assessment (ICTA) and other parties entitled, Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (ICTA Petition).[20] In addition to other resources, the Task Force also considered the US Government-wide evaluation of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials (NNI 2006c)[21] in developing this discussion and these recommendations.

Issue: Understanding Interactions of Nanoscale Materials with Biological Systems

Comments

Many comments noted that nanoscale materials can have a wide variety of properties that are markedly different from the same materials in larger scale forms. Some comments suggested that the definition of "nanomaterial" should be limited to those materials that have some unique, qualitatively different, properties derived from their physical scale. Some comments noted that although the nature and unique properties of many nanoscale materials are not well understood, some nanoscale materials have been observed to be toxic in certain assays and under some specified conditions, or, based on their behavior in biological systems, raise suspicions of potential toxicity. .

Some comments stated that nanoscale materials have a unique ability to interact with proteins and other essential biological functional elements. Some noted: that nanoscale materials can be more biologically active than non-nanoscale materials; that basic research is needed on such issues as interactions with subcellular structures and dose/concentration; and that such research should take an interdisciplinary approach, making use of experts in toxicology, materials science, medicine, molecular biology and bioinformatics. The comments pointed out that there are differences in dose-response curves depending on whether the curves are expressed by mass, number of particles, or surface area.

Some comments essentially stated that, because properties or safety of nanoscale materials cannot be assumed or inferred from larger-scale forms, nanoscale materials will need to be directly and adequately evaluated. Some comments highlighted that this lack of proven safety may be a particularly significant concern for ingested products.

Other comments noted that there is a great deal of knowledge about behavior of many types

[20] FDA is currently reviewing this petition. FDA has not yet reached a decision on the petition because it raises complex issues requiring extensive review and analysis by agency officials, and in relation to which the agency is seeking public input. While this report addresses some issues raised in the petition, this report reflects only the views of the Task Force, and does not constitute an agency answer to the petition in whole or in part.

[21] National Nanotechnology Initiative (NNI). 2006. Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. Available at www.nano.gov.

of nanoscale materials, that there are established methods for assessing their safety and effectiveness, and that the novelty of the scientific issues posed by nanoscale materials is exaggerated. One comment stated that the nanoscale materials contained in some newer sunscreens have been well tested by industry already and have had their safety established. Some comments noted that the use of nanoscale materials may enable development of more targeted drugs and biological products, which may be safer and more effective than otherwise possible, and development should not be impeded.

Some comments highlighted the need for FDA to have adequately trained and educated staff to review products that may contain nanoscale materials.

Analysis

Issues Relevant to all Regulated Products

There may be a fundamental difference in the kind of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way that testing is performed. For conventional chemicals, there is a relatively long history of exploring, and a correspondingly relatively robust understanding, of interactions of molecular classes (such as compounds with particular structures or functional groups) with biological systems. In some cases, screening test methods are used to define what additional tests may need to be performed to gain sufficient knowledge about safety and/or effectiveness. For example, there are screening tests available to help identify whether DNA damage is a possible outcome from exposure to a certain chemical. Other tests can tell how the chemical is distributed in the body and in what forms it is present in various tissues. FDA has an expectation relevant to molecular forms of materials used in products that FDA regulates that if the molecule does not cause DNA damage during *in vitro* testing, or if it is metabolized quickly and does not reach sensitive organs, or if it is not absorbed, then it is less likely to present certain kinds of health hazards. This expectation is based on long experience with, and consequent understanding of, basic biological interactions of molecular forms of chemicals and of how these interactions correlate with the results of current testing methods.

The testing methods for different product types also may need to be evaluated to determine whether or how they can be used in assessing the bioavailability of nanoscale materials in humans. This issue is not so much one of whether the tests are valid (as discussed under "Adequacy of testing approaches…" below). Rather, it speaks to the familiarity with the predictive value of the tests. There is, comparatively speaking, more familiarity with the predictive value of such tests for molecules than for nanoscale materials. As FDA and the scientific community develop familiarity with different nanoscale material types, it may be possible to predict, for example, that specific variations in characteristics of a type of nanoscale material may cause it to be reactive in the same way that it is known that addition of a chemical-specific functional group may cause a molecule to be reactive.

Several recent scientific reviews conclude that the state of knowledge for biological interactions of nanoscale materials is generally in need of improvement to enhance risk assessments and better support risk management decisions.[22] For example, the information

[22] http://www.nano.gov/NNI_EHS_research_needs.pdf; http://www.nanotec.org.uk/finalReport.htm

available on biological interactions for nanoscale materials primarily applies to the specific materials tested, and the agency is not aware of models for how the information might be applied more broadly to other nanoscale materials. At this stage, it is important to monitor individual hazard studies of specific nanoscale materials and, where possible, seek to synthesize a common understanding of more general material properties from these studies.

There is a potential to develop and organize information using physiologically based pharmacokinetic (PbPk) models or quantitative structure activity relationship (QSAR) models, to enable formulation of generalized principles for the behavior of classes of nanoscale materials. Integration of information with respect to given material characteristics (for example, material type, size, charge, surface modification) could be of particular benefit in improving general understanding. Such models are useful in predicting biological interactions of molecules and may provide the same sort of value for nanoscale materials. At present, however, the agency is not aware of models such as these for nanoscale materials.

Further, even though there is a broad array of ongoing research across a wide variety of disciplines, the different disciplines and laboratories employ different methods, standards and ontologies. As mentioned previously, in 2002 alone there were 22,000 scientific publications relating to nanotechnology.[23] Managing this information is a formidable task, but data mining would likely yield a wealth of information relevant to the FDA's review of nanotechnology-based products. For these reasons, the development of a comprehensive database employing standardized ontologies, or other means of integration, could be very valuable.

Rendering appropriate regulatory decisions requires up-to-date training and information. FDA's ability to accomplish its mission depends in part on having staff with expertise in areas such as pharmacology, materials science, biology, physics, chemistry, medicine, and toxicology. New and emerging nanotechnology-based products highlight the possible need for new expertise for some review areas. For example, characterization methods for nanoscale materials (e.g., describing size, shape, surface topography) generally require use of different equipment than would be used for characterizing molecules. The data produced by this equipment are different than those generated by chemical analysis methods typically seen by most FDA reviewers. Particularly in light of the evolving nature of scientific knowledge and technical capacity relating to nanotechnology, it will be important to ensure ongoing training, as well as dissemination of new information within review centers and more broadly across the agency, to ensure timely, informed consideration of the most current science.

Products Subject to Premarket Authorization

As discussed more fully below in the Regulatory Policy Issues section, for products subject to premarket authorization, such as drugs, devices, biologics, and food and color additives, FDA reviewers can require manufacturers to provide the necessary scientific information to support regulatory decisions. The evolving scientific understanding of nanoscale materials would generally be expected to inform assessment of what data are needed. For example,one currently would expect the information needed to assess biological interaction to change as

[23] Heinze, T. 2004. Nanoscience and nanotechnology in Europe: Analysis of publications and patent applications including comparisons with the United States. *Nanotechnology Law & Business* **1**(4): 10.

size decreases because, as discussed above, data from larger particles may not necessarily predict behavior for smaller particles. However, a precise size boundary where scientific information based on larger particles becomes less relevant for a particular question or material is not currently apparent. Similarly, research identifying short and long-term toxicity issues relevant to particular nanoscale materials could aid FDA in determining what, if any, additional testing a manufacturer should conduct. In short, a greater understanding of the properties of nanoscale materials and of trends in material development and uses would help focus data and testing requirements.

