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Reassessing Safety for Nanotechnology Combination Products: What do Biosimilars Add to Regulatory Challenges for the FDA

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**REASSESSING SAFETY FOR NANOTECHNOLOGY COMBINATION
PRODUCTS: WHAT DO BIOSIMILARS ADD TO REGULATORY
CHALLENGES FOR THE FDA?**

JORDAN PARADISE*

ABSTRACT

Amidst sweeping changes to the United States health care system ushered in by the Patient Protection and Affordable Care Act (“ACA”), the Food and Drug Administration (“FDA”) continues to struggle to apply often centuries-old product categorizations to emerging technological innovations. The ACA’s introduction of a “biosimilar” pathway to market for biological products, modeled on abbreviated pathways to market for drugs and medical devices, further complicates the assessment of “safety” and measures of equivalence and similarity that allow products to enter the market faster. One area where this is particularly acute is nanobiotechnology, which has enabled a set of products that drift uncomfortably at the interface of drugs, medical devices, and biologics, blending unique and novel biological properties at the nanoscale that integrate chemical, mechanical, and biological aspects into a wide range of consumer medical and health care products.

This Article will argue that the creation of the biosimilar pathway will prove to be the straw that breaks the camel’s back unless the FDA develops new dynamic models to properly assess and regulate nanomedical combination products. This Article will examine the existing frameworks of FDA oversight for medical and health care products, highlight nanotechnology (and nanobiotechnology and nanomedicine) specifically as an area where products are currently straddling traditional boundaries between FDA product categories, discuss recent FDA initiatives and Agency procedures regarding nanotechnology, and will suggest an approach for the FDA to respond to nanobiotechnology, including more effective federal coordination; reorganization of the FDA either through congressional action or

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Commissioner action in order to properly classify, assess, monitor, and regulate emerging nanomedical technologies and products; and changes to FDA policy regarding data requirements and post-market reporting from industry to address concerns about the scope of safety in the context of nanomedical products.

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INTRODUCTION

The Patient Protection and Affordable Care Act (“ACA”)¹ brought sweeping changes to the U.S. health care system, triggering immediate challenges to the constitutionality of the legislation and seemingly limitless questions regarding its practical implementation. The ACA also ushered in a new era for the oversight of biological products within the purview of the U.S. Food and Drug Administration (“FDA”), creating a pathway for approval of products that are “biosimilar” or “interchangeable” with an existing biological product (“biologic”).² In doing so, Congress has deposited a major regulatory challenge in front of the FDA during a time in which the FDA faces daily onslaught for its perceived inability to assure safety and efficacy of drug and medical device products.³ This challenge is amplified by advancements at the intersection of nanotechnology and medicine and health care, which pose novel problems for safety assessment of drugs, medical devices, and biologics.

Product classification is a touchstone of regulation by the FDA. The classification of a new medical advancement as a drug, medical device, or biologic determines the FDA center to which it is allocated and therefore which approval process it will follow.⁴ This, in turn, determines the financial investment required to bring it to market and the extent and type of requirements imposed on industry, particularly requirements governing measures of safety to ensure that benefits outweigh risks for each product. Each route to market has its own requirements and process and its own set of ensuing controversies.⁵ Recent high-profile product recalls, outcry over improper scientific data, and challenges to the adequacy of post-market monitoring have plagued the FDA in the context of drug and biologic oversight.⁶ Medical device oversight has similarly been subject to increased scrutiny by Congress and the Institute of Medicine (“IOM”) with regard to the FDA’s overwhelming use of the 510(k) clearance process rather than requiring full-scale safety and efficacy review and approval.⁷ The FDA’s assessment and treatment of scientific and technical information guides oversight of product areas, dependent largely on sometimes-irrational categorical and

1. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010) (codified in scattered sections of the U.S. Code).

2. *Id.* § 7002(b), 42 U.S.C. §§ 262(i)(2)–(3) (Supp. IV 2010).

3. *See, e.g.*, INST. OF MED., MEDICAL DEVICES AND THE PUBLIC’S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS 193 (2011).

4. *See infra* Part II.A–D.

5. *See infra* Part II.A–D.

6. *See, e.g., infra* Parts II.A, II.C.

7. *See* INST. OF MED., *supra* note 3, at 4; *infra* Part II.B.

definitional divisions that structure the Food, Drug, and Cosmetic Act (“FDCA”).⁸

Recognizing the swift integration of drug, device, and biologic elements in medical and health care advancements, Congress created the FDA’s Office of Combination Products (“OCP”) to assess emerging technologies at the interface of these three product realms.⁹ The OCP classifies a product as a drug, medical device, or biologic according to its “primary mode of action,” directing it to the appropriate FDA Center and route to market based on this determination.¹⁰ The combination product process itself faces ongoing criticisms, flowing both from perceived shortcomings in the three product classifications (drug, device, or biologic), and the resulting silo effect of the FDA’s determination for products that integrate chemical, biological, and mechanical mechanisms of action in often novel and innovative ways.¹¹

Congress has now added yet another layer to the FDA’s regulatory challenge with the enactment of the recent health care legislation. The Biologics Price Competition and Innovation Act of March 2010¹² (part of the ACA) creates an additional route to market for biologics—the “follow-on” or “biosimilar” biologics approval pathway—and gives broad implementation authority to the FDA.¹³ The creation of this biosimilar pathway, coupled with the abbreviated pathways to market for both drugs (the abbreviated new drug approval pathway) and medical devices (the 510(k) clearance process), and the combination products mechanism, poses significant implementation challenges for the FDA.

It is now useful to take one step back and ask: is the “combination products” approach and availability of abbreviated routes to market the right conceptual framework to assure product safety for new, category-busting products? One area that highlights the effects of category confusion is nanomedicine, the interface of nanotechnology with human health and medicine, where emerging products promise to combine aspects of two or even all three product areas. Utilizing scientific and technical properties of nanotechnology, medical innovations are now pressing the traditional bounds of the FDA’s product classification scheme, integrating multiple and dynamic

8. Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

9. *See infra* Part II.D.

10. *See infra* Part II.D.

11. *See, e.g.*, Susan Bartlett Foote & Robert J. Berlin, *Can Regulation be as Innovative as Science and Technology? The FDA’s Regulation of Combination Products*, 6 MINN. J.L. SCI. & TECH. 619, 622–23, 631, 640–41 (2005).

12. Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (codified in scattered sections of 42 U.S.C. & 21 U.S.C. (Supp. IV 2010)).

13. 42 U.S.C. §§ 262(k)(8)(A)–(B) (Supp. IV 2010).

features.¹⁴ While U.S. federal agencies are busy grappling with the science and scope of nanotechnology, research and development is swiftly moving forward.¹⁵ As the gatekeeper to entrance of most medical and health care products to the U.S. market, the FDA will play a large role in assessing the applications of nanomedicine.

This Article will argue that the creation of the biosimilar pathway will prove to be the straw that breaks the camel's back unless the FDA develops new dynamic models to properly assess and regulate nanomedical combination products. This Article will examine the existing frameworks of FDA oversight for medical and health care products, highlight nanotechnology (and nanobiotechnology and nanomedicine) specifically as an area where products are currently straddling traditional boundaries between FDA product categories, discuss recent FDA initiatives and agency procedures regarding nanotechnology, and will suggest an approach for the FDA to respond to nanobiotechnology, which has enabled a set of products that drift uncomfortably at the interface of drugs, medical devices, and biologics.

Part I will situate nanomedicine within the “nano” landscape, setting out its scope and relationship to other technologies. Part II will examine the traditional oversight frameworks of the FDA for drugs, biologics, and medical devices; address the role of the FDA in protecting public health and safety in development and use of those innovations in medicine and health care; and identify key statutory provisions and regulations in the FDA realm. This part will also identify core challenges and concerns regarding abbreviated routes to market available for these types of products—the abbreviated new drug approval process for drugs, the 510(k) process for medical devices, and the newly created “biosimilar” and “interchangeable” route for biologics. It will also set forth the framework for combination products, a streamlining process tied directly to the drug, medical device, and biologic pathways. Part III will examine the responses of the FDA to nanotechnology developments, including the initiation of an agency-wide nanotechnology task force, internal policy changes to gather nano-specific information from new drug applications, draft guidance to industry on considerations for nanotechnology products, increased requests for public comment and public meetings for input on specific aspects of nanotechnology, and research partnerships. Part IV will then suggest several approaches for the FDA to pursue in overseeing emerging products blending drug, medical device, and biological aspects. These suggestions include more effective use of the National Nanotechnology Initiative (“NNI”),

14. Jordan Paradise et al., *Exploring Emerging Nanobiotechnology Drugs and Medical Devices*, 63 FOOD & DRUG L.J. 407, 417–20 (2008).

15. See, e.g., KK Jain, *Advances in the Field of Nanooncology*, BMC MEDICINE, Dec. 13, 2010, at 1, <http://www.biomedcentral.com/content/pdf/1741-7015-8-83.pdf> (discussing advances in the use of nanotechnology in cancer treatment).

the federal body tasked with aiding in nanotechnology research and development, not only to promote and fund research but also to facilitate collaboration on topics of oversight; reorganization of the FDA either through congressional action or Commissioner action in order to properly classify, assess, monitor, and regulate emerging nanomedical technologies and products; and changes to FDA policy regarding data requirements and post-market reporting from industry to address concerns about the scope of safety in the context of nanomedical products. This will be followed by a brief conclusion.

I. SITUATING NANOMEDICINE IN THE NANO SPECTRUM

A. *The Nanoscale and Nanotechnology*

The nanoscale is the scale range below the microscale—traditionally measured as under 100nm (or 10^{-9} m, or one billionth of a meter).¹⁶ Scientists and commentators have found interesting ways to illustrate this scale in a manner comprehensible to the general public, including comparing the nanoscale to the width of a human hair (where a strand of human hair is approximately 40,000 nm in diameter)¹⁷ or the thickness of a sheet of paper (where a sheet of paper is 100,000 nm thick).¹⁸ Simply put, nanoscale is all about the size.

The term nanotechnology encompasses an array of technologies at the nanoscale. The NNI defines “nanotechnology” as involving three inter-related (and inseparable) aspects: (1) “[r]esearch and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1–100 nanometer” range; (2) “creat[ing] and us[ing] [] structures, devices and systems that have novel properties and functions because of their small and/or intermediate sizes”; and (3) “ability to be controlled or manipulated on the atomic scale.”¹⁹ Thus, a key feature of nanotechnology is that while size matters, it is not everything. To be truly nanotechnology, unique physical, chemical, and/or biological properties must be present at the nanoscale that make the particle or material function in a manner that can be harnessed and controlled to utilize those unique properties.²⁰ Thus, rather than merely connoting size, nanotechnology is all

16. NAT'L INST. OF STANDARDS & TECH., U.S. DEP'T OF COMMERCE, INTERNATIONAL SYSTEM OF UNITS (SI) 29 (Barry N. Taylor & Ambler Thompson eds., 2008).

17. *Nanotechnology Basics*, NANOTECHNOLOGY NOW, <http://www.nanotech-now.com/basics.htm> (last updated June 27, 2009).

18. Nat'l Nanotechnology Initiative, *Size of the Nanoscale*, NANO.GOV, <http://www.nano.gov/nanotech-101/what/nano-size> (last visited Nov. 22, 2011).

