FDA Regulation of Nanotechnology

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About the Editor

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CHAPTER 1: INTRODUCTION TO FDA REGULATION OF NANOTECHNOLOGY*

Nanotechnology is sometimes defined as the understanding and control of matter at the nanoscale, at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications.[1] There is no standard definition of "nanomaterial" or "nanotechnology."[2] The Food and Drug Administration (FDA) has not adopted a regulatory definition, but it has identified points to consider in deciding whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology:

1. Whether an engineered material or end product has at least one dimension in the nanoscale (approximately 1 nm to 100 nm); or

2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.[3]

Although FDA has already approved products using nanotechnology throughout various product categories, the small stream of approved nanotechnology-based products is but a precursor to the flood of those in the pipeline or expected to enter the pipeline in coming years. Some estimates predict that the combined market for nano-enabled medicine, including drug delivery, therapeutics, diagnostics, and nanobiomaterials, will surge to well over $100 billion over the next few years.[4] Nanotechnology-based products may also include cosmetics, foods and food ingredients, packaging materials, and other additional health-related categories.

While nanotechnology leaps forward, concerns regarding the safety of nanomaterials have also grown. Governmental entities, non-governmental organizations, and others are on guard against the unknown effects that the new and tiny particles may have once they enter or come in contact with the body. In some cases, subtle changes in the size of the particles used in the nanoscale materials may create very different properties, including degrees of toxicity. The small size of engineered nanomaterials may also facilitate their uptake into and between various cells or cell components, allowing for transport to sensitive target sites the body, including bone marrow, spleen, heart, and brain. In addition to size, the shape, solubility, surface chemistry, and

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* This chapter was prepared by Mark N. Duvall and Alexandra M. Wyatt, Beveridge & Diamond, P.C.

[1] National Nanotechnology Initiative, What is Nanotech?, www.nano.gov.

[2] Twenty-four definitions of "nanomaterial" are summarized in Table 2 of ICCR, REPORT OF THE ICCR JOINT AD HOC WORKING GROUP ON NANOTECHNOLOGY IN COSMETIC PRODUCTS: CRITERIA AND METHODS OF DETECTION (2010), *available at* http://www.fda.gov/downloads/InternationalPrograms/HarmonizationInitiatives/UCM235485.pdf.

[3] FDA, DRAFT GUIDANCE FOR INDUSTRY, CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY (June 2011), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

[4] Press Release, World Nanomedicine Market to Cross $160 Billion by 2015, According to New Report by Global Industry Analysts, Inc. (June 25, 2009), *available at* http://www.bio-medicine.org/biology-technology-1/World-Nanomedicine-Market-to-Cross--$160-Billion-by-2015--According-to-New-Report-by-Global-Industry-Analysts--Inc--12778-1/.

surface area of nanoscale particles may increase inflammation and tissue damage.[5] Yet these properties are not always considered in depth when FDA evaluates hazards and health effects for regulation or oversight.

Many of the most exciting—and potentially risky—nanotechnology-based products on the horizon will fall under the authority of FDA, which must play a pivotal role in ensuring that these products are safe. FDA is responsible for protecting the public health by assuring the safety, and sometimes the efficacy, of drugs, medical devices, radioactive products, cosmetics, food, and related products. FDA also promotes medical innovations and aims to ensure that the public receives accurate information regarding medicines, food, and supplements.[6] These roles sometimes conflict. FDA must reconcile the values of bringing innovative, effective products to the public quickly and ensuring that only products whose benefits outweigh the risks reach the public. In reconciling those values in the context of nanotechnology-based products, FDA will encounter a number of dilemmas which span across product categories.

As discussed in the following chapters, a key consideration in FDA's review of nanotechnology-based products subject to its jurisdiction is the differing statutory authority it has with respect to different categories of products, most notably with respect to whether or not it has pre-market review authority. It has pre-market review authority for color additives, food additives, drugs, devices, and for new dietary ingredients. It does not have pre-market review authority for cosmetics, most dietary supplements, or food. FDA has indicated that it intends to incorporate attention to nanomaterials in its product-specific pre-market reviews. For products not subject to pre-market review, FDA encourages manufacturers to consult with it to reduce the risk of unintended harm to human or animal health.[7]

One significant regulatory dilemma posed by products based on nanotechnology is the necessity of properly classifying and distinguishing them for oversight by one of FDA's Centers. Although the current FDA classification system functions adequately with other emerging technologies that span regulatory boundaries, the miniaturization of products will amplify deficiencies in the classification procedure. Current distinctions between "chemical," "mechanical," and "biological" activity, for example, may be rendered ineffectual by nanotechnology.[8] FDA has broad latitude to make jurisdictional determinations and to implement pre-clinical and clinical testing requirements that may be significantly more burdensome for nanoscale products than conventional therapies.[9] Its classifications will significantly impact the difference in the time and cost a prospective product will incur prior to

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[5] *See* generally FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 9-19 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter FDA NANOTECHNOLOGY TASK FORCE REPORT].

[6] *What We Do*, FDA (last updated 2010), http://www.fda.gov/AboutFDA/WhatWeDo/default.htm.

[7] FDA, DRAFT GUIDANCE FOR INDUSTRY, CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY (June 2011), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

[8] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 5.

[9] Stuart Portnoy and Steven Koepke, *Regulatory Strategy: Preclinical Testing of Combination Products*, MDDI MAG. (May 2005), *available at* http://www.mddionline.com/article/regulatory-strategy-preclinical-testing-combination-products.

market entry as well as the amount of pre-market and post-market safety scrutiny the product will undergo. Because of the uncertainty of the science and the rapid development of applications for FDA-regulated products, it is critical for FDA to have a transparent, consistent, and predictable regulatory pathway for nanotechnology-based products.[10] FDA has offered guidance on classification decisions, but it is not specific to nanotechnology-based products.[11]

Within given regulatory classifications, FDA experts believe, nanotechnology-based products generally present challenges similar to those FDA faces with other emerging technologies.[12] These challenges may be magnified, however, because "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."[13] Some, therefore, urge FDA to regulate all engineered nanomaterials as new substances, arguing that they categorically behave differently from their larger-scale counterparts; this approach would subject nanotechnology-based products to the highest level of FDA scrutiny. Others advocate for the continued application of a risk-based approach to nanotechnology-based products. They urge that instead of subjecting all nanotechnology-based products to increased scrutiny and possible delay, different levels of precaution should be assigned for different substances based on the importance of their potential use, thereby expediting approval and ensuring public safety.[14] These nanotechnology regulation dilemmas reflect a broader debate about the roles of FDA and industry self-regulation in balancing the values of innovation and safety.

The Obama Administration has intervened in that debate, calling for a risk-based approach to the extent consistent with law. In 2011, the Executive Office of the President a set of principles related to regulation and oversight of emerging technologies (mentioning nanotechnology in particular) which called for scientific integrity, public participation, communication, awareness of benefits and costs, flexibility, risk assessment and risk management, coordination between agencies, and international cooperation, as well as detailed guidance on regulation of emerging technologies.[15] These principles were reiterated and explained in a second set of principles specific to nanotechnology, which stated in summary:

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[10] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 5.

[11] *See, e.g.*, FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES (June 2011), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM258957.pdf; FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: INTERPRETATION OF THE TERM "CHEMICAL ACTION" IN THE DEFINITION OF DEVICE UNDER SECTION 201(H) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (June 2011), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM259068.pdf.

[12] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 5. at 20.

[13] Jennifer Whitney, *Sizing Up the Potential of Nanotechnology*, MED. PROD. OUTSOURCING (Sept. 2007), *available at* http://www.mpo-mag.com/articles/2007/09/sizing-up-the-potential-of-nanotechnology.

[14] *See, e.g.*, Jonathan M. Gilligan, *Flexibility, Clarity, and Legitimacy: Considerations for Managing Nanotechnology Risks*, 36 ENVTL. L. INST. 10924 (2006), *available at* http://www.vanderbilt.edu/ees/images/gilligjm/Gilligan-Flexibility-Clarity-and-Legitimacy.pdf.

[15] EXECUTIVE OFFICE OF THE PRESIDENT, PRINCIPLES FOR REGULATION AND OVERSIGHT OF EMERGING TECHNOLOGIES (Mar. 11, 2011), *available at* http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf.

> Nanomaterials should not be deemed or identified as intrinsically benign or harmful in the absence of supporting scientific evidence, and regulatory action should be based on such scientific evidence. Where there is evidence of either safety or likely harm, the corresponding regulatory actions are usually clear. For some statutes, the mere existence of a hazard, regardless of the probability of it causing harm, may trigger some form of regulatory action. In general, however, and to the extent consistent with law, regulation should be based on risk, not merely hazard, and in all cases the identification of hazard, risk or harm must be evidence-based. In applying these principles, regulators should use flexible, adaptive, and evidence-based approaches that avoid, wherever possible, hindering innovation and trade while fulfilling the Federal Government's responsibility to protect public health and the environment.[16]

Citing those principles, FDA has declared that it "does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful."[17]

FDA has been working to develop information needed to help it regulate nanomaterials in all its programs effectively. It held a public meeting on nanotechnology in 2006,[18]another in 2008,[19] and another in 2010.[20] A key step forward was the 2007 report by an FDA Nanotechnology Task Force, which made numerous recommendations.[21]

Much work needs to be done. Many of the recommendations of the 2007 Nanotechnology Task Force report remain to be implemented. For example, a 2010 FDA document admits that "[b]ecause development of nanotechnology-based drugs is still in its infancy, there are no established standards for the study or regulatory evaluation of these products."[22] The President's Council of Advisors on Science and Technology has called on FDA to "clarify the development pathway" and increase its "emphasis on transitioning nanotechnology to commercialization, including making sustained meaningful investments in focused areas to help accelerate technology transfer to the marketplace."[23]

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[16] EXECUTIVE OFFICE OF THE PRESIDENT, POLICY PRINCIPLES FOR THE U.S. DECISION-MAKING CONCERNING REGULATION AND OVERSIGHT OF APPLICATIONS OF NANOTECHNOLOGY AND NANOMATERIALS (June 9, 2011), *available at* http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf.

[17] FDA, DRAFT GUIDANCE FOR INDUSTRY, CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY (June 2011), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

[18] 71 Fed. Reg. 46,232 (Aug. 11, 2006).

[19] 73 Fed. Reg. 46,022 (Aug. 7, 2008).

[20] 75 Fed. Reg. 51,829 (Aug. 23, 2010).

[21] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 5.

[22] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF PHARMACEUTICAL SCIENCE, REPORTING FORMAT FOR NANOTECHNOLOGY-RELATED INFORMATION IN CMC REVIEW, MANUAL OF POLICIES AND PROCEDURES 5015.9 (June 3, 2010), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf.

[23] EXECUTIVE OFFICE OF THE PRESIDENT, PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, REPORT TO THE PRESIDENT AND CONGRESS ON THE THIRD ASSESSMENT OF THE NATIONAL NANOTECHNOLOGY INITIATIVE 31 (Mar. 12, 2010), *available at* http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-nano-report.pdf.

Funding is a critical constraining factor in accomplishing this work.[24] In fiscal year (FY) 2009 FDA received $6.5 million for nanotechnology-related projects, and it was expected to receive $7.3 million in FY 2010. An increase to $15 million for FY 2011 was included in a supplement to the President's 2011 Budget. These funds are to be used for agency-wide priorities: (1) laboratory and product testing capability, (2) scientific staff development and training, and (3) collaborative and interdisciplinary research to address product characterization and safety. They are focused on enabling the agency to characterize nanotechnology-based products, develop models for safety and efficacy assessment, and study the behavior of nanomaterials in biological systems and their effects on human health.[25] The President's 2012 Budget included $14.3 million for similar nanotechnology-related activities throughout the agency.[26]

The FDA Food Safety Modernization Act (FSMA), enacted on January 4, 2011,[27] authorizes FDA to collect fees to reimburse costs of implementing certain food-related programs.[28] FDA also has authority to collect user fees for drugs[29] and medical devices.[30] Such fees can be a helpful supplement to FDA's congressional appropriation.

The chapters that follow address how FDA can, and to some extent, has, regulated nanomaterials in products falling under its multiple areas of responsibility: cosmetics, color additives, food additives, dietary supplements, food and feed, drugs, medical devices, biologics, and combination products. Radiological products are not addressed. Generally, each identifies products that already feature nanomaterials; reviews FDA's regulatory program for the specific product category (such as particular pre-market and post-market controls); then discusses how that program might apply to nanomaterials. In a number of cases, references are made to how the European Union is addressing similar issues.

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[24] MICHAEL R. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? 45-50 (Oct. 2006), *available at* http://nanotechproject.org/file_download/files/PEN5_FDA.pdf.

[25] THE NATIONAL NANOTECHNOLOGY INITIATIVE, RESEARCH AND DEVELOPMENT LEADING TO A REVOLUTION IN TECHNOLOGY AND INDUSTRY: SUPPLEMENT TO THE PRESIDENT'S FY 2011 BUDGET 8, 21 (2010), *available at* http://www.nano.gov/NNI_2011_budget_supplement.pdf.

[26] DEPARTMENT OF HEALTH AND HUMAN SERVICES, FISCAL YEAR 2012 FOOD AND DRUG ADMINISTRATION JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES (2011), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM243370.pdf.

[27] FDA Food Safety Modernization Act, Pub. L. 111-353, 124 Stat. 3920 (2011) (amending various parts of the FFDCA), and adding 21 U.S.C. §§ 2201-52.

[28] FSMA § 107(a), adding FFDCA § 743, 21 U.S.C. § 379j-31.

[29] FFDCA § 736, 21 U.S.C. § 379h.

[30] FFDCA § 738, 21 U.S.C. 379j.

CHAPTER 2: COSMETICS*

I. INTRODUCTION

Cosmetic manufacturers are increasingly marketing products containing ingredients made using nanomaterials. According to the Food and Drug Administration (FDA), "[c]osmetics represent one of the fastest growing areas for the application of this emerging technology."[1] Using the nanoscale version of some common macroscale ingredients, or some ingredients that only exist at the nanoscale, may allow manufacturers to offer cosmetics that produce superior results as compared to cosmetics made without nanomaterials because the physical and chemical properties of such ingredients are different from those of macroscale ingredients. However, it remains unclear if such properties may present risks to human health or the environment. These safety concerns, in turn, have led some observers to question whether cosmetics incorporating nanomaterials should be subject to greater regulation and scrutiny or should even be allowed on the market. Currently, the regulatory framework governing cosmetics does not require advance approval by FDA before a product is marketed. In addition, cosmetic manufacturers, not FDA, bear the responsibility of ensuring that the safety of their products is adequately substantiated. As a result, a debate has emerged concerning the sufficiency and effectiveness of cosmetic product regulations as applied to those products employing nanomaterials.

This chapter explores that debate, beginning by providing background on the use of nanomaterials in cosmetics as well as on the current FDA regulatory framework. It then examines the various tools available to FDA in overseeing cosmetics which incorporate nanomaterials.

II. REGULATION OF COSMETIC PRODUCTS: A BRIEF OVERVIEW

Through its Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition, FDA regulates the safety and effectiveness of cosmetic products under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended,[2] and its implementing regulations. Cosmetic products are defined in the FFDCA as "(1) articles 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 appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap."[3] By this definition, cosmetics encompass a broad range of products. A few of the most common examples include makeup, face and body lotions, nail polishes, shampoos and conditioners, hair dyes, toothpastes, mouthwashes, deodorants, baby powders, and perfumes.[4]

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* This chapter was prepared by Philip A. Moffat, now with Verdant Law, PLLC, and Michael R. Neilson, now with Lonza, Inc.

[1] DEPARTMENT OF HEALTH AND HUMAN SERVICES, FISCAL YEAR 2012 FOOD AND DRUG ADMINISTRATION JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES 120 (2011), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM243370.pdf.

[2] 21 U.S.C. §§ 301-399d.

[3] FFDCA § 201(i), 21 U.S.C. § 321(i).

[4] Not all consumer products applied to the skin fall within the definition of cosmetics, including new products making use of nanotechnology. For example, FDA regulates sunscreens, antiperspirants, dandruff shampoos, and

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As compared to FDA's other regulated products, cosmetics are governed relatively lightly, and (except for color additives[5]) only after introduction to the market. The FFDCA prohibits the marketing of cosmetic products deemed to be adulterated or misbranded.[6] Adulterated cosmetics are those which (1) contain poisonous or deleterious substances rendering the cosmetics injurious, (2) contain filthy, putrid, or decomposed substances, (3) have been prepared, packaged, or held under unsanitary conditions, or (4) have containers composed of poisonous or deleterious substances. Except for special provisions for hair dyes, a cosmetic product will also be deemed adulterated if it contains an "unsafe" color additive.[7] Misbranded cosmetics generally are those which (1) have false or misleading labeling, (2) have labels without all required information displayed prominently and conspicuously, or (3) have containers made, formed, or filled as to be misleading.[8] Through the Department of Justice, FDA may take regulatory action to remove cosmetic products deemed adulterated or misbranded from the marketplace. FDA may seize violative products, as well as issue restraining orders to halt further distribution.

The FFDCA does not subject cosmetic products to FDA pre-market approval prior to their introduction into the marketplace. Manufacturers are individually responsible for ensuring that only safe products are commercially marketed. Under the misbranding provisions, FDA regulations impose a substantive performance requirement on cosmetic manufacturers by requiring the safety of their products to be "adequately substantiated" by the manufacturer prior to marketing: "Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel: Warning—The safety of this product has not been determined."[9] However, the FFDCA does not authorize FDA to require affirmative proof from a manufacturer that any cosmetic ingredient is safe. Rather, in an adjudicatory proceeding, FDA would have to prove that a cosmetic ingredient is unsafe.

The industry standard for substantiation is through an independent ingredient safety assessment conducted by the Cosmetic Ingredient Review (CIR), an industry-funded but independent expert panel founded in 1976.[10] CIR publishes the results of its work in peer

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acne treatments as drugs under FDA's monograph system. 21 C.F.R. Parts 347, 350, 352, 358. *See also* 72 Fed. Reg. 49,070, 49,110 (Aug. 27, 2007) (notice of proposed rulemaking requesting comments on nanoscale components of sunscreens).

[5] *See* Chapter 3 – Color Additives.

[6] FFDCA §§ 601-602, 21 U.S.C. §§ 361-362.

[7] FFDCA § 601, 21 U.S.C. § 361. Note also that FDA has declared at least some substances to be so toxic that their presence above trace amounts in cosmetics will render the cosmetic adulterated. *See, e.g.*, 21 C.F.R. § 700.13 (restricting use of mercury).

[8] FFDCA § 602, 21 U.S.C. § 362.

[9] Warning Statements, 21 C.F.R. § 740.10.

[10] *See* PERS. CARE PRODS. COUNCIL, QUESTIONS AND ANSWERS - CONSUMER COMMITMENT CODE (2008), http://www.personalcarecouncil.org/sites/default/files/FinalCouncilCodeQ&A0608.pdf [hereinafter PCPC, CCC Q&A]; Robert L. Elder & Jonathon T. Busch, *The Cosmetic Ingredient Review*, *in* 2 COSMETIC SCIENCE AND TECHNOLOGY SERIES, THE COSMETIC INDUSTRY: SCIENTIFIC AND REGULATORY FOUNDATIONS, 203 (Norman F.
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reviewed scientific literature.[11] CIR generally assesses high-priority ingredients based on chemistry, use, general biology, and animal toxicology. A final assessment is made as to whether a product is safe or unsafe based on the panel's research. FDA and industry consider cosmetic ingredients reviewed by CIR to have met the adequate substantiation requirement.

FDA does not mandate reporting adverse events that may occur once a cosmetic product is on the market. FDA post-market regulatory mechanisms include inspections,[12] enforcement actions against adulterated or misbranded products, and best practices guidance. Because the FFDCA provides FDA with limited authority to regulate cosmetic products, industry-initiated programs and assessments largely supplement cosmetic product oversight through voluntary reporting programs.

A bill to strengthen FDA's regulation of cosmetics in various ways, including a provision on labeling of nanomaterials in cosmetics, was introduced in the 112th Congress.[13]

III. BACKGROUND ON NANOMATERIALS IN COSMETICS

Some suggest that "cosmetic products claiming use of nanomaterials are among the most prominent early entries into the U.S. consumer marketplace."[14] The cosmetic industry is using and marketing numerous personal care products containing nanoscale ingredients. The range of products incorporating nanoscale ingredients include blemish concealers, skin creams, powder cosmetics, foundations, wrinkle removers, makeup removers and cleansers, and body wash products.[15] As of March 2011, the Project on Emerging Nanotechnologies has inventoried 143 cosmetics as containing nanoscale ingredients, including, for example, BIONOVA Cosmetics by Barneys New York, Chanel's Calming Emulsion, and Lancôme's Primordiale Nanolotion.[16]

Nanoscale ingredients are anticipated to increase the stability of cosmetic products so that they do not break down and are longer lasting in their intended application. They are also said to offer improved "skin feel." On the other hand, some observers contend that nanomaterials are

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Estrin ed., Marcell Dekker, Inc. 1984) (explaining the establishment and history of the Cosmetic Ingredient Review).

[11] Elder & Busch, *supra* note 10, at 204.

[12] FFDCA § 704, 21 U.S.C. § 374.

[13] Safe Cosmetics Act of 2011, H.R. 2359, 112th Cong. (2011).

[14] MICHAEL R. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? 45-50 (Oct. 2006), *available at* http://nanotechproject.org/file_download/files/PEN5_FDA.pdf.

[15] *Id*. at 18-24.

[16] *Consumer Products Inventory*, PROJECT ON EMERGING NANOTECHNOLOGIES, http://www.nanotechproject.org/inventories/consumer/search/ (enter product name then search the database). Available estimates regarding the number of cosmetics with nanoscale ingredients vary significantly, ranging from a 2006 Friends of the Earth report that identified 71 cosmetics as containing nanoscale ingredients (*see* FRIENDS OF THE EARTH, NANOMATERIALS, SUNSCREENS, AND COSMETICS: SMALL INGREDIENTS BIG RISKS (May 2006), *available at* http://www.foe.org/pdf/nanocosmeticsreport.pdf [hereinafter FRIENDS OF THE EARTH]), to a 2006 survey by the Environmental Working Group (EWG), which identified nearly 9,800 products containing nanoscale ingredients or ingredients that may contain a nanoscale fraction (*see* EWG Comments to FDA on Nano-Scale Ingredients in Cosmetics (2006), *available at* http://www.ewg.org/node/21738 [hereinafter "EWG Comments to FDA"]).

likely to present unique hazards.[17] Friends of the Earth's 2006 report declared that "nanoparticles present higher risks of toxicity than larger sized particles."[18] That report and others suggest that the higher risk is a result of the compounds' different physical and chemical properties. Their smaller size is believed to enhance their ability to penetrate the skin or gain access to the blood stream through inhalation or ingestion. Nanoscale cosmetic product ingredients intended only for dermal exposure might nevertheless reach internal tissues and organs. The uncertainty regarding the effects of nanomaterials on human health and the environment has prompted a debate as to the sufficiency of cosmetic regulations in this context.

FDA participates in the International Cooperation on Cosmetic Regulation (ICCR), a group of cosmetic regulatory authorities that also include Japan, the European Union, and Canada. Nanotechnology has been an ongoing topic of discussion at ICCR since its first meeting in 2007. In 2009, ICCR held an international workshop on regulatory issues on the use of nanomaterials in cosmetics. A breakout session from that workshop concluded that a complete characterization of nanomaterials, as would be needed for a scientific characterization, would be far more detailed than that needed within a regulatory framework. In 2011, ICCR accepted a report that adopted the following working definition of "nanomaterial" for purposes of cosmetics regulation:

> For purposes of the International Cooperation on Cosmetic Regulation, a substance used in a cosmetic is considered a nanomaterial if it is an insoluble ingredient, intentionally manufactured, with one or more dimensions in the realm of 1 to 100 nanometers in the final formulation and is sufficiently stable and persistent in biological media to allow for the potential of interaction with biological systems.[19]

Currently, cosmetic products containing nanoscale materials are regulated under the same framework as those containing their bulk scale counterparts. Opinions vary on the adequacy and potential applicability of the current framework of regulation and industry initiatives as applied to cosmetics employing nanotechnology.

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[17] *See, e.g.*, FRIENDS OF THE EARTH, *supra* note 16; TIM LITTLE, ET AL., BENEATH THE SKIN: HIDDEN LIABILITIES, MARKET RISK AND DRIVERS OF CHANGE IN THE COSMETICS AND PERSONAL CARE INDUSTRY (2007), *available at* http://www.iehn.org/filesalt/IEHNCosmeticsReportFin.pdf; EUROPEAN COMM'N, SCIENTIFIC COMM. ON CONSUMER PRODUCTS, OPINION ON SAFETY OF NANOMATERIALS IN COSMETIC PRODUCTS (2007), *available at* http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_123.pdf [hereinafter SCCP OPINION 2007].

[18] FRIENDS OF THE EARTH, *supra* note 16, at 6.

[19] ICCR, REPORT OF THE ICCR JOINT AD HOC WORKING GROUP ON NANOTECHNOLOGY IN COSMETIC PRODUCTS: CRITERIA AND METHODS OF DETECTION (2010), *available at* http://www.fda.gov/downloads/InternationalPrograms/HarmonizationInitiatives/UCM235485.pdf, at 1, 3. This report , offered at ICCR-4 in 2010, was accepted at ICCR-5 in 2011. ICCR, *International Cooperation on Cosmetic Regulation (ICCR) Outcome of the Meeting Held June 28 to July 1, 2011* (2011), *available at* http://www.fda.gov/Cosmetics/InternationalActivities/ConferencesMeetingsWorkshops/InternationalCooperationonCosmeticsRegulationsICCR/ucm262211.htm.

IV. PRE-MARKET MECHANISMS TO REGULATE COSMETICS USING NANOMATERIALS

A. *ADEQUATE SAFETY SUBSTANTIATION BY COSMETIC MANUFACTURERS*

1. Criticisms of the Lack of Testing and Information

The requirement that cosmetic products must be "adequately substantiated for safety prior to marketing" applies equally to cosmetics containing nanoscale ingredients. As mentioned above, manufacturers, rather than FDA or other regulatory bodies, bear the responsibility for adequately substantiating the safety of their cosmetic products.

CIR does not review every ingredient used in cosmetics. Even where CIR testing has been conducted, FDA lacks legal authority to obtain and review the safety substantiation data. In October 2008, Consumers Union wrote a letter to FDA requesting that it "require a full safety assessment on the use of engineered nanoparticles particularly in cosmetics, sunscreens, and sunblocks . . . ."[20] Based on Consumers Union's self-commissioned testing, the letter asserted that manufacturers were exposing consumers to the widespread use of nanoscale particles and making erroneous assertions about the presence of such particles.[21] In assessing FDA's capacity to enforce safety and testing requirements, one author classified this regulatory tool as "weak" because "cosmetic products bearing nanotechnology claims are on the market without FDA review or knowledge about their actual composition or safety-related properties."[22]

2. Criticisms of Substantiation Testing Methods

Another debate surrounds the appropriate testing procedures. FDA has not indicated the types of testing it considers appropriate for adequately determining the safety of nanoscale ingredients in cosmetics. Some feel that if testing has only been performed on bulk scale materials, such testing cannot serve to substantiate the safety of nanoscale ingredients. Few toxicological or exposure studies have been conducted to examine systematically the role of particle size and surface area in influencing toxicity to support conclusions either way.[23] The lack of data on nanomaterial risks is particularly acute regarding long-term exposure or chronic risk.

Some studies considering the safety of nanoscale materials in cosmetics are based on animal testing.[24] Some research exists, however, to indicate that animal testing overstates nanoparticle effects on the human skin and is therefore an inappropriate testing method.[25] The

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[20] Letter from Michael Hansen, Senior Scientist, Consumers Union, to Andrew C. von Eschenbach, FDA Commissioner (Oct. 30, 2008), *available at* http://www.consumersunion.org/pub/core_product_safety/006254.html. *See also* EWG Comments to FDA, *supra* note 16.
[21] Letter from Michael Hansen, *supra* note 20.
[22] *See* TAYLOR, *supra* note 14, at 29.
[23] *See, e.g.*, Bethany Halford, *Fullerene for the Face: Cosmetics Containing C_{60} Nanoparticles Are Entering the Market, Even if Their Safety is Unclear*, CHEM. & ENG'G NEWS, Mar. 27, 2006, at 47, *available at* http://pcss.xmu.edu.cn/users/xlu/group/courses/ce/cen/8413sci1.pdf.
[24] *See* FRIENDS OF THE EARTH, *supra* note 16, at 6.
[25] SCCP OPINION 2007, *supra* note 17, at 20 ("Animal skins are generally not suitable for testing cosmetics.").

European Union's Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) found that there was insufficient scientific information available to generally characterize the risks to human health and the environment from nanomaterials.[26] The EU's Scientific Committee on Consumer Products (SCCP, since renamed the Scientific Committee for Consumer Safety (SCCS)) opined that smaller particle size, and the resulting increase in the ratio of surface area to mass, may increase biological activity.[27] Nevertheless, the SCENIHR opinion stated that "[t]he hypothesis that smaller means more reactive and thus more toxic cannot be substantiated by the published data."[28]

3. Industry Response

Industry has argued that the current regulatory framework sufficiently governs cosmetics employing nanotechnology. Indeed, according to the Personal Care Products Council (PCPC, formerly the Cosmetic, Toiletry, and Fragrance Association), FDA "has ample authority to regulate the safety of 'nanotechnology' in personal care products."[29] PCPC's comments to FDA emphasize that under the FFDCA, cosmetics on the market are required to be safe and properly labeled. Such products are regulated based on their intended use, and not on the particular technology they employ. PCPC further contended that FDA "has ample authority to take action on cosmetics that are unsafe" and therefore, "consumers can be assured of the safety of the personal care products they use."[30] In response to a 2006 citizen petition filed on behalf of several organizations that claimed nanomaterials are unsafe based on their diminished size,[31] PCPC argued that "reduction in particle size does not necessarily correlate with increased safety risk. Rather, the data indicate that particle size is but one factor that may affect safety."[32]

B. *LABELING*

Cosmetics must be properly labeled or risk being considered misbranded. Without adequate substantiation, cosmetics may be misbranded if they do not conspicuously bear a warning statement indicating that the product's safety has not been determined. Additionally,

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[26] EUROPEAN COMM'N, SCIENTIFIC COMM. ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS (SCENIHR), RISK ASSESSMENT OF PRODUCTS OF NANOTECHNOLOGIES (adopted Jan. 19, 2009), *available at* http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf [hereinafter SCENIHR OPINION 2009].
[27] SCCP OPINION 2007, *supra* note 17, at 11.
[28] SCENIHR OPINION 2009, *supra* note 26 at 10.
[29] Comments of the Cosmetic, Toiletry, and Fragrance Association (CTFA) Regarding the Scientific and Legal Issues Associated with Nanotechnology in Personal Care Products 9, http://www.uvnatural.com/australia/CTFANanotechnologyCommentstoFDA.pdf [hereinafter "CTFA Comments"].
[30] *Id.* at 13.
[31] International Center for Technology Assessment et al., Petition Requesting FDA Amend Its Regulations for Products Composed of Nanomaterials Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (2006), *available at* http://www.icta.org/doc/Nano%20FDA%20petition% 20final.pdf [hereinafter "ICTA Nanoparticle Citizen Petition"].
[32] CTFA Comments, *supra* note 29, at 19.

cosmetic products may be misbranded if their labels are false or misleading,[33] or if they fail to reveal a material fact.[34]

Reports indicate that manufacturers are not posting warning statements and, at times, are not identifying the nanomaterials on the product labels. EWG comments to FDA indicate that "[n]one of the products [it] assessed bears [the] warning label."[35] The Consumers Union report also indicates that some cosmetic manufacturers are commercially marketing products with nanoscale ingredients without warning labels.[36] Currently, it remains unclear if such lack of warning has any effect or significance, but manufacturers could be hesitant due to reports of consumer resistance to the use of nanomaterials in cosmetics.[37]

In response to a petition which requested FDA to require all nanoparticle ingredients in nanomaterial-containing products to be labeled and identified as such, PCPC contended that such labeling is difficult without clear guidance and has the potential to confuse or alarm consumers.[38] It indicated that words such as "nanomaterial" or "nanoparticle" on an ingredient label may influence a consumer's belief as to the safety of products that are adequately substantiated. As a result, consumers may avoid perfectly acceptable products.[39]

FDA has not required manufacturers to disclose the presence of nanomaterials in their products. The agency's Nanotechnology Task Force, in its 2007 report, stated that "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, [it] does not believe there is a basis for saying that, as a general matter, a product containing nanoscale materials must be labeled as such."[40] A bill introduced in the U.S. House of Representatives in 2011 sought to require cosmetic ingredient labels to indicate the presence of nanomaterials if "not less than 1 percent of the ingredient particles in the cosmetic are 100 nanometers or smaller for not less than 1 dimension." The bill also sought to have other ingredients in the cosmetic designated with "scale-specific information" on the label or list if such ingredients possess scale-specific hazard properties."[41]

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[33] FFDCA § 602(a), 21 U.S.C. § 362(a).
[34] FFDCA § 201(n), 21 U.S.C. § 321(n).
[35] EWG Comments to FDA, *supra* note 16.
[36] In some instances, manufacturers, such as that of "Zelens Fullerene Day Cream," have stated that the product has been the subject of extensive in vitro and human safety testing. *See* Halford, *supra* note 23.
[37] *See* Simon Pitman, *Consumers Are Still Suspicious of Nano Cosmetics*, COSMETICS DESIGN-EUROPE.COM (Dec. 21, 2007), http://www.cosmeticsdesign-europe.com/Formulation-Science/Consumers-are-still-suspicious-of-nano-cosmetics.
[38] CTFA Comments, *supra* note 29, at 57.
[39] *Id.*
[40] FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 35 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter FDA NANOTECHNOLOGY TASK FORCE REPORT].
[41] Safe Cosmetics Act of 2011, H.R. 2359, 112th Cong. (2011).

C. *Comparison: Pre-market Regulation of Nanomaterials in Cosmetics in the European Union*

Politicians, policy makers, and others in Europe are likewise concerned about a lack of data on nanomaterials and the use of nanomaterials in the cosmetics industry without consumer knowledge.[42] This concern translated into the addition of significant new requirements for nanoscale ingredients in cosmetics. The European Union "recast" its earlier Cosmetics Directive[43] into a new and more streamlined Cosmetics Regulation,[44] and made a number of important changes to the overall cosmetics regulatory framework when it did so. (During the initial phase-in period for the Cosmetics Regulation, companies can generally apply either the Regulation or the Directive until 2013, at which time the Directive will be repealed.)

Under both the earlier Cosmetics Directive and the new Cosmetics Regulation, cosmetic ingredients are listed in Annexes as banned, restricted, or permitted. The EU does require pre-market notification. As in the United States, manufacturers are generally responsible for testing and ensuring the safety of their products. The new Cosmetics Regulation centralizes that responsibility in a designated "responsible person" and clarifies the safety assessment information requirements.

The Cosmetics Regulation also, for the first time, directly addresses nanomaterials. In general, case-by-case assessment of cosmetics is maintained. The regulation defines nanomaterials,[45] mandates new safety testing and assessment procedures for products containing them,[46] and requires their presence, specifications, and toxicological properties to be made known in a product's pre-market notification six months before being placed on the market. If the European Commission has concerns regarding the safety of a nanomaterial, it is to publicly request a safety opinion from the SCCS, and the SCCS is to respond within six months. The Cosmetics Regulation also adds a nanomaterials labeling requirement: any nanomaterials

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[42] *See, e.g.*, European Parliament Comm. on the Env't, Pub. Health & Food Safety, Report on Regulatory Aspects of Nanomaterials, EUR. PARL. DOC. (2008/2208(INI)) (Apr. 7, 2009), *available at* http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A6-2009-0255+0+DOC+PDF+V0//EN&language=EN (advocating "nano-specific" laws).

[43] Council Directive 76/768/EEC (1976), COM(2008)0049, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52008PC0049R(01):EN:HTML. Because it is a Directive rather than a direct Regulation, this law is implemented somewhat differently in different countries in the EU.

[44] Regulation 1223/2009, 2009 O.J. (L 342) 59 (EC), *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF. The Cosmetics Regulation entered into force on January 11, 2010.

[45] *Id.* Under article 2.1(k), "'nanomaterial' means an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm." However, article 2.3 provides that "[i]n view of the various definitions of nanomaterials published by different bodies and the constant technical and scientific developments in the field of nanotechnologies, the Commission shall adjust and adapt point (k) of paragraph 1 to technical and scientific progress and to definitions subsequently agreed at international level."

[46] The testing requirements do not generally apply to nanomaterials used as colorants, UV-filters or preservatives. *Id.* at art. 16.2.

present in cosmetics must be mentioned in the list of ingredients on the packaging.[47] In addition, the regulation establishes a nanomaterials database.

V. *POST-MARKET MECHANISMS*

A. *GOOD MANUFACTURING PRACTICES*

FDA's Good Manufacturing Practices (GMPs) require manufacturers to take prescribed steps to ensure that their products are safe and effective. For cosmetic manufacturers, however, FDA generally lacks the statutory authority to impose GMPs and, instead, offers "Cosmetic GMP Guidelines" as a voluntary standard.[48] The Cosmetic GMP Guidelines strive to help firms identify and implement practices that will minimize the risk of adulteration or misbranding that could occur through contamination. These guidelines are general in nature. For example, they require inspectors to assess whether raw materials are stored and handled in an appropriate manner and that containers of materials are labeled properly to identify their contents. The Cosmetic GMP Guidelines offer best practice principles and do not specifically address the use of nanomaterials.

FDA has not yet issued any regulations or guidance specific to nanoscale materials in cosmetics. The 2007 FDA Nanotechnology Task Force recommended that FDA issue guidance specific to products not subject to pre-market authorization, including cosmetics. The report identified the need for development of guidance on two points that may inform the Cosmetic GMP Guidelines.[49] First, the Task Force recommended that FDA issue guidance "describing safety issues that manufacturers should consider to ensure that cosmetics made with nanoscale materials are not adulterated." In addition, the Task Force indicated that guidance should be issued encouraging manufacturers to consider whether and how the presence of nanoscale materials affects the manufacturing process. With regard to the latter recommendation, the Task Force urged manufacturers to consider situations where the product contains nanoscale ingredients, as well as those situations where any part of the manufacturing process involves nanoscale ingredients, even if those materials do not become part of the finished product.[50] Such recommendations could also be considered in industry-established GMPs and quality assurance guidelines to address the use of nanoscale ingredients.[51]

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[47] *Id.* art. 19.1(g) ("All ingredients present in the form of nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets.").
[48] *See* FDA, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, COSMETIC GOOD MANUFACTURING PRACTICE GUIDELINES/INSPECTION CHECKLIST (updated Apr. 24, 2008), http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GoodManufacturingPracticeGMPGuidelinesInspectionChecklist/default.htm.
[49] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 40, at 33-34.
[50] *Id.* at 33-34.
[51] *See, e.g.*, COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION, CTFA TECHNICAL GUIDELINES - QUALITY ASSURANCE GUIDELINES, *available at* http://webstore.ansi.org/RecordDetail.aspx?sku=CTFA+Quality+Assurance+Guidelines.

FDA has drafted guidance on the use of nanomaterials in cosmetics, which it intends to publish in 2011.[52]

B. *INSPECTIONS*

FDA has general authority to inspect cosmetic product manufacturing facilities to assure product safety and to determine whether any cosmetics are adulterated or misbranded.[53] Specifically, Section 704(a)(1) of the FFDCA allows unannounced inspections, provided they are conducted at a reasonable time and in a reasonable manner. Inspectors may enter and inspect cosmetics establishments, factories, warehouses, and vehicles, as well as all pertinent equipment, materials, containers and associated labeling.[54] Inspectors may also collect samples to evaluate compliance.[55] The statute does not, however, authorize the inspection of most records.[56] FDA uses this authority to evaluate compliance with the applicable laws and regulations, such as labeling and packaging requirements or ingredient use restrictions and conditions to ensure product safety. FDA also uses its inspection authority to determine whether practices such as sanitary storage, handling, and manufacturing are being observed to prevent the introduction of adulterated or misbranded products into commerce.

With regard to cosmetics containing nanomaterials, FDA's inspection authority may provide some post-market oversight. FDA may evaluate whether finished cosmetic products are at risk of adulteration or misbranding because of their being produced, handled, stored, or transported in an improper manner. Additionally, FDA inspections also may ensure that other cosmetics are not being contaminated with nanoscale ingredients or materials. FDA's Nanotechnology Task Force has suggested that the agency develop guidance on several of these topics, which could improve the quality of facility inspections.[57]

FDA's inspection authority does not, however, assist in ensuring compliance with its safety substantiation requirements. An inspector may not require access to records that "adequately substantiate" the safety of cosmetics or their ingredients to determine whether the warning in 21 C.F.R. § 740.10 is required. If an inspector has concerns that the safety of a product containing nanomaterials has not been adequately substantiated, the inspector may collect samples for analysis to determine the product's ingredients. Once the ingredients are identified through analysis, FDA could determine whether these ingredients have been reviewed for safety through the CIR process and whether their use is consistent with the results of that

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[52] DEPARTMENT OF HEALTH AND HUMAN SERVICES, FISCAL YEAR 2012 FOOD AND DRUG ADMINISTRATION JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES 120 (2011), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM243370.pdf.
[53] *See* FFDCA § 704, 21 U.S.C. § 374.
[54] FFDCA § 704(a)(1), 21 U.S.C. § 374(a)(1).
[55] *Id.*
[56] Section 704 of the FFDCA allows inspections at facilities manufacturing cosmetics, but does not grant the authority to inspect *records* pertaining to cosmetics manufacturing. *Id.* There is an exception for interstate shipping records concerning FDA-regulated products. *See* FFDCA § 703, 21 U.S.C. § 373.
[57] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 40, at 33-34.

review. For ingredients that have not undergone the CIR process, FDA could review the published literature or its own data, assuming either of these is available.

For cosmetics containing nanomaterials, FDA's inspection authority may prove a limited regulatory tool. Inspecting and/or collecting samples places additional administrative and financial burdens on FDA at a time when some experts have concluded that the agency's budget is incapable of meeting the expanding regulatory role.[58] The costs of analysis may prove prohibitive, especially for specialized analytic techniques that may be required to properly characterize a nanomaterial.

C. *VOLUNTARY REPORTING*

FDA has no statutory authority to require post-marketing monitoring of cosmetics or to require the reporting of adverse events that may occur.[59] Instead, PCPC, in conjunction with FDA, established the Voluntary Cosmetics Registration Program (VCRP). Through the VCRP, manufacturers, distributors, and packers of cosmetics in commercial distribution in the United States may register manufacturing establishments and ingredients. In the event that FDA obtains information demonstrating that a particular cosmetic ingredient may pose a risk of harm, FDA will notify VCRP participants of this information, thereby enabling them to reassess the safety of the ingredient or remove it from their products.

A critical component of the VCRP's success, however, is that FDA be aware of such adverse information. FDA may lack access to such information. Indeed, FDA's Nanotechnology Task Force specifically recommended that the agency "issue a notice in the Federal Register requesting submission of data and other information addressing the effects on product safety of nanoscale materials . . . ."[60] FDA may request safety data from cosmetics firms, but because FDA lacks the statutory authority to require production of the data, a firm may choose not to provide any data or may choose to provide only a limited summary.

To encourage industry to provide data, PCPC instituted a Consumer Commitment Code (CCC) and has encouraged all cosmetic manufacturers and marketers to provide a written statement of their support and recognition of the CCC. The CCC offers two avenues of information submission that may be useful in the gathering of information on nanomaterials. First, adherents to the CCC are encouraged to "provide FDA with the information on manufacturing establishments and ingredient usage called for by the [VCRP]," and "immediately inform the FDA of any serious and unexpected adverse experience from the use of a product marketed in the U.S."[61] Accordingly, if a cosmetic product containing a nanomaterial causes a

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[58] TAYLOR, *supra* note 14, at 7 ("Even more so than legal authority, the issue affecting FDA's readiness to regulate nanotechnology products is resources . . . . [The] harsh budget reality threatens FDA's ability to effectively oversee nanotechnology.").

[59] *See* FFDCA §§ 601-604, 21 U.S.C. §§ 361-364. The EU's new Cosmetic Regulation would, in contrast, provide authority to require responsible parties and even distributors to report serious adverse events. Regulation (EC) 1223/2009,,*supra* note 44.

[60] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 40, at 33-34.

[61] PCPC, CCC Q&A, *supra* note 10. The CCC adopts the definitions of "serious" and "unexpected" from the FDA's regulations for drugs that are found in 21 C.F.R. § 314.80(a). "Serious" events include death, as well as

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"serious" health effect that has not been identified in the product labeling, then an adherent of the CCC should disclose that information to FDA. This mechanism could aid in enabling FDA, with industry's cooperation, to accomplish a certain amount of post-market surveillance. However, in the absence of a publicly available database concerning the potential health effects of nanomaterials and a mechanism, such as labeling, to identify cosmetic products containing nanomaterials, a medical doctor or other expert may have insufficient information to attribute a "serious" health effect to a cosmetic product containing nanomaterials, especially if that effect were unique to the nanomaterials and "unexpected" (i.e., not disclosed on the label), or if the effect were chronic.[62]

Second, the CCC encourages companies to "maintain a Safety Information Summary related to product and ingredient safety that is available for inspection by FDA under specified circumstances."[63] Manufacturers completing summary sheets should include information concerning (1) product identification codes so that individual products can be related back to the relevant safety sheet for that formulation; (2) the semi-quantitative formula for the formulation, using the International Nomenclature for Cosmetic Ingredients (INCI) to identify raw materials and their concentration ranges; (3) raw material specifications; (4) finished product specifications; (5) a summary of the manufacturing process; (6) a statement that the product was manufactured using GMPs as established in the CCC's Quality Assurance Guidelines; (7) a statement that the product's safety has been substantiated in accordance with the principles of the CCC's Safety Testing Guidelines, and a summary of the elements that form the basis of the safety assessment, with relevant citations; and (8) a computation of the incidence of adverse effects in the United States that have been "medically confirmed" as being caused by the product.[64] Adherents of the CCC are encouraged to provide this information upon receiving a written request from the FDA District Director for inspection at a mutually agreed location and within a reasonable time after receiving the request.[65]

(Continued …)
those that are considered life-threatening, or result in in-patient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. "Unexpected" are those "adverse . . . experience[s] that [have] not previously been observed (i.e., included in the labeling) . . . ." 21 C.F.R. § 314.80(a).