Products Not Subject to Premarket Authorization

For products not subject to premarket authorization by FDA, such as cosmetics and dietary supplements, the agency generally does not receive data, including safety data, before the products are marketed. Furthermore, there are no post-marketing reporting requirements for adverse events associated with cosmetics. Therefore, FDA receives only cosmetic adverse event reports that are submitted voluntarily. Similarly, for dietary supplements, to date FDA has received only voluntarily submitted adverse events, although recently enacted legislation will give FDA greater access to dietary supplement adverse event reports in the future.[24]

The agency may have far less baseline data than with products subject to premarket authorization. As a result, the agency may have a comparatively difficult burden in assembling the necessary data to support a product removal action under these authorities (whether the product contains nanosized or other materials).

Also as discussed above, there may be general differences in properties relevant to evaluation of safety and effectiveness (as applicable) of products using nanoscale materials compared to products using other materials. For example, size, shape, and charge of a nanoscale material can affect disposition or toxicity in the body in ways that differ from molecular forms of materials and that may be generalizable across different particle or other material types. Knowledge of such generalized differences could, for example, help inform FDA's: assessments of whether to take regulatory actions against products not subject to premarket authorization; efforts to obtain and develop further information; and efforts to develop guidance on data needs for products not subject to premarket authorization.

Recommendations for Consideration

The Task Force recommends strengthening FDA's promotion of, and participation in, research and other efforts to increase scientific understanding, to facilitate assessment of data needs for regulated products. Such activities should, where appropriate, be coordinated with and leveraged against activities supported by other Federal agencies, the private sector, or other countries. This would include:

- Promoting efforts, and participating in collaborative efforts, to further understanding of biological interactions of nanoscale materials, including, as appropriate the development of data to assess likelihood of long term health effects from exposure to

[24] Beginning December 22, 2007, any serious adverse events associated with a dietary supplement reported to the product's manufacturer, packer, or distributor will have to be submitted to FDA. In addition, firms will have to keep records of all dietary supplement adverse events, serious or non-serious, and FDA will have access to those records during inspections.

specific nanoscale materials;

- Assessing data on general particle interactions with biological systems and on specific particles of concern to FDA;
- Promoting and participating in collaborative efforts, to further understanding of the science of novel properties that might contribute to toxicity, such as surface area or surface charge;
- Promoting and participating in collaborative efforts to further understanding of measurement and detection methods for nanoscale materials;
- Collecting/collating/interpreting scientific information, including use of data calls for specific product review categories (see Regulatory Policy Issues section);
- Building in-house expertise;
- Building infrastructure to share and leverage knowledge internally and externally, seeking to collect, synthesize, and build upon information from individual studies of nanoscale materials; and
- Ensuring consistent transfer and application of relevant knowledge through establishment of an agency-wide regulatory science coordination function for products containing nanoscale materials.

Issue: Adequacy of Testing Approaches for Assessing Safety and Quality of Products Containing Nanoscale Materials

Comments

Several comments expressed the concern that existing toxicology screening methods will not adequately assess toxicologic properties of nanoscale materials, and that these methods cannot be used in their present form to assess engineered nanoscale materials. Some comments pointed out that pharmacokinetics and pharmacodynamics of nanoscale particles are different from those of larger particles and that existing toxicity screening studies do not take these differences into account. Several comments further recommended that cellular assays should reflect exposure media (e.g., air, water, food), route of exposure, and portal-of-entry toxicity (e.g., toxicity to lungs, skin, mucus membranes), as well as systemic responses.

Comments stated that most toxicology tests are short-term, and might leave long-term effects unevaluated, especially because the long-term toxicity and effects for most nanoscale materials remain unknown. These comments noted that appropriate endpoints for *in vitro* assays can be difficult to determine, as single cell types are often not sufficient for evaluation of the function or health of organs or tissues that are made up of multiple cell types, and given that various types of tissues are exposed in the body.

Other comments were directed to the inadequacy or absence of currently available and

standardized product characterization methodologies for nanoscale materials. A comment highlighted that FDA has limited ability to detect nanoscale material components in some products. Another comment emphasized that FDA's ability to inspect products is also presently significantly limited with regard to products that may contain nanoscale materials. One comment recommended that nanoscale material be characterized with respect to size (surface area and size distribution), chemical composition (such as purity and crystallinity), surface structure (surface reactivity, surface groups, inorganic/organic coatings, etc.), solubility, shape and aggregation. Other comments noted that detection of nanoscale materials requires expensive and sophisticated equipment, and it is often unclear which parameters are relevant to toxicity.

Comments also encouraged FDA to work with other government agencies to develop rapid screening tools for these types of products. Several comments noted that the Nanotechnology Characterization Laboratory, run by the National Cancer Institute, will be very useful in helping to characterize nanoscale materials and to develop standards and standardized methods for measuring nanoscale materials.

Analysis

Assays to Develop Biological Effects Data

Established *in vitro* and *in vivo* assays and predictive models are available to evaluate a variety of endpoints relevant to the establishment of hazard(s) and the identification of further testing needs. The results of these tests are often used in a tiered approach in an overall data development process for understanding the toxicity and effectiveness of a product such that, for example, a "positive" response may lead to a conclusion of hazard or the initiation of additional studies and a "negative" response would not (the obverse may also be true). However, because many of these tests were developed for molecular forms of materials, and nanoscale materials may behave differently, the ability of these tests to support decisions about biological effects or further testing requirements need to be evaluated.

For example, data to support understanding of dose-response developed through *in vitro* test systems might not be appropriate for particles where sedimentation velocities and diffusion can change the delivered dose.[25] Similarly, in some cases it may be necessary to develop information to evaluate whether current short-term tests provide sufficient predictive value regarding the need for chronic or other long-term toxicity testing, and in some cases the only way to get this information may be to actually conduct long-term toxicity testing. In addition, development of new testing methods may be necessary to develop data to support decisions for nanoscale materials that may have novel biological responses.

Existing information for nanoscale materials does not appear to indicate a need for revision to all tests however. Accordingly, a tiered or staged approach to evaluation would seem appropriate. The first stage of such an approach would be to determine whether any specific tests may need evaluation. Subsequent stages would call for data to assess individual test methods as needed.

[25] Teeguarden,J.G., Hinderliter, P.M., Orr, G., Thrall, B.D., and Pounds, J.G. 2007. Particokinetics in vitro: Dosimetry considerations for in vitro nanoparticle toxicity assessments. *Toxicol. Sciences* **95**: 300-312.

Standard approaches for handling of materials for testing will also need to be evaluated and may need to be modified, with respect to such factors as appropriate solvents and dosing formulations, methods to prevent agglomeration of particles, stability conditions, and other variables that may affect test results when nanoscale materials are tested. Such adjustments may be needed to improve the reliability, repeatability, reproducibility and accuracy of assays and methods.