19. U.S. ENVTL. PROT. AGENCY, NANOTECHNOLOGY: AN EPA RESEARCH PERSPECTIVE FACTSHEET (2007), available at <http://epa.gov/ncer/nano/factsheet/nanofactsheetjune07.pdf>.

20. *Id.*

about how the size contributes to unique and controllable properties and functions.

Two other variations of the “nanotechnology” definition will factor into discussions later in this Article. While all twenty-five agencies that make up the NNI support the NNI definition, many have adapted it to deal with product or process-specific issues facing that Agency. For example, the FDA’s Center for Drug Evaluation and Research (“CDER”) hinges its scope of nanotechnology to nanomaterials and nanoscale materials, which the Agency defines as “any materials with at least one dimension smaller than 1,000 nm.”²¹ While the FDA acknowledges consultation of the existing NNI definition,²² the CDER chose to designate the nanoscale as exceeding the traditionally delineated 100 nm maximum by a tenfold difference, perhaps because the Agency is observing drug products utilizing novel properties at numbers higher than 100nm and prefers to be over-inclusive, rather than under-inclusive for long-term tracking purposes. In fact, Abraxane, one of the first marketed nanodrugs, has a 130nm mean particle size;²³ other products may deviate from the 100nm ceiling depending on the size of the actual drug product compared to the total size of the particle containing the drug product and any encapsulating material or adjuvant.²⁴

The term nanotechnology itself and its use in scientific circles have evolved. First entering into the technical and scientific lexicon in 1974, the term “nano-technology” described the process of scaling down to an advanced level of precision in the field of engineering (known as the “top-down approach”)²⁵; the term was further applied by K. Eric Drexler, a renowned physicist, in 1986 to describe the scaling up of particles (known as the

21. CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES 5015.9: REPORTING FORMAT FOR NANOTECHNOLOGY-RELATED INFORMATION IN CMC REVIEW 3 (2010) [hereinafter MAPP 5015.9 REPORTING FORMAT], available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf>.

22. *Id.* at 7. Attachment B is titled “Search Terms for Populating the CDER Nanotechnology Drug Product Database” and includes the National Nanotechnology Initiative definition of “nanotechnology” as well as related definitions from professional organizations, the FDA itself, scholarly scientific publications, and textbooks. *Id.*

23. See ABRAXIS BIOSCIENCE, INC., ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING BRIEFING PACKAGE: ABRAXANE 5 (2006), available at <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4235B2-01-01AbraxisBioscience-background.pdf>.

24. *Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm> (last visited Jan. 22, 2011) [hereinafter *Draft Guidance for Industry*].

25. Norio Taniguchi, *On the Basic Concept of ‘Nano-Technology’*, 2 PROC. OF THE INT’L CONF. ON PRODUCTION ENGINEERING 18, 18 (1974).

“bottom-up approach”).²⁶ Today, both top-down and bottom-up processes are employed in order to arrive at the nanoscale and the unique properties that emerge at that size; the choice of approaches varies by material and scientific discipline.²⁷ Unique nanoscale properties include electrical, where nanoscale particles and materials can hold considerably more energy than conventional sized materials because of their large surface area (e.g., carbon nanotubes (“CNTs”) have an increased efficiency at conducting heat—carbon becomes a superconductor at the nanoscale);²⁸ optical, where linear and nonlinear optical properties can be finely tailored by controlling the crystal dimensions and surface chemistry (e.g., gold nanoparticles and quantum dots);²⁹ chemical, where nanoparticles can be used as catalysts³⁰ and exhibit enhanced chemical activity (e.g., silver at the nanoscale excels as an antimicrobial germ-killer and nanoscale particles for drug delivery can cross into tumor vasculatures);³¹ and mechanical, where nanomaterials exhibit increased hardness, fracture toughness, scratch resistance, and fatigue strength (e.g., CNTs and C₆₀ fullerenes).³²

Depending on the particular area of development, nanotechnology may include the use of nano-sized technology or processes to create specific products or applications, the inclusion of nano-sized particles or materials, or both. Products on the market that claim to be nanotechnology include aerosols, pesticides and chemicals, air filtration systems, medical devices (such as dental adhesives and diagnostic systems), robotics, pharmaceuticals, cosmetics, and coatings and materials integrated into a wide variety of consumer products (such as antibacterial coatings on wound dressings and baby products, stain-resistant pants, high durability tennis rackets, and no-stick

26. K. ERIC DREXLER, ENGINES OF CREATION 3–20 (1986).

27. O. G. Schmidt et al., *Nanotechnology—Bottom-up Meets Top-down*, in 42 ADVANCES IN SOLID STATE PHYSICS 231, 231–32 (Bernhard Kramer ed., 2002).

28. See, e.g., Ray H. Baughman et al., *Carbon Nanotubes—The Route Toward Applications*, 297 SCI. 787, 787, 791 (2002); Younan Xia et al., *One-Dimensional Nanostructures: Synthesis, Characterization, and Applications*, 15 ADVANCED MATERIALS 353 (2003).

29. Xiaohu Gao et al., *In Vivo Cancer Targeting and Imaging with Semiconductor Quantum Dots*, 22 NATURE BIOTECHNOLOGY 969 (2004).

30. See, e.g., Robert W. J. Scott et al., *Synthesis, Characterization, and Applications of Dendrimer-Encapsulated Nanoparticles*, 109 J. PHYSICAL CHEMISTRY B 692, 696–702 (2005).

31. See, e.g., Döne Demirgöz et al., *PR_b-Targeted PEGylated Liposomes for Prostate Cancer Therapy*, 24 LANGMUIR 13,518 (2008); Ashish Garg et al., *Targeting Colon Cancer Cells Using PEGylated Liposomes Modified with a Fibronectin-Mimetic Peptide*, 366 INT’L J. PHARMACEUTICS 201 (2009); Todd O. Pangburn et al., *Peptide- and Aptamer-Functionalized Nanovectors for Targeted Delivery of Therapeutics*, J. BIOMECHANICAL ENGINEERING, July 2009, at 074005-1, 074005-2.

32. Erik T. Thostenson et al., *Advances in the Science and Technology of Carbon Nanotubes and Their Composites: A Review*, 61 COMPOSITES SCI. AND TECH. 1899, 1899, 1905–07 (2001).

cooking pans).³³ It is often impossible to discern whether they are truly nanotechnology products or whether the marketing claims are merely painting the product in a space-age light.

As compared to the three-pronged NNI definition of nanotechnology, the prefix “nano” is typically used to denote anything at the scale of under 100nm, independent of whether there are novel characteristics or functions and an ability to control. For example, materials and particles at the nanoscale are called such terms as nanomaterials and nanoparticles, indicating merely that they exist at the scale range under 100nm.³⁴ The lesson to take away from this is that not everything “nano” (think size) is “nanotechnology” (think size, *plus* novel properties, *plus* ability to control).

Nanotechnology has garnered much attention from the federal government, enjoying considerable funding and publicity which only promises to increase as the technologies advance. In fact, the actual 2011 NNI budget provided \$1.85 billion in funding that supports nanoscale science and engineering research and development spread across fifteen federal agencies.³⁵ The cumulative federal investment in nanotechnology through the NNI since 2001 is approximately \$14 billion.³⁶

33. The Woodrow Wilson Center’s Nanotechnology Consumer Products Inventory is a useful resource that collects information on the “nano” marketing claims of consumer products both in the United States and internationally. Woodrow Wilson International Center for Scholars, *Nanotechnology Consumer Products Inventory*, NANOTECHPROJECT.ORG, <http://www.nanotechproject.org/inventories/consumer/> (last visited Nov. 30, 2011). The Inventory divides products into multiple categories, including appliances, automotive, electronics and computers, food and beverage, children’s goods, health and fitness, and home and garden. *Id.* While all of these products share the common thread that the manufacturer or other source touts that they contain or utilize “nanotechnology,” this is not necessarily the case.

34. See *Nanotechnology Basics*, *supra* note 17. The word “nano” is commonly related to a Greek word meaning “dwarf.” Christian Joachim, *To Be Nano or Not to Be Nano?*, 4 NATURE MATERIALS 107, 108 (2005).

35. Nat’l Nanotechnology Initiative, *NNI Budget*, NANO.GOV, <http://www.nano.gov/about-nni/what/funding> (last visited Nov 30, 2011). The largest investments have been delivered to the Department of Energy (energy technologies), National Science Foundation (science and engineering generally), National Institutes of Health (biomedical research in the life and physical sciences), the Department of Defense (defense and dual-use capabilities), and the National Institute of Standards and Technology (measurement and fabrication tools, analytical methodologies, and metrology). *Id.*

36. NNI Strategic Plan 2010; Request for Information, 75 Fed. Reg. 38,850, 38,851 (July 6, 2010). The total, including the NNI’s 2012 requests, would be \$16.5 billion since 2001. SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., NAT’L SCI. & TECH. COUNCIL, THE NATIONAL NANOTECHNOLOGY INITIATIVE: RESEARCH AND DEVELOPMENT LEADING TO A REVOLUTION IN TECHNOLOGY AND INDUSTRY: SUPPLEMENT TO THE PRESIDENT’S 2012 BUDGET 7 (2011), available at http://nano.gov/NNI_2012_budget_supplement.pdf.

B. *The Nano/Bio Interface and “Nanomedicine”*

Nanobiotechnology is a narrower application of nanotechnology—“a field that applies the nanoscale principles and techniques to understand and transform biosystems (living or non-living) and which uses biological principles and materials to create new devices and systems integrated from the nanoscale.”³⁷ This is essentially the application of nanotechnology to living systems or the use of nanotechnology to create systems that mimic living systems; this marriage makes inherent sense as biological cells and systems often exist at the nanoscale naturally. For example, the largest amino acid (tryptophan) measures 1.2nm,³⁸ ribosomes measure approximately 2–4nm,³⁹ DNA measures 2.5nm in width,⁴⁰ and proteins typically measure between 1–20nm.⁴¹

Given the natural relationship between the nanoscale and internal properties and functioning of the human body, improvement of human health and advancements in medicine are prime targets for nanotechnology.⁴² The unique and far-ranging properties of nanostructures and nanotechnology have facilitated breakthroughs in the pharmaceutical and medical device realms—a confluence termed nanomedicine.⁴³ The National Institutes of Health (“NIH”) defines nanomedicine as a “highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve.”⁴⁴ The FDA defines nanomedicine as “[t]he use of nanoscale materials for medical applications.”⁴⁵ Nanomedicine is a vastly growing field in the United States, with projections that the market will reach \$53 billion in 2011.⁴⁶ Massive amounts of federal funding are being directed to nanomedicine research through the NNI—the NIH alone devoted \$200 million to nanotechnology research in 2008.⁴⁷ Many biological phenomena

37. Mihail C. Roco, *Nanotechnology: Convergence with Modern Biology and Medicine*, 14 CURRENT OPINION BIOTECHNOLOGY 337, 337 (2003).

38. KEWAL K. JAIN, THE HANDBOOK OF NANOMEDICINE 3 tbl.1.2 (2008).

39. *Id.*

40. *Id.*

41. *Id.*

42. *See, e.g.*, Volker Wagner et al., *The Emerging Nanomedicine Landscape*, 24 NATURE BIOTECHNOLOGY 1211, 1215, 1217 (2006).