[62] *See, e.g.*, THE ROYAL SOCIETY AND THE ROYAL ACADEMY OF ENGINEERING, NANOSCIENCE AND NANOTECHNOLOGIES: OPPORTUNITIES AND UNCERTAINTIES 73 (July 2004), *available at* http://www.nanotec.org.uk/report/Nano%20report%202004%20fin.pdf (recommending that the ingredients lists of consumer products should identify the fact that manufactured nanoparticulate materials are included); BRITISH STANDARDS INSTITUTION, PAS 130:2007 – GUIDANCE ON THE LABELLING OF MANUFACTURED NANOPARTICLES AND PRODUCTS CONTAINING MANUFACTURED NANOPARTICLES 1 (2007), *available at* http://www.nanointeract.net/x/file/PAS130-labellingguidelines.pdf (recommending product labeling to "facilitate traceability and the monitoring of health and environmental impacts."); *see also* THE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND, STATEMENT BY THE UK GOVERNMENT ABOUT NANOTECHNOLOGIES 20 (2008), *available at* http://www.bis.gov.uk/assets/bispartners/goscience/docs/s/statement-nanotechnologies.pdf (implicitly supporting the recommendation of the UK Royal Society and BSI's publication of guidance for labeling products containing manufactured nanomaterials).

[63] PCPC, CCC Q&A, *supra* note 10.

[64] *See* PCPC, SAFETY INFORMATION SUMMARY PROGRAM GUIDELINE, *available at* http://www.cosmeticsinfo.org/fdapartner_ccc3.php.

[65] *Id.*

The CCC's Safety Information Summary Program provides a self-regulatory effort that industry representatives maintain will enable FDA to evaluate the safety of cosmetic products and ingredients and to assure itself and the public of their safety.[66] However, some consumer groups have questioned the CCC's ability to achieve these goals, calling the CCC and the Safety Information Summary Program essentially a commitment to maintain the status quo.[67] Adherence to the CCC is voluntary, and PCPC confirms that it "will not terminate Council membership for noncompliance."[68] The success of the program may depend largely on the level and quality of participation by cosmetic manufacturers and marketers. Secondly, when requesting safety information from manufacturers, the FDA District Director must assert a "legitimate and specific" safety concern to justify the request for the information.[69] With regard to nanomaterials, FDA currently operates on limited information and may not be able to meet this standard. The agency may be unable to identify which products contain nanomaterials without undertaking sampling and potentially expensive laboratory analysis. FDA's Nanotechnology Task Force acknowledged the limitations FDA faces when attempting to identify the presence of nanomaterials in cosmetics.[70]

D. *RECALLS*

FDA also lacks the statutory authority to require the recall of a cosmetic product. Cosmetic manufacturers or distributors may, however, undertake product recalls on their own initiative or at the request of FDA.[71] FDA can request a recall for "misbranded" or "adulterated" products that present a risk of illness, injury, or gross consumer deception, or in actions where it is necessary to do so for the protection of human health and welfare.[72] Generally, cosmetic manufacturers or distributors will undertake a recall to avoid negative publicity from FDA,[73] or to avoid FDA-initiated legal action requesting the seizure of "adulterated" or "misbranded" cosmetics.[74]

FDA has promulgated guidance to assist with the recall process.[75] This guidance requires FDA to classify the recall by the degree of hazard the product may pose.[76] For FDA-requested recalls, the agency develops a recall strategy that defines the extent of the recall and the necessity

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[66] *Id.*
[67] *See, e.g.*, Ryan Nelson, *Campaign for Safe Cosmetics Unimpressed by CTFA Consumer Commitments*, THE ROSE SHEET (Mar. 19, 2007) http://www.safecosmetics.org/article.php?id=101; *see also* Kara Alaimo, *Cosmetics Industry Ramps Up Safety P.R.*, WOMEN'S ENEWS (Mar. 23, 2007) http://www.womensenews.org/article.cfm?aid=3106.
[68] *Id.*
[69] *See* PCPC, SAFETY INFORMATION SUMMARY PROGRAM GUIDELINE, *supra* note 65.
[70] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 40, at 33-34.
[71] *See* 21 C.F.R. § 7.40 ("Recall is a voluntary action that takes place because manufacturers and distributors carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective.").
[72] 21 C.F.R. § 7.45.
[73] *See* FFDCA § 705, 21 U.S.C. § 375 (authorizing FDA to cause the dissemination of information concerning cosmetics and other products when there is "an imminent danger to health or gross deception to the consumer.").
[74] *See* FFDCA § 304, 21 U.S.C. § 334.
[75] *See* 21 C.F.R. §§ 7.40-7.59.
[76] 21 C.F.R. § 7.41.

and nature of any public warnings.[77] For firm-initiated recalls, the firm develops the strategy with FDA's review and comment.[78] The guidance also describes the content of recall communications to customers of the recalling firm, as well as FDA's obligations to publish information describing and classifying the recall.[79] FDA guidance also calls for the submission of periodic status reports to facilitate FDA monitoring of the recall process.[80] FDA will initiate legal action to seize a "misbranded" or "adulterated" cosmetic product if it does not consider the voluntary recall an effective tool or if the manufacturer or distributor refuses to recall the product subsequent to an FDA request.[81]

VI. CONCLUSION

Nanomaterials may have the potential to offer benefits when incorporated in cosmetics and other personal care products, improving their performance and enhancing results. However, these novel materials may also pose unknown safety and health risks. The current regulatory structure limits FDA's roles and relies heavily on the personal care product industry.

Some are of the opinion that nanomaterials in cosmetics are risky and may be unsafe, and therefore a new approach to their regulation should be considered. Industry commenters have disagreed and find the current framework to be sufficient overall. Because nanotechnology is an emerging field, it has been difficult to confirm the safety of such nanomaterials. Thus, to date, FDA and other governmental entities are requesting and collecting more data on the safety of such nanomaterials in efforts to determine what, if any, action should be taken. The ability of FDA and industry to assure the safety of nanotechnology-based cosmetics, and thereby promote public confidence in the technology, will ultimately help determine whether the benefits of nanotechnology to cosmetics can reach their full potential.

[77] 21 C.F.R. §§ 7.42, 7.45.
[78] 21 C.F.R. §§ 7.42, 7.46.
[79] 21 C.F.R. §§ 7.49, 7.50.
[80] 21 C.F.R. § 7.53.
[81] *See* FFDCA § 304, 21 U.S.C. § 334; *see also* 21 C.F.R. § 7.46.

CHAPTER 3: COLOR ADDITIVES*

I. INTRODUCTION

Nanotechnology offers unique opportunities for manufacturers to control their products on a molecular scale to an unprecedented degree, including controlling the coloring of products in new and sophisticated ways. The Food and Drug Administration (FDA) regulates color additives through its Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition. Therefore, FDA must address a number of new technical and regulatory issues raised by color additives containing nanotechnology-based products and nanomaterials. Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended,[1] new color additives must be approved by FDA before they can enter United States markets. Companies that utilize nanoscale color additives should be aware of FDA regulations in order to obtain pre-market approval from FDA and avoid any regulatory obstacles once approved. FDA, in turn, should ensure that the issues raised by nanotechnology are addressed and nanoscale color additives are regulated effectively.

II. BACKGROUND ON COLOR ADDITIVES

Color additives play a vital role in both the utility and the psychological appeal of consumer products regulated by FDA. Consumers' perceptions of a food's taste, desirability, and other properties are dramatically affected by its colors.[2] The value of many cosmetic products is also dependent upon how well they can impart color to the skin or hair. In addition, manufacturers of medical devices and drugs have utilized color additives to make products appear in ways that are helpful to medical professionals or beneficial to patients.[3]

A color additive is generally defined by the FFDCA as a dye, pigment, or other substance made by chemical or natural means that is capable (alone or through interaction with another

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[1] 21 U.S.C. §§ 301-399d.

[2] *See e.g.*, JoAndrea Hoegg & Joseph W. Alba, *Taste Perception: More than Meets the Tongue*, 33 J. CONSUMER RES. 490-98 (2007), *available at* http://www.slideshare.net/guest0b700f/taste-perception-more-than-meets-the-tongue; *More Than Meets The Tongue: Color Of A Drink Can Fool The Taste Buds Into Thinking It Is Sweeter*, SCIENCEDAILY (Feb. 16, 2007), http://www.sciencedaily.com/releases/2007/02/070212182136.htm ("Given two cups of the same Tropicana orange juice, with one cup darkened with food coloring, the members of the researcher's sample group perceived differences in taste that did not exist. However, when given two cups of orange juice that were the same color, with one cup sweetened with sugar, the same people failed to perceive taste differences."). *See also* Judy Hevrdejs, *An Eye for Color: Foodmakers Tempt Our Palates With Their Palettes*, CHI. TRIB., July 14, 2000, at 1, *available at* http://articles.chicagotribune.com/2000-07-14/features/0007140003_1_color-food-science-banana ("People are strongly influenced by perception based on sight . . . . If you put yellow food coloring in vanilla pudding, before they even taste it, they will think it will be lemon or banana. They will tell you it is lemon or banana even after tasting it because they are so strongly perceiving it as lemon or banana.").

[3] *Summary of Color Additives Listed for Use in the United States in Food, Drugs, Cosmetics, and Medical Devices*, FDA, http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm (last updated Oct. 8, 2010).

substance) of imparting color when added to a food, drug, cosmetic, or to the human body.[4] Under the FFDCA, an ingredient will not qualify as a color additive if FDA determines that the use of the ingredient is *solely* for a purpose other than coloring.[5]

After various health risks were associated with certain color additives,[6] Congress passed the Color Additive Amendments of 1960.[7] This law amended the FFDCA and required FDA approval of any color additive to be added to a food, drug, or cosmetic before it can enter the market. Unlike the regulations for food additives, there is no exception to the pre-market approval process for a color additive that could be generally recognized as safe (GRAS). Thus, only those color additives that have been specifically listed by FDA in the Code of Federal Regulations (CFR) Parts 73 or 74 as suitable and safe for a given use in foods, drugs, cosmetics, and medical devices may be used.[8] Each color additive listed by FDA has its own regulation that specifies use, labeling, and certification requirements.

Any person who wants FDA to list a new color additive or a new use for a listed color additive must submit to FDA a color additive petition.[9] This petition must include data establishing that the color additive is safe for the proposed use.[10] FDA publishes a notice describing the petition in the Federal Register,[11] and FDA then has ninety days, subject to extension, to review the petition.[12] During its consideration of the petition, FDA can request any

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[4] FFDCA § 201(t), 21 U.S.C. § 321(t); *see also* 21 C.F.R. § 70.3(g). Note that a colorant added to a food packaging material or other food contact substance is regulated as a food additive, not as a color additive. Julie N. Barrows et al., *Color Additives: FDA's Regulatory Process and Historical Perspectives*, FOOD SAFETY MAG., Oct./Nov. 2003, *available at* http://www.fda.gov/ForIndustry/ColorAdditives/RegulatoryProcessHistoricalPerspectives/default.htm.

[5] FFDCA § 201(t), 21 U.S.C. § 321(t); *see also* 21 C.F.R. § 70.3(g) ("[T]he material must be used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. (It is not enough to warrant exemption if . . . the primary purpose of the material is other than to impart color).").

[6] *See, e.g.*, Barrows et al., *supra* note 4 ("In the fall of 1950, many children became ill from eating an orange Halloween candy containing 1-2% FD&C Orange No. 1 . . . .").

[7] Color Additive Amendments of 1960, Pub. L. 86-618, 74 Stat. 397 (1960).

[8] FFDCA § 721(a), 21 U.S.C. § 379e(a), states:

> A color additive shall, with respect to any particular use (for which it is being used or intended to be used or is represented as suitable) in or on food or drugs or devices or cosmetics, be deemed unsafe . . . unless –
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> > (1) (A) there is in effect, and such additive and such use are in conformity with, a regulation issued under subsection (b) of this section listing such additive for such use, including any provision of such regulation prescribing the conditions under which such additive may be safely used, and (B) such additive either (i) is from a batch certified, in accordance with regulations issued pursuant to subsection (c), for such use, or (ii) has, with respect to such use, been exempted by the Secretary from the requirement of certification; or
> > (2) such additive and such use thereof conform to the terms of an exemption which is in effect pursuant to subsection (f) of this section.

See also 21 C.F.R. pt. 71.

[9] *See* 21 C.F.R. § 71.1; Color Additive Petition Submission Form, http://www.fda.gov/downloads/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm094235.pdf.

[10] 21 C.F.R. § 71.1.

[11] 21 C.F.R. § 71.2(b).

[12] 21 C.F.R. § 71.6.

additional information it needs to make its safety determination.[13] FDA also encourages petitioners to consult with FDA prior to submitting a petition in order to streamline the process and ensure that all of the appropriate information is provided.[14]

FDA has leeway to consider a variety of factors in making its determination that a color additive is safe enough to enter the market. Generally, "[s]afe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive."[15] This "reasonable certainty" standard is not intended to be insurmountable.[16] In determining whether a color additive is safe, FDA is to consider a number of factors, including but not limited to:

(i) the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or devices, or cosmetics because of the use of the additive;
(ii) the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet;
(iii) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data; and
(iv) the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug or device, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive.[17]

The burden of demonstrating that the proposed use of a color additive will be safe under the specified conditions falls on the color additive's manufacturer.[18]

Besides pre-approving color additives, FDA also certifies batches of certain color additives.[19] Such certification is required unless the color additive has been exempted by FDA.[20] Under the certification process, a manufacturer submits a sample from a batch needing certification. FDA then tests this sample to determine that the sample meets the requirements for

[13] 21 C.F.R. § 71.4.
[14] FDA, GUIDANCE FOR INDUSTRY PRE-PETITION CONSULTATIONS FOR FOOD ADDITIVES AND COLOR ADDITIVES (Apr. 2005), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm055270.htm.
[15] 21 C.F.R. § 70.3(i).
[16] *See* H.R. Rep. No. 86-1761 (1960), *reprinted in* 1960 U.S.C.C.A.N. 2,887, 2,890-91.
[17] FFDCA § 721(b)(5)(A), 21 U.S.C. § 379e(b)(5)(A).
[18] FFDCA § 721(b)(4), 21 U.S.C. § 379e(b)(4).
[19] FFDCA § 721(c), 21 U.S.C. § 379e(c); 21 C.F.R. pt. 80.
[20] FFDCA § 721(a)(1)(B), 21 U.S.C. § 379e(a)(1)(B); *see also* 21 C.F.R. pt. 73 (Listing of Color Additives Exempt from Certification) and pt. 74 (Listing of Color Additives Subject to Certification).

composition and purity. Once a batch has been certified, FDA issues a certification lot number and the batch may be used as a color additive.[21]

III. NANOSCALE COLOR ADDITIVES

Nanotechnology offers the potential for a wide and exciting range of color additive possibilities. Some nanoscale color additives already exist—and some, like carbon black, have existed for many years—but for the most part these color additives were not engineered at a molecular level through nanotechnology.[22] These existing nanoscale color additives highlight the potential difficulty of defining nanotechnology for purposes of regulation, but the new and developing nanotechnology-based color additives go far beyond these previous materials in their level of innovation as well as in the resulting scope of regulatory and technical issues they raise for FDA.

For example, scientists have discussed the possibility of creating a drink product that utilizes nanotechnology so that consumers can change the color and flavor of their drink based on personal preferences. This nano-engineered drink would contain various nanoscale capsules enclosing different molecules of color and flavor. Specific capsules could then be opened by the consumer based on his or her preferences so, for example, a drink could become a red-colored cherry soda or a brown-colored tea.[23] Researchers are also exploring the creation of nanotechnology-enhanced food and drug products that could automatically change color when they spoil or are exposed to insanitary conditions. These products would contain small nanoparticles designed to change color when certain odors are detected or when the product is exposed to oxygen.[24]

Nanotechnology is also being used by manufacturers to color their products in other ways. Scientists have utilized nanoparticles to impart color to products in situations where using larger particles would negatively affect the product's properties. For example, manufacturers of color contact lenses have utilized nanoparticles of inorganic pigment to impart color onto the lens while managing to avoid affecting the other physical properties of the product.[25]

Nanotechnology is also enabling scientists to create concentrated amounts of naturally occurring color additives from sources using nano-engineered filters. In one case, scientists were

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[21] 21 C.F.R. pt. 80.

[22] *See* Jane Hollenberg, JCH Consulting, Cosmetic Color Additives, Nanotechnology FDA Public Meeting (Sept. 8, 2008), http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=0900006480706819 (listing iron oxides (primary particle size 20-300 nm), titanium dioxide (10-250 nm), zinc oxide (20-250 nm), and D&C Black #2 ("carbon black," 20-30 nm) as approved nanoscale color additives in cosmetics).

[23] David Rowan, *How Technology Is Changing Our Food*, THE OBSERVER (May 16, 2004), *available at* http://www.davidrowan.com/2004/05/observer-how-technology-is-changing.html; *see generally* Ronald J. Versic, *Flavor Encapsulation: An Overview*, *available at* http://www.rtdodge.com/dodge_fl-ovrvw.html.

[24] John Dunn, *A Mini Revolution*, FOOD MANUFACTURE (Sept. 9, 2004), *available at* http://www.foodmanufacture.co.uk/news/fullstory.php/aid/472/.

[25] Bethany Halford, *Nanotech Makes Your Brown Eyes Blue*, CHEM. & ENG'G NEWS (Oct. 10, 2005), at 42-43, *available at* http://pubs.acs.org/cen/science/83/8341sci2.html.

able to extract just the coloring from beetroot, which is used as a natural coloring agent, while leaving out any flavoring that can usually accompany the additive.[26]

In addition, nanotechnology is allowing manufacturers to remove colors from a product that would normally appear in the product. Sunscreen manufacturers have engineered nanoparticles of zinc oxide and titanium dioxide so that their sunscreens are transparent instead of opaque white.[27] These particular uses of nanoparticles would probably not be regulated as color additives since they do not *impart* color. Moreover, they are regulated as drugs.[28]

While these technologies have promise, some observers are concerned that nanotechnology-based color additives will present greater risks to consumers. The small size of nanomaterials might allow them to pass through various protective barriers of the body,[29] and travel through the body in unknown ways with unknown side effects.[30] Some also argue that it is unknown how nanomaterials released into the environment would accumulate and how they would affect the environment. They point to some evidence of negative effects on microorganisms and other environmental components to conclude that nanoparticles could pose a danger to the environment at large.[31]

IV. PRE-MARKET REGULATION OF NANOSCALE COLOR ADDITIVES

A. *PRE-MARKET DATA SUBMISSION AND REVIEW OF NANOSCALE COLOR ADDITIVES*

In contrast to its more limited regulation of other products like foods and cosmetics, FDA has pre-market approval authority to ensure that a new color additive is safe before it can enter the market. FDA has stated that it is confident that this legal authority allows it to require

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[26] Dunn, *supra* note 24 ("Dr Meirion Jones at the University of Wales in Swansea, is working on nano-filters for extracting food colouring and flavouring. 'Beetroot is a well-known food colouring material but beetroot also has a flavour. It's not very nice, a bit earthy. However, using nano-filter technology we have been able to filter out just the colour, leaving it tasteless.' In other experiments, Jones has used nano-filtration to turn red wine into white and he has been able to extract the colours from red cabbage and onions to produce natural pH indicator dyes – an alternative, maybe, to chemicals such as phenolphthalein, which has come under fire as a possible carcinogen.").

[27] *See* International Center for Technology Assessment (ICTA) et al., Petition Requesting FDA Amend Its Regulations for Products Composed of Nanomaterials Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (2006), *available at* http://www.icta.org/doc/Nano%20FDA%20petition%20final.pdf [hereinafter "ICTA Nanoparticle Citizen Petition"]. In 2011, ICTA and other petitioners filed suit against FDA for alleged failure to respond within a reasonable time to the 2006 petition. *International Center for Technology Assessment v. Hamburg*, No. CV 11-6592 (D.D.C., filed Dec. 21, 2011), http://www.centerforfoodsafety.org/wp-content/uploads/2011/12/1-Pls-Complaint.pdf.

[28] *See* Chapter 7 - Drugs.

[29] *See, e.g.*, Wim H. De Jong & Paul J. A. Borm, *Drug Delivery and Nanoparticles: Applications and Hazards*, 3 INT'L J. NANOMEDICINE 133-149 (2008), *available at* http://www.dovepress.com/articles.php?article_id=1836.

[30] *See, e.g.*, JENNIFER SASS, NANOTECHNOLOGY'S INVISIBLE THREAT: SMALL SCIENCE, BIG CONSEQUENCES 2 (NRDC Issue Paper, May 2007), *available at* http://www.nrdc.org/health/science/nano/nano.pdf.

[31] *See, e.g.*, FRIENDS OF THE EARTH, OUT OF THE LABORATORY AND ON TO OUR PLATES: NANOTECHNOLOGY IN FOOD & AGRICULTURE 29-31 (2nd ed. 2008), *available at* www.foeeurope.org/activities/nanotechnology/Documents/Nano_food_report.pdf [hereinafter FRIENDS OF THE EARTH].

whatever studies are necessary to provide it with adequate evidence to ensure that a nanoscale additive is safe before being used. As stated in the report by FDA's Nanotechnology Task Force,

> 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 . . . . 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.[32]

Other FDA officials have suggested that there would only need to be minor changes to the current regulatory scheme to fully enable FDA to take appropriate measures to ensure that only safe color additives can enter the market. These suggested changes would include requiring supplementary data on the characteristics of the nanomaterial and requiring data on absorption, distribution, metabolism, and excretion of nanomaterials in the initial safety assessment package.[33]

Even with the ability to require adequate pre-market studies of new nanotechnology-based color additive products, FDA will still need to determine what those studies will be and what level of risk is acceptable to allow for nanotechnology color additives to enter the market. Commenters and FDA differ on the degree of change that nanotechnology necessitates for existing study protocols.[34] FDA guidelines on these issues, based on stakeholder input and outlining generally what studies would be required of nanotechnology-based color additives, could lead to greater clarity for commercial manufacturers. In response to a recommendation of the FDA Nanotechnology Task Force,[35] FDA now encourages companies to provide information about nanoscale color additives earlier in the product development process (i.e., well ahead of color additive petition submission), to give FDA earlier insight into potential risks.[36]

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[32] FDA, NANOTECHNOLOGY: REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 35 (2007), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter FDA NANOTECHNOLOGY TASK FORCE REPORT].

[33] T. Scott Thurmond, *Are There Potential Safety Concerns For the Use of Nanosized Food Additives or Color Additives Used in Foods?* CSL/JIFSAN Joint Symposium 2007 at 26-27 (2007), *available at* www.jifsan.umd.edu/presentations/csl_2007/PDF/Thurs/2.S.Thurmond_JIFSAN_CSL_Symp.pdf.

[34] *E.g.*, ICTA Nanoparticle Citizen Petition, *supra* note 27, at 13-14, 19-24.

[35] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 32, at 27, 30.

[36] FDA, GUIDANCE FOR INDUSTRY: COLOR ADDITIVE PETITIONS - FDA RECOMMENDATIONS FOR SUBMISSION OF CHEMICAL AND TECHNOLOGICAL DATA ON COLOR ADDITIVES FOR FOOD, DRUGS, COSMETICS, OR MEDICAL DEVICES (revised 2009), *available at* http://www.fda.gov/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm, § III.A.

B. *Determining That Nanoscale Color Additives Are Safe*

There is ongoing debate regarding the nature of tests that can adequately support a "reasonable certainty of no harm" safety standard when nanomaterials are involved. As noted in the Nanotechnology Task Force Report, some observers "expressed the concern that existing toxicology screening methods will not adequately assess toxicologic properties of nanoscale materials," due in part to their failure to account for long-term effects, novel pharmacodynamic properties, different exposure media and routes, and the difficulty of detecting nanoscale materials.[37] For example, Europe's Scientific Committee on Emerging and New Identified Health Risks (SCENIHR) concluded that effects data on bulk materials cannot be adequately extrapolated to nanoscale materials.[38] The Task Force did acknowledge that some improvements may need to be made to testing procedures, but recommended "a tiered or staged approach to evaluation" of the test methods.[39]

The American Chemistry Council's Nanotechnology Panel also "anticipates that current testing methods (e.g., OECD [Organisation for Economic Co-operation and Development] guidelines) will be determined by others . . . to be acceptable for the assessment of hazard potential. However, with discrete particles, there may be a need to complement the assays with additional dosing characterization, endpoints and/or enhanced study designs . . . ."[40] Other commenters dispute the adequacy of this case-by-case approach, recommending across-the-board changes to tests for all nanomaterials, such as reduced exposure thresholds.[41]

The safety assessment of nanoscale color additives may also potentially implicate the "Delaney Clause,"[42] which imposes a strict ban on any color additive found to induce cancer in man or animal no matter how small the risk.[43] The lack of a *de minimis* exception could pose a barrier for nanotechnology-based color additives likely to be carcinogens.

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[37] FDA Nanotechnology Task Force Report, *supra* note 32, at 16-17.

[38] European Comm'n, Scientific Comm. on Emerging and Newly Identified Health Risks, Risk Assessment of Products of Nanotechnologies 11, 56 (adopted Jan. 19, 2009), *available at* http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf [hereinafter SCENIHR Opinion 2009]; *see also* European Comm'n, Scientific Comm. on Emerging and Newly Identified Health Risks, Modified Opinion on the Appropriateness of Existing Methodologies to Assess the Potential Risks Associated with Engineered and Adventitious Products of Nanotechnologies 6 (adopted Mar. 10, 2006), http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf [hereinafter SCENIHR Opinion 2006] ("Experts are of the unanimous opinion that the adverse effects of nanoparticles cannot be predicted (or derived) from the known toxicity of material of macroscopic size, which obey the laws of classical physics.").

[39] FDA Nanotechnology Task Force Report, *supra* note 32, at 17.

[40] Comments from Sharon H. Kneiss, Vice President, American Chemistry Council, for ACC's Nanotechnology Panel on FDA's Product-Specific Questions, FDA Docket 2008-N-0416, New and Emerging Scientific Issues in Nanotechnology (Oct. 24, 2008), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0416-0030.

[41] *E.g.*, Comments from Michael Hansen, Senior Scientist, Consumers Union, on Breakout Session on Food and Color Additives, Including Food Contact Substances 4 (Sept. 8, 2008), *available at* http://www.consumersunion.org/pdf/Nanotech-FDA-Comm-08.pdf.

[42] FFDCA § 721(b)(5)(B), 21 U.S.C. § 379e(b)(5)(B). Similar clauses govern food additives and animal drugs.

[43] *See, e.g.*, Public Citizen v. Young, 831 F.2d 1108 (D.C. Cir. 1987) (requiring FDA to ban Orange No. 17, which posed a one in nineteen billion chance of causing cancer).

C. *NANOSCALE VERSIONS OF PREVIOUSLY APPROVED COLOR ADDITIVES*

Another issue arises when a previously approved color additive is reduced to the nanoscale. This raises the question of whether the nanoscale version is "new," requiring a new color additive petition. One could take the position that once FDA has approved a substance as a color additive and listed it in the Code of Federal Regulations, FDA has implicitly approved nanoscale versions of the same color additive since there is no size limit to these approvals.

Alternatively, it could be argued that a prior determination that a macroscale color additive is safe has no relevance to the safety of that additive's nanoscale version, since adverse effects related to a nanoscale version of a substance may not be adequately inferred from the known toxicity of the bulk material.[44] Accordingly, that prior determination should not obviate the need for a new petition for the nanoscale version.

FDA has not provided guidance on its views on this matter. Its Nanotechnology Task Force has commented on the potential that nanoscale versions of approved color additives may create the need to amend the prior approvals:

> 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. 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.[45]

Indeed, there is already a push for legislation that would give FDA increased regulatory control over previously approved color additives that utilize nanotechnology to ensure that FDA can control the safety of these products. In 2010, a bill was introduced in Congress to establish a program that would investigate the use of nanoscale materials in FDA-regulated products, including nanomaterials' potential toxicity, biological effects, and interactions with biological systems.[46] This legislation did not pass.

D. *CERTIFICATION OF BATCHES OF NANOSCALE COLOR ADDITIVES*

Another issue FDA may consider in the future is whether to require batch certification for any color additive that is engineered using nanotechnology. In the present scheme, batch certification has generally only been required for those color additives that are not obtained

[44] *See, e.g.*, SCENIHR OPINION 2006, *supra* note 38, at 6.
[45] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 32, at 27.
[46] Nanotechnology Safety Act of 2010, S. 2942, 111th Cong. (2010).

primarily from mineral, plant, or animal sources.[47] This classification scheme may make less sense when the additives are derived through nanotechnology.

Additionally, FDA may call for additional testing requirements for certification of nanoscale color additive products to address the possibility of enhanced absorption and accumulation of nanoparticles within the body. Because nanoparticles may show a greater toxicity per mass dose given their high surface-to-volume ratio, the usual toxicity studies may be inadequate and dosage margins may have to be altered.[48] Furthermore, additional testing requirements may be needed to support certification of color additives that are used for external drugs and cosmetics to study possible skin penetration, absorption into blood stream, UV interaction, and other reactions.

V. POST-MARKET REGULATION OF NANOSCALE COLOR ADDITIVES

In general, FDA has much less power to control a color additive once it has been approved. Before a color additive has been approved, FDA can demand data and studies to determine that the color additive is safe prior to market entry. Once FDA has approved a color additive, it can only remove the product from the market by going through rulemaking procedures or through seizure, and it has far less authority to require submission of information.

A. *LABELING REQUIREMENTS FOR NANOSCALE COLOR ADDITIVES*

The FFDCA does grant FDA some authority, through its regulations that list each color additive, to require labeling of consumer products containing certain color additives.[49] FDA also requires color additive manufacturers to provide more extensive information on the additives' labels, though this information (including any expiration dates, batch lot numbers, or various use limitations) generally does not also appear on the labels of the consumer products in which the color additives are used.[50] Moreover, a food, drug, device, or cosmetic is deemed misbranded if its label is false or misleading in any particular, including a failure to reveal material facts.[51] However, currently, there is no statutory or regulatory requirement that a manufacturer disclose whether a color additive utilized nanotechnology.

In its citizen petition on nano-engineered sunscreens, the International Center for Technology Assessment (ICTA) argued that a product that did not state that it contained a nanotechnology-based color additive was misbranded because the product's labeling was misleading in that it did not disclose a material fact.[52] It appears doubtful that FDA would agree with the arguments made in the petition, given FDA's refusal to require disclosure statements on

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[47] *See* Barrows et al., *supra* note 4 ("Color additives exempt from certification generally include those derived from plant or mineral sources."). *See also* 21 C.F.R. pt. 73 (listing those color additives exempt from batch certification); 21 C.F.R. pt. 74 (listing those color additives that must be batch certified).
[48] *See, e.g.*, SCENIHR OPINION 2009, *supra* note 38, at 13, 23; Hansen, *supra* note 41.
[49] FFDCA §721(b)(3), 21 U.S.C. § 379e(b)(3).
[50] 21 C.F.R. § 70.25.
[51] FFDCA §§ 201(n), 301, 21 U.S.C. §§ 321(n), 331.
[52] ICTA Nanoparticle Citizen Petition, *supra* note 27, at 26-28; *see also* FFDCA § 403(a), 21 U.S.C. § 343-1; FFDCA § 201(n), 21 U.S.C. § 321(n).

products that utilize similarly controversial technology, such as bioengineered food and food derived from cloned animals.[53] Furthermore, the 2007 FDA Nanotechnology Task Force did not support a disclosure statement for nanomaterials. The Task Force stated:

> 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.[54]

Some continue to advocate requiring labels of FDA regulated products to disclose the presence of nanoparticles.[55]

B. *POST-MARKET MONITORING OF NANOSCALE COLOR ADDITIVES*

Manufacturers of color additives, including those at the nanoscale, are required to report to FDA only those adverse events that are related to drugs or medical devices.[56] FDA encourages manufacturers of color additives to voluntarily report adverse events even when not required by regulations.[57] FDA encourages consumers to report adverse events related to color

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[53] FDA, News Release, FDA Issues Documents on the Safety of Food from Animal Clones (Jan. 15, 2008) *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116836.htm; FDA, GUIDANCE FOR INDUSTRY: VOLUNTARY LABELING INDICATING WHETHER FOODS HAVE OR HAVE NOT BEEN DEVELOPED USING BIOENGINEERING; DRAFT GUIDANCE (Jan. 2001), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm059098.htm ("FDA is therefore reaffirming its decision to not require special labeling of all bioengineered foods.").

[54] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 32, at 35.

[55] *See, e.g.*, FRIENDS OF THE EARTH, *supra* note 31, at 44-45 ("Public engagement initiatives and experimental studies suggest that once provided with information about nanotechnology, the public is concerned about many of the same issues identified in relation to [genetically engineered] food: a lack of transparency, a lack of choice about exposure, risks to health and the environment, unfair distribution of risks and benefits, a lack of socially useful applications and a lack of public participation in decision making . . . . Mandatory labelling of all nanofoods is required to enable people to make an informed choice about whether or not to eat them.").

[56] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 32, at 27 n.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.").

[57] The FDA Food Safety Modernization Act (FSMA), Pub. L. 111-353, 124 Stat. 3920 (2011), includes a provision that requires an owner, operator, or agent in charge of a facility to "identify and evaluate known or reasonably foreseeable hazards that may be associated with the facility, including . . . unapproved food and color additives" and to develop a written analysis of the identified hazards, implement preventive controls, and monitor their effectiveness. FSMA § 103, adding FFDCA § 418, 21 U.S.C. § 350g. However, there is still no requirement for adverse event reporting for color additives in the FSMA.

additives as well, either to FDA district offices or through the Center for Food Safety and Applied Nutrition Adverse Event Reporting System.[58]

In addition, "any interested person" who desires FDA to conduct scientific studies in order to regulate a nanoscale color additive may submit a request to FDA to do so. However, FDA is not required to act on such requests.[59]

VI. CONCLUSION

FDA has considerable authority over nanoscale color additives, especially prior to their approval, to ensure that these additives are safe. Some are advocating for additional guidance on the regulatory issues that nanoscale color additives raise to make it easier for companies to innovate in this area.

[58] *See How Safe are Color Additives?*, FDA, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048951.htm (last updated May 27, 2011).
[59] 21 C.F.R. § 70.55.

CHAPTER 4: FOOD ADDITIVES AND RELATED SUBSTANCES*

I. INTRODUCTION

Industry is actively exploring the potential role of nanomaterials as direct food additives and in food contact materials such as food packaging. Nanoscale food additives have the potential to help improve the safety, shelf-life, and convenience of food, but they raise challenging questions for the Food and Drug Administration (FDA) and food manufacturers. As a result, FDA has been analyzing how it should regulate such nanomaterials.

FDA has significant, though incomplete, statutory and regulatory authority to control nanoscale food additives. Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended[1] manufacturers of new food additives must obtain pre-market approval from FDA. This pre-market approval requirement does not extend to substances that are generally recognized as safe (GRAS), substances that have been prior sanctioned, or certain other substances which function in a manner similar to food additives. These gaps in pre-market approval authority are likely to be more apparent with respect to nanomaterials added to food or used in food packaging. While FDA has only limited post-approval oversight authority for nanoscale food additives, it does have the ability to oversee certain good manufacturing practice requirements, to inspect manufacturing facilities, to enforce the regulations, and to require certain statements to appear or not to appear on the labeling of the food. FDA lacks any mandatory post-approval monitoring or reporting authority, but it has a voluntary reporting system in place. So far, FDA has indicated it will use its regulatory authority to address issues posed by nanotechnology on a case-by-case basis.

II. GENERAL BACKGROUND ON FOOD ADDITIVES AND GRAS SUBSTANCES

The term "food additive" has a complicated definition in the FFDCA. In principal part the definition reads:

> The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food . . .), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use . . . .[2]

Food additives are to be distinguished from color additives, dietary supplements, and foods, which are discussed in other chapters. Nanomaterials engineered with multiple functions may

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* This chapter was prepared by Mark N. Duvall, Beveridge & Diamond, P.C.

[1] 21 U.S.C. §§ 301-399d.

[2] FFDCA § 201(s), 21 U.S.C. § 321(s).

render application of this distinction more difficult, potentially leading to disputes about characterization and necessitating FDA guidance, but many nanomaterials will clearly fall under the definition of "food additive."

Food additives can be either direct or indirect. A direct food additive is a substance added directly to food. An example is the common preservative BHT.[3] New direct food additives must receive pre-market approval in the form of a food additive regulation from FDA through notice-and-comment rulemaking. An indirect food additive is a substance that is not intended to become a component of food, but whose usage is reasonably likely to result in it becoming a component of food anyway, if only in minute quantities. Many indirect food additives are components of food packaging. New indirect food additives must also receive pre-market approval from FDA, but many are eligible for an expedited review process called a food contact notification (FCN) instead of rulemaking.

Some food substances have the same functions as food additives but are exempt from pre-market approval due to their status, such as GRAS substances. FDA has implemented a mechanism whereby sponsors may notify FDA of their determinations that a substance is GRAS, and FDA is given an opportunity to object if appropriate. After a food additive or related substance is placed on the market, it remains subject to limited FDA regulation.

III. EXAMPLES OF NANOSCALE FOOD ADDITIVES

Nanotechnology as applied to direct food additives and food packaging has become an object of intense research and development interest, as well as commentary.[4] Potential applications include:

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[3] *See* 21 C.F.R. § 172.115. "BHT" stands for butylated hydroxytoluene. FDA approvals for direct food additives appear in 21 C.F.R. pt. 172. FDA approvals for secondary direct food additives appear in 21 C.F.R. pt. 173; an example is ion-exchange resins, *see* 21 C.F.R. § 173.20.

[4] *See, e.g.*, MICHAEL R. TAYLOR, PROJECT ON EMERGING NANOTECHNOLOGIES & GROCERY MFRS. ASS'N, ASSURING THE SAFETY OF NANOMATERIALS IN FOOD PACKAGING: THE REGULATORY PROCESS AND KEY ISSUES (July 2008) [hereinafter TAYLOR, NANOMATERIALS IN FOOD PACKAGING], *available at* http://www.nanotechproject.org/publications/archive/nano_food_packaging/; FRIENDS OF THE EARTH, OUT OF THE LABORATORY AND ONTO OUR PLATES: NANOTECHNOLOGY IN FOOD & AGRICULTURE (2nd ed. 2008) [hereinafter FRIENDS OF THE EARTH], *available at* http://www.foe.org/pdf/nano_food.pdf; JOCHEN WEISS, STATE OF FOOD NANOTECHNOLOGY IN THE UNITED STATES IN 2007, *available at* http://www.worldfoodscience.org/cms/?pid=100405; INT'L UNION OF FOOD SCI. & TECH., NANOTECHNOLOGY AND FOOD, EQUIVALENCE IN FOOD SAFETY MANAGEMENT (Dec. 2007), *available at* http://www.iufost.org/sites/default/files/docs/IUF.SIB.Equivalence.pdf; Jennifer Kuzma, University of Minnesota, PowerPoint Slides Accompanying Presentation of "Oversight Policy for Agrifood Nanotechnology: Bridging Science, Risk, and Society," AAAS Meeting (Feb. 16, 2007), *available at* http://cs3.msu.edu/d/pubs/AAAS_Presentation_Oversight.pdf; MICHAEL R. TAYLOR, PROJECT ON EMERGING NANOTECHNOLOGIES, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? (Oct. 2006) [hereinafter REGULATING THE PRODUCTS], *available at* http://nanotechproject.org/file_download/files/PEN5_FDA.pdf; Jochen Weiss et. al, *Functional Materials in Food Nanotechnology*, J. FOOD SCI. 71:R107-R116 (2006), *available at* http://www.ift.org/knowledge-center/read-ift-publications/science-reports/scientific-status-summaries/functional-materials-in-food-nanotechnology.aspx?page=viewall; TIJU JOSEPH & MARK MORRISON, INST. OF NANOTECHNOLOGY, EUROPEAN NANOTECHNOLOGY GATEWAY, NANOFORUM REPORT: NANOTECHNOLOGY IN AGRICULTURE AND FOOD 10 (May

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- Nanoscale self-assembled structured liquids which allow penetration of healthy components (such as vitamins, minerals, and phytochemicals) that are insoluble in water or fats.
- Flavors, antioxidants, thickeners, and other direct food additives at the nanoscale.
- Barrier food packaging films of nano-clay or nano-titanium dioxide to block gases and moisture from passing through, thereby extending freshness and shelf life of food.
- Plastic beverage bottles incorporating nanocrystals to prevent the escape of oxygen.
- Nanosensors or "electronic tongues" to detect substances in parts per trillion or even single molecules and trigger a color change to show contamination or spoilage.
- Nanoscale antimicrobials in food packaging, typically based on nanoparticles of silver.
- Nanoscale antimicrobial carriers in food packaging.
- "Intelligent" food packaging that uses a nanoscale bioswitch to release a preservative if food begins to spoil.
- Radiofrequency identification tags incorporating nanoscale components.
- Nanoscale bar codes for tracking and tracing food.

The Project on Emerging Nanotechnologies' inventory of nanotechnology-based consumer products currently on the market identifies multiple products claiming to utilize nanoscale direct food additives or nanoscale components of food packaging to provide a variety of benefits.[5] By one estimate, the nanotechnology-based food and beverage packaging market will reach $7.3 billion by 2014.[6]

To date, FDA is known to have approved at least one nanoscale indirect food additive: nanoscale titanium nitride, for use as a barrier in polyethylene terephthalate (PET) bottles.[7] This same indirect food additive was also approved for defined uses in the European Union by the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) of

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2006), *available at* www.nanoforum.org/dateien/temp/nanotechnology%20in%20agriculture%20and%20food.pdf?11072006040222; HELMUT KAISER CONSULTANCY, NANOTECHNOLOGY IN FOOD AND FOOD PROCESSING INDUSTRY WORLDWIDE 2006-2010-2015 (2004), *available at* http://www.hkc22.com/nanofood.html; ETC GROUP, DOWN ON THE FARM: THE IMPACT OF NANO-SCALE TECHNOLOGIES ON FOOD AND AGRICULTURE (2004), *available at* http://www.etcgroup.org/en/node/80.

[5] *See Consumer Products Inventory*, PROJECT ON EMERGING NANOTECHNOLOGIES [hereinafter *Consumer Products Inventory*], http://www.nanotechproject.org/inventories/consumer/search/ (enter product name then search database).

[6] *Nano-Enabled Food and Beverage Packaging Market Expect to Reach $7.30 Billion by 2014*, AZONANO.COM, http://www.azonano.com/news.asp?newsID=12748 (published July 22, 2009) (citing INNOVATIVE RESEARCH & PRODUCTS, INC., NANO-ENABLED PACKAGING FOR THE FOOD AND BEVERAGE INDUSTRY - A GLOBAL TECHNOLOGY, INDUSTRY AND MARKET ANALYSIS (July 2009), outline *available at* http://www.innoresearch.net/report_toc.aspx?id=68&pg=107&pd=7/1/2009).

[7] *See* FCN 818 (effective July 29, 2008), replacing FCN 716, *available at* http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=fcsListing. In 2010, the Government Accountability Office (GAO) reported, "From 2007 through September 2009, FDA has had eight presubmission meetings concerning food contact substances that companies have described as incorporating engineered nanomaterials. As a result, FDA has received food contact substance notifications for four of these substances and two--applications of titanium nitride added to a certain kind of plastic--have been approved." GAO, FOOD SAFETY: FDA SHOULD STRENGTHEN ITS OVERSIGHT OF FOOD INGREDIENTS DETERMINED TO BE GENERALLY RECOGNIZED AS SAFE 30 (Feb. 2010) [hereinafter GAO REPORT], *available at* http://www.gao.gov/new.items/d10246.pdf.

the European Food Safety Authority (EFSA).[8] The CEF has also approved a silicon dioxide coating on the inner surface of PET articles. The coating is intended to provide gas barrier properties. The maximum thickness is 100 nm.[9]

IV. PRE-MARKET CONTROL OVER NANOSCALE FOOD ADDITIVES

The FFDCA provides FDA with substantial pre-market control over nanoscale food additives. This section discusses (a) the safety requirement; (b) pre-market review of nanoscale direct food additives; (c) pre-market approval of nanoscale indirect food additives; and (d) whether new nanoscale versions of previously-approved macroscale food additives are covered by those approvals. Exceptions to the pre-market approval requirement are discussed in the next section.

A. *THE USE OF NANOSCALE FOOD ADDITIVES MUST BE PROVEN SAFE*

Under the FFDCA, the safety of a food additive must be established to a reasonable degree of certainty. To ensure that this occurs, the statute prohibits the sale of such food additives unless FDA determines that safety has been established.

The FFDCA prohibits introducing adulterated food into interstate commerce.[10] A food is deemed to be adulterated if it is, or bears, or contains, "any food additive that is unsafe within the meaning of section 409 . . . ."[11] Section 409 provides that a direct or indirect food additive is deemed unsafe unless there is a food additive regulation in effect covering its use or, for food-contact substances, there is a food contact notification in effect covering its use.[12] In other words, a food additive (including a nanoscale food additive) is deemed to be adulterated, and thus prohibited from introduction into commerce in food, unless FDA has acted affirmatively to find that its intended use would be safe.

Safety is a judgment that takes into account information on the specific additive under likely patterns of use, together with any chemically or pharmacologically related substances in the diet. That judgment must consider, among other factors,

> (A) the probable consumption of the additive and of any substance formed in or on food because of the use of such additive;

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[8] European Food Safety Auth. (EFSA), *CEF Scientific Opinion of the Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on 21st List of Substances For Food Contact Materials*, EFSA J. 888-890 (adopted Nov. 27, 2008), *available at* http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/cef_op_ej888-890_21stlist_en,3.pdf?ssbinary=true.

[9] European Food Safety Auth. (EFSA), *AFC Scientific Opinion of the panel on food additives, flavourings, processing aids and materials in contact with food on 14th List of Substances For Food Contact Materials*, EFSA J. 452-454 (adopted Feb. 6&7, 2007) [hereinafter *AFC Opinion*], *available at* http://www.efsa.europa.eu/en/efsajournal/doc/452.pdf.

[10] FFDCA § 301(a), 21 U.S.C. § 331(a).