Metrology - Characterization of Particles in the Nanoscale Range

Currently, ability to detect nanoscale materials in the body or in products regulated by FDA is limited, and development of appropriate analytical methods for classes of products and of nanoscale materials may require substantial effort. Further, new analytical methods, and methods that FDA reviewers are generally less familiar with, are often used to characterize nanoscale materials. The strengths and limitations of these methods may vary in ways relevant to evaluating characteristics such as particle size, size distribution, surface charge, surface properties, and particle interactions (such as aggregation) that may be relevant to dose, stability, or other characteristics significant to biological interaction or product quality.

Inspection

Tests used for inspections and product surveillance will need to be evaluated to determine whether modifications are warranted to address nanoscale materials. Increased use of materials in the nanoscale range may present particular challenges, for example, relating to tests that assess product stability or development of potentially hazardous byproducts. Further, as with any product, scaling up to full production rates may affect such factors as purity, particle behavior, size distribution, and general batch-to-batch consistency, and it may be necessary to evaluate the adequacy of existing testing to assess such consequences of scale-up for products using nanotechnology.

Standardization of Tests and Data Reporting

In many cases, methods currently used to characterize nanoscale materials have not been standardized through recognized standard development organizations. There is a need to develop standard particle characterization methods. Furthermore, given the range of methods being used and being developed for nanoscale materials, there is a need to develop consistent nomenclature and measurement types and formats for use across studies and data submissions similar to the "MIAME" approach developed for microarray data.[26] Consistent reporting approaches will make data from one laboratory or for one material type more readily comparable to data from other laboratories and more useful to subsequent consideration of properties of the same type of material or other material types.

Recommendations for Consideration

To be marketed, FDA regulated products must be safe and, as applicable, effective. FDA-

[26] Minimum Information About a Microarray Experiment www.mged.org/Workgroups/MIAME/miame.html. Consistent reporting approaches can be established and instituted without adopting substantive definitions for "nanotechnology" and related terms for regulatory purposes (the merits of which may take some time to evaluate as explained above).

regulated products must also meet all applicable good manufacturing practice and quality requirements. Adequate testing methods are needed regardless of whether a product is subject to premarket authorization or not. Accordingly, the following recommendations are relevant to all categories of FDA-regulated products. The agency should:

- Evaluate the adequacy of current testing approaches to assess safety, effectiveness, and quality of products that use nanoscale materials;
- Promote and participate in the development of characterization methods and standards for nanoscale materials; and
- Promote and participate in the development of models for the behavior of nanoscale particles *in-vitro* and *in-vivo*.

The Task Force recommends encouraging manufacturers to consult with the agency regarding the appropriateness of testing methodologies for evaluating products using nanoscale materials.

Regulatory Policy Issues

Background

FDA regulates a broad range of products under the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Public Health Service Act (PHS Act). The agency's statutory authorities subject some types of products to premarket authorization requirements, either individually or by category, while permitting other products to be marketed without prior agency authorization.[27]

Products subject to premarket authorization include drugs, biological products, devices, and food and color additives. As detailed below, new drugs,[28] biological products, and devices receive marketing authorization on a product-by-product basis. FDA authorizes food additives and color additives for marketing by issuing a regulation approving a substance that meets prescribed identity and quality specifications for specified food additive or color additive uses under specified conditions. Once such a regulation is in place, it covers all products that comply with the regulation, and individual premarket review of such products

[27] For purposes of this report, the term "premarket authorization" is used to refer to a number of regulatory actions that the FFDCA and the PHS Act and agency regulations may refer to by other names, including "approval," "clearance," "licensing," and "listing." As used in this report, "premarket authorization" includes both premarket approval for an individual product (e.g., under an NDA, BLA, or PMA) and regulations permitting the marketing or use of an ingredient or substance for specified uses under specified conditions (e.g., a food additive regulation, OTC drug monograph, or color additive listing regulation). Among other issues concerning the use of nanotechnology, this report focuses on how to treat nano versions of existing products that fall under such a regulation and makes recommendations to guide agency consideration of that issue.

[28] Generally, a drug is regulated as a "new" drug under section 505 of the FFDCA if it is not generally recognized to be safe and effective.

is not required. Drug ingredients can similarly be reviewed for inclusion in monographs authorizing their marketing over the counter (OTC monographs) as generally recognized as safe and effective (GRAS/E) for specified conditions of use. Once the monograph is in place, it covers all products that comply with it, and individual premarket review of such products is not required. FDA-regulated products not subject to premarket authorization include dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS). Although premarket authorization does not apply, premarket notification is required in some cases for dietary supplements containing new dietary ingredients,[29] and premarket notifications may be submitted at the option of the manufacturer for GRAS food ingredients.[30]

In all cases, whether subject to premarket authorization or not, FDA-regulated products cannot be marketed unless they satisfy specified statutory requirements. In addition to other such requirements, drugs, biological products and devices must be safe and effective; and foods (including dietary supplements and food additives), color additives, and cosmetics must be safe.[31]

As discussed in the State of the Science section, the Task Force believes that nanoscale materials will present regulatory challenges that are similar to those posed by other new technologies FDA has dealt with in the past, such as biotechnology products, but also some potentially new challenges. The Task Force began its regulatory policy inquiry by reviewing the agency's authorities to meet any unique challenges that may be presented by FDA-regulated products containing nanoscale materials. Although FDA's authorities may be adequate to meet these challenges, in some cases the evolving state of the science regarding nanotechnology may warrant a case-by-case approach to assess whether sufficient evidence exists to show that products satisfy the applicable statutory and regulatory standards.

The Task Force has made recommendations that seek to address the challenges nanoscale materials may present. The guidances the Task Force is recommending would give affected manufacturers and other interested parties timely information about FDA's expectations, so as to foster predictability in the agency's regulatory processes, thereby enabling innovation and enhancing transparency, while protecting the public health.

The very nature of nanoscale materials – their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications – may permit the development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for "combination products"[32] may need to be assessed to ensure predictable determinations

[29] A "new dietary ingredient" is a dietary ingredient that was not marketed in the United States before October 15, 1994. New dietary ingredients require a premarket notification to FDA unless the ingredient has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered." 21 U.S.C. 350b.

[30] Notifications of a GRAS determination can also be submitted on a postmarket basis.

[31] Under section 351 of the PHS Act, FDA will approve a biologics license application on the basis of a demonstration that, among other things, the biological product that is the subject of the application is safe, pure, and potent. Potency has long been interpreted to include effectiveness. 21 CFR 600.3(s).

[32] A combination product is a product that is a drug-device, drug-biologic, device-biologic, or a drug-device-biologic. The assignment of a "lead center" that will have primary jurisdiction for its regulation is

of the most appropriate pathway for such highly integrated combination products.

Continuing agency efforts to gather together and share scientific knowledge of nanoscale materials, across centers and divisions, will be important to facilitate informed regulatory activity in light of the evolving state of this scientific knowledge. Such coordinated assessment and dissemination of information will enable informed determinations of how best to approach premarket review, including identification of appropriate regulatory pathways for such highly integrated combination products. Among other uses, it will also support assessment of postmarket surveillance of products using nanoscale materials.