43. *Id.* at 1212.

44. *Nanomedicine: Overview*, NAT’L INST. OF HEALTH COMMON FUND, <http://commonfund.nih.gov/nanomedicine/overview.aspx> (last updated Jan. 1, 2011).

45. MAPP 5015.9 REPORTING FORMAT, *supra* note 21, at 3.

46. Raj Bawa & Summer Johnson, *The Ethical Dimensions of Nanomedicine*, 91 MED. CLINICS N. AM. 881, 882 (2007) (citing Freedomia Grp., NANOTECHNOLOGY IN HEALTHCARE (2007)).

47. NANOTECHNOLOGY TASK FORCE, NAT’L INSTS. OF HEALTH, 2008 STATEMENT OF PURPOSE (2008), *available at* http://www.nibib.nih.gov/nibib/file/Research/Nanotechnology/NIH_Nanotechnology_Task_Force_Plan_FINAL_Jan09.pdf.

naturally occur at the nanoscale; however, nanomedicine refers to materials or particles fabricated at this scale to take advantage of manifest properties (e.g., optical, chemical, and mechanical).⁴⁸ Products at the nanoscale are emerging that utilize and integrate nanoscale properties, have the ability to mimic biological systems, and will, in time, be able to functionally evolve in response to bodily feedback.

Research at the nanoscale illustrates that as particle size decreases, and surface area increases, the biological activity of particles increases.⁴⁹ The resulting unique physical properties at the nanoscale are extremely promising for medical applications in that they may solve some of the most difficult barriers for effective therapeutics and diagnostics.⁵⁰ In terms of *in vitro* and *in vivo* imaging, nanoscale properties involving optical absorbance, fluorescence, and electrical and magnetic conductivity are key to locate and visualize internal functioning;⁵¹ for drug delivery and formulation of drugs, nanoscale properties involving pharmacokinetics, biodistribution, and cell permeability will assist in getting the drug load to the exact location, and faster;⁵² and for implants, bone and dental restoratives, and coatings for wound care and various other applications, the size and shape, surface modification, and direct interaction with tissues will increase efficacy.⁵³ The interface of nanomedicine and nanobiotechnology has introduced widespread research activity in the areas of biomolecule and biomimetic devices, biosensors, molecular motors, biomolecular fabrics, engineered enzymes and proteins, and drug discovery and delivery.⁵⁴

As will be discussed in Part III, little to nothing is yet known about the health, safety, and environmental impacts of nanomaterials and nanoparticles. Scientists and regulators alike are struggling to quantify and characterize these materials in an effort to create appropriate toxicological testing and assessment tools.⁵⁵ Specific to human safety and public health, there are broad questions

48. *Nanomedicine: Overview*, *supra* note 44.

49. Andre Nel et al., *Toxic Potential of Materials at the Nanolevel*, 311 SCI. 622, 622 (2006); *see also* Andre E. Nel et al., *Understanding Biophysicochemical Interactions at the Nano-Bio Interface*, 8 NATURE MATERIALS 543, 554 (2009) (discussing particle size, surface area, and bioreactivity in the context of pulmonary inflammation).

50. Nagender Reddy Panyala et al., *Gold and Nano-Gold in Medicine: Overview, Toxicology and Perspectives*, 7 J. APPLIED BIOMEDICINE 75, 75 (2009).

51. *Id.* at 76–77, 84.

52. Pawan Malhotra & Aneeta Singh, *Nano Medicine—A Futuristic Approach*, 12 JK SCI. 3, 3 (2010), <http://www.jkscience.org/current/Nano%20Medicine-%20A%20Futuristic%20Approach.pdf>.

53. *See id.* at 4 (noting that nanomachines that enter cells are able to more effectively make “modifications of faulty [cell] structure”).

54. Alan L. Porter et al., *Refining Search Terms for Nanotechnology*, 10 J. NANOPARTICLE RES. 715, 718 fig.1 (2008).

55. *See infra* Part II.

about the toxicity of nanoparticles in humans and whether animal research findings are an adequate measure to draw conclusions for risks of human exposure,⁵⁶ the effect of various exposure routes and routes of administration, possible unintended effects on non-target areas given the ability of nanoparticles to cross the blood-brain barrier, possible long-term effects of nanoparticles introduced to the human body,⁵⁷ and potential interaction of various nanoparticles and nanomaterials within the human body.⁵⁸ Struggles to develop mechanisms to identify, quantify, and assess the health and environmental impacts of nanotechnology are not confined to the United States; this is a global challenge.⁵⁹ While developing and developed countries alike are channeling funding into nanotechnology research and development, resulting in a vast spectrum of consumer products entering the market, the scientific and regulatory questions abound. The U.S. government, through the NNI, is currently funding targeted research studies within core research institutes and agencies on a number of environmental and public health and safety implications.⁶⁰ It is also, however, spending over ninety-three percent of its current budget on development and support of nanotechnology applications.⁶¹

As nanotechnology advances, particularly in the realm of medicine and human health, ample attention to scientific developments in characterizations and assessment, adverse event reporting specific to nanocharacteristics, and post-market surveillance are necessary to investigate and respond to the effects of these products on the public. Several key federal agencies, including the FDA, the Environmental Protection Agency (“EPA”), and the Occupational Safety and Health Administration, are situated to play a large part in generating, tracking, and disseminating this information. Part II provides an

56. See David B. Resnik & Sally S. Tinkle, *Ethical Issues in Clinical Trials Involving Nanomedicine*, 28 CONTEMP. CLINICAL TRIALS 433, 434–37 (2007) (noting limitations of animal experimentation in discerning long-term effects and differing reactivity between animals and humans).

57. Bawa & Johnson, *supra* note 46, at 885.

58. Christian Lenk & Nikola Biller-Andorno, *Nanomedicine—Emerging or Re-Emerging Ethical Issues? A Discussion of Four Ethical Themes*, 10 MED. HEALTH CARE & PHIL. 173, 176 (2007).

59. See *infra* Part III.A.

60. See, e.g., SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., NAT’L SCI. & TECH. COUNCIL, NATIONAL NANOTECHNOLOGY INITIATIVE STRATEGIC PLAN 29–30 (2011), available at <http://www.nano.gov/nnistrategicplan211.pdf>.

61. This is based on the NNI’s 2011 budget of a total of \$1.76 billion, with \$117 million for environmental, health, and safety research. SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., NAT’L SCI. & TECH. COUNCIL, THE NATIONAL NANOTECHNOLOGY INITIATIVE: RESEARCH AND DEVELOPMENT LEADING TO A REVOLUTION IN TECHNOLOGY AND INDUSTRY, SUPPLEMENT TO THE PRESIDENT’S 2011 BUDGET 11 (2010), available at http://nano.gov/sites/default/files/pub_resource/nni_2011_budget_supplement.pdf.

overview of the FDA's oversight of drugs, medical devices, and biologics, highlighting the abbreviated approval pathways to market and in particular the biosimilar pathway introduced in the ACA, and the mechanisms of overseeing products that combine aspects of these three product areas.

II. TRADITIONAL FOOD AND DRUG ADMINISTRATION OVERSIGHT FRAMEWORKS FOR MEDICAL AND HEALTH CARE PRODUCTS

One of eleven agencies within the Department of Health and Human Services ("DHHS"), the FDA is tasked with enforcing a broad range of federal statutes with products accounting for a quarter of all consumer spending in the United States, including eighty percent of the national food supply and all human drugs, medical devices, cosmetics, vaccines, tissues for transplantations, and radiation-emitting products.⁶² In addition to overseeing products, the FDA is also "responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to . . . improve their health."⁶³ Recent legislation also provides both increased authority over tobacco products⁶⁴ and a new approval pathway for follow-on biologics⁶⁵ that further enlarges the FDA docket.

The FDCA delineates three product categories applicable to nanomedicine: drugs, medical devices, and biologics.⁶⁶ These are the three most heavily regulated consumer products throughout the pre- and post-marketing phases

62. *Regulatory Information: Legislation*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Legislation/default.htm> (last updated May 4, 2011); Press Release, U.S. Food & Drug Admin., The Food and Drug Administration Celebrates 100 Years of Service to the Nation (Jan. 4, 2006), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108572.htm>.

63. *What We Do*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/default.htm> (last visited Jan. 22, 2012).

64. Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776, 1776-1852 (2009) (codified in scattered sections of the U.S. Code).

65. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804-821 (2010) (codified at 42 U.S.C. § 262 (Supp. IV 2010) & 21 U.S.C. § 355(a) (Supp. IV 2010)). The biosimilars provisions are found in Title VII: Biologics Price Competition and Innovation. The new follow-on biologics provisions create statutory mechanisms to provide for approval of a biological product that is "biosimilar" and/or "interchangeable" with a biologic reference product already on the market. This status is to be based on whether a follow-on product is "highly similar" to the reference product. *Id.* A biologic is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, 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." 42 U.S.C. § 262(i) (2006).

66. *See infra* Part II.A-C.

with substantial data requirements and a spectrum of compliance and enforcement mechanisms in the FDA's arsenal. However, the extent of regulation varies according to a multitude of factors, including whether a drug is a new drug or a generic drug, whether a medical device must go through the premarket approval process or is substantially equivalent to a device already on the market,⁶⁷ and, following the 2010 health care legislation, whether a biologic product is biosimilar and thus able to progress through a streamlined (and yet to be developed) approval process.⁶⁸ A broad overview of the pathway to market for drugs, medical devices, and biologics is below.

A. *Human Drugs*

Oversight of both human drugs and medical devices is set out in the FDCA.⁶⁹ The new drug application ("NDA") process involves the most rigorous review of any FDA-regulated product and is overseen by the CDER.⁷⁰ It can take upwards of sixteen years and cost over a billion dollars to bring a new drug to market.⁷¹ The touchstone measures of this process are ultimately safety and efficacy but oversight by the FDA spans identification, synthesis, and purification of an active pharmacological ingredient; pre-clinical and animal testing; clinical trials; manufacturing processes; review of the product for final approval; and post-market performance.⁷² New human drugs⁷³ must

67. An extended discussion of the FDA drug and medical device review, approval, and clearance processes are outside the scope of this article. They are addressed extensively elsewhere in the literature.

68. 42 U.S.C. § 262(i)(2)–(3) (Supp. IV 2010).

69. Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended in scattered sections of 21 U.S.C.).

70. *About the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm> (last visited Jan. 22, 2012).

71. Chris L. Waller et al., *Strategies to Support Drug Discovery Through Integration of Systems and Data*, 12 DRUG DISCOVERY TODAY 634, 634 (2007).

72. 21 U.S.C. § 355 (2006).

73. A drug is defined as:

(A) articles recognized in the official United States Pharmacopeia . . . ; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Id. § 321(g)(1). A new drug is defined as:

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.

Id. § 321(p)(1).

satisfy safety, efficacy, and manufacturing standards, among other substantive requirements.⁷⁴ Applicants must progress through key stages in the approval process including an investigational new drug application (“IND”) based on animal studies and three core stages of clinical trials, culminating in an NDA.⁷⁵ The FDA also maintains significant post-market authority over approved drug products as a result of 2007 amendments.⁷⁶

Under the NDA umbrella, there are three routes for drugs to enter the market faster where they are intended to treat serious or life-threatening diseases: priority review, fast track, and accelerated approval.⁷⁷ These have been established either by agency policy, regulation, or statute.⁷⁸ Each route is distinct, but they share the underlying goal of speeding up the availability of the drug based on its treatment promise.⁷⁹ Priority review is a designation given to new drug applications by FDA reviewers in order to speed up the time of review by a few months for drugs that appear to offer major advances in treatment or will provide treatment where there is currently no adequate therapy.⁸⁰

74. *Id.* § 355.