[11] FFDCA § 402(a)(2)(C)(i), 21 U.S.C. § 342(a)(2)(C)(i).

[12] FFDCA § 409(a), 21 U.S.C. § 348(a).

(B) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substances in such diet; and

(C) safety factors which experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.[13]

The burden of demonstrating that the proposed use of a nanoscale food additive will be safe under the specified conditions of use falls on its manufacturer.[14] Thus, the gate-keeping setup of the FFDCA provisions on food additives provides FDA with an important means of obtaining information on nanoscale food additives. However, some analysts have argued that the FFDCA does not provide FDA with sufficient ability to obtain information on products in earlier development stages.[15]

Despite the heavy emphasis on proving safety, the safety requirement is not intended to be insurmountable. Absolute safety is not required.[16] One aim of the Food Additives Amendment of 1958 was to encourage innovative technology that could deliver benefits to consumers and food processors. It sought to avoid the situation where FDA would

> unnecessarily proscribe the use of additives that could enable the housewife to safely keep food longer, the processor to make it more tasteful and appetizing, and the Nation to make use of advances in technology calculated to permit the use of additives as our technological scientists may produce and which may benefit our people and our economy when proposed usages of such additives are in amounts accepted by the Food and Drug Administration as safe.[17]

FDA incorporates these concepts in its regulatory definition of "safe."[18]

What "safe" means in the context of a nanoscale food additive is still somewhat unclear. The FDA Nanotechnology Task Force has identified two broad scientific issues related to the question of establishing safety for any FDA-regulated nanomaterial: understanding the

[13] FFDCA § 409(c)(5), 21 U.S.C. § 348(c)(5).
[14] FFDCA § 409(c)(3)(A), 21 U.S.C. § 348(c)(3)(A).
[15] *E.g.*, TAYLOR, REGULATING THE PRODUCTS, *supra* note 4, at 36, 38.
[16] The legislative history of the Food Additives Amendment of 1958, Pub. L. 85-929, explained that "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance." S. REP. NO. 85-2422, at 6 (1958), *reprinted in* 1958 U.S.C.C.A.N. 5,300, 5,305. However, the "Delaney Clause," added to FFDCA § 409 in 1958 and codified at 21 U.S.C. § 348(c)(3)(A), *does* impose an absolute standard: "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal . . . ." There is no *de minimis* threshold. *See, e.g.*, Public Citizen v. Young, 831 F.2d 1108 (D.C. Cir. 1987). The Delaney Clause could eventually hinder some of nanotechnology-based food additives, before or after entry into U.S. markets.
[17] S. REP. NO. 85-2422, at 2 (1958), *reprinted in* 1958 F 5,300, 5,301.
[18] 21 C.F.R. § 170.3(i).

interactions of nanomaterials with biological systems, and the adequacy of testing approaches for assessing safety and quality of products containing nanomaterials.[19] FDA has explained:

> From the standpoint of safety evaluation, FDA's concern about engineered nanomaterials is not their size per se. It is rather the fact that, by design, they typically have properties that are different from the conventional-scale versions of the same chemical substance, coupled with the current scientific uncertainty regarding differences in biological interactions between nano- and conventional-scale materials and how to test the safety of the often novel properties associated with nanomaterials.[20]

An FDA scientist has said:

> At present there is insufficient data publicly available to reach meaningful conclusions on the potential toxicity of food or color additives incorporating nanomaterials, although the available information does not give us cause for concern.
>
> The present approach is considered sufficient for safety assessment of food-related nanoproducts for regulatory approval, with minor changes.

In particular, the scientist suggested some "minor changes" to the information required for safety assessments, including supplemental data on physical and chemical characteristics of the nanomaterial and submission of absorption, distribution, metabolism and excretion data on nanomaterials in the initial safety assessment package.[21] Other observers dispute the sufficiency of the present approach.[22]

The Project on Emerging Nanotechnologies and the Grocery Manufacturers Association co-sponsored a series of case studies to examine the scientific and regulatory issues involved in FDA's review of the safety of nanoscale food contact substances. The final report on the case studies provides a detailed discussion of chemistry issues such as the adequate characterization of a nanoscale material's identity and properties, definition and description of impurities, and migration study methodology and validation. The toxicology issues addressed in the report include the appropriateness of current exposure triggers for toxicity testing, toxicological data requirements and testing protocols, and the usefulness of data on conventional scale versions of nanoscale materials.[23]

FDA is not alone in addressing the safety of nanoscale food additives. The European Commission, for example, asked EFSA to produce a scientific opinion on the need for specific

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[19] FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 12-18 (July 25, 2007) [hereinafter FDA NANOTECHNOLOGY TASK FORCE REPORT], *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf.

[20] GAO REPORT, *supra* note 7, at 55, 67.

[21] T. Scott Thurmond, FDA, PowerPoint Slides Accompanying Presentation of "Are There Potential Safety Concerns for the Use of Nanosized Food Additives and Color Additives Used in Foods?" (2007), *available at* http://www.jifsan.umd.edu/presentations/csl_2007/PDF/Thurs/2.S.Thurmond_JIFSAN_CSL_Symp.pdf.

[22] *See, e.g.*, FRIENDS OF THE EARTH, *supra* note 4.

[23] *See generally* TAYLOR, NANOMATERIALS IN FOOD PACKAGING, *supra* note 4.

risk assessment approaches for processes and applications of nanoscience and nanotechnologies in the food and feed area (including food additives). The requested opinion, adopted in 2009, identified the nature of possible hazards associated with actual and projected applications in the food and feed area and provided general guidance on data needed for the risk assessment of such technologies. EFSA concluded that hazard and exposure data are lacking, "the adequacy of currently existing toxicological tests to detect all aspects of potential toxicity of [nanomaterials] has yet to be established," and uncertainty factors used in risk characterization should reflect these data and technology limits.[24]

As for the adequacy of testing approaches for nanomaterials (in food additive applications and otherwise), an issue raised by the FDA Nanotechnology Task Force, the European Commission's Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) has expressed the opinion that current risk assessment methodologies "are generally likely to be able to identify the hazards associated with the use of nanoparticles." Nevertheless, the Opinion called for those methodologies to be adapted to the new challenges in assessing the safety of nanomaterials, and for the evaluation of nanoparticle formulations to be considered on a case-by-case basis.[25]

B. *New Nanoscale Direct Food Additives*

Manufacturers of new nanoscale direct food additives must obtain pre-market approval from FDA in the form of a food additive regulation adopted through notice and comment rulemaking. To do so, they must submit a food additive petition (FAP). FDA has a regulation[26] and procedural guidance[27] that describe the information it expects to see in an FAP to enable it to make a safety assessment. Development of the information requested by FDA can be expensive and time-consuming. FDA recommends pre-petition conferences.[28] The FDA Nanotechnology

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[24] European Food Safety Auth. (EFSA), *Scientific Opinion of the Scientific Committee on the Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety*, 958 EFSA J. 1 (2009), *available at* http://www.efsa.europa.eu/en/scdocs/doc/sc_op_ej958_nano_en,3.pdf.

[25] European Comm'n, Scientific Comm. on Emerging and Newly Identified Health Risks (SCENIHR), Opinion on the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials (June 21-22, 2007), *available at* http://ec.europa.eu/health/ph_risk/committees/04_scenihr/scenihr_cons_04_en.htm.

[26] 21 C.F.R. § 171.1.

[27] *See, e.g.*, FDA, Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions (revised Mar. 2009) [hereinafter Direct Food Additives Chemistry Guidance], *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm124917.htm; FDA, Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food (June 2006), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm054658.htm; Procedural regulations for a food additive petition appear in 21 C.F.R. pt. 171.

[28] *See* FDA, Guidance for Industry: Pre-Petition Consultations for Food Additives and Color Additives (Apr. 2005), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm055270.htm.

Task Force report recommended that FDA issue new or amended guidance on what additional or distinct information should be submitted to FDA or generated for food additives made with nanoscale materials, as well as on the appropriateness of testing methodologies for evaluating products made with nanomaterials.[29] In 2009, FDA amended its guidance to collect information related to nanoscale direct food additives.[30]

Within 15 days of receipt of an FAP, FDA determines whether the information included is adequate for filing and notifies the petitioner in writing. If it files the FAP, FDA publishes a notice in the Federal Register to announce it. Data and information submitted in an FAP are available for public disclosure once a filing notice for the petition has been published. Once an FAP is filed, FDA has 90 days (subject to a 90-day extension) to respond to the FAP.[31] If the petitioner delivers additional substantive information to FDA, either in response to FDA reviewer questions or on the petitioner's own initiative, the petition is given a new filing date and the statutory clock begins to run anew. Once FDA concludes its safety review, it publishes an order in the Federal Register. Such order either includes a regulation that lists the conditions of use for the food additive FDA has determined to be safe (not necessarily what the petitioner had asked for), or denies the petition. In either case, the order gives the reasons for the regulatory decision. A food additive may not be legally marketed for the petitioned use until FDA publishes an authorizing regulation.[32]

Once approved, a food additive regulation is available for use by anyone (subject to any applicable patent protection). Thus, the petitioner for a food additive regulation, including a petitioner for a nanoscale food additive regulation, risks making a substantial investment in data production, only to find at the end of the regulatory process that its competitors may reap the benefits of its investment.

C. *NEW NANOSCALE INDIRECT FOOD ADDITIVES*

Rather than use the FAP process, manufacturers of most new nanoscale indirect food additives must seek pre-market approval through a food contact notification (FCN). The FCN alternative was intended to expedite approval of indirect food additives that qualify as food contact substances (FCSs) except where a food additive petition is required or FDA and the notifier agree that a petition is needed. A food contact substance is defined as:

> any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.[33]

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[29] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 19, at 19, 32-33.
[30] DIRECT FOOD ADDITIVES CHEMISTRY GUIDANCE, *supra* note 27, §§ III.A.7 and III.C.5.
[31] FFDCA § 409(c)(2), 21 U.S.C. § 348(c)(2); 21 C.F.R. § 171.100(a).
[32] *See generally* 65 Fed. Reg. 43,269, 43,270 (July 13, 2000). The prescribed time periods can extend much longer in practice. *See, e.g.*, 73 Fed. Reg. 35,142 (June 20, 2008) (announcing the withdrawal of an FAP filed in 1986); 75 Fed. Reg. 39,699 (July 10, 2010) (announcing the withdrawal of an FAP filed in 2004).
[33] FFDCA § 409(h)(6), 21 U.S.C. § 348(h)(6); 21 C.F.R. § 170.3(e)(3).

An example of a food contact substance is a polymer that is used as food packaging and which contains unreacted residuals of monomer that might migrate from the packaging into food.

FDA does not allow use of the FCN process in some situations. One such situation is where the use of the FCS increases the cumulative dietary concentration to a certain level. The level is 200 parts per billion (ppb) in the daily diet for antimicrobials and 1 part per million (ppm) in the daily diet for other substances. Another situation is where FDA has not reviewed an available bioassay on the FCS and the bioassay is not clearly negative for carcinogenic effects.[34]

Procedures for the FCN process appear in the FFDCA and in FDA's regulations.[35] The manufacturer or supplier of a new FCS must notify FDA at least 120 days before marketing the FCS. The notification must include information on the identity and intended use of the FCS and describe the basis for the notifier's determination that the intended use is safe. As with the FAP process, the burden is on the notifier to demonstrate the safety of the intended use of the FCS. If the information in the notification does not support the notifier's determination of safety, FDA has 120 days from the date of receipt of the notification to object and thereby to prevent marketing of the substance. If FDA does not object to the notification within the 120 days, the substance may be legally marketed for the notified use. FDA must keep confidential any information submitted in an FCN for the 120-day review period. Once the 120-day review period ends, information in the FCN is subject to public disclosure except for trade secret and confidential commercial information.

FDA has provided guidance on what information it expects to see in an FCN to permit it to make its safety evaluation.[36] The guidance on chemistry aspects was revised in 2007 to solicit information related to nanoscale food contact substances.[37]

Unlike the FAP process, FDA does not publish an order announcing the agency's decision or an authorizing regulation for FCNs. Instead, FDA posts limited information about FCNs that have become effective on its website.[38]

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[34] 21 C.F.R. § 170.100(c).

[35] FFDCA § 409(h), 21 U.S.C. § 348(h); 21 C.F.R. pt. 170, subpt. D. *See* 65 Fed. Reg. 43,269, 43,270-71 (July 13, 2000).

[36] FDA, GUIDANCE FOR INDUSTRY: PREPARATION OF PREMARKET SUBMISSIONS FOR FOOD CONTACT SUBSTANCES: CHEMISTRY RECOMMENDATIONS (Dec. 2007) [hereinafter FOOD CONTACT SUBSTANCES CHEMISTRY RECOMMENDATIONS], *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm; FDA, GUIDANCE FOR INDUSTRY: PREPARATION OF PREMARKET SUBMISSIONS FOR FOOD CONTACT SUBSTANCES: TOXICOLOGY RECOMMENDATIONS (revised Apr. 2002), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081825.htm; FDA, GUIDANCE FOR INDUSTRY: PREPARATION OF FOOD CONTACT NOTIFICATIONS: ADMINISTRATIVE (revised May 2002), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081807.htm. Additional guidance documents appear at http://www.fda.gov/Food/FoodIngredientsPackaging/FoodAdditives/default.htm.

[37] FOOD CONTACT SUBSTANCES CHEMISTRY RECOMMENDATIONS, *supra* note 36, §§ II.A.5 and II.C.

[38] FDA, INVENTORY OF EFFECTIVE FOOD CONTACT SUBSTANCE (FCS) NOTIFICATION, *available at* http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm116567.htm. Effective FCNs for nanotechnology-based FCSs include FCNs 302 and 818. The FCN database and the submissions therein

(Continued …)

Also in contrast to the FAP process, an FCN is not effective for a similar or identical substance manufactured or prepared by anyone other than the manufacturer identified in the notification. Thus, additional manufacturers who wish to market the same FCS for the same use must submit their own FCN to FDA. This can work to the advantage of the submitter of an FCN for a nanoscale FCS, since it has more of an advantage over its competitors than it would have under the FAP process.

D. *Whether Existing Food Additive Regulations Apply to Nanoscale Versions of Listed Food Additives*

FDA has already granted many FAPs approving the use of direct food additives[39] and indirect food additives (mostly before implementation of the FCN process).[40] A key question is whether any of the resulting food additive regulations may be regarded as applying to nanoscale versions where the FAP related only to macroscale versions. Some may say no, since the FDA safety assessment did not consider either the effects or exposure that may result from the food additive or its component being at the nanoscale.[41] Others may say yes, since the food additive regulations generally by their terms do not have size parameters that would preclude application to nanomaterials otherwise fitting the description of the approved food additive.[42] Stakeholders have urged FDA to issue guidance clarifying when specific applications of nanotechnology in food additives would be regarded as novel for safety evaluation purposes.[43]

This question only arises if the regulation describes the food additive and its intended use in a manner that matches those of the nanoscale version. In many cases, the substance description will not match, due to the need to modify macroscale materials chemically to take advantage of the properties at the nanoscale. Relatively simple chemicals, such as silicon dioxide, are more likely to raise this question than complex ones. Intended uses may also differ. For example, silicon dioxide already has numerous approvals as a direct food additive,[44] a

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(Continued …)
frequently do not make clear whether nanomaterials are involved. For example, FCN 932, intended for a substance to be used as a "gas barrier in monolayer PET bottles," was jointly submitted by a Japanese company and Nanocor, Inc., the latter being a developer and supplier of nanomaterials. However, it is not clear whether the substances submitted under FCN 932 contain nanomaterials, or to what extent.

[39] 21 C.F.R. pts. 172-173, 180.

[40] 21 C.F.R. pts. 175-178, 180.

[41] *See, e.g.*, International Center for Technology Assessment et al., Petition Requesting FDA Amend Its Regulations for Products Composed of Nanomaterials Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (2006), *available at* http://www.icta.org/doc/Nano%20FDA%20petition%20final.pdf [hereinafter "ICTA Nanoparticle Citizen Petition"]. In 2011, ICTA and other petitioners filed suit against FDA for alleged failure to respond within a reasonable time to the 2006 petition. *International Center for Technology Assessment v. Hamburg*, No. CV 11-6592 (D.D.C., filed Dec. 21, 2011), http://www.centerforfoodsafety.org/wp-content/uploads/2011/12/1-Pls-Complaint.pdf.

[42] *See, e.g.*, TAYLOR, NANOMATERIALS IN FOOD PACKAGING, *supra* note 4, at 34-35.

[43] *E.g.*, Comments by Grocery Manufacturers Association, to FDA Re: Docket No. 2008-N-0416 (Oct. 24, 2008); News Release, Experts Argue Nano Food-Additives Require New Oversight, Project on Emerging Technologies, Woodrow Wilson Int'l Ctr. for Scholars, No. 85-08 (Dec. 18, 2008), *available at* http://www.nanotechproject.org/process/assets/files/7055/penpressrelease081218final.pdf.

[44] *See* 21 C.F.R. §§ 172.230(a)(2) (use as a microcapsule for flavoring substances), 172.480 (multiple uses).

secondary direct food additive,[45] and an indirect food additive.[46] EFSA has approved a use of nanoscale silicon dioxide as a coating on the inner surface of PET articles,[47] but that use would not appear to be covered by existing FDA approvals.

FDA has granted FAPs allowing the use of silver chloride-coated titanium dioxide as a preservative in certain applications, at a level not to exceed 2.2 ppm (based on silver ion concentration).[48] Silver ions exist at the nanoscale, as do virtually all ions. It is unclear if these regulatory provisions support the claims made for some food-contact materials purporting to use "nanosilver" as an antimicrobial.[49]

If an existing food additive regulation were considered to apply by its terms to a nanoscale version and its intended use, FDA could amend the regulation to exclude use of a nanoscale material not established to be safe in its intended application.[50] In a rulemaking initiated by FDA to amend existing food additive regulations to address nanoscale versions, FDA would have the burden of justifying the amendments. Rulemaking also consumes time and agency resources. The FDA Nanotechnology Task Force recognized this issue:

> For an approved food additive, FDA publishes a final regulation establishing conditions under which the substance may be safely used . . . . 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.[51]

Following the Task Force's recommendation,[52] FDA requested submission of data and comments and held a public meeting addressing, among other topics, when a food additive's regulatory status might change due to the presence or use of nanomaterials.[53]

This issue is unlikely to arise in connection with an effective FCN. Since an FCN is product-specific, including a specific manufacturing process, an FCN for a macroscale material

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[45] 21 C.F.R. § 173.340 (use as a defoaming agent).
[46] 21 C.F.R. §§ 175.105(c)(5) (use in adhesives), 175.390 (zinc-silicon dioxide matrix coatings), 177.2250(a) (use in microporous polymeric filters), 177.2420 (use as an adjuvant in polyester resins).
[47] *AFC Opinion*, *supra* note 9, at 3.
[48] 21 C.F.R. §§ 175.300(b)(3)(xxxiii) (resinous and polymeric coatings), 175.320(b)(3)(iv) (resinous and polymeric coatings for polyolefin films), 176.170(a)(5) (components of paper and paperboard in contact with aqueous and fatty foods).
[49] *See Consumer Products Inventory*, *supra* note 5.
[50] See FFDCA § 409(d), 21 U.S.C. § 348(d) (regulation issued on FDA's initiative); 21 C.F.R. § 170.15 (same).
[51] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 19, at 26.
[52] *Id.* at 32.
[53] Consideration of FDA-Regulated Products That May Contain Nanoscale Materials; Public Meeting, 73 Fed. Reg. 46,022-23 (Aug. 7, 2008); *FDA Nanotechnology Public Meeting, Sept. 8, 2008*, FDA, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForce/ucm129416.htm.

would probably not cover a nanoscale version thereof. If a food manufacturer nevertheless claims that a nanotechnology-based FCS is covered by a macroscale FCN, FDA could declare the FCN no longer effective.[54]

V. EXCEPTIONS TO PRE-MARKET APPROVAL REQUIREMENTS

While food additives must receive pre-market approval, some nanomaterials may escape pre-market review on the basis that they fit within certain exceptions to the definition of "food additive" in the FFDCA. The main exceptions are for prior-sanctioned and GRAS substances and for substances that do not become components of food.

A. *PRIOR-SANCTIONED FOOD INGREDIENTS*

The statutory definition of "food additive" does not include a food ingredient used in accordance with a sanction or approval granted prior to September 6, 1958.[55] A prior sanction exists only for the specific level, condition, product, etc. for which FDA or the U.S. Department of Agriculture issued its sanction or approval prior to that date.[56] FDA has published a list of all known prior sanctions.[57]

Since nanoscale food ingredients were not known to be in use until recently, FDA could argue that sanctions prior to September 6, 1958 would not have considered the use of nanoscale materials, so no prior sanction would apply to nanoscale materials. On the other hand, a food company could argue that if a prior sanction has no size limitation, it would apply to nanoscale versions of prior sanctioned substances.

For example, one listed prior sanction is for titanium dioxide used in the manufacture of paper and paperboard products for food packaging, where under normal conditions of use, the substance would not reasonably be expected to migrate to food.[58] A question is whether this prior sanction would apply to nanoscale titanium dioxide when intended for that use. In this case the "no migration" restriction could be a matter needing proof (and in any case would be an independent basis for not considering it to be a food additive; see below). In addition, FDA could amend the prior sanction regulation to limit or prohibit use of nanoscale titanium dioxide in that application based upon scientific data or information that shows that its use may be injurious to health.[59]

B. *GRAS SUBSTANCES*

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[54] 21 C.F.R. § 170.105.
[55] FFDCA § 201(s)(4), 21 U.S.C. § 321(s)(4); 21 C.F.R. § 181.1(a).
[56] 21 C.F.R. § 181.5(a).
[57] 21 C.F.R. pt. 181, subpt. B.
[58] 21 C.F.R. § 181.30. *See also* Kathy Jo Wetter, ETC Group, "100 Years after The Pure Food & Drug Act: FDA's Current Regulatory Framework Inadequate to Address New Nano-Scale Technologies," Presentation at FDA Nanotechnology Public Meeting (Oct. 10, 2006), *available at* http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForce/ucm118910.htm (describing issues related to nanoscale titanium dioxide).
[59] 21 C.F.R. § 181.1(b).

Another exception to the statutory definition of "food additive" applies to any substance that is:

> generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use[.][60]

A substance is GRAS only with respect to "the conditions of its intended use." Arguably, use at the nanoscale must be GRAS for a nanoscale food ingredient to be GRAS; general recognition of the food ingredient's safety in particular macroscale applications may not be sufficient. This limits the relevance for nanoscale food ingredients of this exception to pre-market approval requirements. For example, silicon dioxide is GRAS as a substance migrating to food from paper and paperboard food packaging,[61] but whether a nanoscale version of the compound used for that application would be covered by that regulation is debatable, because the consensus of safety presumably did not consider nanoscale silicon dioxide.

FDA considers that to qualify as GRAS, a food ingredient must have the same quantity and quality of scientific evidence as FDA requires for approval of a food additive petition. FDA also considers that "general recognition" will ordinarily require published studies, which may be corroborated by unpublished data.[62] GRAS food ingredients may be identified as such through a GRAS affirmation regulation, through a self-affirmed GRAS determination by the food manufacturer, or through a GRAS notification to FDA. Those that are the subject of a GRAS affirmation regulation must also meet additional requirements, such as complying with any applicable food grade specifications in the Food Chemicals Codex.[63]

FDA has issued regulations affirming some food ingredients as GRAS, [64] but they are not exhaustive.[65] The regulations mostly reflect a consensus confirmed in the 1960s and 1970s, and hence are unlikely to be relevant to nanoscale food ingredients. Moreover, use under conditions significantly different from those described in the GRAS regulation means that the food manufacturer may not rely on the GRAS regulation.[66]

FDA recognition of GRAS status is not mandatory. Thus, the manufacturer or processor of a nanotechnology-based food ingredient may make its own determination that the ingredient is GRAS. Nevertheless, as a commercial matter, food companies are likely to demand that suppliers claiming nanoscale food ingredients to be GRAS notify FDA of that claim and give FDA an opportunity to object.

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[60] FFDCA § 201(s), 21 U.S.C. § 321(s).
[61] 21 C.F.R. § 182.90.
[62] 21 C.F.R. § 170.30(b).
[63] 21 C.F.R. § 170.30(h).
[64] 21 C.F.R. pts. 182, 184, 186.
[65] 21 C.F.R. § 170.30(d).
[66] 21 C.F.R. §§ 184.1(b)(1), 186.1(b)(1).

FDA has implemented a voluntary GRAS notification procedure based on a 1997 proposed rule, although that proposed rule has never been made final.[67] Under this procedure, a person may submit a statement that it has determined that under the intended conditions of use a food ingredient is GRAS, and a detailed discussion of the reasons for that determination. FDA will acknowledge receipt of the notice within 30 days, and will respond to the notifier in writing within 90 days. FDA posts information about GRAS notifications on its website, together with its response letters. Where FDA does not object to the notification, the response letter says simply that FDA "has no questions at this time" about the notifier's conclusion about GRAS status. The FDA response letter is specific to the conditions specified in the notification, so it would not apply to different conditions (such as use of a nanoscale version of a notified macroscale food ingredient). After evaluating comments solicited in the Federal Register, FDA may publish a notice determining that a substance is not GRAS and is a food additive.[68] Thus, FDA has a remedy for what it considers to be inappropriate GRAS claims for nanoscale food ingredients.

Under this procedure, FDA has approved as GRAS synthetic amorphous silica (SAS), including colloidal silica, which was described as a stable aqueous dispersion or sol of discrete amorphous particles having diameters of 1 to 100 nm for both direct and indirect uses. The submitter notes that most SAS particles range from 0.1 to 1 micrometer and do not exist as easily dispersible nanoparticles.[69]

In 2010, FDA reopened the comment period on the 1997 proposal,[70] with the intention of finalizing it in response to a GAO recommendation.[71] In the notice reopening the comment period, FDA asked for comments on whether the final rule should require submission of information characterizing engineered nanomaterials.[72]

Even with this remedy, however, concerns about the GRAS concept as applied to nanotechnology remain. As Michael R. Taylor (who was named in July 2009 as senior advisor to the FDA Commissioner[73]) stated at the 2008 FDA Nanotechnology Public Meeting,

> I am concerned that the public credibility of the regulatory process . . . is jeopardized by the fact that the system includes, at least theoretically, the opportunity for technology developers and users to make independent GRAS determinations and go to market without even notifying FDA. One way to reduce

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[67] Proposed 21 C.F.R. § 170.36, 62 Fed. Reg. 18,938, 18,960-62 (Apr. 17, 1997). See generally the guidance documents at http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm.
[68] 21 C.F.R. § 170.38(a).
[69] *See* FDA GRAS Notice Inventory Nos. 321 and 298, *available at* http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing (last updated Jan. 31, 2011).
[70] 75 Fed. Reg. 81,536 (Dec. 28, 2010)
[71] GAO REPORT, *supra* note 7, at 35.
[72] 75 Fed. Reg. at 81,540.
[73] Press Release, FDA, Food Safety Expert Michael R. Taylor Named Advisor to FDA Commissioner (July 7, 2009), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm170842.htm. Taylor was previously the FDA's Deputy Commissioner for Policy from 1991 to 1994, and had also held senior positions related to food safety at the U.S. Department of Agriculture.

this vulnerability would be for FDA to make clear through guidance to the industry its position on the applicability of the GRAS concept to food-related uses of nanotechnology.[74]

Similarly, the GAO recommended that FDA develop a strategy for monitoring the appropriateness of non-notified GRAS determinations and ensuring the safety of engineered nanomaterials that companies market as GRAS substances without notifying FDA.[75]

C. *THRESHOLD OF REGULATION*

A third exception to the pre-market approval requirements for food additives applies to substances used in food-contact articles that are present at such low levels that they are deemed not to be components of or to otherwise affect food. Nanoscale substances used in food-contact articles may qualify for this exception, particularly if they are used with barriers preventing their migration into food.

The statutory definition of "food additive" includes only substances "the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component . . . of any food . . . ." Under the diffusion principle, an aspect of the second law of thermodynamics, any two substances that are in contact will tend to diffuse into each other at a rate that will be determined as a function of time, temperature, and the nature of the substances. In a pivotal 1979 decision, a federal appeals court ruled that Congress did not intend that the "component" requirement of the definition of "food additive" would be satisfied by a mere recitation of the diffusion principle, i.e., a finding of any contact whatsoever with food. Instead, "[f]or the component element of the definition to be satisfied, Congress must have intended [FDA] to determine with a fair degree of confidence that a substance migrates into food in more than insignificant amounts."[76]

FDA has promulgated a "threshold of regulation" rule and related guidance that define what it considers to be "insignificant amounts."[77] To be eligible, a substance must not be a carcinogen, must not have carcinogenic impurities, and must present no other health or safety concern, i.e., because its intended use has been shown to result in dietary concentrations of 0.5 ppb or less. The threshold of 0.5 ppb is based on experience and could be changed by FDA in light of new experience (or lack thereof) with nanoscale components of food-contact articles.

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[74] Michael R. Taylor, Food-Related Applications of Nanotechnology: Regulatory Issues, Statement at the FDA Nanotechnology Public Meeting (Sept. 8, 2008), *available at* http://www.nanotechproject.org/process/assets/files/7037/taylorstatement.pdf.

[75] GAO REPORT, *supra* note 7, at 35.

[76] Monsanto Co. v. Kennedy, 613 F.2d 947, 955 (D.C. Cir. 1979).

[77] 21 C.F.R. § 170.39; FDA, GUIDANCE FOR INDUSTRY: SUBMITTING REQUESTS UNDER 21 CFR 170.39 THRESHOLD OF REGULATION FOR SUBSTANCES USED IN FOOD-CONTACT ARTICLES (revised Apr. 2005), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081833.htm.

The rule and related FDA guidance call for submission of notifications to FDA of determinations that the intended use of a substance does not exceed the threshold of regulation, enabling FDA to respond. FDA responses are posted on its website.[78] FDA has posted relatively few threshold of regulation determinations in recent years, suggesting that the FCN process has largely superseded the threshold of regulation process. An example of this may be the FCN for nanoscale titanium nitride, which involved use of a barrier layer that effectively prevented migration into food.

In addition, food manufacturers may make threshold of regulation determinations without notifying FDA, but the marketplace may not accept them for nanoscale components of food-contact articles.

D. *Other Exceptions*

FDA may by regulation exempt from pre-market approval any food additive intended solely for investigational use by qualified experts.[79] FDA has adopted regulations providing for an exemption in limited research circumstances.[80] If nanoscale food additives do not fit within those circumstances, the usual pre-market approval requirements apply.

VI. Post-Approval Oversight

In contrast to its substantial pre-market control over nanoscale food additives, FDA has limited options for post-approval oversight of nanoscale food additives and related substances.

A. *Good Manufacturing Practices*

FDA has rudimentary good manufacturing practice requirements (GMPs) for food additives.[81] These food additive GMPs do not provide the level of detail of FDA's GMPs for drug products and medical devices,[82] but FDA could use them to challenge nanoscale food additives on the basis that they have objectionable impurities or are otherwise not suitable for use in food.

B. *Inspection and Enforcement Authority*

FDA has authority to inspect the facilities and records of food manufacturers producing or using nanoscale food additives and related substances.[83] In practice, FDA regards food

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[78] FDA, Threshold of Regulation Exemptions (updated Apr. 2011), *available at* http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm093685.htm.
[79] FFDCA § 409(j); 21 U.S.C. § 348(j).
[80] 21 C.F.R. § 170.17.
[81] Direct food additive GMPs include that the food additive must be "of appropriate food grade" and "prepared and handled as a food ingredient." 21 C.F.R. § 172.5(a)(2). Indirect food additive GMPs include that the food additive must "be of a purity suitable for its intended use." 21 C.F.R. § 174.65(a)(2).
[82] 21 C.F.R. pts. 210, 211, 820.
[83] FFDCA §§ 414, 703, 704, 21 U.S.C. §§ 359c, 373, 374.

additive inspections to be of low priority, but it might regard nanoscale food additives and related substances to be worth investigating, particularly in light of any complaints received.

Following an inspection finding potential violations, FDA may issue a warning letter or take other action. Warning letters are posted on FDA's website[84] and often receive publicity. FDA can encourage a food company to recall adulterated or misbranded food.[85] In extreme cases, FDA may seize an adulterated or misbranded article of food[86] or seek an injunction.[87] Thus, FDA can move against nanoscale food additives and related substances that it considers to be in violation of FDA requirements.

C. *LABELING*

Food containing a nanoscale food additive or related substance is misbranded if its labeling is false or misleading in any particular.[88] The term "misleading" includes the failure to reveal materials facts.[89] Some commentators have called for FDA to mandate labeling for regulated products to identify any nanomaterials therein.[90]

The FDA Nanotechnology Task Force report did not endorse mandatory labeling requirements for all regulated products containing nanomaterials, although it recognized that in some cases such labeling might be appropriate:

> 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:
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> - Address on a case-by-case basis whether labeling must or may contain information on the use of nanoscale materials.[91]

The Task Force's conclusion that nanomaterial labeling is not necessary across the board is consistent with FDA's earlier decision not to require labeling of all bioengineered food as such.[92] This recommendation is based on FDA's conclusion that safety is the main reason for labeling. Some have called for labeling of food that contains nanomaterials on the basis of social or other considerations, as well as safety. For example, Friends of the Earth has stated:

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[84] *See Warning Letters*, FDA, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.
[85] 21 C.F.R. pt. 7, subpt. C.
[86] FFDCA § 304, 21 U.S.C. § 334.
[87] FFDCA § 302, 21 U.S.C. § 332.
[88] FFDCA § 403(A), 21 U.S.C. § 343(a).
[89] FFDCA § 201(n), 21 U.S.C. § 321(n).
[90] *See, e.g.*, ICTA Nanoparticle Citizen Petition, *supra* note 41, at 26-28.
[91] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 19, at 35.
[92] *See* 66 Fed. Reg. 4,706, 4,711 (Jan. 18, 2001).

> [E]arly surveys show that once given information about nanotechnology, people do not want to eat nanofoods or foods wrapped in packaging that contains manufactured nanomaterials.
>
> Public engagement initiatives and experimental studies suggest that once provided with information about nanotechnology, the public is concerned about many of the same issues identified in relation to GE [genetically engineered] food: a lack of transparency, a lack of choice about exposure, risks to health and the environment, unfair distribution of risks and benefits, a lack of socially useful applications and a lack of public participation in decision making . . . .
>
> Mandatory labelling of all nanofoods is required to enable people to make an informed choice about whether or not to eat them.[93]

EU legislation to require food using such nanomaterials to be labeled as such is pending at the time of this writing.[94]

D. *POST-MARKETING SURVEILLANCE*

FDA has no authority to require the reporting of adverse effects thought to be connected with food additives,[95] but it does include food additives in its voluntary reporting program, the Center for Food Safety and Nutrition Adverse Events Reporting System.[96] FDA has also "elicited agreements from sponsors to conduct post-market monitoring as a condition of approval," but "enforceability of these agreements is questionable."[97]

VII. CONCLUSION

FDA's pre-market review authority over nanoscale food additives is substantial. While there are some exceptions to that authority, the exceptions may be of little relevance to nanoscale food additives.

FDA's post-marketing oversight authority over nanoscale food additives is considerably less substantial. To the extent that this authority proves inadequate to protect consumers, FDA does have the option of removing or modifying its pre-market approval, generally through rulemaking, an option that takes time and agency resources.

In the fifty-plus years since it enacted the Food Additives Amendment of 1958, Congress has not substantially strengthened FDA's post-marketing oversight authority for food additives.

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[93] FRIENDS OF THE EARTH, *supra* note 4, at 44-45.
[94] Documents related to the legislation are located at http://www.europarl.europa.eu/oeil/file.jsp?id=5592852. .
[95] *See* TAYLOR, REGULATING THE PRODUCTS, *supra* note 4, at 37.
[96] *See* Letter from Joseph A. Levitt, Director, FDA Center for Food Safety and Applied Nutrition, to Stakeholders Announcing CAERS - the CFSAN Adverse Event Reporting System (2002). An archived copy of the letter is *available at* http://archives.foodsafety.ksu.edu/fsnet/2002/9-2002/fsnet_september_5.htm#LETTER%20TO%20STAKEHOLDERS.
[97] *See* TAYLOR, REGULATING THE PRODUCTS, *supra* note 4, at 37.

This may reflect an understanding that the current alignment of authority and burdens on FDA with respect to food additives adequately protects the public. At this time there is no sign that nanoscale food additives are likely to change that alignment. Congress is likely to act only if experience with nanoscale food additives in the future should demonstrate that FDA's authority in this area is insufficient.

CHAPTER 5: DIETARY SUPPLEMENTS*

I. INTRODUCTION

Some in the dietary supplements industry see nanotechnology as a new, more effective method for delivering the benefits of dietary supplements.[1] Others are concerned about the possibility of unintended impacts from ingestion of nanoscale materials.[2] While this debate continues, the use of nanotechnology in dietary supplements increases. The Project on Emerging Nanotechnologies (PEN) has predicted that the dietary supplements industry is one of the biggest potential growth areas for nanotechnology.[3] This chapter looks at the ways that the Food and Drug Administration (FDA) can use its existing authority to regulate nanomaterials in dietary supplements, and the ongoing debates over whether FDA needs new statutory authority to ensure the safety of dietary supplements containing nanomaterials.

II. BACKGROUND ON DIETARY SUPPLEMENTS

Dietary supplements are regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended.[4] A dietary supplement is defined in the FFDCA as a product that is intended to supplement the diet that contains one or more of the listed kinds of dietary ingredients, which include vitamins, minerals, herbs or botanicals, amino acids, or "a dietary substance for use by man to supplement the diet by increasing the total daily intake."[5] It also must either be labeled as a dietary supplement and must be intended for "ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form," or, if in another form, not be "represented [for use] as conventional food … or as a sole item of a meal or of the diet."[6] Topical applications are not considered dietary supplements.

The overlap of the "dietary supplement" category with other categories is somewhat complex. For most purposes, a dietary supplement is also deemed a food.[7] Items approved as new drugs, licensed as biologics, or authorized for clinical investigations under an

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* This chapter was prepared by Sara Beth Watson, Steptoe & Johnson LLP.

[1] For example, Health Synergy Group (HGS) markets dietary supplements which use its NanoSynergy™ Delivery System. HGS claims that its Spray for Life® Nano Multivitamin Spray "is the new generation of multivitamins that provides all its benefits plus the highest level of activity, penetration into tissues, organs and cells and metabolic availability never before achievable by any former known technology." *Multi Vitamin*, HEALTH SYNERGY GROUP, http://www.sprayforlife.com/products/multivitamin.html.

[2] *See, e.g.*, *Big environment risks from nano*, FRIENDS OF THE EARTH, http://nano.foe.org.au/node/212.

[3] Comments from David Rijeka, Project on Emerging Technologies, Woodrow Wilson Int'l Ctr. for Scholars, on FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials (July 19, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC7-Attach-1.pdf.

[4] 21 U.S.C. §§ 301-399d. In particular, *see* FFDCA §§ 401-417, 761, 21 U.S.C. §§ 341-350f, 379aa-1. The amendments pertaining to dietary supplements are: the Nutrition Labeling and Education Act of 1990, Pub. L. No. 101-535, 104 Stat. 2353 (1990); the Dietary Supplement Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992); the Dietary Supplement Health Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (1994); and the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006, Pub. L. No. 109-462, 120 Stat. 3469 (2006). Implementing regulations are found in 21 C.F.R. pts. 101, 109, and 190.

[5] FFDCA § 201(ff)(1)(E), 2l U.S.C. § 321(ff)(1)(E).

[6] FFDCA § 411(c)(1)(B)(i)-(ii), 21 U.S.C. § 350(c)(1)(B)(i)-(ii); FFDCA § 201(ff)(2), 21 U.S.C. § 321(ff)(2).

[7] FFDCA § 201(ff), 21 U.S.C. § 321(ff).

Investigational New Drug Application (IND) cannot be marketed as dietary supplements, with one exception: if the product was previously marketed as a dietary supplement or food before the approval, licensing, or authorization under an IND, it may be marketed as a dietary supplement afterwards.[8] Claims by a manufacturer that its dietary supplement product will cure, mitigate, treat, or prevent a disease causes the product to cease to be a dietary supplement and become a drug subject to pre-market FDA approval.[9] Claims that a dietary supplement has a relationship to a disease or health-related condition, however, are classified as "health claims" and are subject to prior approval by FDA under the dietary supplement regulations.[10] Claims that a dietary supplement can affect the structure or function of the body are subject to notification and substantiation requirements.[11]

III. EXAMPLES OF DIETARY SUPPLEMENTS CONTAINING NANOMATERIALS

Nanotechnology offers dietary supplements the ability to provide, or at least promise, superior properties such as increased nutrient absorption or biological activity. Dietary supplements which claim to use nanotechnology range from vitamins to herbal extracts to weight-loss drinks. Health Synergy Group markets seven supplements under its Spray for Life® product line, all of which claim to use a NanoSynergy™ Delivery System.[12] The Ma'at Shop sells Crystal Clear Nano Silver, a colloidal silver product claiming that as a result of nanotechnology, the danger of taking too much colloidal silver has been eliminated, since "[t]he silver particles are simply too small to get stuck in our glands and organs."[13] In all, while the uses of engineered nanoparticles in the dietary supplement market are not fully known, the Project on Emerging Nanotechnologies estimates that more than fifty supplements now on the market claim to contain nanoscale ingredients.[14]

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[8] FFDCA § 201(ff)(3), 21 U.S.C. § 321(ff)(3). *See also* Chapter 7 – Drugs, Chapter 9 – Biologics.

[9] *See, e.g.*, Press Release, FDA, FTC and FDA Act Against Internet Vendors of Fraudulent Diabetes Cures and Treatments Measures are Part of Coordinated Effort by United States, Mexico and Canada (Oct. 19, 2006), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108772 (Among other actions, FDA sent warning letters to 24 firms marketing dietary supplement products with claims to treat, cure, prevent or mitigate diabetes, with threat of further enforcement action, including seizure of the violative products and/or injunctions against the manufacturers and distributors, if violations are not corrected.)

[10] FFDCA §§ 403(r)(5), (6), 21 U.S.C. §§ 343(r)(5), (6); 21 C.F.R. §§ 101.14, 101.70.

[11] FFDCA § 403(r)(6), 21 U.S.C. § 343(r)(6); 21 C.F.R. § 101.93.

[12] *Building Consumer Confidence*, HEALTH SYNERGY GROUP., http://www.sprayforlife.com/products.

[13] Drunvalo Melchizedek, The Ma'at Shop, *Crystal Clear Nano Silver*, http://www.spiritofmaat.com/maatshop/n2_silver.htm. Colloidal silver is an "alternative medicine" claimed by its users to prevent a wide range of diseases, but can cause argyria (permanently blue-gray skin) and other effects if taken in large amounts.

[14] *Consumer Products Inventory - Food and Beverage Supplements*, PROJECT ON EMERGING NANOTECHNOLOGIES, http://www.nanotechproject.org/inventories/consumer/browse/categories/food_beverage/supplements/. A list of dietary supplements which purport to use nanotechnology is also included in William B. Schultz & Lisa Barclay, PROJECT ON EMERGING NANOTECHNOLOGIES, A HARD PILL TO SWALLOW: BARRIERS TO EFFECTIVE FDA REGULATION OF NANOTECHNOLOGY-BASED DIETARY SUPPLEMENTS 26-28 (Jan. 2009), *available at* http://www.nanotechproject.org/process/assets/files/7056/pen17_final.pdf. *See also* FRIENDS OF THE EARTH, OUT OF THE LABORATORY AND ONTO OUR PLATES: NANOTECHNOLOGY IN FOOD & AGRICULTURE, 56-57 (2nd ed. 2008), *available at* http://www.foe.org/publications/reports?page=3 (listing 38 dietary supplements purporting to use nanotechnology).

IV. FDA REGULATION OF DIETARY SUPPLEMENTS

A. *PRE-MARKET REGULATION OF DIETARY SUPPLEMENTS*

FDA has no general authority to regulate the safety of dietary supplements prior to their introduction to the market. It lacks the authority to review, approve or require testing of, dietary supplements. However, there is one area in which FDA does have pre-market review authority: new dietary ingredients.

Section 413 of the FFDCA[15] defines a "new dietary ingredient" as one not marketed in the United States before October 15, 1994.[16] A dietary supplement which contains a new dietary ingredient "shall be deemed adulterated" unless it meets the requirements of either Section 413(a)(1) or 413(a)(2).[17] Under Section 413(a)(1), a dietary supplement containing a new dietary ingredient is not adulterated if it "contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered."[18] If it cannot meet the stringent requirements of Section 413(a)(1), it is deemed adulterated unless it meets the requirements of 413(a)(2).

Section 413(a)(2) has two requirements. First, for the new dietary ingredient, there must be a "history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe."[19] Second, at least 75 days before marketing the dietary supplement containing the new dietary ingredient, the manufacturer must provide FDA with a new dietary ingredient notification (NDIN) containing "information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe."[20] The FFDCA defines "safe" with respect to dietary supplements as not presenting "a

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[15] FFDCA § 413(a), 21 U.S.C. § 350b(a), states:

> IN GENERAL.—A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:
>
> (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.
>
> (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.
>
> The Secretary shall keep confidential any information provided under paragraph (2) for 90 days following its receipt. After the expiration of such 90 days, the Secretary shall place such information on public display, except matters in the information which are trade secrets or otherwise confidential, commercial information.

[16] FFDCA § 413(c), 21 U.S.C. § 350b(d).

[17] FFDCA § 413(a), 21 U.S.C. § 350b(a).

[18] FFDCA § 413(a)(1), 21 U.S.C. § 350b(a)(1).

[19] FFDCA § 413(a)(2), 21 U.S.C. § 350b(a)(2).

[20] FFDCA § 413(a)(2), 21 U.S.C. § 350b(a)(2).

significant or unreasonable risk of illness or injury under—(i) conditions of use recommended or suggested in labeling, or (ii) . . . under ordinary conditions of use."[21]

Under Section 413(a)(2), the manufacturer is required to present FDA with information which supports the manufacturer's conclusion that the dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. If a dietary supplement contains a new dietary ingredient and does not meet the requirements of Section 413(a)(1), a manufacturer's failure to present the information required by Section 413(a)(2), or a finding by FDA that the information submitted is insufficient to establish that the supplement is reasonably expected to be safe, makes the product adulterated. In other words, Section 413(a)(2) places the information burden on the manufacturer, and not on the FDA.