As the recommendations below reflect, the Task Force believes communication between regulated entities and the agency early in the product development process, particularly with regard to highly integrated combination products, will help ensure timely consideration of any potentially novel issues that products using nanoscale materials may raise. In addition, to assist the agency to be well-positioned to enable the development and premarket review of such highly integrated combination products, the Task Force recommends that FDA seek public input on the adequacy of agency policies and procedures.

Discussion

The Task Force has considered four broad regulatory policy questions that concern FDA in relation to the presence of nanoscale materials in FDA-regulated products. These questions are:

- Is FDA able to determine whether particle sizes or material features of products extend into the nanoscale range?
- What is the scope of the agency's authority regarding the evaluation of the safety and effectiveness of products containing nanoscale materials?
- Should product labeling declaring the presence or amount of nanoscale materials be either required or permitted?
- Does the use of nanoscale materials in FDA-regulated products raise any issues under the National Environmental Policy Act (NEPA)?

After summarizing the agency's general authorities, we address each question in turn below, taking into account relevant comments submitted to the public docket for the FDA Nanotechnology Task Force's October 2006 public meeting and to the docket opened in response to the ICTA Petition.

Summary of Agency Oversight Authorities by Product Type

Following are concise summaries by product type of certain agency statutory and regulatory

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based on a determination of the "primary mode of action" of the combination product. FDA regulations define the primary mode of action of a combination product as "the single mode of action . . . that provides the most important therapeutic action of the combination product" (21 CFR 3.2(m)) and define therapeutic action or effect to include "any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body" (21 CFR 3.2(k)).

authorities relating to product safety, effectiveness (as applicable), and quality. This discussion is relevant, in particular, to the Task Force's analyses and recommendations with respect to the first and second questions presented above.

New Drugs and Biological Drug Products

Sponsors are required to submit an Investigational New Drug (IND) application to FDA in accordance with 21 CFR Part 312 prior to conducting human clinical studies of most drugs.[33] INDs are required to contain detailed information about the investigational new drug, including chemistry, manufacturing, and controls information, such as information about its active ingredients and structural formula, and pharmacological and toxicological results from studies of the drug in animals. During FDA's review of the data contained in the IND submission, the agency may identify additional information necessary to assure the safety of subjects and assure that the study design is adequate to permit an evaluation of the drug's safety or effectiveness in humans. FDA has the authority to request such additional safety data from the sponsor, including particle size data, when it is needed to support the IND.

After a drug has been adequately studied in humans, the applicant must submit a new drug application (NDA) to obtain approval to market the drug (21 CFR § 314.50). For biological products regulated under section 351 of the PHS Act, an applicant must submit a biologics license application (BLA) (21 CFR § 601.2). Applicants are required to submit in NDAs and BLAs detailed technical information about their products, including chemistry, manufacturing, and controls information, the results of animal pharmacology and toxicology studies, bioavailability data, and extensive data on safety and effectiveness generated in clinical investigations of the drugs in humans.

Applicants may also seek FDA approval of an abbreviated new drug application (ANDA) to market a generic version of a drug for which the agency has previously approved an NDA. ANDAs contain detailed technical information about the product, including chemistry, manufacturing, and controls information, and bioavailability and bioequivalence data, but do not include extensive human data from clinical investigations (21 CFR § 314.94).

During FDA's review of these applications, the agency may call for additional data from the sponsor needed to support the applications, including particle size data, if not supplied in the original application. FDA requests information on particle size when the agency considers such information relevant to determining whether a particular human drug product or class of human drug products is safe and effective. If FDA determines such data are needed for a class of drugs, FDA may issue guidance to applicants recommending that they be submitted in the original application.

Drugs, including biological drugs, are also subject to current good manufacturing practice requirements found in 21 CFR Parts 210 and 211. These requirements govern the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug. They are intended to ensure that the drug meets the safety

[33] A biological product that is subject to licensure under section 351 of the Public Health Service Act (PHS Act) may meet the definition of "drug" under the FFDCA and thus be subject to certain provisions of drug regulation such as the IND regulations.

requirements of the FFDCA, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

In accordance with 21 CFR § 314.70, 21 CFR § 314.97, and 21 CFR § 601.12, after a human drug or biologic product is approved for marketing, the sponsor must notify FDA about each change in each condition established in the approved application. Significant changes require a supplement to the NDA, ANDA, or BLA, and prior FDA approval. Significant changes include a change in drug substance, drug product, production process, quality controls, equipment or facilities that has a substantial potential to have an adverse effect on the drug product. Changes to a product to introduce nanoscale ingredients or processing would trigger change notification chemistry supplements and permit FDA to review and approve the revised formulation. Depending on the change, the resulting product might be considered a new product for which a new approval is needed.

OTC Monograph Drugs

Over-the-counter drug monographs establish the active ingredients and conditions of use for OTC drugs that qualify as generally recognized as safe and effective. Additional active ingredients can be added to an OTC drug monograph in response to a citizen petition (under 21 CFR § 10.30) or a time and extent application for eligibility (under 21 CFR § 330.14) followed by evaluation of data supporting GRAS/E status. Both processes require the submission of safety and effectiveness data. FDA can require data and information to determine if these proposed additional ingredients contain nanoscale materials and, if so, require safety and effectiveness data directly related to particle size to determine whether the ingredient qualifies for inclusion in the monograph.

If a manufacturer does not have an approved NDA for a drug product that has not been marketed in the United States, that manufacturer generally cannot market that drug product unless FDA has published a final OTC monograph that includes the drug product's active ingredient for the intended use.[34] Products containing active ingredients that are already included in a monograph and that bear labeling published in a monograph may be marketed without product-specific premarket authorization. FDA can take various actions however, if the agency learns that a new version of a drug product marketed under an OTC monograph raises a safety or effectiveness concern. A new version that might raise such concerns could be a drug product that contains a monograph ingredient whose particle size has been reduced to the nanoscale range To address this situation, for example, the agency can issue a call for data on the safety and effectiveness of the changed version of the OTC drug ingredient. In addition, under 21 CFR Part 330, FDA can conduct rulemaking to determine whether a nanoscale version of a monograph ingredient should be considered nonmonograph (i.e., not GRAS/E), and therefore to require submission of data in an NDA to establish its safety and effectiveness.

New Animal Drugs and Animal Feed Containing a New Animal Drug

New animal drugs, including new animal drugs for use in animal feed, are regulated under section 512 of the FFDCA and are subject to a premarket authorization process intended to

[34] Under certain circumstances, FDA does not object to the marketing of OTC drugs with active ingredients being considered for inclusion in an OTC monograph as part of the "OTC drug review."

establish the products' safety and effectiveness that is in many respects similar to the process used for new human drugs and biological drug products. An applicant must submit a new animal drug application (NADA) to obtain approval to market the animal drug and the requirements for the contents of NADAs are found in 21 CFR Part 514. Animal drugs must also be manufactured in accordance with current good manufacturing practice requirements found in 21 CFR Part 211. FDA has the authority to require information that will adequately characterize the drug formulation, identify quality-indicating specifications, and ensure that factors affecting the quality, purity, strength and potency are adequately understood and controlled. This authority includes the ability to require the submission of a product's particle size, where the particle size might have an impact on the safety or effectiveness of the animal drug.