75. Details of the NDA process are detailed elsewhere. Following FDA approval of an Investigational New Drug (“IND”) application, clinical trials involve three key phases. Phase I studies are conducted on healthy subjects for basic metabolism, pharmacology and initial safety and dosage measures. Phase II studies are larger scale (several hundred people) and collect initial measures of effectiveness and continues safety, toxicology, and dosage measures. The sponsor meets with the FDA at the end of Phase II in order to continue into Phase III, which enroll up to several thousand subjects for large-scale safety and efficacy measures, and specifically to identify rare adverse events in a larger population. *The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited Jan. 22, 2012).

76. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.). The Food and Drug Administration Amendments Act (“FDAAA”), among other provisions, expanded the scope of clinical trial registration and post-market surveillance in response to growing concerns about public availability of trial information and is viewed as a strong step forward in efforts to increase transparency. Many question the utility of the information in the face of limited public understanding and ability to interpret results and urge more efforts to promote public understanding of clinical trial information that is put into the public domain. *See, e.g.*, Deborah A. Zarin & Tony Tse, *Moving Toward Transparency of Clinical Trials*, 319 *SCI.* 1340, 1342 (2008).

77. *Fast Track, Accelerated Approval and Priority Review*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (last visited Jan. 22, 2012) [hereinafter *Fast Track*].

78. *Id.*

79. *Id.*

80. This designation and process is established in agency policy and effectively sets the goal for time of review at six months rather than ten months for standard review. *Id.* For examples of agency policy regarding expedited drug approval, see CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES 6020.3:

Fast Track is defined by the FDA as “a process designed to facilitate the development, and expedite the review of drugs to treat serious diseases and fill an unmet medical need.”⁸¹ The FDA considers factors such as the impact on day-to-day functions and survival or the likelihood that, if left untreated, the disease will become more serious in order to determine whether it is serious or life-threatening.⁸² Where no treatments exist, this is clearly an “unmet need”; where therapies do currently exist, the drug must show that it performs some advantage over that existing product.⁸³ This approval process typically requires post-approval studies and the progress of these studies, as well as the plan for completion or termination and any reasons for delay, must be described in the annual report to the FDA.⁸⁴ The FDA may also waive the IND application requirement and may accept a continuous application during the Fast Track process, where portions of the NDA may be submitted before a full NDA is prepared, allowing frequent feedback and interactions throughout the development process.⁸⁵

Accelerated review allows the earlier approval of drugs that are intended to treat serious diseases or life-threatening diseases and fill an unmet medical need based on a surrogate endpoint rather than a traditional clinical trial outcome measure.⁸⁶ The FDA may also impose post-market studies as part of the accelerated approval, tasking the drug sponsor to “study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.”⁸⁷ The regulations provide circumstances under which the FDA may withdraw the approved drug from the market, subject to

REVIEW OF CLASSIFICATION POLICY: PRIORITY (P) AND STANDARD (S) (2007); *SOPP 8405: Complete Review and Issuance of Action Letters*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073481.htm> (last visited Jan. 22, 2012).

81. *Fast Track*, *supra* note 77. This process was established by statute. 21 U.S.C. § 356(a) (2006).

82. *Fast Track*, *supra* note 77.

83. *Id.*

84. 21 U.S.C. § 356(b) (outlining the requirements for the reports of post-marketing studies). This provision requires that the company’s annual report identify each Phase IV commitment (post-market studies) for the approved product, describe the progress being made, and indicate the plan for completion or termination. *Id.*

85. *See Fast Track*, *supra* note 77.

86. This process was established by regulation. 21 C.F.R. §§ 314.500–560, 601.40–601.46 (2010). Surrogate endpoints are physiological assessments recognized as validated indicators of clinical benefit (i.e., a biomarker). *Id.* § 314.510. Examples include reduced blood pressure for anti-hypertensives, reduced fractures for osteoporosis, and reduced cholesterol levels for lipid-altering drugs.

87. *Id.* § 314.510.

notice and a hearing. These include failure to verify clinical benefit and failure to perform a required post-market study with due diligence.⁸⁸

Increasing concern about the failure to assure that industry fulfill post-approval commitments led to the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).⁸⁹ Pre-2007, the FDA relied on two statutory provisions broadly dealing with maintenance of records and reports as the basis for requests for post-approval nonclinical or clinical studies (aside from those required under the accelerated approval regulations).⁹⁰ With enactment of FDAAA, the authority of the FDA to require post-approval studies has been explicitly provided; the FDA can now rely on new provisions to require further studies for safety and efficacy, along with increased authority to review these commitments.⁹¹ Risk evaluation and mitigation strategies (“REMS”) come in many forms: they can require a Medication Guide for patients, prescription physician information, implementation plans, communications to health care providers and pharmacies, and various limitations on labeling, promotion, and prescribing to assure safe use.⁹² These amendments provide significant enforcement mechanisms for violations, which are deemed to be misbranding and carry additional civil money penalties for violations.⁹³ The FDAAA also provides additional requirements for the industry regarding the entry of clinical trial information into existing clinical online databases and creation of new online reporting resources for adverse events as a means to bolster transparency to the public.⁹⁴

However, problems with industry adherence to post-market requirements linger. In September 2009, the U.S. Government Accountability Office (“GAO”) issued a report addressing perceived problems with the FDA’s accelerated approval program.⁹⁵ The report details that while the FDA approved ninety drug applications based on surrogate endpoints between 1992 and November 2008, only two-thirds of the required post-market studies have been fulfilled and deemed “closed” by the FDA.⁹⁶ Pointing out weakness in monitoring and enforcement, the GAO urged the FDA to clarify conditions for withdrawal if sponsors fail to complete the required studies or if the studies fail

88. *Id.* § 314.530.

89. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

90. *See* 21 U.S.C. §§ 355(e), (k) (2006).

91. *See* 21 U.S.C. §§ 355(o)–(p), 355-1 (Supp. IV 2010).

92. *Id.* § 355-1.

93. *Id.* § 352(y)–(z); *Id.* § 333(f)(4).

94. *Id.* § 355(k).

95. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-090-866, NEW DRUG APPROVAL: FDA NEEDS TO ENHANCE ITS OVERSIGHT OF DRUGS APPROVED ON THE BASIS OF SURROGATE ENDPOINTS (2009) [hereinafter FDA NEEDS TO ENHANCE ITS OVERSIGHT].

96. *Id.* at 14.

to demonstrate the drug's clinical effectiveness.⁹⁷ Likely as a result of this report critical of the FDA's handling of these products, the FDA recently asserted this withdrawal authority for the first time, notifying Shire Pharmaceuticals and generic manufacturers of the Agency's proposal to withdraw ProAmatine (and the generic midodrine) from the market based on a lack of required post-marketing data confirming the clinical benefit of the drug.⁹⁸ The FDA has since opened a public docket on the matter.⁹⁹

A drug sponsor may also apply for changes to a drug approval utilizing a supplemental NDA ("sNDA")¹⁰⁰ where an approved application exists that underwent a full premarket approval process and the sponsor wishes to make changes to that marketed drug.¹⁰¹ These are termed "prior approval" supplements and FDA approval is required before changes are implemented.¹⁰² Only major changes require a sNDA: changes to the drug or the manufacturing process, facilities, or equipment that have "a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."¹⁰³ These are typically changes to the active ingredient or active product, including major labeling changes such as a new indication or new dosing and major manufacturing changes such as formulation or synthesis changes.¹⁰⁴

The generic drug approval process, termed the abbreviated new drug application ("ANDA"), was implemented in 1984 with the Hatch-Waxman Act.¹⁰⁵ The ANDA process combines patent term extension and data exclusivity provisions with authorization for the FDA to approve generic versions of already-approved pioneer drugs.¹⁰⁶ These provisions were applicable only to conventional small molecule drugs and did not include

97. *Id.* at 36.

98. *Midodrine Update*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/ucm225444.htm> (last visited Jan. 22, 2012).

99. *Id.*; see also *Trials to Verify and Describe Clinical Benefit of Midodrine Hydrochloride; Establishment of Public Docket*, 76 Fed. Reg. 1620 (Jan. 11, 2011).

100. 21 U.S.C. § 356a(c)(1) (2006).

101. 21 C.F.R. § 314.70 (2010).

102. CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 3 (2004), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf> [hereinafter CHANGES TO AN APPROVED NDA OR ANDA].

103. 21 C.F.R. § 314.70(b)(1) (2010).

104. CHANGES TO AN APPROVED NDA OR ANDA, *supra* note 102, at 12–13.

105. The Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) established the abbreviated new drug application process at 21 U.S.C. § 355(j) (2006). Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, sec. 101, 98 Stat. 1585, 1585–92 (codified at 21 U.S.C. § 355(j) (2006)).

106. 21 U.S.C. § 355(j).

biologics, which are regulated under the rubric of the Public Health Services Act.¹⁰⁷ An ANDA does not generally require preclinical and clinical data to establish safety and efficacy but must demonstrate that the product is “bioequivalent” and performs in the same manner as the pioneer drug in terms of active ingredient, dosage and route of administration, and strength and conditions of use.¹⁰⁸ A showing of bioequivalence requires “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”¹⁰⁹ The FDA may approve an ANDA for a generic version of a pioneer drug after all relevant patents have expired for the pioneer drug and all relevant periods of market exclusivity for the pioneer drug have also expired.¹¹⁰ The Orange Book is the key resource to guide the ANDA applicant and includes patent listings and information on generic drug approvals and the corresponding pioneer drug.¹¹¹ State substitution laws allow pharmacists to dispense the generic (i.e., therapeutic equivalent) drug when a physician prescribes the pioneer, except if explicitly directed otherwise by physician.¹¹²

Nanodrugs are currently being evaluated by the FDA via the NDA process. However, a number of them have benefited from accelerated approval because of their application in treatments for serious or life-threatening illnesses.¹¹³ The GAO report’s Appendix I lists the drugs approved under the accelerated approval process during the 1992 to November 2008 time period, including the

107. Jordan Paradise, *The Devil is in the Details: Health-Care Reform, Biosimilars, and Implementation Challenges for the Food and Drug Administration*, 51 JURIMETRICS J. 279, 282 (2011).

108. 21 U.S.C. § 355(j)(2)(A)(ii)–(iii).

109. 21 C.F.R. § 320.1(e) (2010). Bioavailability is defined as “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of [drug] action.” *Id.* § 320.1(a). The drug product is defined as the “finished dosage form . . . that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.” *Id.* § 320.1(b). Pharmaceutical equivalents are defined as drug products “that contain identical amounts of the identical active drug ingredient.” *Id.* § 320.1(c). And pharmaceutical alternatives are defined as “drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form.” *Id.* § 320.1(d).

110. 21 U.S.C. § 355(j)(5)(A)–(E).

111. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (THE ORANGE BOOK) (31st ed. 2011), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>. The Orange Book lists patent and exclusivity information for pioneer and generic drugs. The searchable electronic version is available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

112. Jesse C. Vivian, *Generic-Substitution Laws*, U.S. PHARMACIST, June 2008, at 30, 32–33.

113. See *infra* Figure 1.

drugs Doxil (approved both for treatment of Kaposi's sarcoma in specific patients with Acquired Immunodeficiency Syndrome and for treatment of metastatic carcinoma of the ovary in specific patients) and DepoCyt (approved for treatment of lymphomatous meningitis).¹¹⁴ Both drugs utilize nanotechnology.¹¹⁵ As companies with existing NDAs for nanotechnology-based drugs pursue additional indications, dosages, and patient populations, many will utilize the sNDA route to achieve this. For example, Abraxis Biosciences reported in early 2010 that it was near completion of Phase 3 clinical trials for a second indication of Abraxane (active ingredient paclitaxel) originally approved in 2005, which the company projected would be the subject of an sNDA sometime in 2011.¹¹⁶ Ortho Biotech has also utilized the sNDA process for several subsequent new or modified indications of Doxil (active ingredient doxorubicin hydrochloride), as well as labeling changes.¹¹⁷

B. Medical Devices

Medical devices¹¹⁸ are subject to a tiered classification system based on perceived level of risk. Most medical devices considered low and medium risk can be marketed with merely a premarket notification to the FDA if "substantially equivalent" to an already marketed device or may be exempt from premarket notification altogether; higher-risk Class II or Class III devices that are not substantially equivalent must go through a pre-market process

114. Both drugs were approved using response rate as the surrogate endpoint. See FDA NEEDS TO ENHANCE ITS OVERSIGHT, *supra* note 95, at 42, 44 tbl.5.

115. Paradise et al., *supra* note 14, at 411–12; see *infra* Figure 1.

116. Press Release, Abraxis Bioscience, Abraxane Meets Primary Endpoint in Phase 3 Trial for Advanced Non-Small Cell Lung Cancer, (Mar. 17, 2010), available at http://www.nanotech-now.com/news.cgi?story_id=37282 (last visited Aug. 8, 2011). Celgene acquired Abraxis Biosciences in June 2010. Andrew Pollack, *Prominent Drug Chief to Sell Abraxis BioScience to Celgene for \$2.9 Billion*, N.Y. TIMES, July 1, 2010, at B3.

117. Doxil Label and Approval History, U.S. FOOD & DRUG ADMIN., <http://www.access.data.fda.gov/scripts/cder/drugsatfda/index.cfm> (search the drug name "Doxil"; then follow "Label Information" hyperlink) (last visited Jan. 22, 2012).

118. A medical device:

means an instrument, apparatus, any component, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part, or accessory which is –

- (1) recognized for use in the official National Formulary, or . . . ,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h) (2006).

demonstrating safety and efficacy as set forth in regulations.¹¹⁹ The Center for Devices and Radiological Health (“CDRH”) oversees medical devices.¹²⁰

Class III is the highest risk classification for medical devices, requiring a pre-market approval (“PMA”) filing prior to marketing in the United States unless it is a product amenable to the 510(k) clearance process based on classification listings and “substantial equivalence,” described below.¹²¹ Class III PMA devices are those that are life-sustaining and life-supporting.¹²² Similar to an NDA for a new drug, the PMA must list uses and indications of the specific product, warning and contraindications, product labeling, results of clinical trials gathered following approval of an investigational device exemption (comparable to an IND for a new drug), and information regarding manufacturing processes.¹²³ Examples of high-risk Class III products subject to the PMA process include heart valves, implantable cardioverter defibrillators, and pacemakers.¹²⁴ Clinical studies for a Class III medical device can take four to five years and cost fifteen to twenty million dollars.¹²⁵

Premarket notification is required for most Class II and III devices, which is termed a 510(k) clearance in reference to the FDCA section that establishes the process.¹²⁶ These devices pose an increased, moderate level of risk.¹²⁷ This process does not mandate a drug-like clinical trial and PMA process as is required for Class III highest risk devices. Rather, it requires a submission that

119. 21 U.S.C. § 360(c).

120. *About the Center for Devices and Radiological Health*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm> (last visited Jan. 22, 2012).

121. The established 510(k) classifications for device manufacturers are listed in 21 C.F.R. §§ 862–880 (2010). If a new device has the same intended use and meets the general description of the device in the classification, then the new device will fall under that regulation scheme. If the device is not currently listed, it will be considered a Class III device and subject to premarket approval requirements until the FDA determines otherwise.

122. Edward C. Wilson, Jr. & Laurie A. Clarke, *The Medical Device Approval Process*, in *A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION* 127, 129 (Kenneth R. Piña & Wayne L. Pines, eds., 2d ed. 2002). These products must typically first complete clinical testing under an investigational device exemption (“IDE”), which is similar in content and requirements to the drug IND but generally involves fewer participants and less extensive clinical trials. Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 J.L. MED. & ETHICS 598, 602 (2009).

123. 21 U.S.C. § 360e(c) (2006).

124. See Alan M. Garber, *Modernizing Device Regulation*, 362 NEW ENG. J. MED. 1161 (2010).

125. Andrew S. Baluch, *Angstrom Medica: Securing FDA Approval and Commercializing a Nanomedical Device*, 2 NANOTECHNOLOGY L. & BUS. 168, 172 (2005).

126. 21 U.S.C. § 360(k) is also expressed as Food, Drug, and Cosmetic Act § 510(k). Some Class II devices are exempt as classified in the Federal Register. See 21 C.F.R. §§ 862–892 (2010).

127. 21 U.S.C. § 360(k).

a device is “substantially equivalent” to a device already on the market and provides for special controls,¹²⁸ which include performance standards, post-market surveillance, patient registries, development of guidelines, recommendations and other actions deemed appropriate by the FDA to “provide reasonable assurance of safety and effectiveness.”¹²⁹ Substantial equivalence is defined as either: (1) having the same intended use and the same technological characteristics of an existing device; or (2) having the same intended use and different technological characteristics but the information submitted to the FDA does not raise new questions of safety and efficacy and demonstrates that the device is at least as safe as the legally manufactured device.¹³⁰ Review times are approximately three months for a 510(k) submission and eight and a half months for a Class III PMA device.¹³¹ Reportedly, of the first six nano-medical devices to enter the market, none were approved through the PMA approval process but instead the 510(k) process based on substantial equivalence to an existing device.¹³² The FDA website reveals that the overwhelming majority of medical devices utilizing the term “nano” (and appropriately described as operating or containing materials at the nanoscale) have been cleared through the 510(k) process.¹³³

Finally, Class I devices are the lowest level of risk, subject typically to general controls which consist of facility registration and product listing with the FDA, record maintenance and filing of marketing reports, adherence to good manufacturing procedures (“GMPs”) and quality system registrations (“QSRs”), and any distribution and use limitations imposed by the FDA.¹³⁴ All devices (Class I–III) are subject to these general controls; additional controls are added as the perceived level of risk increases. All Class I devices undergo either the 510(k) process or are exempt from premarket notification entirely via FDA policy or regulation.¹³⁵

A recent IOM report revealed that a staggering ninety-nine percent of medical devices enter the market either through the 510(k) process or are

128. *Id.* § 360c(a)(1)(B).

129. *Id.*

130. *Id.* § 360c(i)(1)(A).

131. Elizabeth Mansfield et al., *Food and Drug Administration Regulation of in Vitro Diagnostic Devices*, 7 J. MOLECULAR DIAGNOSTICS 2, 3 (2005).

132. Gary E. Marchant et al., *International Harmonization of Regulation of Nanomedicine*, 3 STUD. ON ETHICS L. & TECH art. 6, at 3–4 (2009), <http://www.bepress.com.ezp.slu.edu/cgi/viewcontent.cgi?article=1120&context=selt>.

133. The FDA website has a searchable link for 510(k) and PMA medical devices, arranged by year. For the 510(k) search, visit <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> (last updated Jan. 5, 2012). For the PMA search, visit <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm> (last updated Jan. 5, 2012). See also *infra* Figure 2.

134. 21 U.S.C. § 360c(a)(1)(A) (2006).

135. PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW* 992 (3d ed. 2007).

exempt from any premarket review each year.¹³⁶ The Director of the CDRH indicates that this amounts to approximately 3,000 products passing through the 510(k) process each year.¹³⁷ In response to ongoing criticism and Congress tasking the IOM with a critique of the 510(k) system,¹³⁸ the CDRH has conducted internal investigations of the 510(k) process. The CDRH released two preliminary reports in August 2010 assessing: (1) the existing oversight frameworks for 510(k) medical devices;¹³⁹ and (2) the CDRH's utilization of scientific information in decision-making within the Agency.¹⁴⁰ The 510(k) report addresses long-standing concerns regarding the utilization of substantial equivalence measures rather than requiring premarket approval processes for assuring safety and efficacy.¹⁴¹ One finding highlighted within the report was the inconsistent interpretation of terms such as "substantial equivalence," "intended use," and "different technological characteristics" and the relationship of these terms to the predicate device.¹⁴² This is especially relevant with respect to nanotechnology, as most medical devices utilizing nanotechnology have been cleared via the 510(k) route.¹⁴³ Undoubtedly, these medical devices exhibit new features, properties, and characteristics due to the nanoscale, raising questions about whether the FDA has appropriately allowed them clearance under the 510(k) process.

The second CDRH report acknowledges the needs of the FDA in the face of new scientific information: the need for high-quality and up-to-date information on new science; the need for analytical and technical expertise to assess new science; and the need for operational and organizational

136. INST. OF MED., *supra* note 3, at 4; *see also Protecting Patients from Defective Medical Devices: Hearing on S. 540 Before the S. Comm. on Health, Educ., Labor and Pensions*, 111th Cong. 30 (2009) (testimony of Peter Barton Hutt, Senior Counsel, Covington & Burling LLP).

137. Letter from Jeffrey Shuren, Dir., U.S. Food & Drug Admin. Ctr. for Devices & Radiological Health, to the American Public, *available at* <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM239451.pdf>.

138. *Activity Description, Public Health Effectiveness of the FDA 510(k) Clearance Process*, INST. OF MED., <http://www.iom.edu/Activities/PublicHealth/510KProcess.aspx> (last updated Aug. 1, 2011).

139. CTR. FOR DEVICES AND RADIOLOGICAL HEALTH, U.S. Food & Drug Admin., 1 CDRH PRELIMINARY INTERNAL EVALUATIONS: 510(K) WORKING GROUP PRELIMINARY REPORT AND RECOMMENDATIONS (2010) [hereinafter 510(K) REPORT].

140. CTR. FOR DEVICES AND RADIOLOGICAL HEALTH, U.S. Food & Drug Admin., 2 CDRH PRELIMINARY INTERNAL EVALUATIONS: TASK FORCE ON THE UTILIZATION OF SCIENCE IN REGULATORY DECISION MAKING PRELIMINARY REPORT AND RECOMMENDATIONS (2010) [hereinafter TASK FORCE REPORT].

141. 510(K) REPORT, *supra* note 139.