Section 413(a)(2) does not require FDA to take any action in response to a submission.[22] In particular, Section 413(a)(2) does not require FDA to make a finding that a new dietary ingredient for which a notification has been submitted is safe; accordingly, after 75 days, a submitter is free to introduce a dietary supplement containing the new dietary ingredient into commerce.[23] An FDA regulation declares that FDA's failure to respond, or a statement that it has no further questions, does not constitute a finding by FDA that the new dietary ingredient is safe or that the dietary supplement of which it is a part is not adulterated.[24] On the other hand, FDA guidance indicates that after its review of a new dietary ingredient notification, FDA may notify the submitter that "the information in the notification is inadequate to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury."[25] FDA has used its Section 413 authority to review the information submitted for new dietary ingredients,[26] and has often rejected notifications after finding that the supporting

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[21] FFDCA § 402(f)(1)(A), 21 U.S.C. § 342(f)(1)(A).

[22] The FDA Food Safety Modernization Act of 2011, Pub. L. No. 111-353, 124 Stat. 3920 (2011) (FSMA), does require FDA to notify the Drug Enforcement Administration if it determines that a dietary supplement containing a purported new dietary ingredient is unsafe because it may be, or may contain, an anabolic steroid. FSMA § 113, adding a new FFDCA § 413(c), 21 U.S.C. § 350b(c).

[23] The legislative history of the law which added the new dietary ingredients provision does little to clarify the scope of FDA's powers under Section 413. FFDCA § 413, 21 U.S.C. § 350b, was added by Section 8 of the Dietary Supplement Health Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325 (1994). There is only one committee report on DSHEA: the report of the Senate Committee on Labor and Human Resources, S. Rep. No. 103-410 (1994). The Senate Committee report does not mention new dietary ingredients. Moreover, the sponsors of the bill issued a Statement of Agreement that disclaimed the importance of any other reports or statements in the legislative history. 140 Cong. Rec. 28,961 (1994), *reprinted in* 1994 U.S.C.C.A.N. 3,523.

[24] 21 C.F.R. § 190.6(f).

[25] FDA, NEW DIETARY INGREDIENTS IN DIETARY SUPPLEMENTS (updated Sept. 10, 2001), *available at* http://www.fda.gov/Food/DietarySupplements/ucm109764.htm. A description of additional responses appears in FDA, DRAFT GUIDANCE FOR INDUSTRY: DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENT NOTIFICATIONS AND RELATED ISSUES (JULY 2011) [hereinafter NEW DIETARY INGREDIENT GUIDANCE], *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm, § V.

[26] FDA receives an average of 71 notifications under Section 413 annually. 73 Fed. Reg. 34,940, 34,941 (June 19, 2008).

studies were inadequate to support a conclusion that the new ingredient will reasonably be expected to be safe.[27]

B. *Labeling Requirements for Dietary Supplements*

The basic labeling requirement for dietary supplements is that they must be labeled as "dietary supplements."[28] Other provisions of the FFDCA govern how dietary supplement labels must list nutritional information and ingredients.[29]

In addition, the FFDCA regulates the health claims that can be made with regard to dietary supplements. A claim that a dietary supplement reduces the risk of a disease or health-related condition requires a pre-market petition to and approval from FDA.[30] FDA may take enforcement action against companies making such claims for dietary supplements if FDA becomes aware of the claim.[31]

Separate provisions of the FFDCA govern health claims concerning the structure or function of the body, claims of general well-being, and claims of a benefit relating to a classical nutrient deficiency.[32] Dietary supplement manufacturers must notify FDA within 30 days after marketing a product with one or more of these claimed effects.[33] However, once FDA receives notification of the health claim, FDA does not review the claim to determine whether it is supported by scientific evidence. Dietary supplement labels with such health claims must also have a disclaimer that FDA has not evaluated the claims and that the supplement is not intended to "diagnose, treat, cure or prevent any disease."

C. *Post-Marketing Regulation of Dietary Supplements*

Under the FFDCA, FDA has various tools for regulating dietary supplements after they reach the market. FDA can inspect dietary supplement manufacturing facilities.[34] It is

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[27] *See* Ashish R. Talati, *New Dietary Ingredient Notifications: A Comprehensive Review and Strategies for Avoiding FDA Objections*, 62 FOOD & DRUG L.J. 387 (2007) , *available at* https://litigation-essentials.lexisnexis.com/webcd/app?action=DocumentDisplay&crawlid=1&doctype=cite&docid=62+Food+Drug+L.J.+387&srctype=smi&srcid=3B15&key=a9a389cffb830009c1be34f246b067a2 (analyzing FDA's NDIN acceptance rate, which has dipped below 10%).

[28] FFDCA § 403(s)(2)(B), 21 U.S.C. § 343(s)(2)(B).

[29] FFDCA §§ 403(q)(5)(F), 403(s), 21 U.S.C. §§ 343(q)(5)(F), 343(s).

[30] FFDCA § 403(r)(3), 21 U.S.C. § 343(r)(3); 21 C.F.R. §§ 101.14, 101.70. For an example of an authorized health claim that a nutrient reduces the risk of a condition, *see* 21 C.F.R. § 101.79 (authorizing claims that "diets adequate in folate may reduce the risk of neural tube defects").

[31] *See*, *e.g.*, Letter from Jennifer Thomas, Director, Division of Enforcement, Office of Compliance, Center for Food Safety and Applied Nutrition, to Emy San, All Nature Pharmaceuticals, Inc. (Apr. 8, 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/CyberLetters/UCM213382.pdf (warning the company that FDA review of the company website revealed therapeutic claims making the product a drug subject to pre-market approval and the claim a violation of the FFDCA).

[32] FFDCA § 403(r)(6), 21 U.S.C. § 343(r)(6); 21 C.F.R. § 101.93. The DSHEA Statement of Agreement stated that Section 403(r)(6) "does not permit premarket approval or require premarket review by the FDA of any statement permitted under that provision." 140 Cong. Rec. 28,961 (1994), *reprinted in* 1994 U.S.C.C.A.N. 3,523.

[33] FFDCA § 403(r)(6), 21 U.S.C. § 343(r)(6); *see also* 21 C.F.R. § 101.93.

[34] FFDCA § 704, 21 U.S.C. § 374.

authorized to take action against companies producing adulterated[35] or misbranded[36] dietary supplements. Except for the new dietary ingredient adulteration provisions described above, when taking action against a dietary supplement for adulteration, FDA bears the burden of proof to establish that the product "presents a significant or unreasonable risk of illness or injury."

FDA has adopted a final rule establishing current Good Manufacturing Practice Requirements (cGMPs) for dietary supplements.[37] Under these cGMPs, before using any component in their dietary supplements, manufacturers must "[c]onduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient" unless exempted from doing so.[38] This final rule establishes other quality control measures that manufacturers must follow before marketing dietary supplements.[39]

In addition, manufacturers, packers, and distributors must notify FDA of any serious adverse events associated with their dietary supplements that are reported to them.[40] Dietary supplement firms must keep records of all adverse event reports, both serious and non-serious, and provide FDA access to these records during inspections.[41]

V. APPLYING EXISTING REGULATIONS TO DIETARY SUPPLEMENTS CONTAINING NANOMATERIALS

A. *NEW DIETARY INGREDIENTS*

1. *NEW DIETARY INGREDIENT NOTIFICATION FOR A NANOMATERIAL*

A manufacturer of dietary supplements known to have notified FDA of its use of a nanoscale material as a new dietary ingredient is Nano Port (USA) Inc. (Nano Port). Nano Port submitted information to FDA that it intended to market dietary supplements containing Nano Red Elemental Selenium (under the trade name Nano-Se).[42] Nano Port claimed that the size of selenium in Nano-Se was between 20 and 60 nanometers, and that the selenium exhibited "different biological properties" compared to non-nanoscale selenium.[43]

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[35] FFDCA § 402, 21 U.S.C. § 342.
[36] FFDCA § 403, 21 U.S.C. § 343.
[37] 21 C.F.R. pt. 111.
[38] *Id.* § 111.75(a)(1)(i)-(ii).
[39] *See generally* 21 C.F.R. pt. 111.
[40] FFDCA § 761(b)-(d), 21 U.S.C. § 379aa-1(b)-(d). The adverse event reporting requirements were added to the FFDCA by Section 3 of the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006, Pub. L. No. 109-462, 120 Stat. 3469, 3472 (2006). FDA has issued a guidance document on serious adverse event reporting for dietary supplements. *See* FDA, GUIDANCE FOR INDUSTRY: QUESTIONS AND ANSWERS REGARDING ADVERSE EVENT REPORTING AND RECORDKEEPING FOR DIETARY SUPPLEMENTS AS REQUIRED BY THE DIETARY SUPPLEMENT AND NONPRESCRIPTION DRUG CONSUMER PROTECTION ACT (June 2009), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm171383.htm.
[41] FFDCA § 761(e), 21 U.S.C. § 379aa-1(e).
[42] Letter from Yu Har Fei, President, Nano Port (USA) Inc., to Division of Standards and Labeling Regulations, FDA (May 20, 2003), *available at* http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0196-01-vol144.pdf.
[43] *Id.*

FDA's responses stated that Nano Port's submission did not "provide an adequate basis to conclude that Nano Red Elemental Selenium (Nano-Se), when used under the condition recommended or suggested in the labeling of your product, will reasonably be expected to be safe."[44] FDA based its conclusion on two main deficiencies in Nano Port's submission: first, Nano Port failed to provide adequate information on the chemical identity of Nano-Se; second, Nano Port's health and safety studies did not use Nano-Se as the test substance.[45]

Nano Port then submitted additional information to FDA.[46] In response, FDA noted that Nano Port had not provided any additional information on the chemical identity of Nano-Se, including how Nano-Se was manufactured.[47] Likewise, Nano Port had not included health and safety studies which used Nano-Se as the test substance, as FDA had requested. As a result, FDA once again concluded that Nano Port's submission did not "provide an adequate basis to conclude that Nano Red Elemental Selenium (Nano-Se), when used under the condition recommended or suggested in the labeling of your product, will reasonably be expected to be safe."[48]

It is worth noting that FDA has often concluded that manufacturers of dietary supplements which do *not* contain nanoscale ingredients have failed to provide adequate information to establish that the product will reasonably be expected to be safe. Moreover, FDA often bases its conclusion on the same concerns that it expressed in the letters to Nano Port.[49]

2. *Determining Whether a Nanoscale Dietary Ingredient is "New"*

The application of the reasonable expectation of safety standard to NDINs for nanoscale dietary ingredients, as in the case of Nano-Se, is only a concern when manufacturers of dietary supplements containing nanomaterials actually submit NDINs. There is a larger debate,

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[44] Letter from Susan J. Walker, Acting Division Director, Division of Dietary Supplement Programs, FDA, to Yu Har Fei, President, Nano Port (USA) Inc. (Aug. 19, 2003), *available at* http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0196-01-vol144.pdf; Letter from Susan J. Walker, Acting Division Director, Division of Dietary Supplement Programs, FDA, to Yu Har Fei, President, Nano Port (USA) Inc. (May 7, 2004) at 2, *available at* http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0234-02-Fei-vol166.pdf.

[45] Letter from FDA to Yu Har Fei (Aug. 19, 2003), *supra* note 44.

[46] Letter from Yu Har Fei, President, Nano Port (USA) Inc., to Division of Standards and Labeling Regulations, FDA (Feb. 9, 2004), *available at* http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0234-03-NanoPort-vol166.pdf.

[47] Letter from FDA to Yu Har Fei (May 7, 2004), *supra* note 44, at 2.

[48] *Id.*

[49] *See, e.g.*, letter from Linda S. Pellicore, Senior Toxicologist, Division of Dietary Supplement Programs, FDA, to Mark L. Dreher, Vice President, Pom Wonderful, LLC (July 7, 2006), *available at* www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0349-01-vol270.pdf (concluding that the company Pom Wonderful had failed to provide sufficient information on the chemical identity and safety of a proposed new dietary ingredient, Pom_x, a pomegranate fruit polyphenol extract); letter from Linda S. Pellicore, Senior Toxicologist, Division of Dietary Supplement Programs, FDA, to Robert McKay, Vice President, Seppic, Inc. (July 20, 2006), *available at* www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0353-vol270.pdf (stating that the submission for the proposed new dietary ingredient Extramel did not provide a description of how the ingredient was manufactured, and did not supply information establishing the safety of Extramel).

however, regarding whether nanoscale dietary ingredients must be subject to that requirement. Several commentators have recommended that FDA explore the option of declaring nanoscale versions of ingredients to be new dietary ingredients.[50] Some have gone a step further and have urged FDA to use its Section 413 authority to regulate all nanomaterials in dietary supplements as new dietary ingredients.[51]

This argument is based on the view, acknowledged by FDA, that a nanoscale version of a substance can have very different properties than macroscale substance of identical chemical composition.[52] Nanomaterials have a much higher surface area to mass ratio than non-nanoscale materials; this increased surface area can lead to greater chemical reactivity. . The shape of nanoparticles may differ from non-nanoscale particles, and the shape alone may influence toxicity. Furthermore, particle size can influence the absorption and transport of substances in the body. This is not an exhaustive list of the ways in which nanoscale particles may have novel properties, but rather is intended to illustrate the scientific basis for asserting that a nanoscale version of an ingredient should be treated as a new dietary ingredient.

These commenters have asked under what circumstances FDA will consider a nanotechnology-based dietary ingredient to be a "new dietary ingredient" under the FFDCA. FFDCA Section 413 defines a new dietary ingredient as an ingredient that has not been marketed in the United States prior to October 15, 1994.[53] One can argue that nanoscale dietary ingredients were not marketed prior to that date, and accordingly all nanoscale dietary ingredients are new dietary ingredients.

On the other hand, one could argue that if a macroscale dietary ingredient was marketed prior to that date, a nanoscale version of that ingredient would not be a new dietary ingredient. In what amounts to the same thing, one could also argue that a new nanoscale dietary ingredient is not subject to the Section 413(a)(2) requirement to submit safety information to FDA as it meets the provisions of Section 413(a)(1): "The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in

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[50] *See, e.g.*, William B. Schultz & Lisa Barclay, PowerPoint Slides Accompanying Presentation of "A Hard Pill to Swallow: Barriers to Effective Regulation of Nanotechnology-Based Dietary Supplements" (Jan. 14, 2009), *available at* http://www.nanotechproject.org/process/assets/files/7053/presentationfinal-alex.pdf; comments from Michael R. Taylor, FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials (Oct. 10, 2006), *available at* http://www.nanotechproject.org/process/assets/files/2735/119_taylorfdahearingstatement10_9_06.pdf; William B. Schultz, PowerPoint Slides Accompanying Presentation of "Nanotechnology and Dietary Supplements," FDA Nanotechnology Public Meeting (Sept. 8, 2008), *available at* http://www.nanotechproject.org/process/assets/files/7037/shultz1.pdf.

[51] *See, e.g.*, FRIENDS OF THE EARTH, *supra* note 14, at 3 ("All deliberately manufactured nanomaterials must be subject to new safety assessments as new substances, even where the properties of their larger scale counterparts are well-known.").

[52] *See, e.g.*, FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE at 9-11 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter FDA NANOTECHNOLOGY TASK FORCE REPORT] (acknowledging that particle size may influence toxicity, absorption and transport within the body, and other properties); FDA, "Food and Drug Administration-Regulated Products Containing Nanotechnology Materials; Public Meeting," 71 Fed. Reg. 46,232 (Aug. 11, 2006).

[53] FFDCA § 413(c), 21 U.S.C. § 350b(d).

which the food has not been chemically altered."[54] Under this argument, if a nanoscale substance has the same chemical composition as a macroscale substance which has been part of the food supply, then the nanoscale substance is not subject to the NDIN requirement.

Legislative history supports the view that a chemical change, but not a physical change, in food makes the new dietary ingredient subject to the safety information submission requirement. The legislative history of the Act which added the new dietary ingredients provision[55] states that "the term 'chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyophlization, milling, tincture or solution in water, slurry, powder, or solid in suspension."[56] If a food ingredient which has been milled down to the nanoscale has not been "chemically altered," arguably it is not subject to the submission requirement. On the other hand, some nanoscale new dietary ingredients are likely to be chemically different from macroscale materials used in food; these would presumably be subject to the NDIN requirement.

Currently, nearly all manufacturers of dietary supplements made using nanomaterials appear to take the position that nanoscale versions of existing food ingredients are not new dietary ingredients.[57] In July 2011, FDA issued guidance calling for an evidence-based inquiry as to whether a nanoscale dietary ingredient is new, in light of an Obama Administration principle that "[n]anomaterials should not be deemed or identified as intrinsically benign or harmful in the absence of supporting scientific evidence, and regulatory action should be based on such scientific evidence,"[58] and its own implementing position that it "does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful."[59] The guidance advised companies to contact FDA prior to submitting an NDIN for a nanomaterial or product than involves the application of nanotechnology, since "there is little scientific literature discussing the safety of nanomaterials in dietary supplements."[60] It focused on whether a change in particle size to the nanoscale would alter chemical properties; if so, then the dietary ingredient would be considered to be chemically altered.[61] This will involve a case-by-case analysis. This guidance responds to a 2009 report by the Government Accountability Office that found that FDA should prepare guidance on what kinds or degrees of changes to grandfathered ingredients trigger NDIN

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[54] FFDCA § 413(a)(1), 21 U.S.C. § 350b(a)(1).
[55] The new dietary ingredients provision in FFDCA § 413, 21 U.S.C. § 350b, was added by Section 8 of DSHEA. For a discussion of the legislative history of DSHEA, *see supra* note 23.
[56] 140 Cong. Rec. 28,961 (1994), *reprinted in* 1994 U.S.C.C.A.N. 3,523.
[57] *See* FDA Docket No. 95S-0316, 75-Day Premarket Notification of New Dietary Ingredients, *available at* http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s0316.htm.
[58] EXECUTIVE OFFICE OF THE PRESIDENT, POLICY PRINCIPLES FOR THE U.S. DECISION-MAKING CONCERNING REGULATION AND OVERSIGHT OF APPLICATIONS OF NANOTECHNOLOGY AND NANOMATERIALS (June 9, 2011), *available at* http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf.
[59] FDA, DRAFT GUIDANCE FOR INDUSTRY, CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY (June 2011), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.
[60] *See* NEW DIETARY INGREDIENT GUIDANCE, *supra* note 25, § VI.
[61] *Id.*, § IV.

requirements.[62] In addition, the FDA Nanotechnology Task Force recommended that FDA issue guidance as to whether, and when, a nanoscale version of an existing ingredient would be considered a new dietary ingredient.[63]

B. *LABELING*

While the health claims and disclaimer rules for dietary supplements apply to dietary supplements containing nanomaterials, as in other areas, controversies have arisen regarding whether companies should be required to alert consumers to the presence of nanomaterials in their products. Some advocacy groups stress that without mandatory labeling to indicate the presence of nanomaterials in foods and dietary supplements, "there is no way for anyone to choose to eat nano-free."[64] Under the FFDCA, dietary supplement labels are required to list ingredients by their common names and to not be false or misleading, lest they be deemed misbranded. However, FDA has not declared that the presence of nanomaterials is a material fact, the absence of which on a label would render the label misleading.

C. *POST-MARKET REGULATION*

Post-market regulation of dietary supplements can be applied to dietary supplements containing nanomaterials products in a relatively straightforward way. Inspections of facilities are authorized. The rules regarding good manufacturing practices may benefit from modification, in part, to reflect changes in the manufacture of supplements containing nanomaterials. However, FDA already possesses the necessary statutory authority to adapt its cGMP rules to the manufacture of dietary supplements containing nanomaterials. Likewise, the requirement to keep records of, and report to FDA, serious adverse events should apply to dietary supplements containing nanomaterials, though some commenters advocate expanding FDA's authority to include mandatory reporting of adverse events that do not qualify under the current standards as "serious."[65]

VI. REGULATION OF DIETARY SUPPLEMENTS IN THE EUROPEAN UNION

To gain perspective on the regulation of dietary supplements containing nanomaterials in the United States, it is helpful to examine the regulatory framework in the European Union (EU). The basic regulatory approach to dietary supplements, or food supplements, as they are termed in the EU, is to maintain a "positive list."[66] The European Commission has asked agencies to

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[62] GOVERNMENT ACCOUNTABILITY OFFICE, DIETARY SUPPLEMENTS: FDA SHOULD TAKE FURTHER ACTIONS TO IMPROVE OVERSIGHT AND CONSUMER UNDERSTANDING at 25 (2009), *available at* http://www.gao.gov/new.items/d09250.pdf.

[63] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 52, at 34.

[64] FRIENDS OF THE EARTH, *supra* note 14, at 3.

[65] *See, e.g.*, SCHULTZ & BARCLAY, PEN, *supra* note 14, at 24.

[66] *See* Commission Directive on the approximation of the laws of the Member States relating to food supplements, 2002/46/EC, 2002 O.J. (L183) 51, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:183:0051:0057:EN:PDF. This directive was amended in 2006, 2009, and 2011. *See* http://ec.europa.eu/food/food/labellingnutrition/supplements/index_en.htm.

provide scientific opinions on the risks of nanomaterials in food.[67] These opinions have emphasized that much remains unknown about the health risks of nanomaterials, and that the toxicity of nanoscale materials generally cannot be inferred from the toxicity of macroscale materials of identical chemical composition.[68] Having assessed current legislation that could regulate nanotechnology, the Commission concluded that "[c]urrent legislation covers in principle the potential health, safety and environmental risks in relation to nanomaterials." The Commission recommended regulating nanotechnology by improved implementation of existing laws; the Commission did not suggest the need for new nano-specific legislation. [69]

Before a food supplement can be marketed in the EU, the supplement ingredients must appear on a positive list of approved ingredients.[70] The EU has a separate regulatory scheme for "novel foods." The current Novel Foods Regulation requires pre-market testing and approval of all foods defined as novel.[71] The EU tried for three years to pass a new novel foods legislation that would set a legal definition for "nanomaterials" and require food using such materials to be labeled as such. Other issues led to a collapse of negotiations in March 2011.[72] However, parts of the legislation were salvaged and implemented into the Food Information Regulation, published in the Official Journal in October 2011.[73] The regulation provides a transition period

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[67] The Commission asked for an opinion from the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on the risks of nanotechnology in general. *See* EUROPEAN COMM'N, SCIENTIFIC COMM. ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS (SCENIHR), MODIFIED OPINION (AFTER PUBLIC CONSULTATION) ON THE APPROPRIATENESS OF EXISTING METHODOLOGIES TO ASSESS THE POTENTIAL RISKS ASSOCIATED WITH ENGINEERED AND ADVENTITIOUS PRODUCTS OF NANOTECHNOLOGIES (adopted Mar. 10, 2006), *available at* http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf [hereinafter SCENIHR 2006 OPINION]; EUROPEAN COMM'N, SCIENTIFIC COMM. ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS (SCENIHR), RISK ASSESSMENT OF PRODUCTS OF NANOTECHNOLOGIES (adopted Jan. 19, 2009), *available at* http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf [hereinafter SCENIHR OPINION 2009]. The Commission also requested that the European Food Safety Authority (EFSA) provide an opinion on the risks of nanotechnology in food and feed. The final opinion was adopted in February 2009. *See* EUROPEAN FOOD SAFETY AUTH. (EFSA), SCIENTIFIC OPINION OF THE SCIENTIFIC COMMITTEE ON THE POTENTIAL RISKS ARISING FROM NANOSCIENCE AND NANOTECHNOLOGIES ON FOOD AND FEED SAFETY (adopted Feb. 10, 2009), THE EFSA JOURNAL (2009) 958, 1-39, *available at* http://www.efsa.europa.eu/en/scdocs/doc/sc_op_ej958_nano_en,3.pdf [hereinafter EFSA OPINION 2009].

[68] *See* SCENIHR 2006 OPINION, *supra* note 67, at 55-56, 59-60; EFSA OPINION 2009, *supra* note 67, at 21-23,

[69] EUROPEAN COMM'N, COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE, REGULATORY ASPECTS OF NANOMATERIALS, COM (2008) 366, at 11, *available at* http://ec.europa.eu/nanotechnology/pdf/comm_2008_0366_en.pdf.

[70] Commission Directive 2002/46/EC, *supra* note 66, Art. 4(8).

[71] Commission Regulation 258/97, 1997 O.J. (L43) 1 (EC), *amended by* Regulation 1829/2003, 2003 O.J. (L268) 1-2 (EC); Regulation 1882/2003, 2003 O.J. (L284) 46 (EC). A consolidated version is available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1997R0258:20090120:EN:PDF.

[72] Documents related to the legislation are located at http://www.europarl.europa.eu/oeil/file.jsp?id=5583302. *See also* Press Release, European Parliament, Novel Foods Talks Collapse on Council Refusal to Label Clone-Derived Products (Mar. 29, 2011), *available at* http://www.europarl.europa.eu/en/pressroom/content/20110328IPR16525/html/Novel-Foods-talks-collapse-on-Council-refusal-to-label-clone-derived-products.

[73] Cf. Position of the European Parliament adopted at second reading with a view to the adoption of Regulation (EU) No .../2010 of the European Parliament and of the Council on novel foods, *available at* http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2010-0266, and Regulation 1169/2011, 2011 O.J. (L304) 18 (EU), *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF.

with the first requirements applicable in 2014. The Food Information Regulation establishes information requirements for food, also covering food supplements as per the definition of "food" under the EU Food Law Regulation.[74] The Food Information Regulation establishes labeling requirements for all food ingredients, including engineered nanomaterials. "Engineered nanomaterials" are defined as any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.[75] All ingredients in the form of engineered nanomaterials must be clearly indicated on the ingredients list by listing the ingredient name followed by the word "nano" in brackets.[76] However, section 3 on "nutrition declaration" requirements specifically excludes food supplements.[77] This is a developing area of EU regulation.

VII. CALLS FOR EXPANDED REGULATION OF DIETARY SUPPLEMENTS CONTAINING NANOMATERIALS

In addition to urging FDA to use its existing authority to better regulate nanotechnology, some commentators have proposed that the FFDCA be amended to provide FDA with greater regulatory power over dietary supplements containing nanomaterials. These recommendations to amend the FFDCA fall into three main categories: pre-market approval of dietary supplements containing nanomaterials; mandatory labeling of dietary supplements containing nanomaterials; and increased reporting of health data to FDA and consumers.

A. *PROPOSALS TO GIVE FDA PRE-MARKET APPROVAL AUTHORITY*

According to some commentators, FDA does not possess adequate legal authority to regulate nanoscale ingredients in dietary supplements. To remedy this problem, they have proposed amending the FFDCA to require FDA to approve dietary supplements containing nanomaterials before they could be marketed.[78] Under this view, new risk assessments should be done for all dietary supplements containing nanomaterials, even if the macroscale version of the dietary ingredient is deemed safe.[79] For example, a 2009 report by the Project on Emerging Nanotechnologies recommended that Congress provide FDA with authority to require manufacturers of dietary supplements containing nanomaterials to conduct studies demonstrating

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[74] Regulation 178/2002, 2002 O.J. (L31) 7 (EC) (Art. 2), *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:EN:PDF.
[75] Regulation 1169/2011, *supra* note 73, at 26 (Art. 2(t)).
[76] *Id.* at Art. 18(3).
[77] *Id*. at Art. 29(1)(a).
[78] J. CLARENCE DAVIES, PROJECT ON EMERGING NANOTECHNOLOGIES, NANOTECHNOLOGY OVERSIGHT: AN AGENDA FOR THE NEW ADMINISTRATION at 22 (July 2008), *available at* http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Nanotechnologies/pen13.pdf; FRIENDS OF THE EARTH, *supra* note 14, at 3; Comments from Carolyn Cairns, Senior Project Leader, Consumers Union, on FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials at 7, 9 (Oct. 5, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC14-Attach-1.pdf [hereinafter "Consumers Union Comment"].
[79] *See, e.g.*, FRIENDS OF THE EARTH, *supra* note 14, at 3.

the products' safety prior to FDA's approving the products for sale.[80] These proposals would represent a significant departure from the existing regulation of dietary supplements and be more akin to the way that FDA currently regulates drugs. These proposals have not gained widespread support to date. FDA's Nanotechnology Task Force Report does not include a recommendation that FDA seek statutory authority to conduct pre-market safety assessments of dietary supplements containing nanomaterials.

B. *Proposals to Require Mandatory Labeling of Dietary Supplements Containing Nanomaterials*

In echoes of the debates over genetically modified food, some consumer advocates have called for mandatory labeling of products, including dietary supplements, which contain nanomaterials.[81] They believe that without mandatory labeling of products containing nanomaterials, consumers cannot make informed choices.[82] FDA has not been sympathetic to this argument. The Nanotechnology Task Force stated that it "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."[83] The Report's recommendations, including the recommendation for labeling, were endorsed by the Commissioner of the FDA.[84]

Trade groups have opposed calls for mandatory labeling of products containing nanomaterials. For example, the Food Products Association (FPA) and Grocery Manufacturers Association (GMA) have stated that FDA should use its approach to biotechnology as a model for handling nanotechnology; just as food products using biotechnology are not required to be labeled as containing genetically modified ingredients, so too, food products containing nanomaterials should not have to be labeled as such.[85] On the other hand, presumably for commercial reasons, some manufacturers and retailers have prominently stated that their dietary supplements contain nanomaterials; indeed, the names of some dietary supplements include the word "nano."

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[80] SCHULTZ & BARCLAY, PEN, *supra* note 14, at 24. Under this proposal, FDA would have the authority to "waive pre-market review of safety data for specific classes of dietary supplements containing engineered nanoparticles where it finds that such a waiver is consistent with the protection of public health." *Id.*

[81] *See, e.g.*, Consumers Union Comment, *supra* note 79, at 10.

[82] *See id.* A 2009 report issued by the Project on Emerging Nanotechnologies does not call for mandatory labeling of dietary supplements containing nanomaterials, but does recommend that Congress give FDA the authority to require the registration of all dietary supplements containing engineered nanoparticles. *See* SCHULTZ & BARCLAY, PEN, *supra* note 14, at 24.

[83] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 52, at 35.

[84] Memorandum from Andrew C. von Eschenbach, Commissioner of Food and Drugs, to Deputy Commissioner for Policy and Associate Commissioner for Science on FDA Nanotechnology Task Force Report (July 23, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf.

[85] Comments from Craig Henry, Senior Vice President, FPA, & Mary Sophos, Senior Vice President, GMA, on FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials at 5 (Nov. 9, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC25-Attach-1.pdf.

C. *PROPOSALS TO INCREASE THE INFORMATION PROVIDED TO FDA ON DIETARY SUPPLEMENTS CONTAINING NANOMATERIALS*

Under the FFDCA, the manufacturer of a dietary supplement containing nanomaterials has no legal obligation to notify FDA that its product contains nanomaterials, or to provide FDA with any studies on the health effects of its dietary supplement, provided that the nanomaterials are not deemed new dietary ingredients under Section 413 and do not make a health claim. However, if a manufacturer of a dietary supplement containing nanomaterials sought to make a health claim requiring a pre-market petition,[86] FDA's review of the petition would likely uncover the presence of nanomaterials in the product (if they were not already disclosed by the manufacturer).

Some commentators have expressed concern that FDA is not receiving the data necessary to evaluate the safety of nanomaterials in dietary supplements.[87] The proposals for remedying this perceived information gap tend to be part of proposals for pre-market safety assessments and mandatory labeling. According to this argument, if FDA had legislative authority to perform pre-market safety assessments of dietary supplements containing nanomaterials, it would then have the authority to require health information on nanomaterials in dietary supplements. Additionally, a report by the Project on Emerging Nanotechnologies has recommended increasing the information provided to FDA on dietary supplements containing nanomaterials by proposing that Congress expand the adverse reporting requirement to include all adverse events, not just serious adverse events.[88]

VIII. CONCLUSION

FDA has limited authority over dietary supplements, particularly those that do not make health claims. The pre-market review authority for new dietary ingredients is potentially relevant for nanoscale dietary ingredients, but its use in practice is likely to depend on FDA providing guidance on whether it considers nanoscale versions of macroscale dietary ingredients to be "new" for purposes of that authority.

[86] Claims that a product reduces the risk of a disease or health-related condition requires a pre-market petition to the FDA. *See supra* notes 9-11, 30-33, and accompanying text.
[87] DAVIES, *supra* note 79, at 15, 22; Consumers Union Comment, *supra* note 78, at 3, 9; FRIENDS OF THE EARTH, *supra* note 14, at 3, 46; SCHULTZ & BARCLAY, PEN, *supra* note 14, at 24.
[88] SCHULTZ & BARCLAY, PEN, *supra* note 14, at 24.

CHAPTER 6: FOOD AND ANIMAL FEED PRODUCTS*

I. INTRODUCTION

Nanotechnology appears to hold great promise for the improved safety, shelf-life, nutrition, and convenience of food, while at the same time challenging the adequacy and application of current safety regulation. Some believe that the Food and Drug Administration (FDA) already has adequate authority to regulate nanotechnology-based foods. Others believe that Congress should develop national standards to adequately protect human health from the potentially adverse impacts of nanomaterials in food. Most agree, however, that at a minimum FDA should study the risks associated with nanotechnology-based food and issue further guidance on the safe use of nanomaterials in food production. Presently, FDA addresses food nanotechnology issues on a case-by-case basis. This chapter focuses on the extent of FDA authority to address innovative uses of nanotechnology in key categories of whole foods and animal feed.

II. BACKGROUND

A. *THE FOOD AND NANOTECHNOLOGY DEBATE*

The nanotechnology debate centers on the concern that familiar substances may have dramatically different properties and risks at the nanoscale. Nanomaterials have an extremely high ratio of surface area to volume. As a result, they often display different chemical or physical properties and behaviors compared with larger particles. These differences include "altered magnetic properties, altered electrical or optical activity, increased structural integrity, and increased chemical and biologic activity."[89] Nanomaterials in food are of particular concern because, upon ingestion, they gain access to the bloodstream and may have unprecedented mobility to permeate tissues, cells, and organs.[90] Currently, little research exists on the behavior of nanomaterials upon entering the human body.[91]

The dissimilarities between the properties of nanomaterials and larger materials have led some to conclude that current food regulation, which does not distinguish among products based on particle size or require consumer notification of the presence of nanomaterials, is

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[89] 71 Fed. Reg. 19,523, 19,524 (Apr. 14, 2006).

[90] *See*, e.g., Gh. Amoabediny et al., *Guidelines for Safe Handling, Use and Disposal of Nanoparticles*, 170 J. OF PHYSICS: CONFERENCE SERIES 012037 (Nanosafe 2008: International Conference on Safe Production and Use of Nanomaterials (2009)), *available at* http://iopscience.iop.org/1742-6596/170/1/012037/.

[91] JENNIFER KUZMA & PETER VERHAGE, PROJECT ON EMERGING TECHNOLOGIES, NANOTECHNOLOGY IN AGRICULTURE AND FOOD PRODUCTION: ANTICIPATED APPLICATIONS (Sept. 2006), http://www.nanotechproject.org/publications/archive/nanotechnology_in_agriculture_food/. Notably, this 2006 assessment of nanotechnology-related research could find no studies on the impact of nanomaterials on the gastrointestinal tract, despite the fact that nanomaterials were already appearing in food products sold on the market.

insufficient.[92] Instead, some groups are advocating for nanotechnology-specific regulation to ensure food safety.[93] A major concern is that there is too little information on the properties of nanomaterials and, in particular, on how their very small size might influence toxicity. According to these groups, the lack of toxicity data for nanomaterials warrants a precautionary approach to the regulation of nanotechnology-based food products.

Others, including industry groups and some government officials, remain unconvinced that the development of nanotechnology-based foods should give rise to an entirely new regulatory approach. The Food Products Association (FPA) and Grocery Manufacturers Association (GMA), for example, have stated that they believe FDA has "ample legal authority" to regulate nanotechnology-based foods.[94] If all food is at the nanoscale by the time it enters the blood stream, then nanomaterials in food products are in the same size range as the cells and molecules which FDA reviewers and scientists consider every day. Accordingly, rather than adopting a "size per se" approach, FDA is evaluating nanotechnology-based food products (and nanotechnology applications in general) on a case-by-case basis if there appears to be implications for health and safety.[95]

B. *EXAMPLES OF NANOTECHNOLOGY-BASED FOOD PRODUCTS*

Researchers and food scientists may be on the brink of a revolution in food production. Existing nanotechnology-based food developments have focused on improving tastes and textures of foods and increasing the bioavailability of nutrients in food.[96] Applications of

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[92] *See, e.g.*, Comments from Lydia Straus-Edwards, Straus-Edwards Assocs. Architects, to FDA Comm'r, on FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials (Sept. 21, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06n-0107-c000002-01-vol1.pdf (expressing concern that new properties of nanomaterials create "new risks" like enhanced toxicity and that scientific study of these risks is inadequate).

[93] *See e.g.*, Institute for Agriculture & Trade Policy, Comments to FDA on Docket No. 2006N-0107 (Public Meeting on FDA Regulation of Nanotechnology), Sept. 28, 2006, *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC10-Attach-1.pdf (petitioning FDA to treat nanomaterials as new substances, subject them to "nano-specific paradigms of health and safety testing," and to require manufacturers to delineate all nanoparticle ingredients on product labels). *See also* ETC GROUP, DOWN ON THE FARM: THE IMPACT OF NANO-SCALE TECHNOLOGIES ON FOOD AND AGRICULTURE 54-55 (Nov. 2004), http://www.etcgroup.org/upload/publication/80/02/etc_dotfarm2004.pdf (recommending that all food, feed, and beverage products containing manufactured nanoparticles should be removed from the market until testing and regulatory regimes can account for nanoparticles' special characteristics, and can show that they are safe).

[94] Comments from Craig Henry, Senior Vice President, FPA, & Mary Sophos, Senior Vice President, GMA, on FDA Docket No. 2006N-0107, FDA-Regulated Products Containing Nanotechnology Materials at 5 (Nov. 9, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/06n0107/06N-0107-EC25-Attach-1.pdf. Interestingly, these groups urged FDA to consider establishing a pre-market notification system that would make FDA food safety evaluations a "pre-requisite" for novel applications of nanotechnology materials in food. *Id.*

[95] *See* FDA NANOTECHNOLOGY TASK FORCE, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 33 (2007), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter "FDA NANOTECHNOLOGY TASK FORCE REPORT"] (noting that although agency oversight capacity of products, such as food, that are not subject to pre-market authorization is "less comprehensive," manufacturers remain responsible for ensuring the safety of the products they market).

[96] Qasim Chaudhry et al., *Applications and Implications of Nanotechnologies for the Food Sector*, 25 FOOD ADDITIVES & CONTAMINANTS 241, 243 (2008), *available at*

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nanotechnology on the horizon are exploring the ability to extend the shelf-life of foods, to enable consumers to modify foods depending on their own nutritional needs, and to detect the presence of harmful bacteria or fungi in foods.[97] Specific examples of nanotechnology-based food products (existing and potential) include:

- Nanoemulsions of oil and water that can encapsulate functional ingredients and reduce chemical degradation of the ingredients.[98]
- RBC Life Sciences' *Slim Shake* containing "cocoa clusters" (individual particles of silica 4 - 6 nm in diameter coated with the molecules that give chocolate its flavor) for a better tasting, low sugar diet shake.[99]
- Precooked lasagna, modifiable in color, taste, and proportion of nutrients by adjusting the heating time.[100]
- Edible nano coatings for use on meat, fruit, cheese, and vegetables to provide a barrier to moisture and gas and extend shelf life.[101]
- "Tip-Top" Up bread with nanocapsules containing tuna fish oil, designed to break up only when the capsules hit the stomach in order to avoid the unpleasant taste of the fish.[102]
- Low-fat ice creams developed by decreasing the size of emulsion particles that give ice cream its texture and reducing the need for added fat.[103]
- Canola Active Oil with "nanodrops" that promote absorption of healthy components (such as vitamins, minerals, and phytochemicals) and inhibit the transportation of cholesterol from the digestive tract to the bloodstream.[104]
- Nanotea using "nanomilling" to increase the bioavailability of nutrients in tea and claiming a tenfold release of phytonutrients and selenium.[105]

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http://www.informaworld.com/smpp/content~content=a791090932~db=all~order=page; *Delivering Bioactive Compounds via Nanotechnology*, INST. OF FOOD TECHNOLOGISTS, (June 7, 2009), http://live.ift.org/2009/06/06/delivering-bioactive-compounds-via-nanotechnology/.

[97] Chaudhry et al., *supra* note 96, at 247.

[98] Toni Tarver, Institute of Food Technologists, *Food Nanotechnology*, FOOD TECH. 22, 24 (Nov. 2006), *available at* http://www.ift.org/knowledge-center/read-ift-publications/science-reports/scientific-status-summaries/editorial/~/media/Knowledge%20Center/Science%20Reports/Scientific%20Status%20Summaries/Editorial/editorial_1106_functionalmaterialinfood.pdf.

[99] Andrew Maynard, *Shaking Up the Nano-Food Debate*, 2020 SCI., (Oct. 20, 2008), http://2020science.org/2008/10/20/shaking-up-the-nano-food-debate/.

[100] *Nano-Modified Food: How Much Are Consumers Willing to Accept the Associated Risks?*, SCI. DAILY, July 22, 2008, *available at* http://www.sciencedaily.com/releases/2008/07/080720220640.htm.

[101] FRIENDS OF THE EARTH, OUT OF THE LABORATORY AND ONTO OUR PLATES: NANOTECHNOLOGY IN FOOD & AGRICULTURE 15 (2nd ed. 2008), *available at* http://www.foe.org/pdf/nano_food.pdf [hereinafter FRIENDS OF THE EARTH].

[102] TIJU JOSEPH & MARK MORRISON, INST. OF NANOTECHNOLOGY, EUROPEAN NANOTECHNOLOGY GATEWAY, NANOFORUM REPORT: NANOTECHNOLOGY IN AGRICULTURE AND FOOD 10 (May 2006), *available at* www.nanoforum.org/dateien/temp/nanotechnology%20in%20agriculture%20and%20food.pdf?11072006040222.

[103] *Id.* at 11.

[104] *Consumer Products Inventory - Canola Active Oil*, PROJECT ON EMERGING NANOTECHNOLOGIES, http://www.nanotechproject.org/inventories/consumer/browse/products/canola_active_oil/ [hereinafter PEN, *Canola Active Oil*].

- "Fabuless," a nanoemulsion that delays digestion until lower regions of the small intestine, stimulating satiety and reducing food intake.[106]

Food-based applications of nanotechnology appear to be growing rapidly. While some products are still in the research and development stages, others are already on the market.

III. CURRENT FDA REGULATION OF FOOD AND ANIMAL FEED

In the United States, several agencies share responsibility for food safety. FDA, however, administers the bulk of food safety regulation under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended.[107] The FFDCA extends FDA authority to all "articles used for food or drink for man or other animals."[108] Accordingly, FDA oversees domestic and imported food sold in interstate commerce,[109] including animal feed.[110] Several categories of food, such as meat,[111] poultry,[112] and processed egg products,[113] are excluded from FDA regulatory authority and instead fall under the authority of the U.S. Department of Agriculture's Food Safety and Inspection Service (FSIS).[114] Though FDA regulates substances that fall under the FFDCA's separate "food additive" definition, these substances are subject to separate requirements.[115]

Recommendations that FDA take steps to better regulate nanotechnology-based food products must be considered in light of the relevant statutory framework and the extent of FDA

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[105] Qu Yuan et al., *Application of Ball-Milling Technology for the Preparation of NanoPlant Fines*, QINGHUANGDAO IALJI RING NANO-PROD. CO. LTD., SHENZHEN JINGYENANO-TECH CO. LTD., http://web.archive.org/web/20071217224628/www.369.com.cn/En/Application.htm.

[106] FOOD SAFETY AUTHORITY OF IRELAND, THE RELEVANCE FOR FOOD SAFETY OF APPLICATIONS OF NANOTECHNOLOGY IN THE FOOD AND FEED INDUSTRIES 15 (2008), *available at* http://www.fsai.ie/assets/0/86/204/b81b142b-9ef7-414c-9614-3a969835b392.pdf.

[107] 21 U.S.C. §§ 301–399d.

[108] 21 U.S.C. § 321(f). The FFDCA regulations further define food to include "raw materials" and "ingredients." 21 C.F.R. § 110.3(f). Although no definition is provided for "raw materials" or "ingredients," regulatory language indicates that raw materials are a subset of ingredients. *See* 21 C.F.R. § 110.80(a) (referring to "raw materials and other ingredients").

[109] Food also includes shell eggs, bottled water, and wine beverages with less than 7% alcohol. *Center for Food Safety and Applied Nutrition (CFSAN) - What We Do*, FDA, http://www.fda.gov/AboutFDA/CentersOffices/CFSAN/WhatWeDo/default.htm (last updated May 12, 2010) [hereinafter *CFSAN*].

[110] 21 U.S.C § 321(w). The FFDCA defines "animal feed" as an article "intended for use as food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and which is not limited to a mixture intended to be the sole ration of the animal."

[111] Although meat is generally regulated by the U.S. Department of Agriculture under the Federal Meat Inspection Act, 21 U.S.C. §§ 601–695, FDA regulates game meats, such as venison, ostrich, and snake. *What FDA Doesn't Regulate*, FDA, http://www.fda.gov/AboutFDA/WhatWeDo/WhatFDADoesntRegulate/default.htm (last updated Apr. 27, 2009).

[112] Poultry is regulated under the Poultry Products Inspection Act, 21 U.S.C. §§ 451–472.

[113] Processed eggs and egg products (e.g., liquid, dried, frozen) are regulated under the Egg Product Inspection Act, 21 U.S.C. §§ 1031–1056, while shell eggs (table eggs) remain under FDA jurisdiction. *CFSAN*, *supra* note 109.

[114] *See* FSIS website, http://www.fsis.usda.gov/About_FSIS/index.asp.

[115] 21 C.F.R. §§ 170–189. *See also* Chapter 4 - Food Additives.

regulatory authority under the FFDCA. This section provides an overview of FDA's strongest food safety regulatory tools, notes the key voluntary food safety initiatives, and introduces the Hazard Analysis and Critical Control Point (HACCP) system for ensuring food safety. This section also details the joint system of federal and state regulation of pet food and animal feed.