Devices

Medical devices are regulated under the FFDCA according to a tiered classification system that is largely based on the degree of risk posed by the product. Devices that are low risk, for which safety and effectiveness are generally well-established, are designated as Class I devices. These device types are subject to general controls, such as labeling, good manufacturing practices and adverse event reporting.

Class II devices are more complex, and carry a higher risk than Class I devices. Before marketing the product, manufacturers are usually required to submit a premarket notification under section 510(k) of the FFDCA (510(k) submission) for FDA review. In a 510(k) submission, manufacturers are required to submit data and other information to demonstrate that their device is "substantially equivalent" with regard to safety and effectiveness to a similar device already legally marketed in the United States. The evidence provided usually consists of pre-clinical testing (such as animal, bench, and analytical testing), and occasionally, clinical data (such as data derived from a study using a patient population with a defined clinical condition).

In some cases, manufacturers may make modifications to Class I or Class II devices after FDA clearance without submitting a new 510(k) submission. FDA provides guidance on when a new 510(k) is needed for a modified device in the guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)."[35] Manufacturers of a commercially distributed Class I or Class II device, for which FDA has granted an exemption from the requirement of a 510(k) submission for the generic type of device, must still make such a submission under certain circumstances, such as when the modified device operates using a different fundamental scientific technology than a legally marketed device in that generic type of device. Accordingly, manufacturers would have to make a submission if use of a nanoscale material were to qualify as a use of a different fundamental scientific technology.

Class III devices are the most complex, high risk devices. These devices are reviewed under a premarket approval application (PMA). In a PMA, manufacturers provide detailed evidence that their device provides a "reasonable assurance of safety and effectiveness." The evidence provided usually consists of pre-clinical testing, and clinical data. Class III PMA devices are subject to a pre-approval manufacturing inspection and require submission

[35] http://www.fda.gov/cdrh/ode/510kmod.pdf

of periodic reports. Any modification to a PMA device and its method of manufacture that could affect safety or effectiveness requires approval by FDA through the submission of a PMA supplement. A PMA might be required for a product otherwise within a general category considered Class I or Class II if the inclusion of nanoscale material raises questions of safety or effectiveness warranting clinical studies.

Manufacturers are required to submit information in sufficient detail to describe the device and its intended use. This includes, for example, information on the chemical composition and physical characteristics of materials that comprise the device. In general, devices must be manufactured in accordance with the Quality System Regulation (21 CFR Part 820).

All clinical evaluations of investigational devices, unless exempt, must have an approved investigational device exemption (IDE) before the study is initiated. An approved IDE is required for "significant risk devices" but not for "nonsignificant risk" devices. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject.

Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Clinical studies of devices that pose a significant risk require both FDA and Institutional Review Board (IRB) approval prior to initiation of the study. FDA approval is obtained by submitting an IDE application to FDA (21 CFR § 812.20). If use of a nanoscale material were to pose a potential for serious risk to health, safety, or welfare of a subject, an IDE would, therefore, be required.

Nonsignificant risk devices are devices that do not pose a significant risk to human subjects. Examples include ultrasonic dental scalers, conventional laparoscopes, culdoscopes, hysteroscopes, and foley catheters. A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study, and sponsors are not required to submit an IDE application to FDA for approval. If the IRB disagrees with the sponsor and determines that the device poses a significant risk, the sponsor must report this finding to FDA.

Guidance on distinguishing between significant risk and nonsignificant risk studies is outlined in the FDA guidance document entitled "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies."[36]

Food Additives and GRAS Food Ingredients

FDA regulates food additives and generally recognized as safe (GRAS) food ingredients under sections 201(s) and 409 of the FFDCA. Under these statutory provisions, any substance added to food "directly or indirectly" is a food additive unless the substance is GRAS for its intended use, is a pesticide, or is otherwise excluded from the definition of a food additive. Food additives must receive premarket approval from FDA in the form of a regulation establishing conditions of safe use. Food additives include those substances added directly to food, substances that may become components of food as a result of their

[36] http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf

use in processing, and components of food contact materials that can reasonably be expected to migrate to food.

Section 409 of the FFDCA and 21 CFR Parts 170 and 171 describe in general terms the information and data necessary to establish the safety of food additives and ingredients. These authorities are supplemented by technical guidance documents providing more specific data recommendations. In addition, FDA may require any other information that it determines during its review is necessary to establish safety.

The specific data that FDA can require to establish the safety of food additives include information on: identity, including physical characteristics such as particle size; the physical or chemical technical effect of the additive; analytical methods for determining the quantity of the substance in food; and the safety of the intended use of the substance. These requirements exist regardless of the physical or chemical characteristics or physical state of the additive. Where appropriate to ensure safety, FDA places limitations on the physical and chemical properties of food additives, which include particle size.

For an approved food additive, FDA publishes a final regulation establishing conditions under which the substance may be safely used. Like an OTC monograph, this rule applies to products that satisfy these conditions. FDA can take various actions however, if the agency learns that a new version of a substance being marketed under a food additive regulation raises safety concerns. A new version that might raise such concerns could be a food additive that contains or may contain nanoscale materials. In such a situation, for example, the agency can issue a call for data on the safety of such a version of the substance. In addition, under 21 CFR Parts 170 and 171, FDA can publish a proposed rule to amend the food additive regulation to address under what circumstances the nanoscale version of the substance may be safely used.

GRAS uses of food ingredients do not require premarket authorization by FDA. Nonetheless, the safety data and information to support GRAS uses of food ingredients must be of the same quality and quantity as data needed to establish the safety of a food additive. In addition, the data must be generally available. Finally, for uses of food ingredients to be GRAS, the safety of the ingredient must be generally recognized by scientists qualified to assess the safety of such substances. As part of its GRAS notice process, FDA can inform manufacturers of what data the agency considers necessary to establish the safety of food ingredients.

Color Additives

FDA regulates color additives under sections 201(t) and 721 of the FFDCA. Generally under these statutory provisions, any substance capable of imparting color to any food, drug, cosmetic, or medical device, or the human body is a color additive that requires premarket approval by FDA in the form of a regulation listing (i.e., approving) the color additive for its intended uses. In addition to being used in compliance with an existing regulation, some color additives may require batch certification by FDA. During the premarket approval process for color additives, FDA reviews detailed manufacturing and analytical data to judge whether postmarket batch certification will be required. In many cases this part of the premarket authorization process requires the sponsor to provide batch samples of the color for analysis by FDA color chemists. The judgment regarding whether a color requires batch

certification is ordinarily based on the expected variation in manufactured color and on the degree of concern that such variation raises regarding the safety of the color additive.