142. *Id.* at 4–5. Specifically, the report indicates that “[a]s the 510(k) standard has been applied to a wider range of devices over time, including increasingly varied, complex, and potentially higher-risk technologies, the need for greater clarity with respect to these terms has become even more pressing.” *Id.*

143. *See infra* Figure 2.

infrastructure to support the development of expertise and information and to effectuate communication.¹⁴⁴ The report defines “new science” as “new data about the risk/benefit profile of devices; new information about manufacturing practices and processes; new scientific fields and technologies, such as nanotechnology; and new regulatory science, including analytic, tools.”¹⁴⁵ Specifically, the report presents as a case study a novel technology described as a device under review by the CDRH that is “a first of a kind device that uses a new material with unique or unknown biocompatibility properties.”¹⁴⁶ The report gives examples of novel technology within the report as including advances in nanotechnology and medical robotics.¹⁴⁷ As questions of interest, the report asks what steps should be taken to assure that the novel technologies or novel uses are safe and effective.¹⁴⁸ In order to set the course for future changes to the 510(k) process, the FDA has published an Action Plan, laying out twenty-five specific actions to address problems in the current process.¹⁴⁹ These include guidance to provide clarity on the 510(k) process, criteria for identifying “different questions of safety and effectiveness,” and “technological changes that will generally raise such questions.”¹⁵⁰ The FDA also plans to establish a Center Science Council comprised of external scientific experts to aid in developing responses to new scientific information¹⁵¹ and “address[ing] important scientific issues regarding new medical device technologies.”¹⁵² The Action Plan also directs a number of specific questions to the IOM, including clarification of when a particular device can no longer be used by a 510(k) applicant as a predicate device for purposes of substantial equivalence.¹⁵³

On July 29, 2011, the IOM released its much-anticipated report on the state of the FDA’s 510(k) process.¹⁵⁴ The report came to two core conclusions: (1) the “510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices” and “cannot be transformed into a premarket

144. TASK FORCE REPORT, *supra* note 140, at 3.

145. *Id.* at 39.

146. *Id.* at 45.

147. *Id.* at 13.

148. *Id.* at 45.

149. *Plan of Action for Implementation of 510(k) and Science Recommendations*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHR eports/UCM239450.pdf> (last visited Nov. 30, 2011).

150. *Id.* at 2.

151. *Id.* at 3.

152. Letter from Jeffrey Shuren, Dir., U.S. Food & Drug Admin. Ctr. for Devices & Radiological Health, to the American Public, *available at* <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHR eports/UCM239451.pdf>.

153. *Plan of Action for Implementation of 510(k) and Science Recommendations*, *supra* note 149, at 6.

154. INST. OF MED., *supra* note 3.

evaluation of safety and effectiveness” as long as substantial equivalence is the clearance standard;¹⁵⁵ and (2) “[i]nformation that would allow an understanding of the extent to which the 510(k) clearance process either facilitates or inhibits innovation does not exist.”¹⁵⁶ The IOM did not address the specific questions raised by the FDA in their Action Plan, but considered them in their assessment.¹⁵⁷ The IOM offered eight recommendations to the FDA, urging that any further investment in remedying the 510(k) process would not be prudent, in that resources would be better spent developing a new regulatory framework to replace it.¹⁵⁸ These recommendations included collection of adequate information to guide development of such a new regulatory framework, implementation of a strategy to collect and assess post-market information, review of authority in the post-market realm, development of continuous quality-improvement to track medical devices decisions to assist in addressing emerging issues, commission of an assessment of the effect of regulation of devices on innovation, and developing software-specific procedures.¹⁵⁹

These CDRH movements and the IOM report regarding shortcomings in the 510(k) process generally are extremely relevant to nanotechnology in terms of the uncertainty surrounding the novelty of the technologies involved, the lack of metrics to measure and test, and overall challenges in understanding the differences in scientific and technical aspects of the spectrum of medical devices incorporating nanotechnology. Specifically, there are significant questions of whether substantial evidence is appropriate where the links between the technological differences and safety and efficacy may largely remain unknown.

C. *Biological Products*

Biologics are medical products derived from living sources (animals, human, and microorganisms) and include viruses, therapeutic serums, toxins and antitoxins, vaccines, blood and blood products, and cells, tissues and gene therapy products.¹⁶⁰ While biologics are regulated similarly to drugs following 1997 amendments to the FDCA and the Public Health Service Act

155. *Id.* at 193.

156. *Id.* at 195.

157. *Id.* at xi–xii.

158. *Id.* at 7–8.

159. INST. OF MED., *supra* note 3, at 7–13.

160. A biological product is defined as “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.” 42 U.S.C. § 262(i) (Supp. IV 2010).

(“PHSA”),¹⁶¹ there are several important differences between the two. Aside from their derivation from living sources rather than being chemically synthesized, biologics differ from traditional small molecule drugs in a number of ways—they are more complex macromolecular entities, they are typically manufactured using more sophisticated techniques, and they are more susceptible to variations in final product due to manufacturing processes, storage conditions, and interactions with the human body.¹⁶² The Center for Biologics Evaluation and Research (“CBER”) and the CDER jointly handle biologics.¹⁶³

The 1902 Biologics Act¹⁶⁴ predates the FDCA. The core provisions for the biologics license process are contained in the PHSA rather than the FDCA; in 1997 the Food and Drug Amendments and Modernization Act¹⁶⁵ amended the PHSA and FDCA to create parallels in the approval processes. A biologics license application (“BLA”) is issued by the FDA after finding that the product is safe, pure, and potent and the company assures that the manufacturing process and facility is adequate.¹⁶⁶ Following the 1997 amendments, biologics approval incorporates classical FDCA provisions and structures of NDAs, including good manufacturing practice requirements, INDs, post-market authority, and enforcement mechanisms.¹⁶⁷ Biologics are regulated by both the CDER and CBER and the ultimate approval pathway (BLA or NDA) depends on the type of product.¹⁶⁸ However, these amendments did not include incorporation of any generic approval process or patent and market exclusivity provisions for biologics similar to those created by the Hatch-Waxman Act for drugs.

The ongoing struggle for legislative reform to the U.S. health care system culminated in the March 23, 2010, enactment of the ACA¹⁶⁹ and the partner Health Care and Education Reconciliation Act of 2010, signed into law on

161. See 42 U.S.C. § 262(a) & note (2006) (Amendments).

162. Paradise, *supra* note 107, at 281.

163. *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm> (last visited Jan. 22, 2012) [hereinafter *Transfer of Therapeutic Products*].

164. Biologics Control Act of 1902, Pub. L. No. 57-244, 32 Stat. 728.

165. Food and Drug Amendments and Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

166. 42 U.S.C. § 262(a)(2); 21 C.F.R. § 601.2(a) (2010).

167. 42 U.S.C. § 262.

168. The CDER oversees the following products: monoclonal antibodies for *in vivo* use, proteins for therapeutic use extracted from animals or micro-organisms (except clotting factors), growth factors and enzymes, and non-vaccine therapeutic immunotherapies. CBER oversees allergenics, cellular products, tissue products, gene therapy products, vaccines, and blood & blood products. *Transfer of Therapeutic Products*, *supra* note 163.

169. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

March 30, 2010.¹⁷⁰ In addition to extensive provisions aimed at revamping health insurance, the ACA includes a Biologics Price Competition and Innovation subtitle, authorizing the FDA to implement a regulatory approval process for follow-on biologics (also known as biosimilars).¹⁷¹ The impetus to develop a pathway for biologics akin to the generic drug process was largely the promise of cost savings.¹⁷² The generic drug industry estimates they have saved the U.S. health care system approximately \$734 billion,¹⁷³ with the first generic to enter the market generally offering a price twenty-five percent lower than the pioneer.¹⁷⁴ This rises to eighty percent with multiple generics on the market.¹⁷⁵ Biologics, on the other hand, cost an average of twenty-two times that of ordinary drugs,¹⁷⁶ with the eight top selling biologics in 2008 totaling over \$55.6 billion in sales.¹⁷⁷ In 2008, twenty-eight percent of the pharmaceutical industry's top 100 products came from biologics; projected to be fifty percent by 2014.¹⁷⁸ In 2007, Americans spent \$40.3 billion on biologic drugs (out of a total \$286.5 billion for prescription drugs).¹⁷⁹ These prices result in costs to individual patients. For example, Remicade, a treatment for Rheumatoid arthritis, costs \$20,000 per year;¹⁸⁰ Herceptin, for treatment of breast cancer, costs \$48,000 per year;¹⁸¹ Humira, for treatment of Rheumatoid arthritis or Crohn's disease, costs \$50,000 per year;¹⁸² and Cerezyme, for treatment of Gaucher disease, costs \$200,000 per year.¹⁸³

The ACA's Title VII, Subtitle A, § 7001–7003, amends the PHSA and the FDCA to create an approval pathway for submission of a product that is

170. Health Care and Education Reconciliation Act, Pub. L. No. 111-152, 124 Stat. 1029 (2010).

171. Patient Protection and Affordable Care Act §§ 7001–03, 124 Stat. at 804–21.

172. Steven Kozlowski et al., *Developing The Nation's Biosimilars Program*, 365 NEW ENG. J. MED. 385, 385 (2011).

173. Anthony D. So & Samuel L. Katz, Op-Ed., *Biologics Boondoggle*, N.Y. TIMES, Mar. 8, 2010, at A23.

174. U.S. FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 12 (2009).

175. *Id.*

176. So & Katz, *supra* note 173.

177. These biologics were Avastin (\$9.2 billion), Enbrel (\$8.0 billion), Remicade (\$7.9 billion), Humira (\$7.3 billion), Rituxan (\$7.3 billion), Herceptin (\$5.7 billion), Lantus (\$5.1 billion), and Epogen/Procrit (\$5.1 billion). U.S. FED. TRADE COMM'N, *supra* note 174, at 5 fig.1-1.

178. So & Katz, *supra* note 173.

179. FED. TRADE COMM'N, *supra* note 174, at 3.

180. *Id.*

181. *Id.*

182. So & Katz, *supra* note 173.

183. *Id.*

“biosimilar”¹⁸⁴ and possibly “interchangeable”¹⁸⁵ with an already-approved biologic. The legislation enables the Secretary of the DHHS to issue guidance regarding relevant standards and criteria and to implement an approval processes utilizing public comment.¹⁸⁶ The DHHS Secretary delegates this authority to the Commissioner of the FDA.¹⁸⁷ The amendments give much discretion to the Secretary, and thus the FDA, to determine when clinical studies may not be necessary for a given submission.¹⁸⁸ It also includes incentives to encourage development of biosimilar products. The amendments create twelve years of exclusivity for pioneer biosimilar products,¹⁸⁹ a one-year period of exclusivity for the first interchangeable product,¹⁹⁰ and an additional six months of exclusivity for pediatric studies.¹⁹¹ There are also detailed patent disclosure and litigation provisions.¹⁹²

Topics currently under consideration by the FDA as they determine how to implement the new provisions include scientific and regulatory distinctions between the established generic drug approval processes and the new approval process for follow-on biologics (focusing on differences between traditional drugs and biologics based on size, characteristics, complexity, manufacturing processes, reproducibility, and concepts of similarity and interchangeability) and data, market, and patent exclusivity concerns.¹⁹³ It remains to be seen how

184. Biosimilarity means that “the biological product is highly similar to the reference product notwithstanding minor difference in clinically inactive components” and there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.” 42 U.S.C. § 262(i)(2) (Supp. IV 2010). The biosimilar must “utilize the same mechanism or mechanisms of action for the condition or conditions of use” that have been previously approved for the reference product; must have the same route of administration, dosage form, and strength; and must assure that the product is safe, pure, and potent. *Id.* § 262(k)(2)(A)(i).