A. *FOOD REGULATION*

FDA is the primary regulator of the food industry and is responsible for food safety, prevention of food adulteration, and accurate food labeling under the FFDCA. The adulteration provisions of the FFDCA provide one avenue to ensure the safety of food, granting FDA the authority to promulgate tolerances and action levels for "adulterated" food, i.e., food containing poisonous or deleterious substances that render the food unsafe within the meaning of the statute.[116] FDA's statutory authority to protect the food supply was greatly expanded with enactment of the FDA Food Safety Modernization Act (FSMA) (signed January 4, 2011).[117] New authorities include, among others:

- Increased records inspection authority.[118]
- Increased authority to require registration of food facilities.[119]
- Establishment of HACCP requirements for most food facilities.[120]
- Increased protections against intentional adulteration of imported food occurring outside the United States.[121]
- Enhanced tracking and tracing requirements for food and related recordkeeping.[122]
- Enhanced capability for surveillance of food borne illness.[123]
- Mandatory recall authority.[124]
- Improving the reportable food registry.[125]
- Establishing a foreign supplier verification programs.[126]
- Authority to require import certifications for food.[127]
- Authority to inspect foreign food facilities under agreements with foreign countries.[128]
- Accreditation of third-party auditors for auditing of foreign entities.[129]

These statutory changes will significantly affect FDA regulation of food and feed. For example, until recently, FDA lacked the statutory authority to require a recall of adulterated food and

[116] FFDCA §§ 402, 406, 21 U.S.C. §§ 342, 346.
[117] Pub. L. 111-353, 124 Stat. 3920 (2011).
[118] FSMA § 101, amending FFDCA § 414(a), 21 U.S.C. § 350c(a).
[119] FSMA § 102, amending FFDCA § 415, 21 U.S.C. § 350d.
[120] FSMA § 103, adding FFDCA § 418, 21 U.S.C. § 350g.
[121] FSMA § 106(a), adding FFDCA § 420, 21 U.S.C. § 350i.
[122] FSMA § 204 (not amending the FFDCA), 21 U.S.C. § 2223.
[123] FSMA § 205, 21 U.S.C. § 2224.
[124] FSMA § 206, adding FFDCA § 423, 21 U.S.C. § 350l.
[125] FSMA § 211(a), amending FFDCA § 417, 21 U.S.C. § 350f.
[126] FSMA § 301(a), adding FFDCA § 805, 21 U.S.C. § 384a.
[127] FSMA § 303, amending FFDCA § 801, 21 U.S.C. § 381.
[128] FSMA § 306(a), adding FFDCA § 807, 21 U.S.C. § 384c.
[129] FSMA § 307, adding FFDCA § 808, 21 U.S.C. § 384d.

relied instead on voluntary recall guidelines.[130] The FSMA provided the agency with mandatory recall authority.[131] It is common practice for the food industry to cooperate with FDA and voluntarily recall food FDA has deemed adulterated.

FDA may deem a food "misbranded" if its label is false or misleading or fails to reveal material facts. If food has been misbranded, FDA may take regulatory action against producers. FDA has the authority to file multiple seizure actions—resulting in either the destruction of food products or subjecting the products to FDA-supervised reconditioning procedures—for adulterated food and, in some circumstances, misbranded food.[132] FDA also has limited post-market oversight authority.

In addition to bringing enforcement actions, FDA sets voluntary guidelines and standards to encourage industry to produce safe food in the first instance. FDA's *Food Code*, for example, is not binding but embodies FDA's views on food safety and protection at the retail level.[133] The *Food Code* serves as a model for state development of food safety rules. FDA has also issued nonbinding good manufacturing practices (GMPs) for the food production industry, detailing FDA's recommended approach for facility and equipment maintenance, employee training, and basic sanitation.[134] Despite their nonbinding nature, in practice these standards have become the baseline for industry performance. The FSMA directed FDA to issue contaminant-specific guidance or regulations for different kinds of food and feed.[135]

Within FDA, much of the food-related regulatory activity occurs through the Center for Food Safety and Applied Nutrition (CFSAN). CFSAN is responsible for carrying out FDA's mission of promoting and protecting public health by ensuring that the nation's food supply is safe, sanitary, wholesome, and honestly labeled. Its activities include developing regulations for proper labeling of foods, ensuring that the food industry meets its post-market monitoring requirements, and cooperating with state and local governments on food safety.[136]

CFSAN has pioneered widespread use of the HACCP system. HACCP focuses on placing preventive controls at the most contamination-prone points of production. The key elements of HACCP are hazard analysis and the establishment of critical control points.[137] Hazard analysis involves consideration of both the likelihood that a hazard will occur and the severity of the harm that will result. Critical control points are the aspects of production that, if controlled, ensure food safety. Presently, FDA has adopted HACCP regulations for the processing of seafood[138] and fruit and vegetable juice.[139] The FSMA added a self-executing

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[130] FFDCA § 412(e)(1), 21 U.S.C. § 350a(e)(1); 21 C.F.R. §§ 7.40-7.59.
[131] FFMSA § 206(a), adding FFDCA § 423, 21 U.S.C. § 350l.
[132] FFDCA §§ 304(a), 402(a)(4), 21 U.S.C. §§ 334(a), 342(a)(4).
[133] *See generally* FDA, FOOD CODE (2009), *available at* http://www.fda.gov/Food/FoodSafety/RetailFoodProtection/FoodCode/FoodCode2009/default.htm.
[134] 21 C.F.R. pt. 110.
[135] FSMA § 104, 21 U.S.C. § 2201.
[136] *CFSAN*, *supra* note 109.
[137] Frederick H. Degnan, *The Regulation of Food Safety*, *in* FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT FOODS, VETERINARY MEDICINES, AND COSMETICS VOL. I, 175 (Robert P. Brady et al., eds., 1997).
[138] 21 C.F.R. pt. 123.
[139] 21 C.F.R. pt. 120.

HACCP requirement for all food facilities effective July 2012, by which time FDA is required to have issued minimum HACCP standards.[140]

B. *ANIMAL FEED REGULATION*

For the most part, FDA's statutory authority under the FFDCA to regulate human food also applies to animal feed. FDA has chosen to exercise its authority over feed somewhat differently than with food. The FSMA allows FDA to exempt or modify HACCP requirements for facilities solely engaged in production of feed.[141] Animal feed regulation is a collaborative effort between federal and state agencies. Until 2007, all animals were treated alike under the FFDCA. The Food and Drug Administration Amendments Act of 2007 (FDAAA 2007) carved out a special class of food safety issues for pets.[142] There is, however, no statutory definition of "pet." Early warning of pet food safety problems is now mandatory.

In the same way CFSAN is responsible for the regulation of human food products, the Center for Veterinary Medicine (CVM) is responsible for the regulation of animal food ("feed") products.[143] CVM has primary responsibility for enforcing the FFDCA to ensure that animal foods, including pet foods, are safe and labeled appropriately. The Animal Feed Safety System (AFSS) is a relatively new FDA program aimed at protecting human and animal health by ensuring safe feeds.[144] The AFSS includes oversight of labeling, production, distribution, and administration of all feed ingredients at all stages.[145]

Animal feed can come under even tighter control at the state level, where each state may develop its own feed control laws and regulations. State feed regulators cooperate with FDA to ensure compliance with federal regulations and to complement FDA's efforts with programs geared toward ensuring that feeds are nutritionally adequate and do not cause health problems for animals or economic losses for feed purchasers. Most states require registration of each product and a label review or registration of the producing company prior to placing the product on the market. The label is reviewed to determine whether or not it meets the specific requirements of state laws in terms of the necessary information, and to assure that there are no false or misleading statements on the label.

Non-medicated animal feeds are generally governed by Association of American Feed Control Officials Incorporated (AAFCO) standards, which are published in annual guidebooks

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[140] FSMA § 103(a), adding FFDCA § 418, 21 U.S.C. § 350g.
[141] FSMA § 103(a) adding FFDCA § 418(m), 21 U.S.C. § 350g(m).
[142] Food and Drug Administration Amendments Act of 2007 § 1002, Pub. L. No. 110-85, 121 Stat. 823, 825, 963 (2007).
[143] *See About the Center for Veterinary Medicine*, FDA, http://www.fda.gov/AboutFDA/CentersOffices/CVM/default.htm.
[144] *Animal Feed Safety System*, FDA, http://www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalFeedSafetySystemAFSS/default.htm.
[145] *See* FDA, ANIMAL FEED SAFETY SYSTEM, THIRD EDITION: DRAFT FRAMEWORK OF THE FDA ANIMAL FEED SAFETY SYSTEM (2008), *available at* http://www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalFeedSafetySystemAFSS/ucm053742.htm (last updated Oct. 28, 2009).

called AAFCO Official Publications.[146] Although AAFCO is not a government agency and has no regulatory authority, it has many government participants and is the key forum for standard development in the feed industry. AAFCO has established a uniform code whose components are known as the Model Bill, Model Regulation, and Model Pet and Specialty Pet Food Regulation. It serves as the standard on which the states base their animal feed laws and regulations in order to maintain a substantial degree of uniformity throughout the U.S.[147]

AAFCO has established the uniform definitions of numerous feed ingredients in order to provide a common understanding of what is used in animal feeds. It has drafted model language designed to enhance the process control requirements and inspections for non-medicated feed, which includes specific process control points from plants which manufacture pet food and specialty pet foods. AAFCO also provides test protocols for manufacturers so they can meet state requirements of proof of safety and nutritional quality before a pet food is marketed.

Animal feed that violates animal feed laws or the FFDCA "food" misbranding or adulteration provisions is subject to enforcement action. Although AAFCO is usually the authority on defining what goes into feed, it has no authority to enforce any standards.

IV. FDA REGULATION OF FOOD AND FEED MADE WITH NANOMATERIALS

Novel uses of nanotechnology in food and animal feed production are testing the boundaries of FDA regulatory authority and capability under the FFDCA. This section outlines FDA's regulatory tools, both in the pre-market and post-market contexts, to address the presence of nanomaterials or guard against potential risks of nanomaterials in food products. Potential non-regulatory models that have been used by FDA in other contexts are also considered. Finally, as a point of comparison, this section summarizes key developments in the European Union's study and regulation of nanotechnology-based food applications.

A. *PRE-MARKET CONTROL MECHANISMS*

1. *PRE-MARKET APPROVAL*

FDA's pre-market approval authority does not extend to most food products.[148] As FDA's Nanotechnology Task Force has acknowledged, FDA oversight of products not subject to pre-market approval, such as food and feed, is "less comprehensive."[149]

While the general rule is that FDA lacks pre-market approval authority for food products, the agency can regulate health, nutrient, and structure/function claims on food labels. In

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[146] AAFCO, ORDER AAFCO PUBLICATIONS, http://www.aafco.org/Home/OrderAAFCOPublications/tabid/75/Default.aspx.
[147] *See* AAFCO, HOW PET FOOD IS REGULATED, *available at* http://www.aafco.org/Portals/0/Public/petfood_regulations.pdf.
[148] Infant formula manufacturers, however, must obtain pre-market approval of product changes. FFDCA § 412, 21 U.S.C. § 350a.
[149] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 95, at 33.

particular, if a food label makes a health claim[150] due to nanomaterials in the product, the FFDCA regulations require the manufacturer to file a health claim petition.[151] In the health claim petition, the manufacturer must provide support, including studies, for its conclusion that the substance is safe.[152]

In the absence of pre-market approval authority for most nanotechnology-based food products, FDA and the public must rely on manufacturers to ensure that the products they market are safe. Some commentators advocate for limits on the manufacture, sale, and use of food made with nanomaterials until the nanomaterials can be tested and proven safe.[153] Some of the authority granted by the FSMA may help FDA assure the safety of nanotechnology-based food products.

In contrast to the U.S. system, in the European Union (EU), the Novel Foods Regulation[154] requires pre-market approval for all new food products.[155] The EU tried for three years to pass legislation that would set a legal definition for "nanomaterials" and require food using such materials to be labeled as such. Other issues led to a collapse of negotiations in March 2011.[156] However, other legislation to require food using nanomaterials to be labeled "nano" is pending at the time of this writing.[157]

2. *Review of Manufacturers' Safety Data*

In some instances, FDA has the opportunity to review manufacturers' safety data for food products before they are sold commercially. For example, seafood and juice processors are required to implement a HACCP system, and FDA has construed its authority under the FFDCA to require access to certain records related to the design and operation of the processing system.[158] The FSMA makes the HACCP system mandatory for other foods, including a

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[150] As defined under 21 C.F.R. § 101.14, "*Health claim* means any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including third party references, written statements . . . , symbols . . . , or vignettes, characterizes the relationship of any substance to a disease or health-related condition. Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition."

[151] 21 C.F.R. § 101.70.

[152] *Id.*

[153] *See, e.g.*, Jennifer Sass, Natural Res. Def. Council, Nanotechnology's Invisible Threat: Small Science, Big Consequences 7 (May 2007), *available at* http://www.nrdc.org/health/science/nano/nano.pdf.

[154] Regulation (EC) 258/97.

[155] Commission Regulation 258/97, 1997 O.J. (L43) 1 (EC), amended by Regulation 1829/2003, 2003 O.J. (L268) 1-2 (EC); Regulation 1882/2003, 2003 O.J. (L284) 46 (EC). A consolidated version is available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1997R0258:20090807:EN:PDF.

[156] Documents related to the legislation are located at http://www.europarl.europa.eu/oeil/file.jsp?id=5583302. *See also* Press Release, European Parliament, Novel Foods Talks Collapse on Council Refusal to Label Clone-Derived Products (Mar. 29, 2011), *available at* http://www.europarl.europa.eu/en/pressroom/content/20110328IPR16525/html/Novel-Foods-talks-collapse-on-Council-refusal-to-label-clone-derived-products.

[157] Documents related to the legislation are located at http://www.europarl.europa.eu/oeil/file.jsp?id=5592852. .

[158] Degnan, *supra* note 137, at 176.

recordkeeping requirement,[159] which means records of nanotechnology uses in food processing, other than of the processors specifically required to implement a HACCP system, could be reviewed. Prior to enactment of the FSMA, some commenters called for environment, health, and safety impact assessments of nanomaterials as a "prerequisite to commercialization."[160]

The EU is responding to similar concerns about safety data through its European Food Safety Authority (EFSA), which enlisted a scientific committee to study the risks associated with nanotechnology uses in food and feed. EFSA's scientific committee concluded that while there were substantial uncertainties regarding the application of nanotechnology in food production, its current risk assessment paradigm would apply to nanomaterials. However, the committee noted that risk assessment should consider the specific properties of nanomaterials in addition to those common to their corresponding larger particles.[161]

FDA is also considering its capacity to address nanotechnology-related food safety risks. Its Nanotechnology Task Force concluded that the FDA's existing authority includes sufficient mechanisms for requesting data from manufacturers and sponsors concerning their nanoscale materials with respect to drugs, devices, biological products, and food and color additives.[162] However, with respect to the regulation of whole foods and other products not subject to pre-market approval, the Task Force conceded that FDA has less ability to obtain information about the presence of nanomaterials.[163] In 2008, in response to the Task Force report, FDA issued a broad request for comments and for "available data and information on the effects of nanoscale materials on quality, safety, and . . . effectiveness of products subject to FDA oversight," including food.[164] A Senate bill in 2010 sought to fund an FDA program for scientific investigation of nanomaterials in FDA-regulated products (presumably including food), including their potential toxicity and effects on other biological systems.[165] The bill did not pass, however. Although nanotechnology-based food products were not a focus of the FSMA, FDA could direct some of its authority to addressing the safety of such products.

3. *PRODUCT LABELING*

The statutory structure for food product labeling includes both the FFDCA and the Fair Packaging and Labeling Act (FPLA). FDA implements both of these statutes in the food context, and ensures that food labels meet all of the statutes' basic requirements as well as FDA's additional regulatory requirements before the products are sold on the market. The basic

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[159] FSMA § 103(a), adding FFDCA § 418, 21 U.S.C. § 350g. There are voluntary HACCP programs for dairy plants and for food service and retail establishments. *See Hazard Analysis & Critical Control Points (HACCP)*, FDA, http://www.fda.gov/Food/FoodSafety/HazardAnalysisCriticalControlPointsHACCP/default.htm (last updated Apr. 27, 2011).

[160] SASS, *supra* note 153, at 8.

[161] EUROPEAN FOOD SAFETY AUTH. (EFSA), PUBLIC CONSULTATION ON THE DRAFT OPINION OF THE SCIENTIFIC COMMITTEE ON THE POTENTIAL RISKS ARISING FROM NANOSCIENCE AND NANOTECHNOLOGIES ON FOOD AND FEED SAFETY 22 (endorsed for public consultation on Oct. 14, 2008), *available at* http://files.nanobio-raise.org/Downloads/sc_opinion_nano_public_consultation.pdf [hereinafter EFSA OPINION 2008].

[162] *See generally* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 95.

[163] *Id.* at 30.

[164] 73 Fed. Reg. 46,022-24 (Aug. 7, 2008).

[165] Nanotechnology Safety Act of 2010, S. 2942, 111th Cong. (2010). *See* 156 Cong. Rec. S123 (Jan. 21, 2010).

requirements include the ingredient listing, with information on the presence of artificial coloring or flavoring, and nutrition information. FDA also regulates nutrient content claims, such as "low fat" or "sugar free," and health claims. While the FFDCA does not expressly authorize FDA to require warning labels for food products, FDA has nevertheless required warning labels in some instances. For example, FDA has required warnings for foods in self-pressurized containers as well as warnings cautioning consumers of the risks associated with high-protein, low-calorie diets.[166] Thus, FDA could promulgate food labeling regulations requiring warnings related to nanomaterials, if appropriate.

There is currently no requirement that manufacturers disclose the presence of nanomaterials on food labels. As with bioengineered food, FDA does not require labeling to describe what technique was used in the development of a food, unless the technique is used to significantly change the composition of a food.[167] FDA "regulates products based on their statutory classification rather than the technology they employ," and therefore FDA's review of a nanotechnology product "may not occur until well after the initial development of that technology."[168] A commenter called the lack of nanomaterial labeling of foods in the United States "a blow to the precautionary principle, transparency and the right of consumers to choose nano-free . . . ."[169] In the EU, these concerns have led to European Parliament draft legislation to mandate risk assessment and labeling of nano-scale ingredients in food and food packaging.[170]

The FDA Nanotechnology Task Force rejected the need for universal nanotechnology-related labeling, reasoning that there is a lack of scientific knowledge about the safety concerns, if any, that nanoscale materials present. The Task Force noted that FDA's enforcement authority over false or misleading labeling permits case-by-case review concerning whether companies must include nanotechnology-related information in product labeling.[171] Under the misbranding provisions of the FFDCA, labels for food products, including nanotechnology-based food products, must be "truthful and not misleading." Food labels must also include "material" information, including consequences which may result from the use of the product under the conditions prescribed in the labeling or under customary or usual conditions of use. If FDA were to "determine that a particular use of a specific nanomaterial, or the use of nanomaterials more generally, was a material fact for a category of products, FDA could amend its regulations to require . . . that all members of that category of products include labeling regarding such use of the nanomaterial."[172]

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[166] 21 C.F.R. § 101.17(a)(1), (d).
[167] FDA, Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (May 29, 1992), *available at* http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Biotechnology/ucm096095.htm.
[168] Martin E. Rock, *Nanotechnology: A Key Trend in the Pharmaceutical and Biotech Industries*, INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING (ISPE), http://www.ispeboston.org/technical_articles/boston_area_nanotechnology_a_key_trend_in_the_pharmaceutical_and_biotech_industries.html (2009).
[169] FRIENDS OF THE EARTH, *supra* note 101, at 41.
[170] *See supra* note 66.
[171] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 95, at 35.
[172] *Id*. at 34-35.

Given the lack of scientific data on many nanomaterials used in food, some may argue that claims regarding the use of nanoscale materials are misleading, so manufacturers may want to consult with FDA concerning such labeling to avoid misbranding the product.[173] If the FDA deems the product "misbranded," the product will not be allowed to enter the market.[174]

B. *POST-APPROVAL OVERSIGHT*

FDA's exercise of its post-market enforcement mechanisms may help ensure the safety of nanotechnology-based food products.

1. *GOOD MANUFACTURING PRACTICES*

One tool available to FDA for addressing potential risks from nanomaterials in food is its food-related GMPs. Food GMP regulations are interpretative rules which construe "insanitary conditions," a term found in the FFDCA prohibiting the adulteration of foods.[175] Food GMPs were an attempt by FDA to lead, rather than push, the industry toward making sanitation improvements to serve the statutory goal of avoiding insanitary conditions.[176] The enforcement of GMPs reflects a desire to instill a general standard of quality into the food industry. The GMP rules and quality standards act as a benchmark against which to measure violations when a food processing facility is inspected. FDA's food GMP regulations provide detailed guidance with respect to personnel, buildings and facilities, sanitary operations, equipment, production and process controls, warehousing and distribution, defects, records and reports.[177] GMP regulations have been supplemented by the voluntary HACCP program for analysis of risks within food facilities. Under the FSMA, mandatory HACCP requirements will apply to most food facilities. By studying the points at which the process could expose food to contaminants or other problems, FDA inspectors are able to give positive suggestions for process improvements.

However, the existing umbrella GMP requirements do little to address the safety concerns associated with nanotechnology-based food products specifically. The GMP provisions relating to raw materials and other ingredients are designed to protect against contamination and minimize deterioration, and do not address toxicity, particle size, or other nanotechnology-related concerns. Nevertheless, FDA and industry experience through the development of the food GMPs demonstrates the potential of this mechanism to establish nonbinding but influential standards for manufacturing processes.

2. *INSPECTIONS OF FOOD FACILITIES*

FDA has authority to monitor the safety of food products through inspecting food processing and handling facilities, examining food stuffs for the presence of physical, chemical, and microbial contamination, and determining whether the food products were prepared, packed,

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[173] *Id.* at 35.
[174] *Id.* at 34.
[175] FFDCA § 402(a)(4), 21 U.S.C. § 342(a)(4).
[176] The potential for contamination is sufficient; proof that the food actually was contaminated is, therefore, unnecessary.
[177] 21 C.F.R. pt. 110.

or held under unsanitary conditions or were not manufactured under GMPs. In addition, FDA is empowered to inspect facilities where foods are processed and/or stored, collect samples for testing, and access safety-related records if it has a "reasonable belief" that the food/ingredient "presents a threat of adverse health consequences or death."[178] The FSMA added to FDA's authority to inspect records.[179]

FDA investigators and inspectors visit thousands of facilities each year to ensure that products are made well and labeled truthfully. As part of these inspections, tens of thousands of domestic and imported product samples may be collected for examination by FDA scientists or for label checks. If a company is found violating any of the laws FDA enforces, FDA can encourage the firm to voluntarily correct the problem or recall the faulty product from the market. When a company cannot or will not correct a public health problem with one of its products voluntarily, FDA has had legal sanctions it could bring to bear, such as going to court to force a company to stop selling a product or to have its products seized and destroyed. When warranted, criminal penalties – including prison sentences – are sought against manufacturers and distributors.[180] The FSMA authorizes FDA to require recall food for which there is a reasonable probability that it is adulterated or misbranded.[181] Also, FDA has new authority to require the tracking and tracing of food.[182]

Inspections may be of assistance to FDA in regulating the use of nanotechnology in the food industry. In particular, the ability to access safety-related records may prove useful in evaluating the safety of a nanoscale ingredient. However, because the focus of inspections has traditionally been sanitation, adjustments in FDA procedures and requirements may need to be made to accommodate nanotechnology-related concerns.

3. *Post-Market Monitoring and Reporting*

The FSMA augmented FDA's ability to conduct or enforce post-market monitoring and reporting of food and feed under the FFDCA.

The Food and Drug Administration Amendments Act of 2007 (FDAAA) established additional requirements for food safety. Under the FDAAA, FDA must establish an early warning and surveillance system to identify any adulteration incidents affecting the pet food supply and also to alert the public about any outbreaks of illnesses associated with pet food.[183] The FDAAA further directed FDA to establish an "Adulterated Food Registry." The registry tracks adulterated food and facilitate information gathering of instances of "reportable adulterated food," or food that is "adulterated or presents a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death . . . ."[184] Anyone may submit a food or feed incident

[178] *See* FFDCA §§ 704, 706, 21 U.S.C. §§ 374, 376.
[179] FSMA § 101(a), amending FFDCA § 414(a), 21 U.S.C. § 350c(a).
[180] U.S. FDA, Center for Food Safety and Applied Nutrition, http://vm.cfsan.fda.gov/fdaoview.html.
[181] FSMA § 206(a), adding FFDCA § 423, 21 U.S.C. § 350l.
[182] FSMA § 204, 21 U.S.C. § 2223.
[183] FDAAA § 1002, Pub. L. No. 110-85, 121 Stat. 823, 963 (2007), 21 U.S.C. § 2102.
[184] FDAAA § 1005, adding FFDCA § 417, 21 U.S.C. § 350f.

report.[185] Once FDA receives a report, it must review it and, if appropriate, issue an alert for foods that have had multiple or recurring reports.

The FSMA gives FDA the authority to require responsible parties to submit "consumer-oriented information" regarding reportable foods, and also require grocery stores to post related information, in order to help consumers identify whether they are in possession of such foods.[186] Also, the FSMA requires facility owners, operators, or agents in charge to evaluate hazards related to the facility, install preventive controls, monitor such controls for effectiveness, and take corrective actions where necessary.[187] Beyond its statutory authority, FDA often receives adverse event information when the parties involved believe a significant health issue may result. FDA investigates such voluntary reports to determine the veracity of the report, the nature of the event, the populations at greatest risk, the necessary steps to control the situation, and the appropriate enforcement action to help prevent future occurrences.

These mechanisms may create a de facto notification system for nanotechnology-based food products, since FDA could be able to detect patterns of food safety issues, at least for certain kinds of short-term health effects. However, the ability of FDA to link patterns of food safety to nanomaterials would depend on whether the food products concerned advertise the use of nanomaterials in the products. FDA currently has little way of knowing, other than through marketing claims, whether a food product contains nanomaterials.

4. *RECALLS*

Prior to enactment of the FSMA, FDA had no authority to compel food product recalls, except in the case of infant formula.[188] Recalls therefore have reflected a voluntary decision by a responsible manufacturer to remove from the market food products which may expose the public to some risk of harm to health or economic well-being. Other voluntary options include a "market withdrawal,"[189] a "stock recovery,"[190] or removing the product from the market without informing FDA.[191]

With enactment of the FSMA, FDA now has authority to require the recall of a nanotechnology-based food product if there is a reasonable probability that the product is adulterated or misbranded and the use of or exposure to the product will cause serious adverse health consequences.[192]

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[185] The FDAAA lists the following as parties who may submit a report: 1) federal, state, and local public health officials; 2) an importer; 3) a responsible party; or 4) a consumer or other individual. *Id.*
[186] FSMA § 211, amending FFDCA § 417, 21 U.S.C. § 350f.
[187] FSMA § 103, adding FFDCA § 418, 21 U.S.C. § 350g.
[188] FFDCA § 412(d), 21 U.S.C. § 350a(d).
[189] 21 C.F.R. § 7.3(j).
[190] 21 C.F.R. § 7.3(k).
[191] FFDCA § 518(e), 21 U.S.C. § 360h(e).
[192] FSMA § 206(a), adding FFDCA § 423, 21 U.S.C. § 350l.

C. *NON-REGULATORY U.S. MODELS*

1. *FDA CONSULTATIONS*

FDA's handling of genetically modified (GM) foods may offer a viable pre-market review model for nanomaterials in food as well. FDA recommends (but does not mandate) consultation before marketing GM foods. Given that the adulteration provisions of FFDCA give FDA broad authority to ensure the safety and wholesomeness of food, and that FDA has strongly enforced those provisions, most companies choose to consult with FDA before marketing GM foods. FDA encourages developers of GM foods to consult early in the development phase of their products, and as often as necessary, until the developer accumulates enough information to ensure that the product is safe and complies with the FFDCA. The developer will then be in a position to conclude any ongoing consultation with FDA.

The practice of consultation, if applied in the nanotechnology context, could amount to a limited, voluntary form of pre-market review. If nanotechnology-based foods are established—through the Adulterated Food Registry or otherwise—to be adulterated or misbranded, and FDA consistently pushes for voluntary recalls or requires mandatory recalls, industry may be motivated to participate in consultations. In deciding whether to develop a consultation mechanism in the nanotechnology context, FDA may want to evaluate how effectively its biotechnology policy has provided it with information about GM foods entering the marketplace, as well as whether U.S. consumers are sufficiently confident about the safety of GM foods.

2. *FDA'S FOOD PROTECTION PLAN*

In an effort to modernize food safety protections in the United States, FDA developed a Food Protection Plan outlining its strategy to strengthen the food safety system.[193] The key features of the Plan are prevention, intervention, and response. According to FDA, the Plan "focuses FDA's efforts to prevent problems before they start."[194] In its one year progress summary, FDA described its success in building food safety into best industry practices and standards. Although food using nanotechnology was not featured in the Plan, it could be an appropriate subject for FDA going forward. FDA may update the Plan in light of the FSMA.

V. THE EUROPEAN UNION REGULATORY STRUCTURE

Much like the United States, the EU has no comprehensive regulatory framework governing nanotechnology-based food applications. According to the European Food Law Regulation, all food for consumption must be safe.[195] Although this regulation applies to all foods, including nanotechnology-based foods, if a substance has already been established as safe

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[193] FDA, FOOD PROTECTION PLAN (Nov. 2007), *available at* http://www.fda.gov/Food/FoodSafety/FoodSafetyPrograms/FoodProtectionPlan2007/ucm132565.htm (last updated Apr. 30, 2009).

[194] FDA, FACT SHEET: FOOD PROTECTION PLAN (Nov. 2007), *available at* http://www.fda.gov/Food/FoodSafety/FoodSafetyPrograms/FoodProtectionPlan2007/ucm132705.htm (last updated Apr. 30, 2009).

[195] Regulation 178/2002, 2002 O.J. (L 31) (EC), art. 14(1), *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:EN:PDF.

under the law at the macroscale, there is no regulatory trigger to require safety data for the same substance at the nanoscale.[196]

In recognition that there were gaps in knowledge about the potential risks associated with the presence of nanomaterials in food, the European Parliament's Committee on the Environment, Public Health and Food Safety asked EFSA to provide guidance on these risks.[197] Following this request, EFSA published an Opinion in 2009 assessing a range of issues, including sources of exposure, toxicity, and environmental impacts of nanotechnology in the food and feed sectors.[198] The Opinion concluded that in order to properly assess the risks of nanomaterials in food and feed, the EU would need "comprehensive identification and characterization" of nanomaterials, information on whether they are likely to be ingested in nanoform, and if ingested, whether the materials would remain in nanoform upon absorption.[199]

VI. CONCLUSION

Until enactment of the FSMA, FDA regulation of nanotechnology-based foods was restricted by FDA's limited authority over food. The FSMA does not target nanotechnology-based foods, but it does provide FDA with new regulatory tools that it could use as appropriate with respect to those foods.

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[196] See FRIENDS OF THE EARTH, *supra* note 101, at 38.

[197] Jess Halliday, *EU Parliament Votes for Tougher Additives Regulation*, FOODNAVIGATOR.COM, July 12, 2007, http://www.foodnavigator.com/Legislation/EU-Parliament-votes-for-tougher-additives-regulation.

[198] European Food Safety Authority (EFSA), The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety – Scientific Opinion of the Scientific Committee, 958 EFSA J. 1 (2009), *available at* http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/sc_op_ej958_nano_en.pdf?ssbinary=true.

[199] *Id.* at 2. Additional research and collaboration continue outside the formal regulatory channels. For example, the International Life Sciences Institute (ILSI) Europe has a Novel Foods and Nanotechnology Task Force, which holds information sessions related to nanotechnology, using an expert group to investigate the safety assessment of nanoparticles and nanotechnology in food applications. It follows developments throughout Europe in the risk assessment of nanoparticles. ILSI Europe, Novel Foods and Nanotechnology Task Force, http://www.ilsi.org/Europe/Pages/TF_NovelFoods.aspx.

CHAPTER 7: DRUGS*

I. INTRODUCTION

The development of new, more effective drugs and medical treatments is a high social priority. However, society also demands that drugs be safe and effective. The Food and Drug Administration (FDA), through its Center for Drug Evaluation and Research (CDER), serves as the gatekeeper in ensuring that drugs are both safe and effective before they enter the market, and polices them once they are on the market. The task is a significant one – under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended,[1] drugs are broadly defined to include prescription drugs, diagnostics, over-the-counter medicines, sunscreens, and more.[2] FDA's regulatory authority over prescription drugs is substantial: new prescription drugs and some over-the-counter drugs must be investigated and pre-approved in phases. FDA's monograph system for over-the-counter drugs provides it with somewhat less review authority, though it has the flexibility to adapt monographs to new ingredients and issues.

Nanotechnology offers great potential for augmenting the effectiveness and benefits of drugs. Nanomaterials can have unique properties, different from traditional small-molecule drugs. Yet, due to the unique properties of matter at this scale and because the field is new, nanotechnology also poses special safety concerns for FDA to address. According to FDA:

> Developments in the science of nanotechnology present opportunities for new drug development that challenge existing drug review approaches. CDER is assessing characterization methodologies to better evaluate the physico-chemical properties of products containing nanomaterials, and investigating models and approaches to better predict human responses to such nanomaterials. This work will allow CDER to understand how best to assess the safety and efficacy of drugs based on nanotechnology.[3]

This chapter assesses FDA's regulatory authority for ensuring the safety of nanomedicines while promoting their innovation.

II. NANOMEDICINE

Drugs currently in development incorporate nanotechnology in a wide variety of ways. Manufacturers are designing nanoparticles that alter the delivery or absorption rate of traditional drugs which target and treat cancerous cells, allowing drugs to be applied topically or taken

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[1] 21 U.S.C. §§ 301-399d.

[2] FFDCA § 201(g)(1), 21 U.S.C. § 321(g)(1).

[3] DEPARTMENT OF HEALTH AND HUMAN SERVICES, FISCAL YEAR 2012 FOOD AND DRUG ADMINISTRATION JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES 164 (2011), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM243370.pdf.

orally instead of injected.[4] Eventually, even more advanced technologies may enable treatment of spinal cord injuries and Parkinson's disease.[5] Nanoparticles may also be key in addressing the growing threat of drug-resistant pathogens,[6] and may help in treating heart diseases as well.[7]

Presently, a number of prescription drugs have been approved which incorporate nanotechnology. Nanotechnology-based drugs catalogued by the Project on Emerging Nanotechnologies (PEN)[8] include anti-nausea drug Emend (Merck);[9] immunosuppressant Rapamune (Wyeth Pharms. Inc./Elan);[10] estrogen lotion Estrasorb (Novavax/Graceway);[11] cholesterol-reducer TriCor (Abbott);[12] the cancer drugs Abraxane (Abraxis Bioscience/AstraZeneca)[13] and Doxil (Ortho Biotech);[14] and appetite stimulant Megace ES (Par Pharm.).[15]

In addition, PEN has catalogued more than thirty sunscreens that contain nanomaterials. Other groups have concluded, after additional testing, that many sunscreens contain nanomaterials but do not say so on the label.[16] Sunscreens are regulated as over-the-counter (OTC) drugs. There are few other nanotechnology-based OTC drugs, but Flex-Power pain relief cream, for example, claims to use nanoscale liposomes and comply with FDA OTC requirements.[17] Other nanomaterial-containing OTC drugs, such as acne treatments, are said to be in development.

FDA has recognized that "[b]ecause development of nanotechnology-based drugs is still in its infancy, there are no established standards for the study or regulatory evaluation of these

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[4] *See* PROJECT ON EMERGING TECHNOLOGIES, NANOFRONTIERS: ON THE HORIZONS OF MEDICINE AND HEALTHCARE (May 2007), *available at* http://www.nanotechproject.org/process/assets/files/2702/188_nanofrontiers_newsletter.pdf.

[5] *See* Project on Emerging Nanotechnologies, *Nanotechnology Offers Hope for Treating Spinal Cord Injuries, Diabetes, Heart and Parkinson's Disease* (April 24, 2007), http://www.nanotechproject.org/news/archive/nanotechnology_offers_hope_for_treating/.

[6] IBM, IBM and The Institute of Bioengineering and Nanotechnology Find Breakthrough for MRSA Treatment: New Molecular Structures Could Fight Infectious Diseases Better than Conventional Antibiotics (Apr. 4, 2011), *available at* http://www-03.ibm.com/press/us/en/pressrelease/34144.wss.

[7] *See, e.g.*, Press Release, University of California at Santa Barbara Engineering Department, Nanoparticle Created to Attack Cardiovascular Plaque (June 4, 2009), *available at* http://engineering.ucsb.edu/news/282/.

[8] Project on Emerging Nanotechnologies, *Medicine Inventory - Current Medical Applications*, http://www.nanotechproject.org/inventories/medicine/apps/.

[9] *See* FDA, *Drugs@FDA*, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (New Drug Application (NDA) 021549) (enter application number to search database).

[10] *See id.* (NDA 021110).

[11] *See id.* (NDA 021371).

[12] *See id.* (NDA 021656).

[13] *See id.* (NDA 021660).

[14] *See id.* (NDA 050718 (describing "STEALTH" nanotechnology delivery system)).

[15] *See id.* (NDA 021778).

[16] *See* FRIENDS OF THE EARTH, INT'L CTR. FOR TECH. ASSESSMENT, & CONSUMERS UNION, MANUFACTURED NANOMATERIALS AND SUNSCREEN: TOP REASONS FOR PRECAUTION (Aug. 2009), *available at* http://www.foe.org/sites/default/files/SunscreensReport.pdf.

[17] FLEX-POWER, *How Does Flex-Power Work?*, http://www.flexpower.com/Product%20info/index2.htm.

products."[18] As a step forward, FDA is developing a comprehensive database of products containing nanomaterials that were the subject of drug applications to CDER.[19] A Presidential advisory group has recognized that development of nanotechnology-based drugs may be relatively slow: "It should be pointed out that because of the significant amount of pre-approval studies required by the FDA, developing nanomedicines such as RNA-nanoparticle complexes is the most costly and most long-term endeavor in the nanomedicine context."[20]

III. FDA REGULATION OF NANOTECHNOLOGY IN DRUGS

A. *DRUG CLASSIFICATION AND REVIEW*

A product will be regulated by FDA as a drug if it is recognized in an official Pharmacopoeia; is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or is intended to affect the structure or any function of the body of man or other animals (and is not food).[21] Drugs are distinguished from devices mainly by their chemical, rather than physical, mode of action.[22] Nanotechnology may challenge the drug-device distinction because it can be difficult to distinguish between chemical and physical modes of action at the nanoscale.

A drug may be either prescription or OTC. All new prescription drugs and some new OTC drugs are subject to some form of individual pre-market approval, though drugs that follow on other brand-name drugs can use abbreviated procedures. The remaining OTC drugs are regulated by category, with regulatory OTC monographs dictating the conditions under which new versions may be marketed without having to apply for pre-market approval.

B. *PRE-MARKET APPROVAL FOR NEW DRUGS*

Generally, new drugs must be shown by substantial evidence to be safe and effective under the pre-market approval authority of the FFDCA.[23] A drug is "new" if it is not generally recognized by qualified experts as safe and effective for use under the recommended or prescribed conditions.[24] There are three types of New Drug Applications (NDAs) that can be submitted to FDA, depending essentially on how "new" a new drug is. A full NDA under FFDCA Section 505(b)(1) is an application that contains full reports of investigations of safety and effectiveness. It is required where there is a new molecular entity, significant new indication or label change, new dosage form, or other substantial development over earlier drugs. Data

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[18] FDA CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF PHARMACEUTICAL SCIENCE, REPORTING FORMAT FOR NANOTECHNOLOGY-RELATED INFORMATION IN CMC REVIEW, MANUAL OF POLICIES AND PROCEDURES 5015.9 (June 3, 2010), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf [hereinafter FDA CDER, MAPP 5015.9].

[19] *See generally id.*

[20] PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, REPORT TO THE PRESIDENT AND CONGRESS ON THE THIRD ASSESSMENT OF THE NATIONAL NANOTECHNOLOGY INITIATIVE 53 (2010), *available at* http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-nano-report.pdf.

[21] FFDCA § 201(g)(1), 21 U.S.C. § 321(g)(1).

[22] *See* Chapter 10 – Combination Products.

[23] FFDCA § 505, 21 U.S.C. § 355.

[24] FFDCA § 201(p), 21 U.S.C. § 321(p).

found in a full NDA must be from studies conducted by or for the sponsor, or must be obtained through a "right of reference."[25] An abbreviated NDA (ANDA) is for a proposed generic drug that is comparable to a listed innovator drug and must demonstrate the generic's bioequivalence.[26] A Section 505(b)(2) NDA is something of a hybrid of the full NDA and the ANDA: it proposes a limited change to a previously approved drug, but provides the required substantial evidence of safety and efficacy through reliance on the data of others.

1. *New Drug Applications and Investigational New Drug Applications*

The product-specific approvals under the full Section 505(b)(1) NDA process pose the fewest concerns for FDA assurance of the safety of nanotechnology-based drugs. Pre-market approval begins with an Investigational New Drug (IND) application, which must be supported by prior (preclinical) animal pharmacology and toxicology studies and detailed clinical protocols to demonstrate that the drug is safe to test on humans.[27] After drug investigations have supplied enough information, a drug sponsor may begin applying for marketing approval through the lengthy NDA process. There are three phases. In Phase I, safety data is obtained from human subjects. Phase II generates data on dosing range and effectiveness. Phase III expands on Phases I and II by increasing the sample of subjects, providing the key data on safety and effectiveness for FDA approval. An NDA review then follows.[28] During the NDA review, FDA can call for additional data. FDA has also suggested that it could issue general guidance recommending that particle size data be submitted in the applications for certain classes of drugs, though it has apparently not yet done so.[29]

On request, FDA may require applicants to supply information about a drug's particle size as part of its review of the product's safety early in the IND process.[30] However, since particle size is not expressly required to be disclosed by the applicant, either the applicant must voluntarily disclose that the product is nanotechnology-based or FDA is likely not to become aware the product utilizes nanotechnology until later in the process. In 2010, CDER asked its reviewers in the Office of Pharmaceutical Sciences (OPS) to document nanotechnology-related information received in drug application submissions.[31] However, this procedural update only requires OPS reviewers to gather nanotechnology-related information that is reported on a drug

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[25] *See* Kim Colangelo, FDA, PowerPoint Slides Accompanying Presentation of "Regulatory Pathways: NDA Process" 7 (Jan. 9, 2007), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118448.pdf.
[26] FFDCA § 505(j), 21 U.S.C. § 355(j).
[27] 21 C.F.R. pt. 312; *Investigational New Drug (IND) Application*, FDA, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (last updated Nov. 5, 2010).
[28] 21 C.F.R. pt. 314; *New Drug Application (NDA)*, FDA, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm (last updated Aug. 20, 2010).
[29] FDA, Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force 22 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter "FDA Nanotechnology Task Force Report"].
[30] *Id.* at 24.
[31] *See* FDA CDER, MAPP 5015.9, *supra* note 18.

application and to search internal reporting databases for particular nanotechnology-related terms; it does not create any new reporting or disclosure requirements for those who submit the drug application.

2. *Abbreviated New Drug Applications for Generic Drugs or Changes to Previously Approved Drugs*

For drugs that contain the same or similar active ingredients as previously approved drugs, pre-market approval may proceed via a Section 505(b)(2) application[32] or an ANDA. These applications reference the data supporting previously approved drugs and may require as little as a showing of bioequivalence between the new drug and the previously approved drug. The FFDCA does not differentiate between active ingredients on the basis of particle size, so a nanotechnology-based active ingredient might be considered the same as a traditional drug, thereby shortening the time necessary for approval and, consequently, getting the product to market faster. Concerns arise between the speed of getting a drug to market and safety risks of moving too quickly through the approval process.

To date, there have been no generic nanotechnology-based drugs approved under the ANDA pathway. Because of the potential differences in how the body interacts with a previously approved drug, as opposed to a similar drug in nanoscale form, an applicant with a nanoscale active ingredient may not be able to demonstrate bioequivalence to the listed drug and obtain approval for its product via an ANDA.[33] In other words, because a nanotechnology-based drug will likely exhibit different pharmacokinetic[34] properties than a traditional drug, it may not perform in exactly the same manner.[35] Nanotechnology may also be used to produce inactive ingredients, which could influence absorption or toxicity of the product. Although drugs approved under ANDAs are generally permitted to have different inactive ingredients, their manufacturers must provide information to FDA to demonstrate that the changes in inactive ingredients do not affect the safety or efficacy of the proposed new drug.[36]

The sponsor of a nanotechnology-based drug could submit an application under Section 505(b)(2) of the FFDCA, which references data contained in a previously approved NDA. A sponsor of a Section 505(b)(2) application for a nanotechnology-based drug must meet the same

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[32] FFDCA § 505(b)(2), 21 U.S.C. § 355(b)(2).

[33] Mary C. Till, Michele M. Simkin & Stephen Maebius, *Nanotech Meets FDA: A Success Story about the First Nanoparticulate Drugs Approved by FDA*, 2 NANOTECH. L. & BUS. J. 163 (2005).

[34] "Pharmacokinetic" means the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion. Merriam-Webster Medical Dictionary, http://www.merriam-webster.com/medical/pharmacokinetic.

[35] For example, "[o]ne way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream . . . . This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug." A nanoscale drug is likely to have a different bioavailability due to its size and surface area. *See* FDA, *Abbreviated New Drug Application (ANDA): Generics*, http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/default.htm (last updated Mar. 21, 2011).