Section 721 of the FFDCA and 21 CFR Part 71 describe in general terms the information and data necessary to establish the safety of color additives. These authorities are supplemented by technical guidance documents providing more specific data recommendations. In addition, FDA can generally require the submission of any data that it determines in its review to be necessary to establish safety. The specific data that FDA can require to establish the safety of a color additive include information on: identity, including physical characteristics such as particle size; analytical methods for determining the quantity of the substance in the finished product and for ensuring the purity and consistency of the manufactured color; and the safety of the color additive under its intended conditions of use. These requirements exist regardless of the physical or chemical characteristics or physical state of the color additive. Where appropriate to ensure safety, FDA places limitations on the physical and chemical properties of color additives, which include particle size.

Once FDA has promulgated a regulation listing a color additive, the regulation applies to products that comply with the rule's conditions. However, FDA can take various actions if the agency learns that a new version of a substance being marketed under a color additive regulation raises safety concerns. A new version that might raise such concerns could be a color additive that contains or may contain nanoscale materials.[37] In such a situation, for example, the agency can issue a call for data on the safety of such a version of the substance. In addition, under 21 CFR Part 71, FDA can publish a proposed rule to amend the listing regulation to address under what circumstances the nanoscale version of the substance may be safely used.

Cosmetics

Section 201(i) of the FFDCA defines a cosmetic as an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof 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.[38] This definition includes skin-care creams, lotions, hairsprays, perfumes, lipsticks, fingernail polishes, eye and facial makeup, permanent waves, hair colors, deodorants, baby products (e.g., baby powder, baby oil, wipes), bath oils, bubble baths, and mouthwashes, as well as any material intended for use as a component of a cosmetic product. Under the FFDCA, FDA is not given premarket approval authority for cosmetic products and most cosmetic ingredients (other than color additives). However, FDA's mission includes ensuring that cosmetics are safe and properly labeled. FDA pursues this mission through a combination of activities which include inspection of cosmetic manufacturing establishments and enforcement actions for cosmetic products found to be in violation of the "adulteration" (Section 601) and/or "misbranding" (Section 602) provisions of the FFDCA. For example, if a cosmetic bears or contains any poisonous or deleterious substance which

[37] Although adverse events for color additives marketed as stand-alone products or used in conventional foods and cosmetics do not have to be reported to FDA, adverse events for color additives that are components of a drug or device must be reported as part of the adverse event reporting requirements for the finished product.

[38] However, a product that meets the definition for a cosmetic but is intended to affect the structure or function of the body of man will also be subject to regulation as a drug or device.

may render it injurious to users when used under labeled or customary conditions of use, the product is adulterated.

Dietary Supplements

Dietary supplements are regulated under the FFDCA, as amended by the Dietary Supplement Health and Education Act of 1994, or DSHEA. In addition, there are implementing regulations in 21 CFR Parts 101, 119, and 190. As defined in the statute (21 U.S.C. 321(ff)), a dietary supplement is a product other than tobacco that is intended to supplement the diet and that contains one or more dietary ingredients. A dietary ingredient is any one of the following: a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total daily intake; or a concentrate, metabolite, constituent, extract or combination of any of the other types of dietary ingredients. The requirement to contain a dietary ingredient is only one element of the dietary supplement definition. A dietary supplement must also be labeled as such and must be intended for ingestion. Topical products like lotions and ointments cannot be dietary supplements. A dietary supplement must not be represented for use as a conventional food or as a sole item of a meal or the diet. Generally, articles approved as new drugs, licensed as biologics, or authorized for clinical investigation under an IND cannot be marketed as dietary supplements. However, if the product was marketed as a dietary supplement or as a food before such approval, licensing, or authorization under an IND, it may still be marketed as a dietary supplement afterwards.

With one exception, FDA has no authority to require premarket safety testing or premarket submission of safety information for a dietary supplement. The manufacturer of a dietary supplement must notify FDA at least 75 days in advance of marketing a product if it contains a new dietary ingredient,[39] unless that ingredient has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered" (21 U.S.C. 350(b)). The manufacturer must include in the notification the information on which the manufacturer based its conclusion that a dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. However, the nature of the safety information on which the manufacturer may rely is not specified in the law, and there is no requirement that a manufacturer wait for a safety determination from FDA before marketing the product.

Because the majority of dietary supplements do not contain a new dietary ingredient, most dietary supplement safety issues arise in the post-market context. As with conventional foods and cosmetics, a manufacturer may market a dietary supplement without pre-market authorization from FDA. As part of its responsibility to ensure that FDA-regulated products sold in the U.S. are safe and properly labeled, the agency inspects dietary supplement manufacturing facilities and takes action against dietary supplements that are adulterated (21 U.S.C. 342) or misbranded (21 U.S.C. 343).

Because FDA's regulation of dietary supplements is generally post-market, the agency may not know whether particle sizes or material features used in dietary supplement products are in the nanoscale range, unless the agency becomes aware of the use of such sizes and features, for example, from information submitted in a notification or from the product

[39] A new dietary ingredient is an ingredient not marketed in the U.S. before October 15, 1994.

labeling.

Labeling and Advertising Claims for Conventional Foods and Dietary Supplements

In some cases, FDA may become aware of the use of nanoscale materials or features in a dietary supplement or conventional food because of labeling or advertising claims for the product in the marketplace. These could be claims that explicitly reference the presence of nanoscale materials in the product or claims that describe product characteristics or effects derived from the use of nanoscale materials or nanotechnology.

In addition, there are some labeling claims for conventional foods and dietary supplements that require a premarket petition process or a postmarket notification to FDA. For example, health claims (i.e., claims about reducing the risk of a disease or health-related condition) for a conventional food or dietary supplement require premarket review by FDA. The mechanism for requesting a new health claim is a health claim petition under 21 CFR 101.70, requesting that the agency issue a regulation regarding the claim. Health claim petitions must explain the petitioner's basis for concluding that the substance that is the subject of the requested claim is safe, and petitions must also include studies demonstrating that the substance has the claimed risk reduction effect.

For dietary supplements, the FFDCA (Section 343(r)(6)) specifically authorizes the use of labeling claims concerning effects on the structure or function of the body (structure/function claims), claims of general well-being, and claims of a benefit related to a classical nutrient deficiency disease. These claims do not require premarket review, but they do require notification to FDA within 30 days of marketing. Unlike a health claim petition, however, a postmarket notification for a dietary supplement labeling claim under Section 403(r)(6) of the Act need not include safety information about the substance for which the claim is being made or studies demonstrating that it has the effect claimed.

In summary, FDA review of a labeling claim, such as a structure or function claim or health claim, would not necessarily include information related to use of nanoscale materials. Whether the agency would have the opportunity to review such information would depend on whether the nanoscale material was related to the basis for the labeling claim and, if so, whether the information about the nanoscale material was submitted to the agency, e.g., in a health claim petition as required by 21 CFR § 101.70(f), or voluntarily for other types of claims.

Issue: Ability of FDA to Identify FDA-Regulated Products that Contain Nanoscale Materials

Comments

Several comments stressed the importance of identifying the use of nanoscale materials in FDA-regulated products. One comment suggested that companies generally submit information on particle size. Another comment urged FDA to call for data on uses of nanotechnology for foods. Another comment suggested that FDA establish a mandatory premarket notification system for novel uses of nanotechnology and urged FDA to issue

guidance defining "novel use." Several comments discussed the importance of a clear definition of nanoscale materials in order to eliminate confusion. A few comments stated it was necessary to distinguish between "common" nano-sized food ingredients and those intentionally nano-sized.