185. Interchangeability means that biosimilarity is fulfilled and the biologic “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.” *Id.* § 262(i)(3). To receive interchangeable status, the application must include all of the information to show biosimilarity *plus*: a showing of the expectation to provide the same clinical result as reference product in any given patient; and a showing that where “administered more than once to an individual, the risk in terms of safety of diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alteration or switch.” *Id.* § 262(k)(4).

186. *Id.* § 262(k)(8).

187. Richard M. Cooper, *Introduction*, in *FOOD AND DRUG LAW AND REGULATION*, 7 (David G. Adams et al. eds., 2008).

188. 42 U.S.C. § 262(k)(8)(A)–(B).

189. *Id.* § 262(k)(7)(A).

190. *Id.* § 262(k)(6)(A).

191. *Id.* § 262(m)(2)(A).

192. *Id.* § 262(l).

193. *See, e.g.*, Kozlowski et al., *supra* note 172.

this pathway will play out. Thus far, the FDA has formed a Biosimilar Implementation Committee “to plan the agency’s approach to implementing the statute in order to ensure that the process of evaluation, review and approval of products within this newly-defined product category will be achieved in a consistent, efficient and scientifically sound manner.”¹⁹⁴ The FDA reports formation of a working group¹⁹⁵ and the Office of New Drugs (“OND”) has appointed an Acting Associate Director for Biosimilars to assist in the coordination of the CDER’s implementation efforts.¹⁹⁶ A biosimilars Review Committee has also been created within the CDER, “serv[ing] in an advisory capacity to the OND review divisions as they consider sponsor requests for advice about how to develop a biosimilar product and as they review biosimilar BLAs.”¹⁹⁷ The FDA has also solicited feedback via public meetings held in Washington, D.C. focusing on multiple aspects of the BPCIA confronting the FDA, including scientific and technical factors.¹⁹⁸

These new follow-on biologic provisions raise interesting questions for nanomedicine products; the creation of a quicker route to market for products deemed biosimilar opens up questions regarding measures of “highly similar” and “interchangeable” that mimic those of substantial equivalence and bioequivalence in the context of 510(k) cleared medical devices and generic drugs. Without full-scale purity, potency, and safety requirements as mandated by the BLA and NDA provisions, follow-on biologics will pose tough questions for the FDA. One particular area will be that of combination products, discussed below.

D. Combination Products

The OCP was established in 2002,¹⁹⁹ dividing regulatory responsibilities for products combining elements of drugs, devices, and biologics among the

194. *Implementation of the Biologics Price Competition and Innovation Act of 2009*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm> (last visited Jan. 22, 2012).

195. *Id.*

196. *New Acting Associate Director for Biosimilars in Office of New Drugs*, U.S. FOOD & DRUG ADMIN., (May 17, 2010, 3:29 PM), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm217641.htm>.

197. *Id.*

198. Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 61,497 (Oct. 5, 2010).

199. See Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 107-250, sec. 204, § 4(A) 116 Stat. 1588, 1611 (codified at 21 U.S.C. § 353(g)(4)(A) (2006)); see also *About FDA: Office of Combination Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm> (last visited Jan. 22, 2012). The Safe Medical Device Act of 1990 originally gave primary jurisdiction to the most relevant center to regulate combination products. Pub. L.

relevant Centers—CDER, CDRH, and CBER.²⁰⁰ Where a product contains a drug and a medical device, a drug and a biologic, a medical device and a biologic, or all three, it is termed a “combination product” and regulated according to the primary mode of action (“PMOA”).²⁰¹ The PMOA is defined as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.”²⁰² This categorization will determine the Center that will oversee the product, as well as the amount and type of information that the FDA will require.

This collaborative approach to regulation has provided an important framework for emerging medical technologies that integrate chemical, mechanical, and biological aspects. However, as acknowledged by the FDA²⁰³ and corresponding medical agencies abroad,²⁰⁴ nanotechnology poses a new set of questions as products at the nanoscale may exhibit much more complex mechanisms of action(s) not easily quantified or distinguished that do not adhere to traditional safety, efficacy, or risk measures.²⁰⁵ The major regulatory challenge for the FDA is the fuzziness between chemical, biological, and mechanical aspects and modes of action with nanomedicine products and questions of whether existing safety measures are adequate for novel properties and interactions at the nanoscale.

Particularly important for emerging nanomedicine developments, the FDCA distinguishes between the chemical action of drugs and the mechanical action of medical devices, providing that a device “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.”²⁰⁶ Cutting-edge nanomedicine applications in research and development utilize nanoscale properties in a

No. 101-629, sec. 15, § 503(f)(1), 104 Stat. 4511, 4526 (1990) (codified at 21 U.S.C. § 353(f)(1) (Supp. II 1991)).

200. *About FDA: Office of Combination Products*, *supra* note 199.

201. 21 C.F.R. § 3.2(e), (k) (2010).

202. Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49,848, 49,850 (Aug. 25, 2005). Mode of action is defined as “the means by which a product achieves its intended therapeutic effect or action” where “‘therapeutic’ action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.” *Id.*

203. U.S. FOOD & DRUG ADMIN., NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 19–21 (2007), *available at* <http://www.fda.gov/nanotechnology/taskforce/report2007.pdf>.

204. EUR. MEDS. AGENCY COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, REFLECTION PAPER ON NANOTECHNOLOGY-BASED MEDICINAL PRODUCTS FOR HUMAN USE 4 (2006).

205. For the earliest discussion of these problems in the legal literature, see Frederick A. Fielder & Glenn H. Reynolds, *Legal Problems of Nanotechnology: An Overview*, 3 S. CAL. INTERDISC. L.J. 593 (1994).

206. 21 U.S.C. § 321(h) (2006).

manner that integrate chemical, mechanical, and biological with optical, thermal, and other properties to respond to a given environment or outcome once deployed into the body.²⁰⁷ A single product may initially target specific organs and tissues in the human body, image them or take vitals, diagnose medical conditions, and subsequently provide medical therapies or evolve to address the status detected once deployed into the human body. Rigid categories and time-limited assessment regarding chemical and mechanical aspects, as well as the identification of the primary mode of action, may hinder appropriate classification of evolving nanomedical products and lead to underregulation of novel applications.

III. LEGAL AND REGULATORY RESPONSES TO NANOTECHNOLOGY

The evolution of nanotechnology over the last few decades has met with little attention from the FDA and other federal agencies until about 2000. This is chiefly because the unifying term “nanotechnology” was not in widespread use until the National Science Foundation began using it to package and promote once disparate areas of scientific research into one unifying field based on the size and novel characteristics displayed at the nanoscale.²⁰⁸ With the establishment of the NNI and a resulting massive yearly infusion of funding for research, development, and education, nanotechnology was thrust onto the radar of researchers, industry, and invariably the American public.

Despite rapid advances and the infusion of federal dollars into funding, not all coverage of nanotechnology has been positive nor is there unanimous support for the U.S. government’s aggressive funding efforts. Many commentators proffer that nanotechnology research and development is too risky for workers exposed to nanoparticles and nanomaterials as well as consumers and the general population, based on a lack of information on toxicological, biological, environmental, and ecological effects of particles and materials at the nanoscale.²⁰⁹ Some have urged the application of the precautionary principle, a cry parallel to that of a previous decade in the United States (and adopted in the European Union) regarding genetically modified foods—that no nanotechnology be developed or utilized until it is shown to be

207. See, e.g., Nat’l Cancer Inst. Alliance for Nanotechnology, *Nanoshells*, NAT’L CANCER INST., http://nano.cancer.gov/learn/understanding/nanotech_nanoshells.asp (last visited Nov. 30, 2011).

208. See *National Nanotechnology Initiative*, NAT’L SCI. FOUND., www.nsf.gov/crssprgm/nano/ (last updated June 17, 2011).

209. For a discussion of perspectives on nanotechnology risk, see ANDREW D. MAYNARD, WOODROW WILSON INT’L CTR. FOR SCHOLARS, *NANOTECHNOLOGY: A RESEARCH STRATEGY FOR ADDRESSING RISK* (Project on Emerging Nanotechnologies, PEN 3, 2008) [hereinafter MAYNARD, *ADDRESSING RISK*]; see also Andrew D. Maynard, *Nanotechnology: The Next Big Thing, or Much Ado About Nothing?*, 51 *ANNALS OCCUPATIONAL HYGIENE* 1 (2007).

absolutely safe.²¹⁰ Numerous reports from researchers warn that nanoparticles may have neurological and biological effects similar to asbestos and that the long-term use of nanoproducts could have far-reaching negative impact on the environment as they are excreted or otherwise expelled from the body or from consumer products.²¹¹ While compelling, these concerns are beyond the scope of this Article, and are addressed elsewhere.

Academics, professional organizations, government bodies, and non-profit institutions alike have assessed and written on the adequacy of existing legal and regulatory frameworks for nanotechnology, highlighting gaps in the science and oversight, and identifying aspects necessitating particular investigation.²¹² While nanotechnology necessarily crosses multiple agencies

210. Robert F. Service, *Nanotechnology Grows Up*, 304 SCI. 1732, 1733–34 (2004).

211. For toxicology research on fullerenes, see, for example, J.D. Fortner et al., *C₆₀ in Water: Nanocrystal Formation and Microbial Response*, 39 ENVTL. SCI. & TECH. 4307 (2005); Sarah B. Lovern & Rebecca Klaper, *Dahnia Magna Mortality when Exposed to Titanium Dioxide and Fullerene (C₆₀) Nanoparticles*, 25 ENVTL. TOXICOLOGY & CHEMISTRY 1132 (2006); Eva Oberdörster, *Manufactured Nanomaterials (Fullerenes, C₆₀) Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass*, 112 ENVTL. HEALTH PERSP. 1058 (2004). For toxicology research on carbon nanotubes, see Craig A. Poland et al., *Carbon Nanotubes Introduced into the Abdominal Cavity of Mice Show Asbestos-Like Pathogenicity in a Pilot Study*, 3 NATURE NANOTECHNOLOGY 423 (2008); Lin Zhu et al., *DNA Damage Induced by Multiwalled Carbon Nanotubes in Mouse Embryonic Stem Cells*, 7 NANO LETTERS 3592 (2007).