[36] 21 C.F.R. § 314.94(a)(9)(ii).

safety standard as a full NDA for approval,[37] but can do so by referencing the data contained in a previously approved NDA.[38] A Section 505(b)(2) application will include more data than an ANDA (i.e., it will contain more than just bioequivalency data), but is not required to contain the same amount of data as a full NDA. Of the nanotechnology-based drugs already approved by FDA under a Section 505(b)(2) application, varying degrees of clinical data were required. The amount of clinical data required to support approval seemed to depend on how long the active ingredient had been marketed in traditional form.[39]

3. *PRE-MARKET INSPECTIONS*

If FDA was aware that a drug contained nanoscale ingredients and it had concerns about those ingredients, it could schedule a pre-approval inspection of the facilities used to manufacture the drug. NDAs, as well as ANDAs, must include information on "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug[s]."[40] As part of the drug approval process, manufacturers of new drugs must demonstrate that "the methods used in, and the facilities and controls used for, the manufacture, processing . . . , packing, [and testing] of the drug are [ ] adequate to assure and preserve its identity, strength, quality, and purity."[41] Under this authority, FDA can conduct an inspection of a drug manufacturing facility prior to approval. FDA employs a risk-based approach in determining which sponsors will be subject to a pre-approval inspection. Pre-approval inspections are most likely for manufacturers of drugs that are new molecular entities or manufacturers that are first-time applicants, but can also be conducted for cause.[42]

4. *LABELING AND ADVERTISING*

FDA is the "ultimate authority" with respect to drug labeling and package inserts,[43] charged by Congress to ensure that the labeling for approved drug products appropriately informs users of the risks and benefits of the products. Labeling is essentially "[t]he centerpiece of risk management," since it "communicates to healthcare practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."[44] FDA gives careful consideration to labeling during pre-market review of the safety and efficacy of new drugs, since a drug's safety and effectiveness must necessarily turn on the conditions under which it is used. Labeling is approved by FDA as part of the NDA/ANDA process and must always be disseminated with the drug. FDA may mandate warnings and other precautions as part of the label, which is negotiated on an individual basis. Thus, whether a drug

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[37] FFDCA § 505(d), 21 U.S.C. § 355(d).
[38] FFDCA § 505(b)(2), 21 U.S.C. § 355(b)(2).
[39] Cindy H. Strickland, *Nano-Based Drugs and Medical Devices: FDA's Track Record*, 4 NANOTECH. L. & BUS. J. 179 (2007).
[40] FFDCA §§ 505(b)(1)(D), (j)(2)(vi), 21 U.S.C. §§ 355(b)(1)(D), (j)(2)(vi).
[41] FFDCA §§ 505(d)(3), (j)(4)(A), 21 U.S.C. §§ 355(d)(3), (j)(4)(A).
[42] FDA CENTER FOR DRUG EVALUATION AND RESEARCH, COMPLIANCE PROGRAM GUIDANCE MANUAL 7346.832: PRE-APPROVAL INSPECTIONS (Apr. 2010), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf.
[43] 73 Fed. Reg. 2,848, 2,849 (Jan. 16, 2008).
[44] 71 Fed. Reg. 3,922, 3,934 (Jan. 24, 2006).

would have to or would be permitted to indicate the presence of nanoscale ingredients would be determined by FDA on a case-by-case basis.[45] Class warnings may be required if FDA identifies an issue that affects an entire drug class.

One concern that has been expressed is that FDA will not be able to know when it should require product or class warnings if it is unable to recognize which products employ nanoscale ingredients and which do not. Without proper recognition and identification procedures, it is unlikely FDA would have the ability to respond appropriately to issues or problems relating to the nanomaterial-related aspects of a product.[46] However, there is no clear requirement to disclose that a product is nanotechnology-based. FDA's Nanotechnology Task Force stated that "[b]ecause 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, [it] does not believe there is a basis for saying that, as a general matter, a product containing nanoscale materials must be labeled as such."[47] Some manufacturers have avoided promoting the role nanotechnology plays in the manufacture of their products.[48]

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[49] provides FDA with additional authority to rapidly negotiate changes to drug labels based on new safety information.[50] FDA's regulations now provide that certain labeling changes related to an approved drug may be implemented upon receipt by the agency of a supplemental new drug application that includes the change.[51] These post-approval labeling changes are commonly referred to as "changes being effected supplements" or "CBE supplements." Although CBE supplements permit sponsors to implement labeling changes before FDA approval of the change, a CBE supplement is a mechanism primarily designed to provide information to FDA so that the agency can decide when safety information should be included in the labeling for a product. CBE supplements are intended to apply when the sponsor becomes aware of newly discovered risk information that is appropriate for inclusion in the labeling for the product.[52]

FDA has indicated that it does not view nanotechnology-based products as necessarily having an advantage or disadvantage over their traditionally manufactured counterparts.[53] It is unclear whether FDA would permit a manufacturer to promote the advantages of a nanotechnology-based drug over traditional drug, or to imply a benefit by emphasizing the

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[45] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 29, at 34.
[46] John Monica, *FDA Should Systematically Gather Basic Nanomaterial Information*, FDLI INSIGHTER (Feb. 2008), *available at* http://www.fdli.org/insighter/articles/Monica_021908.pdf.
[47] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 29, at 35.
[48] *See id*. at 34.
[49] Pub. L. No. 110-85, 121 Stat. 823 (2007).
[50] *See* FFDCA § 505(o)(4), 21 U.S.C. § 355(o)(4).
[51] 21 C.F.R. § 314.70(c)(6)(iii).
[52] 73 Fed. Reg. 2,848, 2,850 (Jan. 16, 2008) (defining information appropriate for CBE supplement as "data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product").
[53] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 29, at 33-34.

nanotechnology, without clinical data to support such a comparison.[54] Although FDA does not have the authority to require agency approval of promotional materials prior to their use and dissemination, drug companies are required to submit their promotional materials at the time of dissemination.[55] In this way, FDA may become aware of any objectionable claims that overemphasize the benefits of nanotechnology in a product, minimize its risks, or are otherwise inconsistent with FDA's approved label for the product.

C. *OVER-THE-COUNTER MONOGRAPHS*

1. *OVERVIEW*

OTC drugs are defined as drugs that are safe and effective for use by the general public without seeking treatment by a health professional.[56] Thus, an OTC drug must be specifically safe for use without a practitioner's supervision. "Safe" is defined as "a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability."[57] Safety of an OTC category is generally proven through published studies and the benefit-to-risk ratio.[58]

FDA evaluates whether OTC drugs meet this safety requirement through the OTC Monograph system. An OTC drug product containing ingredients that comply with standards established in an applicable monograph is presumed to be "generally recognized as safe and effective" (GRASE) and does not require specific FDA approval before marketing. The monograph is prepared through a three-phase rulemaking process that covers the formulation, labeling, and testing of the OTC drug in question. An OTC drug product that does not conform to a monograph (different active ingredient, strength, formulation, etc.) is considered a "new drug" and requires an individually approved NDA or ANDA demonstrating safety and effectiveness.

Whether a nanoscale version of a monograph-approved ingredient is the same ingredient and is covered by the monograph is an issue likely to arise. The monographs typically do not refer to particle size. However, monographs are amendable by regulation, on FDA's own initiative or based on a petition.[59] If FDA becomes aware of safety issues related to the marketing of nanotechnology-based OTC drugs, it may issue a call for data and comments on the marketing of such products and propose to amend the appropriate monograph accordingly.

The label of an OTC drug product must provide adequate directions for use, which could include references to, or precautions related to, the inclusion of nanoscale ingredients in the drug.

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[54] *See* 21 C.F.R. § 202.1(e)(4)(ii)(b), (c) (requiring comparative claims in advertisements to be supported by "substantial evidence" or "substantial clinical experience"). "Substantial evidence" and "substantial clinical experience" have been interpreted by FDA to require adequate and well-controlled clinical trials.
[55] 21 C.F.R. § 314.81(b)(3)(i).
[56] FFDCA § 503(b)(1)(A), 21 U.S.C. § 353(b)(1)(A); 21 C.F.R. pt. 330.
[57] 21 C.F.R. § 330.10(a)(4)(i).
[58] *See* 21 C.F.R. § 330.10(a)(4).
[59] 21 C.F.R. § 330.10(a)(12).

For OTC drugs marketed under monographs, their labeling must comply with specific requirements of a monograph, including various warnings and other pre-defined statements. However, there are no monograph provisions requiring a disclosure that the OTC product is nanotechnology-based. FDA could add such a disclosure, or necessary warnings to the information required to be included in a drug's label under a monograph.

2. *Nanotechnology-Based OTC Drugs and Sunscreens*

As indicated above, sunscreens have been one of the most prominent product categories to incorporate nanotechnology. Two of the most common and effective sun blocking ingredients, titanium dioxide and zinc oxide, leave a whitish tint on the skin when applied—except when the sunscreen uses those ingredients at the nanoscale, in which case the sunscreen is clear. However, some stakeholders have clashed over these nanotechnology-based sunscreens.[60] Friends of the Earth, for example, issued a report warning consumers to avoid sunscreens containing nanoparticles due to their unknown health and safety risks.[61] They, the International Center for Technology Assessment, and other nonprofit groups petitioned FDA in 2006 to, among other actions, amend the OTC Sunscreen Drug Monograph to declare sunscreens containing engineered nanoparticles to be new drugs.[62] Consumers Union also requested in 2008 that FDA undertake a comprehensive safety review of nanoparticles in sunscreens and require disclosure of nanoscale ingredients on labels.[63] The otherwise nano-wary Environmental Working Group (EWG), on the other hand, reported in 2009 that nanotechnology-based sunscreens were often among the most effective, and that the sun protection benefits could outweigh any nanotechnology-related risks.[64] As of 2011, EWG continues to recommend some sunscreen products that the Project on Emerging Nanotechnologies indicates contain nanoparticles.[65]

FDA has indicated that it considers products containing micronized titanium oxide and zinc oxide[66] to be covered by the agency's OTC Monograph for Sunscreen Products.[67] FDA

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[60] *See e.g.*, Barnaby J. Feder, *Nanoparticles in Your Sunscreen: Too Hot to Handle?*, BITS BLOG, N.Y. TIMES (Aug. 14, 2007), http://bits.blogs.nytimes.com/2007/08/14/nanoparticles-in-your-sunscreen-too-hot-to-handle/.

[61] FRIENDS OF THE EARTH ET AL., *supra* note 16 .

[62] International Center for Technology Assessment, et al., Petition Requesting FDA Amend Its Regulations for Products Composed of Nanomaterials Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically (2006), *available at* http://www.icta.org/doc/Nano%20FDA%20petition%20final.pdf. In 2011, ICTA and other petitioners filed suit against FDA for alleged failure to respond within a reasonable time to the 2006 petition. *International Center for Technology Assessment v. Hamburg*, No. CV 11-6592 (D.D.C., filed Dec. 21, 2011), http://www.centerforfoodsafety.org/wp-content/uploads/2011/12/1-Pls-Complaint.pdf.

[63] Press Release, Consumers Union, *FDA Should Review Nanoparticles in Sunscreen* (Oct. 31, 2008), *available at* http://www.consumersunion.org/pub/core_product_safety/006259.html.

[64] EWG, *EWG's 2009 Sunscreen Investigation, Section 4: Nanotechnology & Sunscreens* (2009), http://www.ewg.org/nanotechnology-sunscreens.

[65] EWG, *Best Beach & Sport Sunscreens* (2011), http://breakingnews.ewg.org/2011sunscreen/best-sunscreens/best-beach-sport-sunscreens/; PROJECT ON EMERGING NANOTECHNOLOGIES, *Consumer Products Inventory - Sunscreen* (2011), http://www.nanotechproject.org/inventories/consumer/browse/categories/health_fitness/sunscreen/ (both listing, e.g., Blue Lizard brand).

[66] "Micronization" refers to the grinding down of particles. It is not clear what size particles result from the process and whether they are indeed "nanosized." *See* MICHAEL R. TAYLOR, PROJECT ON EMERGING TECHNOLOGIES,

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proposed a revised monograph for OTC sunscreen products in 2007 to address UVA and UVB, but the proposal would not require that the labeling disclose the presence of micronized ingredients or include related warnings.[68] However, in response to comments the agency received and the increased marketing of nanotechnology-based sunscreen products, it specifically requested comments from interested parties on the use of nanoscale ingredients in sunscreens.[69] At the time of this writing, FDA has not issued a final rule or indicated when a final rule would be forthcoming.[70] In the 111th Congress, the "Sunscreen Labeling Protection Act of 2009" (S. 1112) was introduced in 2009 which would, if enacted, have made the proposed rule law unless FDA issued a final rule within 180 days. This legislation did not pass.

D. *POST-MARKET OVERSIGHT*

1. *POST-APPROVAL STUDIES*

With the FDAAA, FDA has authority to require studies, clinical trials, and post-market monitoring after approval of a new drug. Although there has been little discussion of these provisions in the context of nanotechnology specifically, they provide FDA with significant authority to monitor nanotechnology-based drugs after approval. Under the FDAAA, FDA may require "Phase IV" post-market studies or clinical trials to assess or identify known or potential long-term risks associated with use of an approved drug (or approved biologic that is a drug).[71] FDA may require the studies based on scientific data, including chemically or

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REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? 42 (2006), *available at* http://www.nanotechproject.org/process/assets/files/2705/110_pen5_fda.pdf.

[67] FDA, Sunscreen Drug Products for Over-The-Counter Human Use; Final Monograph; Final Rule, 64 Fed. Reg. 27,666, 27,671 (May 21, 1999).

[68] FDA, Sunscreen Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph, 72 Fed. Reg. 49,070 (Aug. 27, 2007). The primary purpose of the proposed revision was to address formulation, labeling, and testing requirements for both ultraviolet B (UVB) and ultraviolet A (UVA) radiation protection.

[69] *Id.* at 49,110.

[70] FDA issued an advance notice of proposed rulemaking related to the monograph at 76 Fed. Reg. 35,669 (June 17, 2011). At the same time it issued a draft enforcement policy indicating the circumstances under which it would exercise enforcement discretion regarding certain OTC sunscreen products pending adoption of a final monograph. FDA, GUIDANCE FOR INDUSTRY: ENFORCEMENT POLICY – OTC SUNSCREEN DRUG PRODUCTS MARKETED WITHOUT AN APPROVED APPLICATION (June 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf. These and related FDA actions did not address the issue of nanomaterials in sunscreens, prompting concerns by Consumers Union, Friends of the Earth, and the International Center for Technology Assessment. *See* Friends of the Earth, news release, *New FDA Sunscreen Rules Called Blind to Nanotechnology* (June 23, 2011), *available at* http://www.foe.org/new-fda-sunscreen-rules-called-blind-nanotechnology. In response, an FDA spokesperson said, "The ingredients in sunscreens marketed today have been used for many years, and FDA does not currently have reason to warn consumers about their safety. This includes nanoparticles." Bureau of National Affairs, Chemical Regulation Reporter, *Groups Criticize FDA's Sunscreen Rules for Not Addressing Nanoscale Ingredients* (*35* CRR 640, June 27, 2011).

[71] FFDCA § 505(o)(1)-(3), 21 U.S.C. § 355(o)(1)-(3); FDA, DRAFT GUIDANCE FOR INDUSTRY ON POSTMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF SECTION 505(O) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (July 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

pharmacologically-related information about the drug.[72] In the case of already approved drugs, FDA may only require a study or trial if it becomes aware of new safety information that indicates the need.[73]

2. *RISK MANAGEMENT PLANS*

Under the FDAAA, as part of the new drug approval process, FDA may also require a Risk Evaluation and Mitigation Strategy (REMS) for a new drug in order to assure that the benefits of the drug outweigh the risks involved with its use.[74] As with post-marketing studies and clinical trials, FDA may require a REMS after approval of a drug, but only if the agency becomes aware of new safety information on the basis of which it determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[75] A REMS is specifically designed to address the risks associated with a particular drug or class of drugs and may involve extensive post-market monitoring, restricted distribution plans, patient labeling, or patient registries. REMS may be applied to entire pharmacological classes of drugs, and generic versions of marketed drugs. FDA has indicated it intends to require REMS under very limited circumstances,[76] and to date has not required REMS for any nanotechnology-based drug.

Where a specific risk is known and can be avoided with careful planning (e.g., preventing pregnant women from taking teratogenic drugs), FDA can mandate a risk minimization action plan, known as a "RiskMAP," as a "strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits."[77] FDA recommends the use of a RiskMAP for a small number of products. It cautions sponsors to carefully tailor a RiskMAP to minimize risks without encumbering drug availability. There are many processes or systems to minimize known safety risks available for use in RiskMAPs. These systems include targeted education and outreach to communicate risks; reminder systems, processes, or forms to foster reduced-risk prescribing and use; and performance-linked access systems that guide prescribing, dispensing and use of the product to the target population.[78] A RiskMAP might include tools from one or more categories, depending on its risk minimization goals. During post-marketing, FDA and the drug's sponsor are guided by the utilization of the RiskMAP and can refine or modify it to further reduce risks. To date, FDA has not required a RiskMAP for any nanotechnology-based drugs. The challenge of applying the RiskMAP program to such drugs will be in determining the associated risks and benefits when scientific consensus and reliable testing methodologies are still to be developed.

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[72] FFDCA § 505(o)(3)(A), 21 U.S.C. § 355(o)(3)(A).
[73] FFDCA § 505(o)(3)(C), 21 U.S.C. § 355(o)(3)(C).
[74] FFDCA § 505-1(a)(1), 21 U.S.C. § 355-1(a)(1).
[75] FFDCA § 505-1(a)(2)(A), 21 U.S.C. § 355-1(a)(2)(A).
[76] *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.
[77] FDA, GUIDANCE FOR INDUSTRY: DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS (Mar. 2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf.
[78] *Id.* at 7.

3. *ADVERSE EVENT REPORTING*

NDA and ANDA sponsors who have received marketing approval for prescription drugs must report adverse events involving their products to FDA. For adverse events that are considered serious (e.g., fatal, life-threatening, incapacitating, or requiring hospitalization) and unexpected (i.e., not described on the drug label), sponsors must notify FDA within 15 days of learning of the adverse event.[79] Sponsors must also submit reports in tabulation form on a periodic basis.[80] Adverse event reporting is also required for OTC drugs under the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006.[81] Under that law, manufacturers of OTC drugs marketed under monographs are required to submit to FDA within 15 days any report of serious adverse events associated with their drugs.[82] These provisions can make FDA aware of serious, acute health and safety risks from nanotechnology-based drugs.

4. *MANUFACTURING FACILITIES*

FDA's regulations establish minimum standards for current good manufacturing practices (cGMPs) that govern production and process controls which can be applied broadly to a wide range of technology, including nanotechnology.[83] FDA could issue guidance addressing the implementation of cGMPs for nanotechnology-based products. The FFDCA authorizes FDA to seize or seek an injunction against the distribution of a drug that is adulterated or misbranded, which could occur if FDA concludes that the drug is not manufactured in accordance with cGMPs.[84] During drug manufacturing facility inspections, FDA is also authorized to view records relating to product safety.

FDA has authority to conduct periodic inspections of drug manufacturing facilities.[85] However, given the competing demands on the agency's resources and time, it may be a struggle for FDA to devote adequate resources to inspections of nanotechnology-related issues.[86]

5. *REMOVING A PRODUCT FROM THE MARKET*

If FDA becomes aware of clinical or scientific data showing that an individually approved drug is unsafe for use, FDA may withdraw approval of an application for the drug.[87] FDA must provide the applicant with notice and the opportunity for a hearing prior to

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[79] 21 C.F.R. § 314.80(c)(1).
[80] 21 C.F.R. § 314.80(c)(2).
[81] Pub. L. No. 109-462, 120 Stat. 3469 (2006) (adding FFDCA § 760, 21 U.S.C. § 379aa).
[82] Pub. L. No. 109-462, §§ 760(c)(1)-(2).
[83] *See* 21 C.F.R. pts. 211 & 212, which govern finished drug products. *See also, e.g.*, FDA, GUIDANCE FOR INDUSTRY: Q7A GOOD MANUFACTURING PRACTICE GUIDANCE FOR ACTIVE PHARMACEUTICAL INGREDIENTS (Aug. 2001), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129098.pdf, and FDA CENTER FOR DRUG EVALUATION AND RESEARCH, COMPLIANCE PROGRAM GUIDANCE MANUAL 7356.002: DRUG MANUFACTURING INSPECTIONS (FEB. 2002), *available at* http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074902.htm.
[84] FFDCA § 501(a)(2), 21 U.S.C. § 351(a)(2).
[85] FFDCA § 704, 21 U.S.C. § 374.
[86] *See* TAYLOR, *supra* note 66, at 47.
[87] FFDCA § 505(e)(1), (2), 21 U.S.C. § 355(e)(1), (2); 21 C.F.R. § 314.150.

withdrawing the NDA. FDA can remove OTC drugs from the market by amending the applicable monographs through rulemaking.

The FFDCA authorizes FDA to seize or seek an injunction against the distribution of a drug that is adulterated or misbranded, which could occur if FDA concludes that the drug is unsafe or if it is not manufactured in accordance with cGMPs.[88] However, FDA is more likely to ask a manufacturer to undertake a voluntary recall. If an applicant has not taken other appropriate action to fix a problem, FDA may request, but not require, a recall of defective or unsafe prescription or OTC drugs, if distribution of the product "presents a risk of illness or injury or gross consumer deception" and agency action is necessary to "protect the public health and welfare."[89] As a general matter, FDA will only request recalls under urgent situations and only when the agency has sufficient evidence to support a legal action such as a seizure.[90] Thus, if a drug manufacturer or distributor were to reject FDA's request to conduct a recall, FDA could probably take legal action against the company.

6. *NON-REGULATORY OVERSIGHT*

In addition to all of the above regulatory authorities, FDA conducts a number of initiatives and programs to enhance drug safety. FDA maintains a number of web pages to disseminate drug safety information, including the Drug Safety Communications webpage[91] and the previous Drug Safety Newsletter.[92] FDA's MedWatch website also distributes Safety Alerts for drugs and other medical products.[93] Thus, any safety issue related to nanomedicines could be circulated and publicized relatively quickly, which raises the stakes for manufacturers of such drugs.

FDA also maintains research programs, several of which are currently conducting research to better understand nanomaterials and nanotechnology in the drug context. For example, FDA's National Center for Toxicological Research has established a Nanotechnology Core Facility which is, among other projects, examining the skin absorption and toxicity of micronized titanium dioxide and zinc oxide used in sunscreens.[94] Nanotechnology has been addressed by a number of efforts under the auspices of FDA's Critical Path Initiative and Advancing Regulatory Sciences Initiative, two of FDA's efforts modernize the scientific processes through which FDA-regulated products are developed, evaluated, manufactured, and

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[88] FFDCA §§ 302, 304, 501-502, 21 U.S.C. §§ 332, 334, 351-352.
[89] 21 C.F.R. § 7.45(a).
[90] FDA, *FDA Requested Recall*, Chapter 7-5-2 in REGULATORY PROCEDURES MANUAL, *available at* http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074312.pdf.
[91] FDA, *Drug Safety Communications*, http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm.
[92] FDA, *FDA DRUG SAFETY NEWSLETTER ISSUES*, http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm096049.htm.
[93] FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, http://www.fda.gov/Safety/MedWatch/default.htm.
[94] FDA National Center for Toxicological Research, *NCTR Research Focus Areas: Nanotechnology*, http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/NCTRResearchPriorities/ucm083162.htm (last updated Apr. 2010).

used.[95] FDA is also a member of the nanotechnology subcommittee of the Interagency Oncology Task Force (IOTF), which also includes the National Cancer Institute and National Institute for Standards and Technology. Under the IOTF umbrella, the agencies are "leveraging resources and expertise to advance the field in the context of oncology."[96]

IV. CONCLUSION

FDA's regulatory authority over nanotechnology-based drugs is considerable, but not without gaps. FDA can obtain large amounts of chemical characterization and safety data through its new drug pre-market approval processes. However, its ability to obtain such data and to act as a gatekeeper for nanotechnology-based drugs using the OTC monograph system is more limited. Continuing controversies over OTC drugs such as sunscreens containing nanoparticles illustrate that FDA may need to issue guidance or, according to some commenters, exercise its regulatory authority to assure consumers of the safety of nanotechnology-based products.[97]

FDA's regulatory framework will continue to shift as it seeks to find a balance between assuring safety and effectiveness of nanomedicines with the need for medical innovation, which nanotechnology promises to accelerate in helpful and even life-saving ways.

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[95] *See* FDA, *Critical Path Initiative 2010 Update: Q's and A's*, http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm204289.htm (last updated Apr. 2011).

[96] *See* FDA, *Critical Path Initiative Spotlight on CPI Projects, Did You Know? Nanotechnology*, http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/spotlightoncpiprojects/ucm083244.htm (last updated June 2009).

[97] It should be noted, however, that in July 2008, when FDA's Center for Drug Evaluation and Research (CDER) convened its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, the committee split 50/50 (with one vote abstaining) when asked whether CDER guidance is needed for the development of nanotechnology-derived drug application. *See* FDA, Summary Minutes of the Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (July 22, 2008).

CHAPTER 8: MEDICAL DEVICES*

I. INTRODUCTION

A number of medical devices currently on the market use nanomaterials. Commentators, as well as the Food and Drug Administration (FDA), expect the number of medical devices using nanomaterials to increase dramatically.[1] As a result of these technological developments, individuals inside and outside FDA have considered the challenges of regulating the application of nanotechnology to medical devices.[2] This chapter examines FDA's existing authority to regulate medical devices, the ways that FDA can use its existing authority to regulate medical devices which use nanotechnology, and debates over whether FDA's existing authority is adequate to regulate nanotechnology-based medical devices.

II. REGULATION OF MEDICAL DEVICES GENERALLY

A. *PRE-MARKET AUTHORITY*

1. *DEFINITION*

Medical devices are regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended.[3] A medical device is an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory" which has at least one of the following three characteristics: (1) it is recognized in the official National Formulary or the United States Pharmacopeia; or (2) it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or (3) it is intended to affect the structure or function of the body but "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and . . . is not dependent upon being metabolized for the achievement of its primary intended purposes."[4]

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* This chapter was prepared by Judi Abbott Curry and Stanley Goos, Harris Beach PLLC, with assistance from Kathleen Knight, now with Pediatrics Medical Group, Inc., and B.J. Demery, now with Bell Helicopter Textron Inc.

[1] *See, e.g.*, Jordan Paradise et al., *Exploring Emerging Nanobiotechnology Drugs and Medical Devices*, 63 FOOD DRUG L.J. 407, 408-410 (2008); *see also* FDA Center for Devices and Radiological Health, Office of Science and Engineering Laboratories, *Toxicology*, *in* FY 2008 OSEL DIVISION DESCRIPTIONS (2009), *available at* http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm164262.htm#_Toc231210940 (stating that a primary focus of the division's work since 2006 has been to evaluate the bioeffects of nanoparticles, and outlining evaluations that have been conducted to date).

[2] *See, e.g.*, FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE (2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter "FDA NANOTECHNOLOGY TASK FORCE REPORT"].

[3] 21 U.S.C. §§ 301-399d. Amendments to the FFDCA which pertain to medical devices include the Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976); the Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511 (1990); the Medical Device Amendments of 1992, Pub. L. No. 102-300, 106 Stat. 238 (1992); the Medical Device User Fee & Modernization Act of 2002, Pub. L. No. 107-250, 116 Stat. 1588 (2002); and the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007), which included the Medical Device User Fee Amendments of 2007.

[4] FFDCA § 201(h), 21 U.S.C. § 321(h). *See* FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: INTERPRETATION OF THE TERM "CHEMICAL ACTION" IN THE DEFINITION OF DEVICE UNDER SECTION 201(H) OF THE

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2. *CLASSIFICATION*

Under FFDCA Section 513, medical devices are divided into three classes: Class I, Class II, and Class III.[5] A medical device is regulated based in part on its classification.

A Class I medical device is defined as a "device for which the controls authorized by or under section 501, 502, 510, 516, 518, 519, or 520 or any combination of such sections are sufficient to provide reasonable assurance of the safety and effectiveness of the device."[6] The specified general controls to which a Class I medical device is subject include a prohibition on adulterated devices; labeling and packaging requirements; a requirement to register as a manufacturer of a medical device; FDA's authority to ban devices if they present substantial deception or a substantial and unreasonable risk of illness or injury; FDA's authority to order a manufacturer to repair, replace, recall, or refund the purchase price of a device; adverse event reporting requirements for device manufacturers and device user facilities; good manufacturing practice requirements; and FDA's authority to restrict the sale, distribution, or use of a device if FDA finds that such restriction is necessary for the safe and effective use of the device. Alternatively, a device is classified as a Class I medical device even if there is inadequate information to establish that the above-mentioned general controls are sufficient to provide reasonable assurance of safety or effectiveness, as long as either of the following is true: the device is not represented for use in supporting or sustaining human life, or for a use which is substantially important in preventing impairment of human health;[7] or the device "does not present a potential unreasonable risk of illness or injury."[8]

A Class II medical device is defined as a device for which the general controls applicable to Class I devices are "insufficient to provide reasonable assurance of the safety and effectiveness of the device," but there is sufficient information to establish that special controls provide reasonable assurance of the safety and effectiveness of the device.[9] Special controls include "the promulgation of performance standards, post-market surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in pre-market notification submissions in accordance with [FFDCA] Section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance."[10]

A device is classified as a Class III device if two conditions are met. First, there is insufficient information to establish that either general controls or special controls "provide reasonable assurance of the safety and effectiveness of the device."[11] Second, the device is

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FEDERAL FOOD, DRUG, AND COSMETIC ACT (June 2011), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM259068.pdf.

[5] FFDCA § 513(a)(1), 21 U.S.C. § 360c(a)(1).
[6] FFDCA § 513(a)(1)(A)(i), 21 U.S.C. § 360c(a)(1)(A)(i).
[7] FFDCA § 513(a)(1)(A)(ii)(I), 21 U.S.C. § 360c(a)(1)(A)(ii)(I).
[8] FFDCA § 513(a)(1)(A)(ii)(II), 21 U.S.C. § 360c(a)(1)(A)(ii)(II).
[9] FFDCA § 513(a)(1)(B), 21 U.S.C. § 360c(a)(1)(B).
[10] *Id.*
[11] FFDCA § 513(a)(1)(C)(i), 21 U.S.C. § 360c(a)(1)(C)(i) .

either "purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," or "presents a potential unreasonable risk of illness or injury."[12]

If a device was not introduced into commerce prior to May 28, 1976, a device is automatically classified as a Class III device unless the device is "substantially equivalent" to a device that was either introduced into commerce before 1976 or is classified as a Class I or Class II device.[13] Additionally, a manufacturer can avoid having the device classified as a Class III device if the manufacturer submits a petition, and FDA responds to the petition and classifies the device as a Class I or II device.[14]

A device is defined by the FFDCA to be "substantially equivalent" to another device (the "predicate device") if the device has the same intended use as the predicate device, and FDA makes one of two sets of findings: either that the device has the same technological characteristics as the predicate device,[15] or that the device has different technological characteristics compared to the predicate device, and the information submitted demonstrates that the device is safe and effective and does not raise different questions of safety and effectiveness than were raised by the predicate device.[16] "Different technological characteristics" means that "there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device."[17]

3. *PRE-MARKET APPROVAL: CLASS III DEVICES*

The classification of a device determines which of two kinds of pre-market procedures applies to a device. A Class III device is subject to pre-market approval as specified in Section 515 of the FFDCA.[18] Under Section 515, an application for pre-market approval (or "PMA") of a Class III device must contain, among other things, information concerning whether the device is safe and effective, a "full statement of the components, ingredients, and properties and of the principle or principles of operation, of such device," and a "full description of the methods used in, and the facilities and controls" used for manufacturing the device.[19]

Upon reviewing an application for pre-market approval of a Class III device, FDA must approve the application if none of the specific grounds for denial of an application applies.[20] If FDA finds any of the following five elements, FDA must deny the application: "there is a lack of a showing of reasonable assurance that such device is safe" under the suggested conditions of use; "there is a lack of a showing of reasonable assurance that the device is effective" under the suggested conditions of use; methods used for the manufacture of the device violate the

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[12] FFDCA § 513(a)(1)(C)(ii)(I-II), 21 U.S.C. § 360c(a)(1)(C)(ii)(I-II).
[13] FFDCA § 513(f)(1)(A)(i), 21 U.S.C. § 360c(f)(1)(A)(i).
[14] FFDCA § 513(f)(1)(B), 21 U.S.C. § 360c(f)(1)(B).
[15] FFDCA § 513(i)(1)(A)(i), 21 U.S.C. § 360c(i)(1)(A)(i); *see also* 21 C.F.R. § 807.100(b).
[16] FFDCA § 513(i)(1)(A)(ii), 21 U.S.C. § 360c(i)(1)(A)(ii); *see also* 21 C.F.R. § 807.100(b).
[17] FFDCA § 513(i)(1)(B), 21 U.S.C. § 360c(i)(1)(B).
[18] FFDCA § 513(a)(1)(C), 21 U.S.C. § 360c(a)(1)(C).
[19] FFDCA § 515(c)(1)(A)-(C), 21 U.S.C. § 360e(c)(1)(A)-(C).
[20] FFDCA § 515(d)(1)(A)(i), 21 U.S.C. § 360e(d)(1)(A)(i).

regulatory good manufacturing practice requirements; the proposed labeling is false or misleading; or the device does not conform to a specified performance standard and deviation from the performance standard is not justified.[21]

4. *PRE-MARKET NOTIFICATION: MOST CLASS I AND II DEVICES*

Unlike Class III devices, Class I and Class II devices are not subject to pre-market approval. Instead, many Class I and Class II devices must comply with the pre-market notification requirements of Section 510(k) of the FFDCA. Ninety days prior to introducing a medical device into commerce, a manufacturer must submit a so-called Section 510(k) notification to FDA setting forth the classification of the device and the manufacturer's compliance with any applicable special controls or performance standards.[22]

The Section 510(k) notification requirement does not apply to Class I devices, other than those Class I devices that are "intended for a use which is of substantial importance in preventing impairment of human health" or that "present[] a potential unreasonable risk of illness or injury."[23] Furthermore, the Section 510(k) requirement does not apply to a Class II device which is of a type for which FDA has issued regulations exempting the type of device from Section 510(k) requirements.[24]

In addition, under the investigational device exemption, FDA may exempt a medical device from the PMA requirement and the Section 510(k) notification requirement in order to allow scientific experts to investigate the device's safety and effectiveness and encourage the discovery and development of new, useful devices.[25]

5. *OTHER PRE-MARKET AUTHORITIES*

Every owner or operator of an establishment engaged in manufacturing, preparing, propagating, compounding, or processing a medical device must register with FDA.[26] Each owner or operator who must register with FDA must also provide FDA with a list of all devices which the owner or operator introduces into commerce.[27]

The FFDCA also requires that labels for medical devices not be false and misleading, and that they list the name and place of business of the manufacturer, list accurately the quantity of the contents of the package, and state directions for use of the device.[28] Any device whose label or packaging does not meet these requirements is deemed misbranded.

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[21] FFDCA § 515(d)(2)(A)-(E), 21 U.S.C. § 360e(d)(2)(A)-(E).
[22] FFDCA § 510(k), 21 U.S.C. § 360(k).
[23] FFDCA § 510(l), 21 U.S.C. § 360(l).
[24] FFDCA § 510(m), 21 U.S.C. § 360(m). FDA's list of types of devices which are classified as Class I and Class II devices and which are exempt from Section 510(k) reporting is at 21 C.F.R. pts.8 62 through 892.
[25] FFDCA § 520(g), 21 U.S.C. § 360j(g). Implementing regulations are at 21 C.F.R. pt. 812.
[26] FFDCA § 510(b)(2), 21 U.S.C. § 360(b)(2).
[27] FFDCA § 510(j), 21 U.S.C. § 360(j).
[28] FFDCA § 502(a), (b), (f), 21 U.S.C. § 352(a), (b), (f). Implementing regulations are at 21 C.F.R. pt. 801.

B. *POST-MARKET AUTHORITY*

FDA has authority to regulate medical devices after they are introduced into commerce. FDA can ban a medical device if it finds that the device "presents substantial deception or an unreasonable and substantial risk of illness or injury."[29] If FDA determines that the deception or risk of illness or injury could have been corrected by proper labeling and FDA so notified the manufacturer, FDA must find that the labeling was not changed in the time allotted by FDA.[30] If FDA makes these required findings, it may issue regulations banning a medical device.[31] FDA also has the authority under Section 518(e) to recall medical devices. FDA must issue an order to halt distribution and use of a device if FDA finds that "there is a reasonable probability" that a device "would cause serious, adverse health consequences or death."[32]

The FFDCA directs FDA to issue regulations regarding reporting of adverse events attributable to the use of medical devices.[33] These regulations require a manufacturer or importer of a device to report to FDA when the manufacturer or importer learns either that the device may have caused or contributed to serious injury or death, or that the device has malfunctioned and a future malfunctioning would likely cause or contribute to serious injury or death.[34] Additionally, device user facilities (such as hospitals) must report to both FDA and the device manufacturer upon learning that a device may have caused or contributed to the death of a patient.[35] Upon learning that a device may have caused serious illness or serious injury, device user facilities must report such information to the device manufacturer, and, only if the device manufacturer's identity is unknown, report such information to FDA.[36] The FDA Modernization Act of 1997 required FDA to issue regulations limiting reporting to a "subset of user facilities that constitutes a representative profile of user reports,"[37] but FDA is continuing to conduct its MedSun system and Sentinel Initiative as pilot programs and has not issued regulations to move away from universal mandatory reporting.[38]

FDA has issued regulations which require manufacturers to comply with Quality Systems regulations (good manufacturing practices for medical devices).[39] Furthermore, every facility registered with FDA is subject to inspection.[40] For each facility which manufactures a Class II

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[29] FFDCA § 516(a)(1), 21 U.S.C. § 360f(a)(1).
[30] FFDCA § 516(a)(2), 21 U.S.C. § 360f(a)(2).
[31] FFDCA § 516(a), 21 U.S.C. § 360f(a).
[32] FFDCA § 518(e)(1), 21 U.S.C. § 360h(e)(1).
[33] FDA's regulations are at 21 C.F.R. pt. 803. FDA has proposed a rule that would amend the medical device post-market reporting regulations to require manufacturers, importers, and user facilities to submit mandatory reports of medical device adverse events to FDA in an electronic format, but has not finalized the rule. 74 Fed. Reg. 42,310 (Aug. 21, 2009).
[34] FFDCA § 519(a)(1)(A)-(B), 21 U.S.C. § 360i(a)(1)(A)-(B); *see also* 21 C.F.R. § 803.50.
[35] FFDCA § 519(b)(1)(A), 21 U.S.C. § 360i(b)(1)(A); *see also* 21 C.F.R. § 803.30.
[36] FFDCA § 519(b)(1)(B), 21 U.S.C. § 360i(b)(1)(B); *see also* 21 C.F.R. § 803.30.
[37] FFDCA § 519(b)(5), 21 U.S.C. § 360i(b)(5).
[38] *See MedSun: Medical Product Safety Network*, FDA, http://www.fda.gov/MedicalDevices/Safety/MedSunMedicalProductSafetyNetwork/default.htm; *FDA's Sentinel Initiative: Transforming How We Monitor Product Safety*, FDA, http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm.
[39] *See* 21 C.F.R. pt. 820. The authority for these regulations is found in FFDCA § 520(f), 21 U.S.C. § 360j(f).
[40] FFDCA § 510(h), 21 U.S.C. § 360(h).

or Class III device, FDA is required to conduct an inspection at least once in the first two years following registration of the facility, and at least once in every successive two-year period.[41]

III. NANOMATERIALS IN MEDICAL DEVICES

The medical device sector is one of the largest fields for nanotechnology advances. "Medical devices have particular potential to benefit from advances in nanotechnology as stronger and more highly functional materials become available for a range of implantable devices, prostheses and diagnostics."[42] One 2008 prediction forecast a 15-20% annual growth rate in the use of nanotechnology-based materials, tools, and devices over the next decade, with medical device technologies eventually accounting for perhaps one-fifth of the nanotechnology market.[43] FDA recognizes the role that nanotechnology will play in the field of medical devices. In early 2011, FDA's Center for Devices and Radiological Health (CDRH) unveiled a "Medical Device Innovation Initiative" that is intended to "support[] the development of innovative products by addressing some of the barriers that can impede a product's timely progress to market." The white paper that explains the initiative specifically mentioned nanotechnology as one of the areas where CDRH needs additional expertise to properly evaluate emerging medical device technologies.[44]

According to the Project on Emerging Nanotechnologies, medical devices on the market which claim to use nanotechnology include medical tools, bone replacement products, diagnostic tests, and imaging devices.[45] Applications include sending nanoscale iron oxide particles through biofilms (where regular drugs have failed before) where they can then kill bacteria within that layer but simultaneously limit damage to other healthy cells, thereby limiting potential side effects.[46] Scientists can also direct implants containing nanoscale sensors to specific locations within the body and use those sensors to gather biochemical information.[47] Carbon nanotubes can communicate cell and tissue conductivity information to an implant that is programmed to release a drug when those monitored conditions reach certain levels.[48]

A White House report noted that nanotechnology-enable advances in analysis of medical samples and imaging are "leading to medically-relevant data sets of unprecedented richness and

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[41] *Id.*
[42] MICHAEL R. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? 39 (Oct. 2006), *available at* http://nanotechproject.org/file_download/files/PEN5_FDA.pdf.
[43] *See* BCC RESEARCH, GROWING ROLE OF NANOTECHNOLOGY IN MEDICAL DEVICES (2008), http://bccresearch.wordpress.com/2008/08/13/growing-role-of-nanotechnology-in-medical-devices/.
[44] *See* FDA, *CDRH Medical Devices Innovation Initiative*, http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHInnovation/default.htm (Feb. 2011). The white paper is available at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHInnovation/default.htm.
[45] Project on Emerging Technologies, *Medicine Inventory - Current Medical Applications*, http://www.nanotechproject.org/inventories/medicine/apps/.
[46] Transcript, FDA Center for Devices and Radiological Health, Public Workshop on Medical Devices and Nanotechnology: Manufacturing, Characterization, and Biocompatibility Considerations 24-25 (Sept. 23, 2010), *available at* www.regulations.gov, under Docket No. FDA-2010-N-0427.
[47] *Id.* at 27.
[48] *Id.* at 27-28.

value."[49] It predicted that "[b]ecause FDA requirements for the approval of diagnostics are not as elaborate as for *in vivo* imaging agents or therapeutics, diagnosis and treatment monitoring are areas of nanomedicine that will most likely be the first to provide 'game-changing' technologies for managing human diseases."[50]

FDA held a public workshop on medical devices and nanotechnology in 2010. The notice calling for the meeting noted that "[t]he scientific hurdles (e.g., biocompatibility and toxicity) for the safe use of nanomaterials in medical devices, including the processes and standards for their manufacture and characterization, are not understood."[51]

IV. REGULATING NANOTECHNOLOGY-BASED MEDICAL DEVICES UNDER FDA'S EXISTING AUTHORITIES

A. *AUTHORITY TO REGULATE PRIOR TO MARKETING*

1. *CLASSIFICATION*

As discussed previously, a device which has not been on the market is presumed to be a Class III device unless it is "substantially equivalent" to a legally marketed Class I or Class II device, or FDA grants a petition requesting that the device be classified as a Class I or Class II device.[52] For a device that uses nanotechnology, does the presence of nanomaterials affect the determination of substantial equivalence? For example, should FDA consider a synthetic bone material utilizing nanomaterials to be "substantially equivalent" to a bone material that does not use nanomaterials?

A device is substantially equivalent if it has the same intended use as a predicate device, and either has the same technological characteristics, or does not raise different questions of safety and effectiveness.[53] One could argue that a medical device which uses nanotechnology has "different technological characteristics" than a medical device which does not use nanotechnology. Since "technological characteristics" is defined to include materials, one could argue that even a change from bulk to nanoscale form of the same substance is a change in material. Under this argument, a nanotechnology-based medical device could be substantially equivalent to a non-nanotechnology-based medical device only if the information submitted demonstrates that the device is safe and effective and does not raise different questions of safety and effectiveness than were raised by the predicate device.[54]

In response, one could first challenge whether a nanotechnology-based medical device will always have different technological characteristics than a medical device which does not use

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[49] PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, REPORT TO THE PRESIDENT AND CONGRESS ON THE THIRD ASSESSMENT OF THE NATIONAL NANOTECHNOLOGY INITIATIVE 52 (2010), *available at* http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-nano-report.pdf.
[50] *Id.*
[51] 75 Fed. Reg. 51,829 (Aug. 23, 2010).
[52] *See supra* notes 13-17 and accompanying text.
[53] FFDCA § 513(i)(1)(A), 21 U.S.C. § 360c(i)(1)(A).
[54] *See* FFDCA § 513(i)(1)(A)(ii), 21 U.S.C. § 360c(i)(1)(A)(ii).

nanotechnology. For example, if a medical device is changed such that it uses a nanoscale version of a bulk substance used in an approved device, one could argue that there is not a significant change in materials—since the same substance is being used, only at the nanoscale—and thus there is no difference in technological characteristics.

Even accepting that a nanotechnology-based device has different technological characteristics, medical device manufacturers could still support substantial equivalence by submitting information demonstrating the device's safety and effectiveness. The issue which is potentially more controversial is whether a nanotechnology-based device raises "different questions of safety and effectiveness than were raised by the predicate device." The phrase "different questions of safety and effectiveness" is not defined or clarified in the FFDCA, nor has FDA issued regulations interpreting this phrase. One could argue that, given the unique properties of substances at the nanoscale, *any* application of nanotechnology raises different issues of safety and effectiveness as compared to a device which does not use nanotechnology. Under this argument, a device using nanotechnology could be substantially equivalent only to another device which uses nanotechnology; otherwise, according to this argument, the device should not be deemed substantially equivalent to a non-nanotechnology-based device. In light of the potential uncertainty surrounding the debate, it may be helpful for FDA to issue guidance on the subject.

Another issue is when, if ever, use of nanomaterials in a device makes the device subject to the PMA process when the device, absent the nanomaterials, would not be subject to that process. The FDA Nanotechnology Task Force Report posed this question, stating that "[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."[55] A device is classified as a Class III device if general or special controls do not provide sufficient information to establish the safety and effectiveness of the device.[56] One could argue that since nanomaterials may have different toxicities and biological interactions than their non-nanoscale counterparts,[57] and given that there are large gaps in knowledge about the health effects of nanomaterials,[58] general and special controls (which do not require clinical studies[59]) cannot establish that the use of nanomaterials in medical devices is safe, and thus such devices must be classified under Class III. This argument appears to have little support at FDA, given that FDA has approved several medical devices which use nanomaterials without subjecting the devices to premanufacture approval.[60]

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[55] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 2, at 25.
[56] FFDCA § 513(a)(1)(C)(i), 21 U.S.C. § 360c(a)(1)(C)(i) .
[57] *See, e.g.*, FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 2, at 9-11.
[58] *See, e.g.*, *id.* at 13 (stating that "[s]everal 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.").
[59] *See supra* notes 6-10 and accompanying text.
[60] *See, e.g.*, FDA CDER, 510(k) Summary for Immunicon Corp. at 1 (Jan. 12, 2006), *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf6/K060110.pdf; FDA CDER, 510(k) Summary for Orthovita, Inc., *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf8/K083033.pdf. Note that while the 510(k) summary for Orthovita does not mention "nanotechnology" specifically, Orthovita states on its website that its Vitoss product family uses nanomaterials. *See Vitoss Bone Graft Substitute - Technical Specifications*, ORTHOVITA, http://www.orthovita.com/vitoss/technicalspecs.aspx.