Analysis

As discussed in the State of the Science section, although the science of nanotechnology is continuing to evolve, it is known that the size of a particle can affect its properties such that versions of the same substance with differing particle sizes can have different properties, such as their interaction with light (e.g., transparency of lotions). To appropriately assess the safety and, as applicable, the effectiveness of products, it will be important in some cases for FDA, or the manufacturer, to take into account whether the product contains nanoscale materials. FDA's authority to obtain information on particle size differs depending on whether products are subject to premarket authorization or not. As indicated above, the agency's authority is comprehensive with regard to products subject to premarket authorization such as drugs, devices, biological products, and food and color additives. FDA's authority is more limited with regard to products that are not subject to premarket authorization, which include cosmetics and dietary supplements.

FDA can require submission of data regarding particle size and other relevant properties when such data are necessary to evaluate the safety or, as appropriate, effectiveness of a product that is subject to premarket authorization. However, the agency might not obtain such information if the manufacturer is uncertain of whether it needs to obtain authorization to market its product or already has authorization to do so (e.g., of whether its product is covered by an existing food or color additive regulation or by an OTC drug monograph). When dealing with products not subject to premarket authorization, the agency has less ability to obtain information about the presence of nanoscale materials.

Recommendations for Consideration

Issue guidance to sponsors regarding identification of the particle size for:

- Products subject to premarket authorization, including OTC drugs (when a new monograph or amendment to a monograph is being proposed), and food and color additives (in petitions to approve new additives or to amend existing approvals); and

- Products not subject to premarket authorization but for which the sponsor is required to provide notice (such as dietary supplements containing certain new dietary ingredients), or may choose to provide notice (such as a GRAS notification).

When warranted, issue a call for data to identify:

- OTC drug products that contain or may contain nanoscale versions of ingredients included in an OTC monograph; and

- Nanoscale versions of previously approved food and color additives.

Issue: Scope of FDA's Authority Regarding Evaluation of Safety

and Effectiveness

Comments

Several comments requested that FDA collect safety information on the use of nanotechnology in regulated products. Most comments stated that there should be disclosure, transparency, and sharing of scientific information. One comment suggested that all existing safety data should be submitted. One comment recommended that FDA request available studies on nano- and micro-scale ingredients to substantiate safety in personal care products. One comment urged cosmetic manufacturers to submit substantiation data voluntarily. Other comments urged obligatory reporting of safety and health problems caused by nanoscale products.

Opinions differed regarding the need to develop a regulatory framework specific to nanotechnology. Most of the comments urged regulation based upon the unique risks of small particle size. One comment, for example, stated that FDA should start with the assumption that nanoscale materials in products behave in a distinct way and, therefore, should be subject to nanospecific paradigms and health and safety testing. On the other hand, many of the comments stated that there was not enough scientific evidence of unique risks posed by products using nanotechnology and therefore disagreed that FDA should establish a distinct regulatory regime for products using nanotechnology. These comments stated that the regulatory pathways currently utilized by FDA based on statutory classification of the products are sufficient to ensure the safety and effectiveness of products using nanotechnology. These comments urged FDA to evaluate products according to consistent, proven safety standards. Still other comments stated the need to address "intentionally produced" nanoscale materials. One comment stressed the need to avoid definitions that failed to distinguish between common, naturally occurring nanoscale food components and those intentionally used components that might, based upon the hazards posed, require modification of existing regulatory frameworks.

Several comments stated that products using nanotechnology should be treated as new products. Some groups wanted all products using nanotechnology to be subjected to safety testing prior to marketing. One comment suggested that use of nanoscale materials could change the regulatory pathway used to ensure safety and that FDA establish criteria for what is "new for legal and regulatory purposes" and "new for safety evaluation purposes."

Some comments focused on the safety standard for products using nanotechnology. One comment suggested that the agency adopt a "reasonable certainty of no harm" standard. Several comments requested guidance on substantiation, one of which recommended that substantiation be based on the "competent and reliable scientific evidence" standard under the Federal Trade Commission Act.

Several comments focused on the process for developing timely and responsible regulations. These comments urged that any regulation to identify and minimize risks should be adopted in an open and transparent process.

One comment stated that FDA has ample legal authority to require food manufacturers to establish safety, substantiate label claims based on sound science, and remove unsafe products from the market.

Analysis

Products Subject to Premarket Authorization

Because nanoscale materials can behave differently than other versions of the same materials, it will be important for FDA to obtain relevant information about the characteristics of products containing nanoscale materials. The guidance recommended in the section above entitled "Ability of FDA to Identify FDA-Regulated Products that Contain Nanoscale Materials" would assist the agency in identifying the particle size and other relevant properties of nanoscale materials in products subject to FDA's review. As stated above, FDA's authority over products subject to premarket authorization is comprehensive and provides FDA with the ability to obtain detailed scientific information needed to assess the safety and, as applicable, effectiveness of products, including relevant effects of nanoscale materials. In some cases, the presence of nanoscale materials may change the regulatory status/regulatory pathway of products. The Task Force believes it is important that manufacturers and sponsors be aware of the issues raised by nanoscale materials and the possible change in the regulatory status/pathway when products contain nanoscale materials.

Recommendations for Consideration

To provide clear guidance to interested parties and to enhance FDA's knowledge base, the Task Force recommends that the agency take the following actions regarding products subject to premarket authorization:

- Issue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety and effectiveness of nanoscale materials in products subject to FDA premarket authorization, including both existing products that are changed to include (or include greater proportions of) nanoscale materials and new products made with nanoscale materials. In addition, the Task Force recommends that FDA seek comment on whether FDA's current policies for determining the appropriate regulatory pathway are optimal for reaching timely and predictable decisions for highly integrated combination products containing nanoscale materials. If commenters believe current policies are not optimal, they would be asked for examples of the kinds of products for which FDA's policies are not optimal and why they are not.

- Issue guidance requesting submission of information on whether and how the presence of nanoscale materials affects the manufacturing process for products subject to premarket authorization, as part of a premarket submission. Relevant information would address situations when the product contains nanoscale materials and when any part of the manufacturing process involves nanoscale materials, even if those materials do not become part of the finished product.

Issue guidance or amend existing guidance to describe what additional or distinct information should be submitted to FDA or generated with regard to the following:

- New food or color additives made with nanoscale materials; and

- Previously approved food or color additives that are now made with nanoscale

materials or to contain greater proportions of nanoscale materials.

Issue guidance describing when:

- A sponsor of a Class I or Class II device, who is otherwise exempt from submitting a 510(k), would need to submit a 510(k) because the presence or amount of nanoscale material would result in the device being outside the scope of the limitations of exemption described in the general provisions of the applicable regulations (see 21 CFR §§ 862.9-892.9);

- A sponsor should submit a new 510(k) for a modification to a previously cleared device that incorporates the use or increased use of nanoscale materials; and

- IRBs, investigators, and industry should seek input from FDA on significant risk/nonsignificant risk decisions regarding investigational devices containing nanoscale materials.