2. *SECTION 510(K) PRE-MARKET NOTIFICATION*

The issue of the "substantial equivalence" of nanotechnology-based devices to non-nanotechnology-based predicate devices impacts not only the initial classification of a nanotechnology-based device, but also whether the device is subject to the Section 510(k) notification requirements. Section 510(k) of the FFDCA requires a manufacturer to notify FDA 90 days prior to introducing a new device into commerce.[61] However, most Class I devices and some Class II devices are exempt from the Section 510(k) reporting requirement.[62] FDA regulations specify the types of devices for which a Section 510(k) notification is not required.[63] However, the exemption does not apply if the new device "operates using a different fundamental scientific technology than a legally marketed device in that generic type of device."[64] FDA has provided the following examples of a different fundamental scientific technology: "a surgical instrument cuts tissue with a laser beam rather than with a sharpened metal blade, or an in vitro diagnostic device detects or identifies infectious agents by using deoxyribonucleic acid (DNA) probe or nucleic acid hybridization technology rather than culture or immunoassay technology."[65] This fundamental scientific technology limitation is included in the regulations for every device type which is exempt from Section 510(k) requirements.[66]

Thus, the issue arises as to whether the application of nanotechnology to a medical device causes a device that would otherwise be exempt from Section 510(k) notification to fall outside the exemption. FDA's Nanotechnology Task Force Report addressed this precise issue, and recommended that FDA issue guidance on 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)" due to the presence of nanoscale materials.[67] To date, FDA has not issued such guidance.

If a new medical device uses nanotechnology, and there are no devices in its device type which use nanotechnology, then one can argue that the device uses a different fundamental scientific technology than a legally marketed device in that device type. Under this argument, the new, nanotechnology-based device would *not* qualify for the exemption, and the manufacturer would have to submit a Section 510(k) notification. Such an analysis will, of course, be device-specific. There may be devices which use nanotechnology in such a way that the nanotechnology is not central to the operation of the device; perhaps then one could argue that the technological difference does not affect the operation of the device, and thus there is no "different fundamental scientific technology."

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[61] FFDCA § 510(k), 21 U.S.C. § 360(k).
[62] FFDCA § 510(l), (m), 21 U.S.C. § 360(l), (m).
[63] *See* 21 C.F.R. pts. 862 through 892. Note also that FDA has exempted certain clinical chemistry and clinical toxicology devices from the Section 501(k) notification requirement. *See* 21 C.F.R. pt. 862.
[64] 21 C.F.R. § 862.9(b).
[65] *Id.*
[66] See 21 C.F.R. §§ 864.9(b), 866.9(b), 868.9(b), 870.9(b), 872.9(b), 874.9(b), 876.9(b), 878.9(b), 880.9(b), 882.9(b), 884.9(b), 886.9(b), 888.9(b), 890.9(b), 892.9(b).
[67] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 2, at 33.

If a new device is not exempt, and the manufacturer must submit a Section 510(k) notification, then the manufacturer must demonstrate that the new device is substantially equivalent to a legally marketed device. If FDA does not agree with that "substantial equivalence" conclusion, the device manufacturer can either petition for FDA to classify the device as a Class I or II device, or go through the PMA process. Both classification by petition and the PMA process are more involved and time-consuming than the Section 510(k) process, and therefore device manufacturers have an interest in FDA concluding that a new device is substantially equivalent to a legally marketed device.

3. *Modification of an Already-Approved Device*

The application of nanotechnology to medical devices raises a related issue: if an already-approved device is changed to incorporate nanotechnology, does that change trigger any regulatory requirements? A "major" change in the intended use of a device requires the manufacturer to submit a new Section 510(k) notification.[68] Similarly, a "significant" change or modification that "could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process" also triggers the need for the manufacturer to submit a new Section 510(k) notification.[69] As with the issue of substantial equivalence, here one could argue that any application of nanotechnology in a medical device could significantly affect the safety or effectiveness of a device, given that substances can behave differently at the nanoscale. Furthermore, one could argue that taking a non-nanotechnology-based medical device and changing it to use nanotechnology constitutes a significant change in design, material, or manufacturing process, in which case changing an already-approved medical device to incorporate nanotechnology should trigger the requirement to submit a new Section 510(k) notification. FDA may not agree with these arguments, however.

FDA has issued guidance on when a modification to an approved device requires submission of a new Section 510(k) notification. The guidance document does not lay out a generally applicable rule. Instead, the guidance suggests that whether a new Section 510(k) notification must be submitted depends on several factors, including the kind of device (implant, non-implantable, etc.), the kind of change (change in materials, energy source, design, etc.), and the device component that is changed (e.g., whether the component comes into contact with human tissue or fluids).[70]

According to the guidance document, certain changes in materials or the formulation of materials require submission of a new Section 510(k) notification.[71] If there is a change in materials, or material formulation, or if the material would come into contact with human tissue or bodily fluid, the guidance states that manufacturers should submit a new Section 510(k)

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[68] 21 C.F.R. § 807.81(a)(3)(ii).
[69] 21 C.F.R. § 807.81(a)(3)(i).
[70] Guidance for Industry and FDA Staff - 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device (2011), *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265274.htm.
[71] *Id.* at 17-22.

notification.[72] Thus, a new Section 510(k) notification would also be necessary if a manufacturer sought to replace a material in an existing, implantable device with either a new nanomaterial or a nanoscale version of the material already used in the device, and the new material would contact human tissue or fluids.

FDA's Nanotechnology Task Force Report raised, but did not answer, this issue of when modification of an approved device to incorporate nanotechnology would require the manufacturer to submit a new Section 510(k) notification.[73] The Task Force Report recommended that FDA issue more specific guidance on when "[a] sponsor should submit a new [Section] 510(k) for a modification to a previously cleared device that incorporates the use or increased use of nanoscale materials."[74] Again, as of this writing, FDA has not issued such guidance.

4. *Examples of Section 510(k) Notifications for Nanotechnology-Based Devices*

Several companies have submitted Section 510(k) notifications to FDA for medical devices which reportedly use nanotechnology. Orthovita submitted a 510(k) notification for its Vitoss Bone Graft Substitute in early 2011, and Immunicon submitted a Section 510(k) notification for CellTracks Analyzer II, mentioned above [75] GfE Medizintechnik GmbH, a German corporation, also submitted a Section 510(k) notification for TiMESH.[76] Yet in all three cases, FDA classified the devices as Class II, determined that they were substantially equivalent to legally marketed devices, and cleared the products for introduction into commerce. In the Section 510(k) decision documents, it is unclear whether FDA examined any information on nanomaterials that may be in the device prior to responding to the submission.

B. *Authority to Regulate After Marketing*

Applying the post-marketing regulations of medical devices to nanotechnology-based devices does not raise any significant new legal issues, although it may raise scientific issues for FDA. For example, FDA may have to acquire new expertise in nanotechnology in order to adapt good manufacturing practices to the manufacture of nanomaterials, but the authority for FDA to set GMPs applies to manufacture of nanomaterials for medical devices. Nanotechnology also appears to raise no significant legal issues with respect to adverse event reporting, good manufacturing practices, inspections, or FDA's authority to ban or recall devices.

V. Regulation of Medical Devices in the European Union

The European Union (EU) experience regulating nanotechnology in medical devices provides useful insight, particularly since the market for such devices is often global. The EU

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[72] *Id.*
[73] FDA Nanotechnology Task Force Report, *supra* note 2, at 24.
[74] *Id.* at 33.
[75] *See supra* note 60 and accompanying text.
[76] FDA CDER, 510(k) Summary for GfE Medizintechnik GmbH (Sep. 29, 2003), *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf3/K031225.pdf.

regulates medical devices through three directives, which regulate medical devices generally,[77] *in vitro* diagnostic medical devices,[78] and active implantable medical devices.[79] There are no EU laws specific to nanotechnology-based medical devices.

The European Commission has asked for several opinions on whether existing regulations are adequate to deal with nanotechnology-based products, including medical devices. The European Group on Ethics in Sciences and New Technologies did not recommend new, broad regulatory structures, but instead stated that the focus should be on implementing existing regulations.[80] Similarly, the report of the Working Group on New and Emerging Technologies in Medical Devices concluded that existing legislation is adequate to deal with nanotechnology-based medical devices.[81] This report included one notable proposal for regulating nanomaterials in medical devices. The report recommended that the European Commission adopt a rule that "[a]ll devices incorporating or consisting of particles, components or devices at the nanoscale are in Class III unless they are encapsulated or bound in such a manner that they cannot be released to the patient's organs, tissues, cells or molecules."[82] To date, the European Commission has not issued such a rule.

The European Commission concluded in 2008 that in general, existing products legislation addresses adequately the risks of nanotechnology in various product categories, including medical devices.[83] However, for medical devices, the Commission stated that it "will examine the possibility to make the placing on the market of devices presenting risks associated with nanomaterials subject to a systematic pre-market intervention."[84]

VI. PROPOSALS TO EXPAND FDA AUTHORITY OVER MEDICAL DEVICES

Many pharmaceutical and device manufacturers believe that FDA's current regulatory framework is "sufficiently comprehensive to accommodate nanoscale materials," including those in medical devices, because the devices are "subject to extensive pre-market studies to characterize safety, effectiveness and quality, to regulatory approval for commercialization, and

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[77] Council Directive 93/42/EEC, 1993 O.J. (L 042) 1, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF.
[78] Council Directive 98/79/EC, 1998 O.J. (L 079) 1, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20090807:en:PDF.
[79] Council Directive 90/385/EEC, 1990 O.J. (L 385) 1, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1990L0385:20071011:en:PDF.
[80] THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES TO THE EUROPEAN COMMISSION, OP. NO. 21, OPINION ON THE ETHICAL ASPECTS OF NANOMEDICINE 57 (Jan. 17, 2007), *available at* http://ec.europa.eu/european_group_ethics/activities/docs/opinion_21_nano_en.pdf.
[81] WORKING GROUP ON NEW AND EMERGING TECHNOLOGIES IN MEDICAL DEVICES, REPORT ON NANOTECHNOLOGY TO THE MEDICAL DEVICES EXPERT GROUP, FINDINGS AND RECOMMENDATIONS 5, 9 (July 2007), *available at* http://ec.europa.eu/enterprise/newsroom/cf/_getdocument.cfm?doc_id=4865.
[82] *Id.* at 10.
[83] EUROPEAN COMMISSION, COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE, REGULATORY ASPECTS OF NANOMATERIALS 11 (June 17, 2008), *available at* http://ec.europa.eu/nanotechnology/pdf/comm_2008_0366_en.pdf.
[84] *Id.* at 6.

to thorough ongoing testing and post-approval pharmacovigilance activities."[85] The FDA Nanotechnology Task Force similarly stated that "the agency's authority is comprehensive with regard to products subject to premarket authorization . . . ."[86] While there are currently no significant legislative or other proposals for amending the FFDCA to provide FDA with greater authority to regulate nanotechnology-based medical devices, there is concern about nanotechnology's effects at large. In 2010, legislation was introduced to call for further study by FDA. Citing FDA's need for "tools and resources to assure the public that nanotechnology-based medical and health products are safe and effective," and the need for "a robust scientific framework" to understand what nanotechnology data to collect and examine, the bill sought to amend the FFDCA to establish "a program for the scientific investigation of nanoscale materials included or intended for inclusion in FDA-regulated products, to address the potential toxicology of such materials, the effects of such materials on biological systems, and interaction of such materials with biological systems."[87] The bill, however, did not pass. Nevertheless, FDA is conducting nanotechnology research.[88]

[85] Comments from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer and Roche, on FDA Docket No. 2008-N-0416, Consideration of FDA-Regulated Products that May Contain Nanoscale Materials (Feb. 10, 2009), *available at* http://www.regulations.gov.

[86] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 2, at 30.

[87] Nanotechnology Safety Act of 2010, S. 2942, 111th Cong. (2010); *see also* 156 CONG. REC. S 123 (Jan. 21, 2010) (statement of Sen. Pryor).

[88] *See, e.g.*, FDA, *Nanotechnology Research at NTCR*, http://www.fda.gov/AboutFDA/CentersOffices/NCTR/WhatWeDo/NCTRResearchPriorities/ucm083162.htm; *FDA Regulatory Science Research*, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm196697.htm.

CHAPTER 9: BIOLOGICAL PRODUCTS*

I. INTRODUCTION

The category of biological products, or "biologics," regulated by the Food and Drug Administration (FDA), comprises a complex and diverse array of mostly biologically-derived tissues and materials, almost all of which also qualify as drugs. Many of these various biologics are being or will be impacted by the innovations of nanotechnology, which offers the potential both for great advances in health care and for unknown risks. FDA and other commenters have analyzed the degree to which FDA's current regulatory practices and procedures can adequately manage the novel issues and risks associated with nanotechnology-based biologics. Overall, while the regulatory scheme for biologics is somewhat complex, FDA has a large amount of both pre-market approval and post-approval oversight authority to assure the safety of nanotechnology-based biologics.

II. FDA REGULATION OF BIOLOGICS

FDA regulates biologics under two statutes: the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended,[1] and the Public Health Service Act (PHSA), as amended.[2] Processes under these two statutes have generally converged over the past century,[3] but there are still some ways in which the distinct statutory framework for biologics remains important.

The PHSA, originally enacted in 1944 and substantially amended since then, defines a "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[4] Determining whether a particular product should be regulated as a biologic can be quite difficult on a case-by-case basis.[5]

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[1] 21 U.S.C. §§ 301-399d.

[2] 42 U.S.C. §§ 201-300jj-38 (the provisions for biological products are under sections 262, 262a, and 263). Biological products intended for veterinary use are regulated under a separate law, the Virus-Serum-Toxin Act, 21 U.S.C. §§ 151-159, which is administered by the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture.

[3] *See* David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 145-185 (2005) (providing historical and theoretical overview of the regulation of drugs and biologics in the context of recombinant DNA technology).

[4] PHSA § 351(i), 42 U.S.C. § 262(i).

[5] *See* Dudzinski, *supra* note 3, at 180-181; Edward R. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 Food Drug L.J. 257, 276-95, 282 (2007) ("[A] maze exists today in classifying and regulating human drug products as biologics."); Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 82-83 (2007). *See also* Chapter 10 – Combination Products.

The core requirement of the PHSA is an effective biologics license for each new biological product. To obtain a biologics license, a manufacturer must submit for approval a biologics license application (BLA) to the Center for Biologics Evaluation and Research (CBER) or to the Center for Drug Evaluation and Research (CDER), depending on the subcategory of biologic.[6] The BLA must demonstrate to the Center's satisfaction that the biological product is "safe, pure, and potent," and that the manufacturing, processing, packing, and holding facilities meet applicable standards.[7]

Because the FFDCA defines "drugs" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" or "articles (other than food) intended to affect the structure or any function of the body of man or other animals,"[8] biologics are also included under the definition of "drugs." Under the PHSA, "[t]he Federal Food, Drug, and Cosmetic Act . . . applies to a biological product subject to regulation under this section, except that a product for which a license has been approved . . . shall not be required to have an approved application under section 505 of such Act."[9] In other words, a biologic that has obtained a biologic license does not need to also submit a new drug application (NDA), but all of the other requirements applicable to drugs also apply to biologics.[10]

Despite being a main point of difference between biologics and other drugs, the BLA and NDA processes are quite similar, especially after Congress in 1997 directed them to be harmonized as much as possible.[11] One important similarity is the convergence of the safety standards for biologics and drugs. "Although licensed under the [PHSA] upon proof of safety, purity, and potency, biologics have been subject to the [FFDCA] requirements of safety and effectiveness for so long that it has been said that the standards for biologics are 'similar, if not identical' to drugs; namely, biologics must be 'safe, pure, potent, and effective.'"[12] Moreover, most BLAs are reviewed by CDER.[13] Additionally, the Biologics Price Competition and Innovation Act of 2009 (BPCI) established an abbreviated approval pathway for biological products that are demonstrated to be "highly similar" (biosimilar) to, or "interchangeable" with, an FDA-licensed biological product, which is similar to the one available for drugs.[14] However, one point of difference is that "BLAs must meet additional requirements concerning manufacturing plant inspection and must demonstrate product stability," while "NDA applicants

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[6] *See* Dinh, *supra* note 5, at 82-83 (describing 2002 reassignment of FDA Centers' review responsibilities); Judy Ciaraldi et al., The Regulation of Biological Products (2008), *available at* http://www.docstoc.com/docs/542532/The-Regulation-of-Biological-Products.
[7] PHSA § 351(a)(1)(A), (a)(2)(C), 42 U.S.C. § 262(a)(1)(A), (a)(2)(C).
[8] FFDCA § 201(g), 21 U.S.C. § 321(g).
[9] PHSA § 351(j), 42 U.S.C. § 262(j).
[10] *See* Chapter 7 – Drugs.
[11] Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, 12 (2006)
[12] Dudzinski, *supra* note 3, at 184 (citations omitted).
[13] Drug and Biological Product Consolidation, 68 Fed. Reg. 38,067, 38,068 (June 26, 2003).
[14] The Biologics Price Competition and Innovation Act of 2009 is found in Sections 7001-7003 of the Patient Protection and Affordable Care Act, Pub. L. 111-148, 124 Stat. 119 (2009). It amends Sections 351 and 409I(a)(1) of the PHSA, 42 U.S.C. §§ 262, 284m, and Sections 505(b)(5)(B), 505(A)(p), 505(B), and 735(1)(B) of the FFDCA, 21 U.S.C. §§ 355(b)(5)(B), 355b(p), 355c, 379g(1)(B).

are required to submit patent information and a statement of the full composition of the drug, requirements that BLA applicants are not subject to."[15]

The post-approval requirements for biologics also generally mirror those for other drugs. The biological product laws and regulations under the PHSA and FFDCA provide more detailed requirements for advertising and labeling, good manufacturing practice and facility condition standards, and concurrent recordkeeping, adverse event reporting, and product recall authority.[16] These requirements are discussed in greater detail below in their potential application to nanotechnology-based biologics.

III. NANOTECHNOLOGY-BASED BIOLOGICS

While some envision a deeply transformative fusion of biology and nanotechnology within our lifetimes,[17] currently there are only a few licensed nanotechnology-based biological products. This is partly due to the fact that most biologics are proteins, which are already in the 1-10 nanometer range.[18] These proteins are already fairly efficiently produced through recombinant DNA technology—technology which will likely remain more cost-efficient for protein synthesis than nanotechnology well into the future.[19] Thus, nanotechnology has a slightly reduced range of opportunities to add value to biologics via either novel product sizes or novel production processes than in other FDA-regulated product categories. Another reason stems from the regulatory definition of biologics, which, as noted above, includes viruses, serums, toxins, antitoxins, vaccines, blood components or derivatives, allergenic products, or analogous products.[20] Within these categories, FDA tends to classify materials that are produced synthetically as drugs rather than as biologics.[21] More generally, it is often difficult to classify biologic versus non-biologic drug products, but manufacturers of nanotechnology-based products that could be interpreted as either may have incentives to submit NDAs rather than BLAs (for reasons that have little to do with stringency of FDA oversight, as that is similar for drugs and biologics).[22]

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[15] Mandel, *supra* note 11, at 12-13.
[16] 21 C.F.R. pts. 600-680.
[17] *See, e.g.*, A.L. Jones, *Rupturing the Nanotech Rapture*, IEEE SPECTRUM (2008), http://www.spectrum.ieee.org/jun08/6271 (describing gulf between those who anticipate a nanotechnology-based "singularity" and current realities of nanotechnology).
[18] Harold P. Erickson, *Size and Shape of Protein Molecules at the Nanometer Level Determined by Sedimentation, Gel Filtration, and Electron Microscopy* 2-4, Biological Procs. Online (2009), *available at* http://www.cellbio.duke.edu/faculty/Erickson/pdf's/Protein hydrodn EM.pdf.
[19] *See* Jones, *supra* note 17.
[20] PHSA § 351(i), 42 U.S.C. § 262(i).
[21] *See* Korwek, *supra* note 5, at 280 (" [P]roducts that are chemically synthesized or synthetic . . . excluding vaccines and allergenics . . . are regulated as non-biological drugs, even when, for example, they are analogues of cytokines, thrombolytics, or other biologics.") (citing *Jurisdictional Update: Intercenter Agreements*, FDA, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm106506.htm (2006)).
[22] *See* Dinh, *supra* note 5, at 63 ("A pioneer probably would rather have its biologic 'drug' be approved under the FDCA than the PHSA because while it may qualify for a patent term extension via either route, only the FDCA offers non-patent-based marketing exclusivities like the three-year new clinical study exclusivity and the five-year new molecular entity exclusivity.").

These factors, along with the regulation of biologics as drugs, have meant that nanotechnology-based biologics have received less commentary from public health or environmental advocates than other nanotechnology-based products. One prominent and otherwise thorough review of FDA regulation of nanotechnology ignored the category altogether.[23]

Nevertheless, abundant potential and actual applications of nanotechnology to biologics do exist and could offer significant opportunities for improvements in health care. Numerous vaccines have been packaged in nanoscale delivery devices made of lipids or other materials, and these novel delivery technologies can enable the development of entirely new vaccines for diseases such as HIV, malaria, or even cancer.[24] Nanotechnology has also enabled synthetic vaccines, "functionalized with the surface proteins of a virus" in order to stimulate the appropriate immune response.[25] Moreover, some nanotechnology developments, such as nano-scaffolding for regenerated tissues[26] or self-assembling nanotechnology sacs for the culture and targeted delivery of stem cells,[27] may stretch the capacity of FDA's rigid categorization of products as biologics, drugs, or devices.

At the more speculative end, if biomimetic, or nature-imitating, applications of nanotechnology progress greatly, the resulting products could become more analogous to biologically-produced materials such as tissues, and could therefore fall more clearly into the "biologics" category. In this field, scientists have been researching nanotechnology-based replication of different kinds of biological materials, like the keratin hairs that allow geckos to cling to smooth surfaces, or, conversely, biological production of nanomaterials, such as nanowires or quantum dots made with viruses.[28]

FDA is dealing with at least one nanotechnology-utilizing biologic through the BLA process. The manufacturer of Cinryze, a "nanofiltered plasma-derived C1 inhibitor product that has been approved by FDA for routine prophylaxis against angioedema [a kind of severe inflammation] attacks in adolescent and adult patients," submitted a supplemental BLA in 2008,

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[23] *See* MICHAEL R. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? (Oct. 2006), *available at* http://nanotechproject.org/file_download/files/PEN5_FDA.pdf (discussing all other categories in this book).

[24] *See, e.g.*, L.J. Peek, C.R. Middaugh, & C. Berkland, *Nanotechnology in Vaccine Delivery*, 60 ADV. DRUG DELIVERY REV. 915-28 (2008), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/18325628.

[25] Jordan Paradise, Gail Mattey DiLiberto, Alison W. Tisdale & Efronsini Kokkoli, *Exploring Emerging Nanobiotechnology Drugs and Medical Devices*, 63 FOOD & DRUG L.J. 407, 414 (2008) (citing Anke Huckriede et al., *The Virosome Concept for Influenza Vaccines*, 23 VACCINE S26 (2005)).

[26] *See e.g.*, Lay Leng Tan, *Biotechnology Brings Hope to Tissue Regeneration: Applying Synthetic Molecules in Regenerative Medicine May Translate to the Repair of Spinal-Cord Injury, Bone, and Heart Tissue*, 5 INNOVATION 2, *available at* http://www.innovationmagazine.com/innovation/volumes/v5n2/coverstory3.shtml; Hemalatha Raju & Jeffrey L. Goldberg, *Nanotechnology for Ocular Therapeutics and Tissue Repair*, 3 EXPERT REV. OF OPHTHALMOLOGY 4: 431-36 (Aug. 2008), *abstract available at* http://www.ingentaconnect.com/content/ftd/eop/2008/00000003/00000004/art00010.

[27] Megan Fellman, *Self-Assembled Materials Form Mini Stem Cell Lab*, STUPP LABORATORY NEWS (2008), http://stupp.northwestern.edu/news/index.html.

[28] *See* Eric J. Lerner, *Biomimetic Nanotechnology: Researchers Mimic Biology To Form Nanoscale Devices*, THE INDUS. PHYSICIST 16-19 (2004), *available at* http://www.aip.org/tip/INPHFA/vol-10/iss-4/p16.pdf.

and received a response from FDA requesting an additional clinical study on effectiveness in 2009.[29]

IV. PRE-MARKET REGULATION OF NANOTECHNOLOGY-BASED BIOLOGICS

A. *BIOLOGICS LICENSE APPLICATIONS FOR NANOTECHNOLOGY-BASED BIOLOGICS*

New nanotechnology-based biologics are subject to essentially the same pre-market testing and approval requirements as those for nanotechnology-based drugs. These requirements involve sequential phases of animal and clinical testing, information submission, and FDA analysis and follow-up.

Because biologics are also drugs, sponsors of biologics are required to submit Investigational New Drug applications (INDs) to FDA prior to conducting each phase of human clinical studies, well before the BLA phase.[30] INDs require submission of detailed information on the biologic (including toxicology) and on the planned studies.[31] The amount of information on a particular drug that must be submitted in an IND to assure safety depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.[32] If FDA determines that other information, such as particle size information, is relevant to evaluation, the sponsor must supply it at FDA's request.[33] Thus, FDA has wide latitude to require information on any nanotechnology-specific risks fairly early in the development of the biologic product. Even prior to clinical testing, FDA has some capacity to obtain information on nanotechnology-based products in the pipeline, according to one commenter:

> Despite the lack of a specific legal tool for accessing information on new technologies and products under development . . . companies facing [drug or biologic approval requirements] have a significant incentive to provide FDA with the information the agency needs to understand and efficiently review new products especially when novel technologies are involved.[34]

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[29] Press Release, ViroPharma Inc., ViroPharma Submits Supplemental Biologics License Application For Cinryze™ To Treat Acute Attacks Of Hereditary Angioedema (Dec. 2, 2008), *available at* http://www.medicalnewstoday.com/articles/131376.php. FDA's response to the SBLA requested an additional clinical study on effectiveness, but did not cite any safety concerns. Press Release, ViroPharma Inc., ViroPharma Receives Complete Response Letter for Cinryze™ Supplemental Biologics License Application for Acute Treatment of Hereditary Angioedema (June 4, 2009), *available at* http://www.drugs.com/nda/viropharma-receives-complete-response-letter-cinryze-supplemental-biologics-license-application-2138.html.

[30] 21 C.F.R. pt. 312; FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 22 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter "FDA NANOTECHNOLOGY TASK FORCE REPORT"].

[31] 21 C.F.R. § 312.23.

[32] *Id.* § 312.22(b).

[33] *Id.* § 312.23(a)(11); FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 30, at 22.

[34] TAYLOR, *supra* note 23, at 44.

The existence of INDs for particular biologics is deemed confidential.[35]

After completing clinical trials, the sponsor of a biologic can submit a BLA including the clinical trial data and other information. Once again, the data requirements are substantial, and FDA can call for additional data wherever relevant to its determination of safety, purity, potency, and effectiveness.[36] While under the statutory scheme biologics lack the requirement of "a statement of the full composition" that applies to drugs[37] (since some biologics like human tissues are impossible to so fully characterize), given the volume of data required to be submitted in INDs and BLAs and the authority of FDA to require additional information as needed, it may be unlikely that the presence of nanomaterials in a biologic would be able to slip under the radar in the review and approval process.

BLA files are fully confidential prior to approval, except that if the existence of a BLA has been disclosed, FDA has discretion to disclose "a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue."[38] After approval, however, information, including ingredients and safety information, is broadly available. Only "(1) [m]anufacturing methods or processes, including quality control procedures, (2) [p]roduction, sales, distribution, and similar data and information, . . . [or] (3) [q]uantitative or semi-quantitative formulas" remain confidential.[39] It is unclear whether these confidentiality provisions on manufacturing processes or formulas could shield nanotechnology-related information from the public.

As with drugs, there is a regulatory process for accelerated approval of biologics "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses"; applicants can use surrogate clinical endpoints in their efficacy studies.[40] Even in this "life-threatening illnesses" pathway, though, FDA has broad authority to restrict a drug for safety reasons and to require additional studies.[41]

B. *Safety, Purity, Potency, and Efficacy Under the FFDCA and PHSA*

Based on the information submitted in a BLA, FDA and its advisory review panels[42] must determine whether a nanotechnology-based biologic meets the safety standards for both biologics, under the PHSA, and drugs, under the FFDCA. As noted above, these standards are essentially the same.[43] "Safety" is most likely the parameter of highest concern for stakeholders

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[35] 21 C.F.R. § 601.50.
[36] *Id.* §§ 601.2, 601.3, 601.20, 601.25; FDA Nanotechnology Task Force Report, *supra* note 30, at 22. Like other applications to FDA, the data requirements also include submission of either an environmental assessment under 21 C.F.R. § 25.40, or a claim for categorical exclusion under 21 C.F.R. §§ 25.30 or 25.31. 21 C.F.R. § 601.2.
[37] FFDCA § 505(b)(1)(C), 21 U.S.C. § 355(b)(1)(C).
[38] 21 C.F.R. § 601.51(d)(1).
[39] 21 C.F.R. § 601.51(e)-(f).
[40] 21 C.F.R. §§ 601.40, 601.41.
[41] 21 C.F.R. § 601.42.
[42] *See* 21 C.F.R. § 601.25(a), (c).
[43] *Supra* notes 11-12 and accompanying text.

concerned about the ability of FDA to regulate nanotechnology-based products effectively. The biologics regulations define "safety" as:

> the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.[44]

This standard is somewhat similar to the "reasonable certainty of no harm" standard sometimes advocated for products using nanotechnology.[45] The advisory panels are also directed to consider the "benefit-to-risk ratio of a biological product" when determining safety and effectiveness.[46]

The procedures for determining that a biologic is "safe and effective" under the FFDCA and that it is "safe, pure, and potent" under the PHSA both require "controlled clinical investigations" and other scientific trials.[47] Conceivably, some of the protocols for pre-clinical or clinical testing and analysis could require modification in light of new issues raised by nanotechnology. To the extent that the safety and efficacy analyses rely on mass-dose bases, for example, procedures may have to be altered to account for the higher active surface area of most nanomaterials per given mass.[48] FDA has noted that it can issue guidance to NDA and BLA applicants recommending particular kinds of data for a class of drugs or biologics.[49]

C. *Application of Existing Biologics Regulations to Nanotechnology-Based Versions of Approved Biologics*

A significant question of concern is whether and when a nanotechnology-based version of an existing product would qualify as "new" and thus subject to greater FDA oversight. This situation could arise if either a company added new nanotechnology-based elements to another manufacturer's licensed biologic, or if the original manufacturer of a biologic modified its manufacturing process to incorporate nanotechnology.

The Biologics Price Competition and Innovation Act of 2009, discussed previously, provides an abbreviated approval pathway for biologics that are determined to be a "biosimilar"

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[44] 21 C.F.R. § 601.25(d)(1).
[45] *See, e.g.*, FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 30, at 31 (discussing comments on safety standards for regulated products).
[46] 21 C.F.R. § 601.25(d)(3).
[47] *Compare* 21 C.F.R. § 314.125(b)(6) (drugs) *with* 21 C.F.R. § 601.25(d)(2) (biologics) (both referencing "controlled clinical investigations," which are described in 21 C.F.R. § 314.126). *See also The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 5 (2004) (statement of Lester M. Crawford, Acting Commissioner of FDA) ("[NDAs and BLAs] require submission of complete reports of clinical and animal data to support approval.").
[48] *See* TAYLOR, *supra* note 23, at 17.
[49] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 30, at 22.

or "interchangeable" compared to a reference product.[50] To be declared "biosimilar," a product must present, among other things, analytical studies showing that it is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[51] An "interchangeable" product must be shown to be biosimilar, is "expected to produce the same clinical result as the reference product in any given patient," and (for biologics administered more than once to an individual) the safety and efficacy risks from switching to the new product must not be greater than the risk of using the reference product.[52] Given the generally unknown behaviors and characteristics of nanoparticles, and given that the purpose behind using nanoparticles in biologics is to achieve effects previously not seen in reference products, it is not clear that nanotechnology-modified biologics would qualify under either standard, and therefore may be ineligible for the abbreviated application process.

In other words, if a biologics manufacturer should change its own processes or qualitative formulation to incorporate nanotechnology, FDA could deem the changes to be major, meaning that the manufacturer would probably have to notify and obtain approval from FDA prior to distributing any product manufactured with the new process or ingredient.[53] "Depending on the change, the resulting product might be considered a new product for which a new approval is needed."[54] Even if the nanotechnology-modified product were not considered new, the manufacturer would still be required to "assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product."[55]

V. POST-APPROVAL OVERSIGHT OF NANOTECHNOLOGY-BASED BIOLOGICS

A. *POST-APPROVAL STUDY REQUIREMENTS*

As with other drugs, FDA can require post-approval study, including Phase IV clinical trials, of biologics in many circumstances. FDA can and often does condition license approval on biologic manufacturers' agreements to conduct post-approval monitoring and data submission, based on both the FFDCA and PHSA.[56] FDA appears to have wide latitude in

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[50] *See supra* note 14 and accompanying text.
[51] BPCI Act of 2009, § 7002(b)(3), 42 U.S.C. § 262(i).
[52] BPCI Act of 2009, § 7002(a)(2), 42 U.S.C. § 262(k)(4).
[53] *See* 21 C.F.R. § 601.12. The requirements apply to "any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product," including changes in the formulation.
[54] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 30, at 23.
[55] 21 C.F.R. § 601.12(a)(2).
[56] *See* Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 343-45, 355 (2006) (discussing, and criticizing, FDA interpretation of FFDCA § 505(j) "records and reports" authority and PHSA § 351(a)(2)(C)-(D) provisions requiring that products and their facilities meet standards "designed to insure [their] continued safety, purity, and potency").

requiring or requesting such studies, and could use this strategy in addressing the particular risks and issues involved with nanotechnology-based biologics.

B. *Good Manufacturing Practices, Recordkeeping, And Facility Inspection*

Facilities that manufacture nanotechnology-based biologics must conform to fairly stringent FDA regulations regarding good manufacturing practices (GMPs), enforced by inspections.[57] The work areas and equipment must continuously meet precautionary standards.[58] Samples from each lot must be tested prior to release[59] for safety, sterility, purity, and identity.[60] Biologics involving blood components are subject to even more rigorous and specific procedural standards.[61] Biologics manufacturers must create and retain records of "each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector [and] as detailed as necessary for clear understanding of each step."[62] They must also submit distribution information to FDA twice a year.[63] In addition, the GMPs for drugs, contained in a separate subchapter in the regulations, "supplement and do not supersede" the regulations specifically for biologics.[64] It is unclear at this time whether any additional guidance regarding these procedural requirements would be necessary to account for issues unique to the manufacturing of nanotechnology-based biologics.

C. *Labeling Requirements*

Labeling, or lack thereof, of products to indicate the presence of nanomaterials has been a focus of heated debate among nanotechnology stakeholders and commenters.[65] Noting that "[t]he FFDCA requires that labeling of FDA-regulated products be truthful and not misleading," the FDA Nanotechnology Task Force found that there was no basis for requiring a product containing nanomaterials to be labeled as such and recommended case-by-case analysis instead.[66] Biologics in particular are subject to the labeling provisions in the regulations under both the PHSA and the FFDCA. Ingredients must be named on the label, but it is generally not the case that a nanoscale version of any ingredient would have to be specifically identified.[67] FDA approval must also be obtained before distribution of a biologic product with a change to its labeling.[68]

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[57] PHSA § 351(c), 42 U.S.C. § 262(c); 21 C.F.R. pts. 600-680.
[58] *See e.g.*, 21 C.F.R. § 600.11.
[59] *Id.* § 610.1.
[60] *Id.* §§ 610.11-610.13.
[61] *Id.* § 610.40; 21 C.F.R. pts. 606-607 and 630-640.
[62] *Id.* § 600.12.
[63] *Id.* § 600.81.
[64] *Id.* § 211.1(b).
[65] *See, e.g.*, FDA Nanotechnology Task Force Report, *supra* note 30, at 34; Jennifer Sass, *Nanotechnology's Invisible Threat: Small Science, Big Consequences* 8-9 (2007), *available at* http://www.nrdc.org/health/science/nano/nano.pdf.
[66] FDA Nanotechnology Task Force Report, *supra* note 30, at 35
[67] 21 C.F.R. § 601.25(d)(5) (citing 21 C.F.R. §§ 610.60-610.68 (biologics) and subpt. D of pt. 201 (drugs)).
[68] 21 C.F.R. § 601.12(f).

D. *ADVERSE EVENT REPORTING*

A holder of a biologic license must, on penalty of license revocation, "develop written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse experiences to FDA" and "promptly review all adverse experience information pertaining to its product obtained . . . from any source . . . including information derived from commercial marketing experience, post-marketing clinical investigations, post-marketing epidemiological/ surveillance studies, reports in the scientific literature, and unpublished scientific papers."[69] Adverse experiences are defined to include:

> Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: An adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.[70]

"Serious" and "unexpected" adverse experiences must be reported within 15 days; others must be reported quarterly for the first three years and then annually, and records must be maintained for ten years.[71] A biologic manufacturer must also report unexpected events or deviations from GMPs, regulations, or specifications "that may affect the safety" of the product.[72] Human cell and tissue products are subject to their own particular adverse reaction reporting requirements, especially for reactions involving communicable diseases.[73] Finally, biologics are also included under FDA's MedWatch system for voluntary adverse event reporting by consumers and health professionals.[74] All of these mechanisms provide FDA with information it could use to manage risks of nanotechnology-based biologics.

E. *RECALLS*

FDA's capacity to remove unsafe products from the market is stronger for biologics than for other drugs. Unlike the FFDCA,[75] the PHSA mandates FDA to "immediately order[] the recall of such batch, lot, or other quantity of" a biologic that "presents an imminent or substantial hazard to the public health," on penalty of severe fines for non-compliance with such an order.[76]

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[69] 21 C.F.R. § 600.80(b).
[70] 21 C.F.R. § 600.80(a).
[71] 21 C.F.R. § 600.80(a), (i).
[72] 21 C.F.R. § 600.14(c).
[73] *Human Cell & Tissue Products (HCT/P) Adverse Reaction Reporting*, FDA Center for Biologics Evaluation & Research, http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/ucm152576.htm (2005); 21 C.F.R. § 1271.350(a).
[74] *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FDA, http://www.fda.gov/Safety/MedWatch/default.htm.
[75] Dinh, *supra* note 5, at 130 (citing 21 C.F.R. §§ 7.40, 7.45(a)(3)).
[76] PHSA § 351(d)(1), 42 U.S.C. § 262(d).

F. *CHANGES, SUSPENSIONS, AND REVOCATIONS OF BIOLOGICS LICENSES*

As with drugs, manufacturers of biologics are required to inform FDA of any changes in the conditions that were established in the BLA; non-compliance can result in revocation.[77] If the changes are significant, prior FDA approval of a supplement to the BLA is required, which supplement must include data demonstrating the lack of adverse effect on "identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness."[78]

FDA also has authority, after giving opportunity for a hearing, to revoke a previously approved BLA if FDA finds that a biologic manufacturer fails to conform to standards in the license or regulations or that the biologic is not safe and effective for all of its intended uses.[79] This authority intersects with the mandatory reporting requirements for changes to the product or its manufacture and for adverse events, which can provide FDA with the data it would need to issue such a revocation notice for nanotechnology-based biologics.

VI. CONCLUSION

While FDA regulation of nanotechnology-based products under its jurisdiction has provoked intense debate, regulation of nanotechnology-based biologics under the FFDCA and PHSA has received less scrutiny for several reasons. First, examples of nanotechnology-based biologics may not be so numerous or obvious as other categories, since so many biologics are characteristically produced by living organisms rather than by manufacturing processes. Second, and more importantly, the regulatory structure for biologics is generally even more comprehensive and flexible than that for non-biologic drugs. It appears to provide FDA with sufficient authority to manage the potential risks and rewards of nanotechnology as it is being and will be applied to this category. FDA's BLA approval process generally holds biologics to safety standards that are equal to or stricter than those for other drugs, and FDA has a great degree of information-gathering capacity to aid its evaluations.. FDA also has a large amount of post-approval oversight authority over biologics and can inspect facilities, issue recalls, or revoke BLAs based on the required finding of risks from nanotechnology.

In sum, nanotechnology is likely to present challenges to FDA's categorization and evaluation of biologics, but the regulatory mechanisms under the FFDCA and PHSA offer multiple ways in which FDA can seek to manage the novel risks of nanotechnology in biologics.

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[77] 21 C.F.R. § 601.5(b)(1)(iii).
[78] *Id.* § 601.5(b)(1).
[79] *Id.* §§ 601.5(b)(1)(iv)-(vi), 601.6.

CHAPTER 10: COMBINATION PRODUCTS*

I. INTRODUCTION

Combination products span multiple product categories under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended,[1] and cross regulatory borders. Many nanotechnology-based products being developed combine drug and device components to address medical issues at the nanoscale, and are therefore combination products. The increasing prevalence of combination products, particularly as nanotechnology-based products, presents the Food and Drug Administration (FDA) with novel regulatory challenges, including how to classify combination products, what part of the agency should have regulatory responsibility, what types of pre-market and post-market regulation should apply, and whether these products can be effectively regulated through current frameworks. Currently, combination products are regulated primarily as drugs, devices, or biologics, but as combination products become more prevalent, FDA might have to develop new rules. This chapter focuses on FDA's ongoing development of a combination products regulatory framework and how nanotechnology-based products may fit into that framework and help to shape it.

II. BACKGROUND ON COMBINATION PRODUCTS

A. *DEFINITION OF COMBINATION PRODUCTS*

A combination product is a product composed of a drug and a device, a biologic and a device, a drug and a biologic, or a drug, a device, and a biologic.[2] A combination product may be a single entity comprising two or more regulated components that are "physically, chemically, or otherwise combined or mixed."[3] Alternatively, the definition of combination product also encompasses two or more drug and device products, device and biological products, or biological and drug products "packaged together and sold in a single package or as a single unit."[4] Finally, a product also may be regulated as a combination product if it is a drug, device,

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* This chapter was prepared by Kathleen Knight, now with Pediatrics Medical Group, Inc., with assistance from Judi Abbott Curry, Harris Beach PLLC.

[1] 21 U.S.C. §§ 301-399d.

[2] FDA, *Frequently Asked Questions About Combination Products*, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm [hereinafter *Frequently Asked Questions About Combination Products*]. *See also* 21 C.F.R. § 3.2(e).

[3] 21 C.F.R. § 3.2(e)(1). Examples include: a monoclonal antibody conjugated to a therapeutic drug; a device coated or impregnated with a drug or biologic, such as a drug-eluting stent or an orthopedic implant with growth factors; and prefilled syringes, insulin injector pens, metered dose inhalers, and transdermal patches. FDA OFFICE OF COMBINATION PRODUCTS, GUIDANCE FOR INDUSTRY AND FDA STAFF: HOW TO WRITE A REQUEST FOR DESIGNATION (RFD) (2011), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf [hereinafter OCP GUIDANCE ON RFDS].

[4] 21 C.F.R. § 3.2(e)(2). Examples include: a drug or biological product packaged with a delivery device, and a surgical tray with surgical instruments, drapes, and antimicrobial swab. OCP GUIDANCE ON RFDS, *supra* note 3, at 3.

or biologic packaged separately from, but intended for use with, another drug, device, or biologic, where both are required to achieve an intended use, indication, or effect.[5]

B. *REGULATORY BACKGROUND*

Combination products provide opportunities for promising new advances in medical care. The combined constituent parts can have synergistic effects and can provide enhanced therapeutic advantages as compared to single entity drugs, devices, or biologics.[6] New combination products are being developed each year, and in fiscal year 2009, FDA received 377 combination product submissions, a five-year high.[7] Moreover, combination products are becoming more sophisticated and are incorporating cutting-edge, novel technologies, including nanotechnology.[8]

Congress introduced the concept of combination products in 1990 by amending the FFDCA with the Safe Medical Devices Act of 1990.[9] In response, in 1991, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), the three FDA centers responsible for regulation of drugs, devices, and biologics, respectively ("lead centers"), entered into Intercenter Agreements (ICAs) to clarify product jurisdictional issues.[10] These agreements served as guidance documents to describe the allocation of responsibility for product categories or specific products.[11]

Congress overhauled the regulation of combination products in 2002, as part of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA).[12] The MDUFMA mandated that FDA create a new Office of Combination Products (OCP), which would be responsible for coordinating and overseeing the regulation of combination products.[13] FDA established OCP in late 2002.[14]

OCP's primary responsibilities are to ensure (1) "the prompt assignment of combination products to agency centers," (2) "the timely and effective pre-market review of such products,"

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[5] 21 C.F.R. § 3.2(e)(3)-(4). Examples include: a photosensitizing drug and activating laser/light source, and an iontophoretic drug delivery patch and controller. Note that other combinations of two products, for example, two or more drugs, a drug and a cosmetic, or a drug and a dietary supplement, do not meet the regulatory definition of a combination product, and therefore are not regulated as combination products. *See Frequently Asked Questions About Combination Products*, *supra* note 2.

[6] FDA, FY 2010 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS 1, *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/PerformanceReports/CombinationProducts/UCM270772.pdf.

[7] *Id.* at 3.

[8] *Id.* at 2.

[9] P.L. 101-629, 104 Stat. 4511 (1990). *See also* FDA, Review of Agreements, Guidances, and Practices Specific to Assignment of Combination Products in Compliance With the Medical Device User Fee and Modernization Act of 2002, Request for Comments, 71 Fed. Reg. 56,988, 56,989 (Sept. 28, 2006).

[10] *Id.* at 56,989; 21 C.F.R. § 3.5(a)(1).

[11] 21 C.F.R. § 3.5(a)(2).

[12] Pub. L. No. 107-250, 116 Stat. 1588 (2002).

[13] 21 U.S.C. § 353(g) (MDUFMA § 204), FFDCA § 503(g).

[14] FDA, *Office of Combination Products*, http://www.fda.gov/CombinationProducts/default.htm.

and (3) "consistent and appropriate post-market regulation of like products."[15] Any dispute regarding the timeliness of pre-market review of a combination product can be settled by OCP.[16] The MDUFMA also required OCP to review all FDA agreements, guidance documents, or practices specific to combination products.[17] As part of its review, OCP found that the ICAs continued to provide some helpful guidance, but they had become incomplete and their usefulness was limited.[18] Instead of revising them, OCP chose to develop and implement new approaches to more clearly articulate how jurisdictional determinations are made and to increase transparency.[19] OCP's responsibilities also expanded in 2003, when it assumed responsibility for all jurisdictional determinations. This change consolidated the jurisdiction program within OCP, and made the entire program more efficient to administer.[20]

III. NANOTECHNOLOGY-BASED COMBINATION PRODUCTS

As nanotechnology develops, FDA anticipates that many of the new nanotechnology-based products will be combination products.[21] Moreover, FDA recognizes that the nature of nanomaterials "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."[22] Already, new combination products involving nanotechnology are in research and development stages and more will be emerging. For example, multiple research groups are developing "nanoshells," which "can potentially combine imaging capabilities and the ability to selectively bind to cancer cells and kill them via heat or light and/or targeted drug delivery using temperature sensitivity."[23] Another research team has developed

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[15] 21 U.S.C. § 353(g)(4)(A)-(D), FFDCA § 503(g)(4)(A)-(D).
[16] 21 U.S.C. § 353(g)(4)(E), FFDCA § 503(g)(4)(E).
[17] 21 U.S.C. § 353(g)(4)(F), FFDCA § 503(g)(4)(F).
[18] 71 Fed. Reg. at 56,989.
[19] *Id.*; FDA, *Intercenter Agreements*, http://www.fda.gov/CombinationProducts/JurisdictionalInformation/IntercenterAgreements/default.htm. In June 2011, FDA reported that it is reviewing the agreements to determine whether it would be appropriate to modify them or replace them with new agreements, and noting that current guidance supersedes those agreements to the extent they are inconsistent. *See* FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES (June 2011) [hereinafter FDA GUIDANCE ON PRODUCT CLASSIFICATION], *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM258957.pdf, at 6.
[20] FDA, Assignment of Agency Component for Review of Pre-market Applications, 68 Fed. Reg. 37,075, 37,076 (June 23, 2003); *see also* 21 C.F.R. § 3.6.
[21] FDA, *FDA Readies for More 'Nanoscale' Challenges – Consumer Update*, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm153723.htm.
[22] FDA, NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 20 (July 25, 2007), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf [hereinafter "FDA NANOTECHNOLOGY TASK FORCE REPORT"].
[23] Jordan Paradise, Gail Mattey Diliberto, Alison W. Tisdale & Efrosini Kokkoli, *Exploring Emerging Nanobiotechnology Drugs and Medical Devices*, 63 FOOD & DRUG L.J. 407, 418 (2008) (citing Tarek M. Fahmy et al., *Nanosystems for Simultaneous Imaging and Drug Delivery to Cells*, 9 AAPS J. E171 (2007), *available at* http://www.springerlink.com/content/t5g5lxl31451n624/fulltext.pdf.). *See also* Max Sherman, *Exploring the World of Nano Medical Devices*, MED. DEVICE & DIAGNOSTIC IND. 142 (May 2006), *available at* http://www.devicelink.com/mddi/archive/06/05/008.html; Christopher Loo et al., *Immunotargeted Nanoshells for Integrated Cancer Imaging and Therapy*, 5 NANO LETTERS 709 (2005); Andre M. Gobin et al., *Near-Infrared*

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"nanoparticles made of chitosan that encapsulate superparamagnetic iron oxide nanoparticles, fluorescent cadmium telluride quantum dots, and pharmaceutical drugs," whose magnetic properties allow for guidance of the drug and fluorescence allows for real-time monitoring as the particles deliver drugs.[24]

The emergence of nanotechnology poses new regulatory challenges for FDA. New categories of products have challenged FDA in the past, as it has struggled to classify the products based on existing definitions.[25] Innovative technologies such as nanotechnology can lead to the development of new manufacturing methodologies or unique safety issues not associated with products manufactured in other ways.[26] FDA has dealt with similar issues surrounding combination products and, thus far, FDA has chosen to regulate combination products under existing frameworks for drugs, devices, and biologics. However, as new highly integrated nanotechnology-based combination products with multiple uses are developed, FDA may have to reassess the adequacy of its current framework.[27]

FDA has taken preliminary steps to address the challenges posed by nanotechnology. In 2006, the agency established a Nanotechnology Task Force to determine "regulatory approaches that encourage development of innovative, safe, and effective FDA-regulated products that use nanotechnology materials."[28] The Task Force released its report in 2007.[29] FDA subsequently held public meetings in 2006, 2008, and 2010 and collected public comments.[30] In its 2007 report, the FDA Nanotechnology Task Force concluded that an entirely new regulatory

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Resonant Nanoshells for Combined Optical Imaging and Photothermal Cancer Therapy, 7 NANO LETTERS 1929 (2007).

[24] Paradise et al., *supra* note 23, at 419 (citing Linlin Li et al., *Magnetic and Fluorescent Multifunctional Chitosan Nanoparticles as a Smart Drug Delivery System*, 18 NANOTECHNOLOGY 405,102 (2007)). Researchers also are developing "nanobubbles," tumor-targeted drug-carrying nanoparticles that coalesce in tumors to form "microbubbles," which release an encapsulated drug when exposed to therapeutic ultrasound. *Id.* at 419 (citing Natalya Rapoport et al., *Multifunctional Nanoparticles for Combining Ultrasonic Tumor Imaging and Targeted Chemotherapy*, 99 J. NAT'L CANCER INST. 1095 (2007)). Another group of nanotechnology-based combination products involves incorporation of microelectromechanical systems (MEMS). MEMS research could provide a near-term application in pacemaker accelerometers; advanced stage research projects, with potential near-term realization, are exploring the potential use of MEMS in implantable pumps (e.g., insulin pumps); and research projects aimed at future practical applications of MEMS are examining MEMS in nano-batteries for artificial retina or MEMS in hearing aids and defibrillators. *See* MedMarket Diligence, LLC, Micro- and Nanomedicine: Technologies, Applications, Industry, and Markets Worldwide, Report #T625 (2006), *available at* http://www.mediligence.com/rpt/rpt-t625.htm.

[25] Susan Bartlett Foote & Robert J. Berlin, *Can Regulation Be as Innovative as Science and Technology?*, 6(2) MINN. J. LAW, SCI. & TECH. 619, 639 (2005).

[26] FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: EARLY DEVELOPMENT CONSIDERATIONS FOR INNOVATIVE COMBINATION PRODUCTS (2006), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm [hereinafter "OCP EARLY DEVELOPMENT CONSIDERATIONS"].

[27] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22, at 20-21.

[28] FDA, Nanotechnology Task Force webpage, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForce/default.htm.

[29] *See* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22.

[30] FDA Nanotechnology Task Force webpage, *supra* note 28. *See also* 73 Fed. Reg. 46,022-24 (Aug. 7, 2008); 75 Fed. Reg. 51,829 (Aug. 23, 2010).

framework or special regulations for nanotechnology were not necessary at the time.[31] For combination products, the Task Force stated that it "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."[32] OCP is coordinating combination product regulation under the current pre-market review and post-market regulation framework, while continuing to solicit internal and external opinions to seek improvements to this framework.[33]

FDA has also begun encouraging intercenter coordination in information sharing and collaboration about nanotechnology-based combination product regulation.[34] Each of FDA's lead centers has established a multidisciplinary nanotechnology working group, and the Office of the Commissioner has established a Nanotechnology Interest Group.[35] This coordinated effort is designed to inform regulatory activity in light of emerging scientific knowledge, and to enable informed decisions from all centers on how best to approach pre-market review and post-market surveillance of nanotechnology-based combination products.[36]

IV. ASSIGNMENT OF COMBINATION PRODUCTS TO AGENCY CENTERS

A. *ASSIGNMENT BY PRIMARY MODE OF ACTION*

A key issue for a nanotechnology-based combination products, like other combination products, is the assignment of a lead center to review the application. Products submitted for FDA approval are assigned to a particular center within FDA that will have primary jurisdiction for reviewing and regulating the product.[37] Products that consist solely of a drug, device, or biologic generally are reviewed and regulated by CDER, CDRH, or CBER, respectively. For a combination product, OCP assigns the product to one of the three lead centers based on the product's "primary mode of action" (PMOA).[38] Because a combination product consists of multiple constituent parts, and each constituent part has a drug, device, or biologic mode of action, the product will operate through more than one "mode of action," or means of achieving an intended therapeutic effect.[39] The combination product's PMOA is "the single mode of action of a combination product that provides the most important therapeutic action," meaning the mode of action expected to make the greatest contribution to the product's overall intended

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[31] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22, at 30.
[32] *Id.* at 21.
[33] *See* FDA, FY 2009 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, *supra* note 6.
[34] NAKISSA SADRIEH, PH.D., FDA OFFICE OF PHARMACEUTICAL SCIENCE, CENTER FOR DRUG EVALUATION AND RESEARCH, NANOTECHNOLOGY: ISSUES AND FUTURE DIRECTIONS (2006), *available at* http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s2_7.ppt.
[35] *Id.*
[36] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22, at 21.
[37] 21 C.F.R. § 3.4.
[38] FFDCA § 503(g)(1), 21 U.S.C. § 353(g)(1); 21 C.F.R. § 3.4(a).
[39] A constituent part's "mode of action" is based on the part's classification, thus, a drug constituent part has a "drug mode of action," a device has a "device mode of action," and a biologic has a "biological product mode of action." *See* 21 C.F.R. § 3.2(m) (definition of "mode of action").

therapeutic effect or action.[40] The agency center assignment can have a major impact on the financial and time costs of regulatory approvals, though the centers can consult and collaborate with one another during the reviews.

FDA realized that in certain situations it can be difficult to determine a combination product's PMOA, perhaps because at the time of submission to FDA it is not clear which mode of action provides the most important therapeutic action, or the product has two completely different modes of action and neither is subordinate to the other.[41] For such cases, FDA created an assignment algorithm whereby OCP will assign the product based on prior designations for similar combination products and each center's relevant experience with the combination product components.[42] First, OCP will attempt to assign the product to the lead center "that regulates other combination products that present similar questions of safety and effectiveness."[43] If there are no similar combination products, OCP will assign the product to the center "with the most expertise related to the most significant safety and effectiveness questions presented by the combination product."[44]

Draft guidance issued in June 2011 does not refer to PMOAs. Instead, it says that if a product meets both the drug and device definitions, FDA generally intends to classify it as a device. If the product meets the drug definition, but there is uncertainty regarding whether it also meets the device definition, FDA generally intends to classify it as a drug. A product meeting the drug definition or both the drug and device definitions and that also meets the definition of a biological product may be classified as a biological product, rather than as a drug or device.[45]

B. *REQUEST FOR DESIGNATION*

If the appropriate classification or assignment of a product is unclear or in dispute, before submitting a marketing application to a lead center, the product's sponsor may request from OCP a determination of the classification or assignment.[46] The sponsor may request an informal determination of jurisdiction, or may submit a Request for Designation (RFD) for a more formal determination of (1) the regulatory identity of a product as a drug, device, biological product, or combination product, or (2) which center will have primary jurisdiction for pre-market review and regulation of a combination product.[47] A pre-market RFD provides the sponsor with the opportunity to recommend the center it believes should have primary jurisdiction, based on the PMOA or the regulatory assignment algorithm.[48] OCP will issue a letter of designation specifying the lead center pre-market, as well as any consultative centers, within 60 days of the

[40] 21 C.F.R. § 3.2(k); 70 Fed. Reg. 49,848, 49,850 (Aug. 25, 2005).
[41] 21 C.F.R. § 3.4(b); 70 Fed. Reg. at 49,850.
[42] 70 Fed. Reg. at 49,850.
[43] 21 C.F.R. § 3.4(b).
[44] *Id.*
[45] *See* FDA GUIDANCE ON PRODUCT CLASSIFICATION, *supra* note 19, at 4-5.
[46] 21 C.F.R. § 3.7(a).
[47] OCP GUIDANCE ON RFDS, *supra* note 3.
[48] 21 C.F.R. § 3.7(c)(3).

filing date.[49] The letter of designation is important to a sponsor because it is a binding agency jurisdictional determination.[50]

C. *ISSUES RAISED BY THE ASSIGNMENT PROCESS*

There are some problems associated with OCP's current approach, though FDA has attempted to address them through the PMOA definition and the RFD process. First, early in development, the PMOA often is unknown. Second, many products have two or more modes of action, neither of which is subordinate to the other. And third, weighing the contributions of each component is imprecise.[51] When OCP evaluates nanotechnology-based combination products, the identification of the PMOA and classification of the product on the basis of PMOA can be even more difficult.

Thus far, generally, a product having a chemical action as its PMOA would be regulated as a drug, while a product having a mechanical action would be regulated as a device.[52] However, integrated nanotechnology-based products may have multiple modes of action that blur chemical and mechanical distinctions at the nanoscale, and FDA will have a more difficult time identifying and characterizing the PMOA of nanotechnology-based products.[53] For example, the chitosan nanoparticles that encapsulate iron oxide nanoparticles, quantum dots, and drugs act mechanically for guidance and monitoring and chemically for drug delivery; therefore, classification is unclear.[54] Nanobubbles also operate as diagnostic tools to locate tumors and as drug delivery systems to attack the tumors.[55] While OCP currently categorizes these and other nanotechnology-based combination products as drugs, devices, or biologics, these categories might not be the best fit, and FDA realizes that the adequacy of the current system may need to be reassessed.[56]

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[49] 21 C.F.R. § 3.8(b). If OCP does not issue a letter of designation within 60 days of the filing date, the sponsor's recommended lead agency becomes the lead agency. *Id.* In fiscal year 2010, applicants filed 45 RFDs. FDA issued 44 assignments, all within 60 days. FY 2010 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, *supra* note 6, at 14-15.

[50] 21 C.F.R. § 3.9. A designation letter is binding only to the particular product described in the RFD. Thus, if the product's configuration, composition, modes of action, intended use, or other key aspect changes after OCP issues the letter, a sponsor may have to submit a new RFD. OCP GUIDANCE ON RFDS, *supra* note 3. In addition, OCP may change the assigned lead agency with the sponsor's written consent, or without consent to protect the public health or for other compelling reasons. 21 C.F.R. § 3.9(b).

[51] Stuart Portnoy & Steven Koepke, *Regulatory Strategy: Preclinical Testing of Combination Products*, MED. DEVICE AND DIAGNOSTIC IND. (2005), *available at* http://www.mddionline.com/article/regulatory-strategy-preclinical-testing-combination-products.

[52] Paradise et al., *supra* note 23, at 418. *See* FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: INTERPRETATION OF THE TERM "CHEMICAL ACTION" IN THE DEFINITION OF DEVICE UNDER SECTION 201(H) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (June 2011), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM259068.pdf.

[53] *Id. See also* Gregory Mandel, *Nanotechnology Governance*, 59 ALA. L. REV. 1323, 1360 (2008).

[54] Paradise et al., *supra* note 23, at 419.

[55] *Id.* As another example, nanoparticles have been used to detect the development of plaque in asymptomatic patients at high-risk of atherosclerotic disease, and the same nanoparticles also can deliver antiangiogenic therapy to slow plaque progression, thus providing monitoring and drug delivery capabilities. *Id.* at 419-20 (citing Gregory Lanza et al., *Nanomedicine Opportunities in Cardiology*, 1080 ANN. N.Y. ACAD. SCI. 451 (2006)).

[56] FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22, at 20.

The question of how best to classify and regulate combination products is not unique to FDA. In the European Union, for example, drugs are regulated under the Medicinal Products Directive (MPD)[57] and devices are regulated under several Medical Devices Directives (MDDs),[58] but for combination products, manufacturers must determine which apply and follow the appropriate directive or directives.[59] For drug-device combination products, if the product is classified as a device intended to administer a medicinal substance, it is governed by the MDD, but if the combination is a single integrated product intended exclusively for use in the combination and is not reusable, then the MPD applies to the entire product and the MDD apply with regard to the safety and performance of the device features.[60] The European Commission recently has made some efforts to address more advanced medical products, for example, through the Advanced Therapies Regulation, which creates a single regulatory framework for new medical products that are based on gene therapy, cell therapy, or tissue engineering,[61] and a guideline on the clinical and non-clinical evaluation of medicinal substances contained in drug-eluting stents.[62] However, classification of the product remains the key first step of the regulatory process and continues to be convoluted.[63]

Having a consistent and reliable classification system in place in the United States is extremely important, because the classification of a product and its subsequent regulation have major repercussions for its economic success. There are large variations between the three lead centers in terms of time and money required to obtain FDA approval, so a combination product's designation to a particular center could have a significant impact on a company's ability to

[57] European Parliament Directive 2001/83/EC, 2001 O.J. (L 311) 67, amended by Directive 2002/98/EC, 2003 O.J. (L 33) 30; Directive 2004/24/EC, 2004 O.J. (L 136) 85; and Directive 2004/27/EC, 2004 O.J. (L 136) 34. For the Directive and additional directives, regulations, and miscellaneous documents related to the regulation of medicinal products for human use, *see* EUROPEAN COMMISSION, ENTERPRISE AND INDUSTRY, PHARMACEUTICALS, EUDRALEX VOLUME 1 - PHARMACEUTICAL LEGISLATION MEDICINAL PRODUCTS FOR HUMAN USE, *available at* http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm.

[58] Active Implantable Medical Device Directive, 90/385/EEC, 1990 O.J. (L 189) 17; Medical Devices Directive, 93/42/EEC, 1993 O.J. (L 169) 1; In Vitro Diagnostic Medical Device Directive, 98/79/EC, 1998 O.J. (L 331) 1. These original directives have been amended numerous times, and the Medical Devices and Active Implantable Medical Devices Directives were amended by Directive 2007/47/EC, which came into force in 2010. For Directives and amendments, *see* European Commission, Enterprise and Industry, Medical Devices Sector – Legislation, http://ec.europa.eu/consumers/sectors/medical-devices/regulatory-framework/index_en.htm.

[59] *See* Corinne Lebourgeois, *Device and Drug Combination Products: A New Regulatory, Reimbursement, and Marketing Challenge*, LIFESCIENCE ONLINE, Mar. 11, 2008, http://www.lifescience-online.com/articles.html?portalPage=Lifescience+Today.Articles&a=1014.

[60] Maria Donawa, *The Evolving Process of European Combination Product Review, Part I*, 19(6) MED. DEVICE TECH. 32, (2008), *available at* www.donawa.com/european-cro/files/MDT_081001%20Comb%20Products%20Pt.1.pdf.

[61] Regulation (EC) No 1394/2007. For a description of the regulation, *see* European Commission, Enterprise and Industry, Pharmaceuticals, Advanced Therapies, http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm.

[62] Maria Donawa, *The Evolving Process of European Combination Product Review, Part II*, 19(7) MED. DEVICE TECH. 26, 26 (2008), *available at* http://www.donawa.com/european-cro/files/Comb%20Prod%20part%20II.pdf.

[63] *See* Lebourgeois, *supra* note 59.

attract financing and to reach its scheduled milestones.[64] Also, products approved as drugs or biologics are eligible for certain forms of patent and market exclusivity protection against competing products, for periods ranging from six months to seven years, while products approved as devices do not enjoy such protections.[65] Therefore, where possible, a combination product may obtain significant strategic advantages if classified as a drug or biologic rather than a device. On the other hand, classification as a device can shorten a product's approval time.[66] Applicants may make strategic efforts to try to direct the products to classifications that lead to the pathway with the least intense statutory or regulatory requirements or to the center that is perceived to be the most lenient, regardless of whether the classification is the most appropriate from a safety standpoint.[67] Some consultants advise applicants to consider carefully the product's regulatory pathway at the outset of the development process.[68]

V. PRE-MARKET REVIEW OF NANOTECHNOLOGY-BASED COMBINATION PRODUCTS

A. *OCP'S ROLE IN PRE-MARKET REVIEW*

OCP has two statutory roles in pre-market review of combination products, including nanotechnology-based combination products.[69] First, OCP oversees the timeliness of pre-market reviews; if a lead center has failed to review and act on an applicant's pre-market submission within the appropriate timeframe, the applicant can contact OCP to help resolve the issue.[70]

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[64] Gabor Garai & Andrew Baluch, *Nanotech Combination Products Challenge Classic Paradigms*, THE CONVERGENCE GUIDE TO LIFE SCIENCES IN NEW ENGLAND (May 7, 2007), http://www.foley.com/files/tbl_s31Publications/FileUpload137/4103/FoleyConvergenceguide.pdf.

[65] FFDCA § 505 (c)(3)(E), 21 U.S.C. § 355(c)(3)(E) (provides exclusive use periods of 3, 4, or 5 years for new molecular entities or new uses); FFDCA § 505(j)(5)(F), 21 U.S.C. § 355(j)(5)(F) (provides a 180-day exclusive use period for the first filed abbreviated new drug application); FFDCA § 505A(a) and (c), 21 U.S.C. § 355A(a) and (c) (provides an additional exclusive use period of 6-months for pediatric studies); FFDCA § 527(a), 21 U.S.C. § 360cc(a) (provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug or biological product).

[66] Though approval times vary widely for individual products, and the centers have different methods for reporting approval times, an examination of approval times for marketing applications can provide an example. In FY 2009, the median approval times were 13 months for standard NDA and BLA submissions and 9 months for priority applications. FDA, CBER & CDER, FY 2010 PERFORMANCE REPORT TO THE PRESIDENT AND THE CONGRESS FOR THE PRESCRIPTION DRUG USER FEE ACT 4, *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf (the report stated that 2010 data were too few for meaningful reporting). For CDRH, in FY 2008, the average total elapsed time for all original pre-market approvals (PMAs) and panel track PMA supplements was approximately 284 days, but the average total elapsed times to final decision for all 180-day PMA supplements were 183 days, and 115 days for Section 501(k) submissions. FDA, OFFICE OF DEVICE EVALUATION, ANNUAL REPORT FISCAL YEAR 2009 at 4-9, *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM223893.pdf.

[67] Mandel, *supra* note 53, at 1361.

[68] Gabor Garai & Andrew Baluch, *Integrated Legal Strategies for Combination Biomedical Products*, THE PULSE, Apr. 10, 2007, http://www.foley.com/files/tbl_s31Publications/FileUpload137/4046/ThePulse_April07.pdf.

[69] FFDCA § 503(g)(4)(c), 21 U.S.C. § 353(g)(4)(C).

[70] *See* FDA, OFFICE OF COMBINATION PRODUCTS, GUIDANCE FOR INDUSTRY AND FDA STAFF: SUBMISSION AND RESOLUTION OF FORMAL DISPUTES REGARDING THE TIMELINESS OF PRE-MARKET REVIEW OF A COMBINATION PRODUCT (2004), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147126.pdf.

Second, OCP coordinates pre-market reviews involving multiple centers. Once OCP assigns a combination product to one of the three lead centers, that center has oversight responsibility for both the review and the regulation of the combination product.[71] However, the lead center does not have to work alone, and lead centers often consult or collaborate with other lead centers or OCP, as appropriate, to identify and evaluate information necessary for review.[72] While each lead center has its own procedures for determining when a consultation or collaboration with another center is required, FDA developed a standard operating procedure to improve intercenter communication and the timeliness and consistency of intercenter consultative and collaborative reviews.[73]

OCP has issued guidance, "Early Development Considerations for Innovative Combination Products," to aid developers in determining the safety and effectiveness information required for a new combination product.[74] Because of the complex scientific and technical issues raised by combination products, there is not a single developmental paradigm for all combination products; rather, an applicant must consider the novel issues associated with its product and the constituent parts, and propose to FDA a developmental approach that addresses these issues without requiring redundant studies.[75] Moreover, because of the novel issues raised by nanotechnology, if a combination product involves a nanotechnology-based constituent part, the product is likely to further challenge existing developmental approaches.[76]

B. *INVESTIGATIONAL APPLICATIONS*

During pre-market review, FDA will review the entire combination product, and if any of the constituents or the product as a whole raises new safety risks, FDA will require an investigational application.[77] FDA requires only one investigational application for a combination product, and in most cases, the appropriate application is that typically required by the lead center. The application must include all relevant information for the product as a whole and for each constituent part. Each center currently is considering how to treat investigational applications for nanotechnology-based products, and whether to incorporate nanotechnology-based products into current frameworks or develop new ones.[78]

In considering whether new issues might be raised when an approved product is part of a combination product, FDA recommends that applicants consider factors such as any potential physical or chemical interactions between constituent parts, any change in formulation, dosage,

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[70] OCP EARLY DEVELOPMENT CONSIDERATIONS, *supra* note 26.
[72] *Id.*
[73] FDA, MANUAL OF STANDARD OPERATING PROCEDURES AND POLICIES: INTERCENTER CONSULTATIVE/COLLABORATIVE REVIEW PROCESS (2004), *available at* http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm.
[74] *See* OCP EARLY DEVELOPMENT CONSIDERATIONS, *supra* note 26.
[75] *Id*.
[76] *Id*.
[77] *Frequently Asked Questions for Office of Combination Products*, *supra* note 2.
[78] *Id*. Therefore, if the product is assigned to CDER, the applicant likely will have to submit an investigational new drug application. If assigned to CDRH, the product likely will require an investigational device exemption. If the product is assigned to CBER, it likely will require a biological IND. For investigational application considerations at CDER, see Chapter 7 - Drugs; for CDRH, see Chapter 8 - Devices; and for CBER, see Chapter 9 - Biologics.

delivery method or route of administration, or whether the product will be used in a new patient population or for a new indication.[79] Thus, if combining a nanotechnology-based constituent with other constituents changes any aspects of any constituent's functionality, an applicant might have to submit an investigational application.

Though combining constituent parts might raise unique scientific and technical issues that an applicant must address, a developer might ensure a more timely and efficient development process by incorporating a currently marketed product as a constituent part and relying on information and data already available for it, even if the part's intended use in the combination product is different than its originally approved use.[80] For nanotechnology-based constituent parts, however, there is the additional issue of whether a nanoscale version of an approved product is a "new product," requiring an investigational application, or similar enough to the approved product to overcome the need for an investigational application. Each lead center may address this issue differently.

For example, Angstrom Medica developed a nano-device called NanOss, a synthetic bone-based orthopedic implant consisting of nanoscale grains of calcium phosphate, a substance used in medical devices for decades. FDA had approved dozens of calcium phosphate products for use in non-weight bearing applications, and the only difference in NanOss was that the calcium phosphate was ordered in nanoscale grains, making it stronger than any calcium phosphate product previously developed. FDA concluded that, despite its nanoscale properties, NanOss was simply calcium phosphate, not a new product, and therefore required only a Section 510(k) notification, which is submitted for a product with "substantial equivalence" to a previously approved product, and not an investigational application.[81] As a result, Angstrom filed its Section 510(k) notification with FDA in January 2005 and was able to receive FDA approval by February 2005.[82] Whether a nanoscale version of an approved drug, device or biologic is considered new will be critical to the type of review a combination product will receive and could greatly impact the time and cost required for pre-market review.

C. *MARKETING APPLICATIONS*

OCP is also working to clarify the number of marketing applications, one or multiple, that should be required for a combination product.[83] As with investigational applications, once OCP has assigned a lead center, that center is responsible for any marketing applications, but OCP can provide assistance to applicants.[84] For marketing applications, if the product is

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[79] OCP EARLY DEVELOPMENT CONSIDERATIONS, *supra* note 26.
[80] *Id.*; Portnoy & Koepke, *supra* note 51.
[81] Andrew Baluch. *Angstrom Medica: Securing FDA Approval and Commercializing a Nanomedical Device*, 2(2) NANOTECH. L. & BUS. J. 168 (2005) *available at* http://www.nanolabweb.com/index.cfm/action/main.default.viewArticle/articleID/76/CFID/5321463/CFTOKEN/45349535/index.html.
[82] *Id.*
[83] FDA OFFICE OF COMBINATION PRODUCTS, CONCEPT PAPER: NUMBER OF MARKETING APPLICATIONS FOR A COMBINATION PRODUCT 1 (2005), *available at* http://www.fda.gov/downloads/CombinationProducts/RequestsforComment/UCM108197.pdf [hereinafter OCP CONCEPT PAPER ON NUMBER OF APPLICATIONS].
[84] *Id.*

assigned to CDER, the applicant will have to submit a new drug application, or an abbreviated new drug application; if assigned to CDRH, the applicant will have to submit a pre-market approval application or a Section 510(k) notification; and if the product is assigned to CBER, it will require a biologic license application.[85] Depending on the nature of the combination product, approval, clearance or licensure might be obtained through a single marketing application or separate marketing applications for the product's constituent parts.[86]

For most combination products, OCP has determined that one marketing application is sufficient to ensure the product's safety and effectiveness and to ensure consistent and appropriate post-market regulation. Under a single marketing application, the lead center would follow the appropriate regulations, standards, and mechanisms applicable to the application used and those directly applicable to the constituent parts, thus addressing the product as a whole and its parts.[87] However, multiple marketing applications might be necessary in some situations, especially involving nanotechnology, if one application does not sufficiently ensure the safety and effectiveness of the product. Moreover, an applicant may wish to submit multiple marketing applications, even if one is sufficient, in order to receive certain benefits that arise only under a particular type of application, such as new drug product exclusivity, orphan drug benefits, or proprietary data protection when two firms are involved.[88]

In June 2011, OCP issued a guidance document addressing the factors it expects to consider in determining whether a combination product applicant should submit a single or multiple marketing applications.[89] In the meantime, OCP expects that many nanotechnology-based products will be regulated under the "traditional" rules for combination products.[90] However, nanotechnology-based combination products seem more likely to require multiple applications, because the constituents are separate and complex products or because of mechanisms with unique regulatory requirements. As examples of the former, OCP lists drugs and implantable delivery devices and a device in combination with a new molecular entity, both of which have nanotechnology-based examples, which were discussed above.[91] For the latter, nanotechnology might have unique regulatory requirements, if the lead centers choose to create them.

D. *MUTUALLY CONFORMING LABELING*

Pursuant to the FFDCA, FDA has the authority to regulate the labeling of drugs, devices, biologics, and combination products.[92] The FFDCA prohibits the sale of any drug, device, or

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[85] For a more thorough discussion of marketing applications for drugs, see Chapter 7 - Drugs; for devices, see Chapter 8 - Medical Devices, and for biologics, see Chapter 9 - Biological Products.
[86] OCP CONCEPT PAPER ON NUMBER OF APPLICATIONS. *supra* note 83, at 1.
[87] *Id.* at 2.
[88] *Id.* at 2-3.
[89] Frequently Asked Questions for Office of Combination Products, *supra* note 2.
[90] *FDA Readies for More 'Nanoscale' Challenges – Consumer Update*, FDA, *supra* note 21.
[91] FDA, OFFICE OF COMBINATION PRODUCTS, CONCEPT PAPER: NUMBER OF MARKETING APPLICATIONS FOR A COMBINATION PRODUCT, *supra* note 83, at 3.
[92] *See* FFDCA § 201(k), 21 U.S.C. § 201(k) (definition of "label"); FFDCA § 201(m), 21 U.S.C. § 201(m) (definition of "labeling").

biologic that is "misbranded,"[93] meaning the product's label includes false or misleading information or fails to include adequate directions for each use of the product.[94] Because of FDA's strict labeling requirements, combination products, particularly those involving constituent parts from two manufacturers, raise "mutually conforming labeling" (or "cross-labeling") issues which FDA is working to address. Nanotechnology-based combination products will face these issues and will shape the way FDA addresses them.

The combination products that raise particular labeling issues are those involving a "drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed."[95] Manufacturers develop numerous combination products where the constituent parts are independently approved, manufactured, and distributed, and in some cases, one product already is approved for a particular indication. Ideally, the sponsors of the two products in a combination product work together to develop safety and effectiveness data and bring the products to market with mutually conforming labeling. To have mutually conforming labeling, the sponsor of the approved product must submit a supplement to its marketing application, or sometimes a new Section 510(k) notification, to amend the product's label to include directions for using the two products together.[96]

In some cases, product sponsors do not work together, but one sponsor develops a product intended to be used with an already approved product from another sponsor. The new sponsor may develop all necessary safety and effectiveness data for the combination product, but if the new product is intended to be used with the approved product in a significantly different way and the sponsor of the approved product refuses to submit a new marketing application, the products would not have mutually conforming labeling.[97] Concerned that valuable new combination products would not be developed because of concerns about mutually conforming labeling, FDA has been considering whether it should approve combination products that do not have mutually conforming labels.[98]

In 2005, FDA held a public workshop entitled "Combination Products and Mutually Conforming Labeling" to address the public health and legal issues raised by cross-labeling.[99] The core issue was "whether FDA should consider reviewing and possibly approving or clearing

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[93] FFDCA § 301, 21 U.S.C. § 331.
[94] FFDCA § 502, 21 U.S.C. § 352.
[95] 21 C.F.R. § 3.2(e)(3).
[96] FDA, Food and Drug Administration/Drug Information Association Cross Labeling; Public Meeting; Combination Products and Mutually Conforming Labeling [hereinafter "Cross Labeling"], 70 Fed. Reg. 15,633, 15,633 (Mar. 28, 2005).
[97] *Id.*
[98] *Id.* at 15,633-34.
[99] *Id.* at 15,633. For meeting agenda and links to speakers' presentations, *see* FDA/DIA Workshop: Combination Products and Mutually Conforming Labeling, May 10, 2005, Agenda, http://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm118182.htm; for transcript of meeting, *see* FDA/DIA Workshop: Combination Products and Mutually Conforming Labeling, May 10, 2005, Proceedings, http://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm135152.htm.

a new product . . . labeled for use in conjunction with an approved product . . . when there is no supplement for the combined use to the marketing application for the approved product, and the labeling of the approved product would not mention the new product, or the use of the two products together."[100] FDA intended to consider all of the information it collected to develop draft guidance on cross-labeling.[101]

OCP is continuing to work on clarifications on the numerous public health and legal issues raised by cross-labeling.[102] In the meantime, OCP is working with the lead centers on a product-by-product basis to resolve public health and legal issues raised when cross-labeling questions arise.[103] Mutually conforming labeling is an important issue for manufacturers because it has the potential to affect both the pre-market review of new combination products, which must address labeling before gaining approval, and the post-market regulation of already approved products that are incorporated into new combination products, whether with the sponsor's cooperation or not. OCP has not released any documents specifically addressing mutually conforming labeling of nanotechnology-based combination products. However, issues relevant to combination products will become more important as manufacturers develop new nanotechnology-based combination products.

VI. POST-MARKET REGULATION OF NANOTECHNOLOGY-BASED COMBINATION PRODUCTS

A. *OCP'S ROLE IN POST-MARKET REGULATION*

Pursuant to the MDUFMA, OCP is responsible for ensuring the consistency and appropriateness of the post-market regulation of combination products.[104] OCP does not have authority to directly regulate combination products after they have reached the market, but OCP has made efforts to streamline post-market regulation by working to develop good manufacturing practices (GMPs) and safety reporting requirements for combination products.

B. *GOOD MANUFACTURING PRACTICES*

The relevant GMPs for a single-entity product or constituent part of a combination product depend on the product's classification. Current good manufacturing practice (cGMP) regulations apply to drug products,[105] quality system regulations apply to devices,[106] and the drug cGMP regulations as well as biological product regulations apply to biologics.[107] While they overlap to some extent, each set of regulations contains express, specific requirements related to the unique characteristics of a drug, device, or biologic. For combination products in which the constituent parts are produced separately, the separate parts must meet applicable GMPs. For

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[100] Cross Labeling, *supra* note 96, 70 Fed. Reg. at 15,634.
[101] *Id.*
[102] FY 2009 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS, *supra* note 6, at 8.
[103] *Id.*
[104] FFDCA § 503(g)(4)(D), 21 U.S.C. § 353(g)(4)(D).
[105] 21 C.F.R. pts. 210 and 211. For a discussion of cGMP regulations, see Chapter 7 - Drugs.
[106] 21 C.F.R. pt. 820. For a discussion of QS, see Chapter 8 - Devices.
[107] 21 C.F.R. pts. 600-80. For a discussion of good manufacturing practices applicable to biologics, see Chapter 9 - Biologics.

combination products joined as a single-entity or packaged together, the relevant GMPs for all constituent parts apply during manufacture and after the products are joined together, so that the products must always meet both sets of regulations.[108]

OCP first addressed GMPs for combination products in 2004, with the publication of a draft guidance document. OCP recognized that most manufacturing facilities operate under one type of GMPs, and therefore production of combination products burdened a facility to some extent; however, OCP believed a facility could meet both sets of regulations fairly easily by generally following one set of regulations and adjusting practices to meet the specific requirements of the other set of regulations. OCP encouraged manufacturers to consult with the agency early and throughout the development process to ensure they would be able to meet all necessary GMPs by the time manufacturing began.[109]

After some delay, OCP proposed a rule in September 2009.[110] In general, the proposed rule codifies the prior FDA guidance and does not propose any new cGMP requirements. For single-entity and co-packaged combination products, the proposed rule would allow firms to demonstrate compliance with GMP requirements by complying with *either* the drug cGMPs or the device QS in some instances. The rule is expected to be finalized in 2011.

C. *Adverse Event Reporting*

OCP also has worked to develop safety reporting guidelines for combination products. Many of the issues relevant to safety reporting mirror those applicable to GMPs, and OCP's involvement also has followed a similar path. As with GMPs, separate and distinct regulatory systems apply for the reporting of adverse events of drugs, devices, and biologics. Adverse effects from a drug must be reported through Adverse Event Reporting ("AER") regulations,[111] device adverse effects are subject to Medical Device Reporting ("MDR"),[112] and adverse effects from biologics are subject to drug AER regulations, as well as some additional regulations specific to biological products.[113] While the adverse event reporting regulations are similar, each has unique requirements based on the products for which they are designed.[114]

Also as with GMPs, in order to ensure consistent and appropriate post-market safety reporting for combination products, OCP has been working to develop a framework for adverse event reporting applicable to combination products.[115] To this end, OCP issued a concept

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[108] FDA, Office of Combination Products, Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products (2004), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.
[109] *Id.*
[110] FDA, Current Good Manufacturing Practice Requirements for Combination Products, 74 Fed. Reg. 48,423 (Sep. 23, 2009); 74 Fed. Reg. 51,099 (Oct. 5, 2009) (correcting docket number).
[111] 21 C.F.R. pt. 314. For a discussion of AER, see Chapter 7 - Drugs.
[112] 21 C.F.R. pt. 804. For a discussion of MDR, see Chapter 8 - Devices.
[113] 21 C.F.R. pts. 600, 606. For a discussion of adverse reporting applicable to biologics, see Chapter 9 - Biologics.
[114] 74 Fed. Reg. 50,744, 50,745 (Oct. 1, 2009).
[115] FY 2009 Performance Report to Congress for the Office of Combination Products *supra* note 6, at 10-11.

paper[116] and in October 2009 issued a proposed rule.[117] Recognizing that safety reporting was similar for drugs, devices, and biologics, OCP intended its combination products framework to supplement, as necessary, the safety reporting requirements ordinarily associated with a product's marketing application.[118] OCP identified what it believed were the most significant differences in safety reporting schemes, and proposed to retain them.[119]

The general requirement would be for a reporter to use the requirements for post-marketing safety reporting associated with the approved or cleared application under which the combination product is marketed.[120] For combination products approved under separate marketing applications, an option would be to attempt to identify the component responsible for the adverse event, and if the adverse event is clearly related to one component, report through the safety reporting mechanism required for that component, while if the component responsible for the adverse event is unclear, the manufacturer would have to satisfy reporting requirements for each constituent part of the combination product.[121] If a manufacturer is one of multiple parties holding applications for the constituent parts in a combination product, then it would need to first comply with the requirements related to the application it holds, then submit information about the adverse event to FDA or the reporter for the other constituent parts within a specified timeframe. A reporter receiving such a notification would then need to investigate and report the event based on the requirements associated with the application it holds.[122]

VII. FUTURE OF NANOTECHNOLOGY-BASED COMBINATION PRODUCTS

As the above discussion demonstrates, the regulatory future for nanotechnology-based combination products is intricately tied to the regulation of combination products generally. Because OCP is still working to develop rules applicable to all combination products, it has not yet set out rules specific to nanotechnology-based combination products. As OCP develops a regulatory framework for combination products, including principles to govern classification, investigational applications, marketing applications, labeling, GMPs, and adverse event reporting, it will have to address any unique issues that arise with nanotechnology. Thus, it appears that any significant near-term developments in the regulation of nanotechnology-based

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[116] FDA, OFFICE OF COMBINATION PRODUCTS, CONCEPT PAPER: POSTMARKET SAFETY REPORTING FOR COMBINATION PRODUCTS 1 (undated), *available at* http://www.fda.gov/downloads/CombinationProducts/RequestsforComment/UCM108195.pdf.

[117] 74 Fed. Reg. 50,744 (Oct. 1, 2009) [hereinafter OCP CONCEPT PAPER ON POSTMARKET SAFETY].

[118] OCP CONCEPT PAPER ON POSTMARKET SAFETY, *supra* note 116, at 1.

[119] *Id.* The differences in the drug, device, and biological product post-market safety reporting regulations that FDA identified as the most significant were those associated with: device malfunction reporting (21 C.F.R. § 803.3(r)(2)(ii), 21 C.F.R. § 803.20); 5-Day MDR reporting (21 C.F.R. § 803.10(c)(2)(i)); drug and biological product "alert" reporting (21 C.F.R. § 314.80(c)(1) and § 600.80(c)(1)); and blood related deaths (21 C.F.R. § 606.170). *Id.* at 2. *See also* 74 Fed. Reg. at 50,747.

[120] 74 Fed. Reg. at 50,747.

[121] *Id*. at 50,749.

[122] *Id*. at 50,749-50. FDA recognizes that it may, in these instances, receive duplicate reports for an adverse event, but "believes these requirements are necessary in order to promote and protect the public health by ensuring consistent and appropriate ongoing postmarketing surveillance of risks, and ensure both manufacturers are aware of and appropriately investigate and follow up on events involving their constituent part(s) of a combination report." *Id.* at 50,750.

combination products likely would occur through either the regulation of combination products or the regulation of nanotechnology-based products. These two processes may eventually join, and FDA or OCP might develop a separate regulatory system for nanotechnology-based combination products. For the near future, however, a nanotechnology-based combination product will be assessed first by OCP as a combination product and then by the assigned lead center as a nanotechnology-based product, if the center chooses to establish a separate regulatory system for nanotechnology-based products.

An alternative to a two-step regulatory process for combination products is the creation of a stand-alone Center for Combination Products.[123] Like the other lead centers, a Center for Combination Products could have full review and regulatory authority over combination products, including nanotechnology-based products. The creation of this new center would obviate the need to force the classification of combination products as drugs, devices, or biologics in order to regulate them.[124] However, creating a new center would require legislative action, could further complicate the regulatory mix, and would require FDA to choose attributes and borrow or acquire a broad range of expertise from the centers to determine the appropriate regulatory pathway for combination products.[125] Indeed, before OCP was established, there were calls for OCP to have the principal responsibility for regulating combination products, not just an advisory role,[126] but Congress did not give OCP such power. A combination products lead center does not appear to be on the near horizon, as FDA and OCP continue to focus efforts on improving the current framework for routing combination products to the three lead centers and offering assistance and advice to the centers when issues and questions arise, including those involving nanotechnology.

In the meantime, the Nanotechnology Task Force's 2007 report provides the fullest discussion of FDA's plans for the future of nanotechnology-based products, including combination products.[127] The report recognized that "[t]he 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. It noted that "the adequacy of the current paradigm for selecting regulatory pathways for 'combination products' may need to be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated combination products."[128] However, the Task Force did not engage in a thorough assessment of the current paradigm, nor did it suggest specific ways FDA should conduct such an assessment, instead deferring to FDA's ongoing reviews. Ultimately, the Task Force concluded that individual consultations between regulated entities and the agency early in the development process of a combination product would ensure appropriate consideration of

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[123] *See* Foote & Berlin, *supra* note 25, at 641.
[124] *Id.*
[125] *Id.*
[126] Kshitij Mohan, *Combination Products: Incrementalism Won't Work*, MED. DEVICE & DIAGNOSTIC INDUSTRY. 52 (May 2002), *available at* http://www.mddionline.com/article/combination-products-incrementalism-wont-work.
[127] *See generally* FDA NANOTECHNOLOGY TASK FORCE REPORT, *supra* note 22.
[128] *Id.* at 20-21.

any novel issues that products using nanoscale materials might raise.[129] OCP continues to rely on this case-by-case approach to assess any combination product it evaluates.

In 2009, FDA senior staff reaffirmed the agency's position that an entirely new regulatory framework for nanotechnology was not currently necessary, but FDA would continue to keep abreast of emerging nanotechnology research and issues. In addition, they confirmed that the agency continued to regard the 2007 Task Force Report as current and had no plans to update the report or to issue regulations specific to nanotechnology.[130] Therefore, multiple component nanoproducts will continue to be regulated as any other combination products, and OCP's framework for regulation of combination products will apply.[131]

VIII. CONCLUSION

The regulation of combination products is still a relatively new endeavor for FDA. Thus far, more questions than answers have developed around combination products, and while OCP is working to produce new guidance to address the many issues surrounding combination products, a complete and coherent regulatory framework will not be in place for some time.

FDA currently is choosing to treat nanotechnology-based products the same as any other products and is taking time to examine relevant issues and formulate responses. Because FDA expects many of the new nanotechnology-based products to be combination products, the need for a robust regulatory framework for combination products is especially important. Whether the lead centers choose to regulate nanotechnology-based products differently or not, OCP will be the first FDA office to examine many such products. Therefore, as more and more nanotechnology-based products emerge, how FDA chooses to regulate combination products will have a significant impact on how the agency regulates all nanotechnology-based products.

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[129] *Id.* at 21.
[130] Ricardo Carvajal, *FDA Stays the Course on Nanotechnology* (2009), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/02/fda-stays-the-course-on-nanotechnology.html (summarizing comments of FDA senior staff at a session of the Food and Drug Law Institute's Second Annual Conference on Nanotechnology Law, Regulation, and Policy).
[131] *FDA Readies for More 'Nanoscale' Challenges – Consumer Update*, FDA, *supra* note 21.