Products Not Subject to Premarket Authorization

Where products are not subject to premarket authorization, manufacturers generally are not required to submit data to FDA prior to marketing, and agency oversight capacity is, therefore, less comprehensive. However, manufacturers are still responsible for ensuring that the products they market are safe. For example, cosmetic manufacturers are required to ensure the safety of their products but are not required to provide safety data to FDA. In light of the evolving state of the science, the Task Force believes an appropriate course of action at this time would be for the agency to work with manufacturers of these products and assist them in identifying data to substantiate the safety of products containing nanoscale materials, including chronic toxicity and other long-term toxicity data as appropriate.

Recommendations for Consideration

We recommend the following regarding products not subject to premarket authorization:

- Issue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety of nanoscale materials in products not subject to premarket authorization. The notice would address both new products made with nanoscale materials and existing products that are changed to include or include greater proportions of nanoscale materials.

- Issue guidance or amend existing guidance to describe what additional or distinct information should be submitted to FDA or generated with regard to:

    - The use of nanoscale materials in food ingredients for which a GRAS notification is submitted or the reduction of particle size into the nanoscale range for food ingredients for which an earlier notification had been submitted and not objected to by FDA; and

    - The use of nanoscale materials in new dietary ingredients.

- Issue guidance recommending manufacturers consider whether and how the presence

of nanoscale materials affects the manufacturing process. Relevant considerations would include both situations when the product contains nanoscale materials and when any part of the manufacturing process involves nanoscale materials, even if those materials do not become part of the finished product.

- Issue guidance describing safety issues that manufacturers should consider to ensure that cosmetics made with nanoscale materials are not adulterated.

- Issue guidance on whether a dietary ingredient modified to include nanoscale materials or include a greater proportion of nanoscale materials would still qualify as a dietary ingredient under 21 U.S.C. 321(ff) (1), and on when the reduction in size into the nanoscale range of an "old" dietary ingredient might trigger the notification process required for a new dietary ingredient on the basis of the presence or amount of nanoscale materials.

Issue: Permissible and Mandatory Labeling

Comments

Several comments urged the disclosure in labeling of the presence of nanoscale materials in FDA-regulated products. A few stressed the importance of clear definitions of "nanoengineered materials and nanotechnology" to enable such disclosure. One group recommended that FDA enforce warning label requirements for cosmetics.

Analysis

Consumers are increasingly exposed to information about nanotechnology products, but they may not always understand whether the use of nanotechnology has a significant effect on the products they purchase. As with many other new technologies, the use of nanotechnology does not mean that a product's safety or effectiveness is necessarily increased, decreased, or affected in any way. As the comments reflect, consumers may have questions regarding the use of nanotechnology for products regulated by FDA. Whether information on such use must be included in product labeling, or can voluntarily be included, depends on whether its inclusion is required or permitted under the FFDCA.

The FFDCA requires that labeling of FDA-regulated products be truthful and not misleading. Labeling must include material information, including with respect to consequences which may result from the use of the product under the conditions of use prescribed in the labeling or under customary or usual conditions of use. The risk information contained in prescription drug labeling is an example of material information. For foods, information about the characteristics of the food can be material, such as nutritional, organoleptic (e.g., taste, smell, or texture), or functional (e.g., storage) properties. If labeling is false or misleading, the product is "misbranded" and cannot be marketed.

For products subject to premarket authorization, the agency generally considers on a case-by-case basis as part of marketing authorization whether labeling contains adequate information to support the safe and, as applicable, effective use of the product. Labeling for products not subject to premarket authorization (for example, cosmetics) also must include material information and not include false or misleading information. Otherwise, these

products would be misbranded. If FDA determined that a particular use of a specific nanoscale material, or the use of nanoscale materials more generally, was a material fact for a category of products, FDA could amend its regulations to require, for example, that all members of that category of products include labeling regarding such use of nanoscale material.

If disclosure of information on the use of nanoscale materials is not material (and, therefore, is not required to be included in the product labeling), the manufacturer may still be able to include such information, as long as the information is not false or misleading. However, because claims regarding the use of nanoscale materials might be misleading and, therefore, misbrand a product, the Task Force would recommend encouraging manufacturers to consult with the agency concerning such labeling to avoid misbranding the product.

Recommendations for Consideration

Because the current science does not support a finding that classes of products with nanoscale materials necessarily present greater safety concerns than classes of products without nanoscale materials, the Task Force does not believe there is a basis for saying that, as a general matter, a product containing nanoscale materials must be labeled as such. Therefore the Task Force is not recommending that the agency require such labeling at this time. Instead, the Task Force recommends that the agency take the following action:

- Address on a case-by-case basis whether labeling must or may contain information on the use of nanoscale materials.

Issue: National Environmental Policy Act

Comments

No comments were submitted to the Task Force's docket or to the docket for the ICTA Petition regarding NEPA obligations.

Analysis

NEPA requires federal agencies to assess the environmental impacts of "major federal actions" and to ensure that the interested and affected public is informed of environmental analyses. Agencies may prepare an environmental assessment (EA) or environmental impact statement (EIS), as appropriate. Agencies can also establish categorical exclusions for categories of major federal actions that have been determined not to individually or cumulatively have a significant effect on the human environment. However, agency procedures must also provide for those circumstances where a normally excluded action may have a significant environmental effect. Examples of such "extraordinary circumstances" are identified in FDA's regulations and include actions for which available data establish that there is the potential for serious harm to the environment and actions that adversely affect an endangered, threatened, or otherwise specially protected species.

Many FDA regulatory actions constitute major federal actions, including: actions to approve or withdraw applications to market new drugs and biological products; actions to approve or prohibit or otherwise restrict the use of a substance in food, or food packaging; and actions

on premarket notifications and premarket applications for devices. Under FDA's regulations, many of these actions can qualify for a categorical exclusion.

The agency requires applicants and petitioners to submit an EA or a claim of categorical exclusion when requesting agency action. An EA must address the relevant environmental issues and contain sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Agency guidance provides recommendations for preparation of EAs and the making of categorical exclusion claims. The science related to the environmental implications of nanoscale materials is evolving. In some cases, the presence of nanoscale materials may warrant a closer look at potential environmental impacts of an FDA-regulated product. Such products may not qualify for a categorical exclusion or an extraordinary circumstance may exist.

As knowledge of nanoscale materials increases, it may be productive for the agency to develop or amend agency NEPA guidance to address expressly nanoscale materials or certain types of nanoscale materials. In light of the current, evolving state of scientific knowledge regarding nanoscale materials, however, the Task Force recommends a case-by-case approach at this time to assessing NEPA requirements for products using these materials, and coordination across the agency to enable consistent determinations informed by the most current science.

Recommendations for Consideration

We recommend that the agency take the following actions:

- Take into account, on a case-by-case basis, whether an FDA-regulated product containing nanoscale materials qualifies for an existing categorical exclusion and whether extraordinary circumstances exist.

- Designate a lead in the agency to coordinate the agency's approach to its obligations under NEPA regarding nanotechnology.