212. See, e.g., LINDA K. BREGGIN & JOHN PENDERGRASS, WOODROW WILSON INT'L CTR. FOR SCHOLARS, WHERE DOES THE NANO GO? END-OF-LIFE REGULATION OF NANOTECHNOLOGIES (Project on Emerging Nanotechnologies, PEN 10, 2007); J. CLARENCE DAVIES, WOODROW WILSON INT'L CTR. FOR SCHOLARS, NANOTECHNOLOGY OVERSIGHT: AN AGENDA FOR THE NEW ADMINISTRATION (Project on Emerging Nanotechnologies, PEN 13, 2008); J. CLARENCE DAVIES, WOODROW WILSON INT'L CTR. FOR SCHOLARS, EPA AND NANOTECHNOLOGY: OVERSIGHT FOR THE 21ST CENTURY (Project on Emerging Nanotechnologies, PEN 9, 2007); J. CLARENCE DAVIES, WOODROW WILSON INT'L CTR. FOR SCHOLARS, MANAGING THE EFFECTS OF NANOTECHNOLOGY (Project on Emerging Nanotechnologies, PEN 2, 2006); E. MARLA FELCHER, WOODROW WILSON INT'L CTR. FOR SCHOLARS, THE CONSUMER PRODUCT SAFETY COMMISSION AND NANOTECHNOLOGY (Project on Emerging Nanotechnologies, PEN 14, 2008); MARK GREENWOOD, WOODROW WILSON INT'L CTR. FOR SCHOLARS, THINKING BIG ABOUT THINGS SMALL: CREATING AN EFFECTIVE OVERSIGHT SYSTEM FOR NANOTECHNOLOGY (Project on Emerging Nanotechnologies, PEN 7, 2007); SAMUEL N. LUOMA, WOODROW WILSON INT'L CTR. FOR SCHOLARS, SILVER NANOTECHNOLOGIES AND THE ENVIRONMENT: OLD PROBLEMS OR NEW CHALLENGES? (Project on Emerging Nanotechnologies, PEN 15, 2008); MAYNARD, ADDRESSING RISK, *supra* note 209; NANOACTION, INTERNATIONAL CENTER FOR TECHNOLOGY ASSESSMENT, PRINCIPLES FOR THE OVERSIGHT OF NANOTECHNOLOGIES AND NANOMATERIALS (2007) available at http://www.icta.org/doc/Principles%20for%20the%20Oversight%20of%20Nanotechnologies%20and%20Nanomaterials_final.pdf; NAT'L NANOTECHNOLOGY INITIATIVE, NAT'L SCI. & TECH. COUNCIL, ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH NEEDS FOR ENGINEERED NANOSCALE MATERIALS (2006) available at http://www.nano.gov/NNI_EHS_research_needs.pdf; NAT'L RES. COUNCIL, REVIEW OF THE FEDERAL STRATEGY FOR NANOTECHNOLOGY-RELATED ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH (2008); WILLIAM B. SCHULTZ & LINDA

that regulate public and worker safety, the environment, national security, and consumer products, the FDA will oversee the majority of nanomedicine products on the market.

Although extremely incremental, the FDA has initiated some agency information-gathering actions to begin to contemplate novel issues raised by nanotechnology products and applications. The FDA has installed a Nanotechnology Task Force,²¹³ fostered intra-agency Center collaborations, begun to implement internal agency policies relating to nanotechnology, and published draft guidance for industry.²¹⁴ Specifically, in May 2010, the FDA's CDER and the Research Office of Pharmaceutical Science issued a policy instructing drug reviewers to collect nanospecific information from new drug applications.²¹⁵ To date, the CDER is the only Center to adopt internal policy regarding nanotechnology.

Although this section will primarily focus on FDA responses to nanotechnology, an initial examination of international, state, and local government actions are instructive to highlight how the piecemeal and uncoordinated efforts at information-gathering and oversight have thus far progressed.

A. *State, Local, and International*

In light of the lack of nano-specific oversight mechanisms at the federal level, the City of Berkeley and the State of California have taken small steps in gathering information on nanotechnology in order to track its use by mandating the reporting of nanoparticle and nanomaterial manufacturing. Berkeley,

BARCLAY, WOODROW WILSON INT'L CTR. FOR SCHOLARS, A HARD PILL TO SWALLOW: BARRIERS TO EFFECTIVE FDA REGULATION OF NANOTECHNOLOGY-BASED DIETARY SUPPLEMENTS (Project on Emerging Nanotechnologies, PEN 17, 2009); MICHAEL R. TAYLOR, WOODROW WILSON INT'L CTR. FOR SCHOLARS, ASSURING THE SAFETY OF NANOMATERIALS IN FOOD PACKAGING: THE REGULATORY PROCESS AND KEY ISSUES (Project on Emerging Nanotechnologies, PEN 12, 2008); MICHAEL R. TAYLOR, WOODROW WILSON INT'L CTR. FOR SCHOLARS, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? (Project on Emerging Nanotechnologies, PEN 5, 2006) [hereinafter TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY]; U.S. ENVTL. PROT. AGENCY, NANOTECHNOLOGY WHITE PAPER (2007), available at <http://es.epa.gov/ncer/nano/publications/whitepaper12022005.pdf>; Kenneth W. Abbott et al., *A Framework Convention for Nanotechnology?*, 36 *Envtl. L. Rep. (Envtl. Law Inst.)* 10,931 (2006); Jordan Paradise et al., *Developing Oversight Frameworks for Nanobiotechnology*, 9 *MINN. J. L. SCI. & TECH.* 399 (2008); Mihail C. Roco, *Possibilities for Global Governance of Converging Technologies*, 10 *J. NANOPARTICLE RES.* 11 (2008); ABA Section of Env't, Energy, & Res., *Nanotechnology Project*, ABA, http://www.americanbar.org/groups/environment_energy_resources/projects_awards/nanotech.html (last visited Nov. 30, 2011).

213. U.S. FOOD & DRUG ADMIN, *supra* note 203, at 5.

214. *See infra* Part III.C.2-4.

215. MAPP 5015.9 REPORTING FORMAT, *supra* note 21, at 3-4.

California requires that manufacturers report yearly to the Toxics Management Division on certain aspects of their manufacturing processes and products.²¹⁶ The California Department of Toxic Substances and Control issued letters in January 2009 to select manufacturers identified as producing nanoparticles or nanomaterials, requesting nano-specific data on carbon nanotubes and methods of worker protection.²¹⁷ The California legislature had authorized the Department to request information on chemicals of concern.²¹⁸ In a joint effort with the California Council on Science and Technology, the California Department of Toxic Substances issued a report in January 2010 detailing enabling legislative provisions, areas of inquiry, and the general status of nanotechnology research and manufacturing in California.²¹⁹ To date, no other state or municipality has followed California's lead.

Internationally, other countries are also at early stages of understanding the scope of the unique legal and scientific questions that nanotechnology may raise. While no countries have enacted nano-specific legislation, there have been some efforts to initiate reporting and tracking mechanisms. A voluntary reporting scheme was implemented in the United Kingdom, but published reports indicate that authorities received an abysmally low number of submissions in response.²²⁰ In 2004, the Royal Society and Royal Academy of Engineering were commissioned by the British government to examine oversight of manufactured nanoparticles and recommended that a ban on free (rather than fixed in a matrix) manufactured nanoparticles in environmental applications be implemented;²²¹ there has been no movement to implement that ban.²²² It appeared from media reports in 2009 that Canada was to claim the

216. BERKELEY, CAL., MUNICIPAL CODE §§ 15.12.040(I), 15.12.050(C)(7) (2008).

217. *Carbon Nanotube Information Call-in*, CAL. DEP'T OF TOXIC SUBSTANCES CONTROL, <http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/CNTcallin.cfm> (last visited Nov. 30, 2011). The Department's future schedule of inquiry to manufacturers in the state over the next few years includes nano silver, reactive nonmetals, dendrimers, and quantum dots.

218. CAL. HEALTH & SAFETY CODE §§ 57019–57020 (West Supp. 2011).

219. CAL. COUNCIL ON SCI. AND TECH., NANOTECHNOLOGY IN CALIFORNIA (2010), available at <http://www.ccst.us/publications/2010/2010Nano.pdf>.

220. DEP'T FOR ENV'T, FOOD & RURAL AFFAIRS, UK VOLUNTARY REPORTING SCHEME FOR ENGINEERED NANOSCALE MATERIALS 4 (2008) (U.K.), available at <http://www.defra.gov.uk/environment/nanotech/policy/pdf/vrs-nanoscale.pdf>; *Archive: Nanotechnology: Policy*, DEP'T FOR ENV'T, FOOD AND RURAL AFFAIRS, <http://archive.defra.gov.uk/environment/quality/nanotech/policy.htm> (last visited Nov. 30, 2011) (stating that DEFRA received only thirteen submissions during the two years of the study).

221. THE ROYAL SOC'Y & THE ROYAL ACAD. OF ENG'G, NANOSCIENCE AND NANOTECHNOLOGIES: OPPORTUNITIES AND UNCERTAINTIES 85 (2004), available at <http://www.nanotec.org.uk/report/Nano%20report%202004%20fin.pdf>.

222. Although the U.K. government issued a response, no further information is available. See The Royal Soc'y & The Royal Acad. of Eng'g, *Nanotechnology and Nanoscience*, NANOTEC.ORG, <http://www.nanotec.org.uk/govRes.htm> (last visited Nov. 30, 2011).

role of being the first country to enact law regarding reporting and monitoring of nanomaterials,²²³ although the bill has yet to become law. Bill C-494, introduced in March 2010, would have amended the Canadian Environmental Protection Act.²²⁴

Australia commissioned Monash University academics to examine that country's existing legal frameworks; they concluded that there were significant gaps when those frameworks were applied to nanotechnology.²²⁵ The European Economic and Social Committee of the European Parliament recommended in a 2005 opinion that the European Commission develop methods to identify nanotechnology risks, setting a recommended timeframe of 2008.²²⁶ Similar to many other countries and regions examining these issues in terms of law and regulations, the European Parliament has not yet responded.

B. Federal Administrative Agencies

As nanotechnology is truly a convergence of scientific fields and disciplines, spanning a vast spectrum of research and product development both in the United States and internationally, U.S. federal agencies have struggled to keep abreast of the rapidly increasing scientific and technological capabilities, applications, and marketed consumer products at the nanoscale. In the face of myriad unknowns regarding health and environmental effects of nanoparticles and nanomaterials, federal agencies have proceeded to measure, evaluate, approve, and monitor nanotechnology processes and products under existing legal and regulatory frameworks. Although a number of U.S. federal regulatory agencies have taken the initiative to either implement voluntary nanotechnology-specific reporting mechanisms,²²⁷ begin expert investigations

223. Victoria Gill, *Nanotechnology Regulation Creeps Closer*, CHEMISTRY WORLD (Feb. 25, 2009), <http://www.rsc.org/chemistryworld/News/2009/February/25020901.asp>.

224. See An Act to Amend the Canadian Environmental Protection Act, 1999, (nanotechnology), Bill C-494 (Historical), 40th Parl., 3d. Session (Can. 2010), available at http://parl.gc.ca/content/hoc/Bills/403/Private/C-494/C-494_1/C-494_1.pdf.

225. KARINNE LUDLOW ET AL., A REVIEW OF POSSIBLE IMPACTS OF NANOTECHNOLOGY ON AUSTRALIA'S REGULATORY FRAMEWORK 8, 100 (2007), available at <http://www.innovation.gov.au/Industry/Nanotechnology/NationalEnablingTechnologiesStrategy/Documents/MonashReport2007.pdf>.

226. *Opinion of the European Economic and Social Committee on the 'Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee—Nanosciences and Nanotechnologies: An action Plan for Europe 2005-2009,'* 2006 O.J. (C 185) 1, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:185:0001:0009:en:pdf>.

227. Although subsequently acknowledging that it has largely failed, EPA instituted a voluntary program for industry to provide information relevant to health and safety for industrial applications of nanotechnology and nanomaterials. OFFICE OF POLLUTION PREVENTION & TOXICS, U.S. ENV'T'L PROT. AGENCY, NANOSCALE MATERIALS STEWARDSHIP PROGRAM: INTERIM REPORT 3, 6 (2009), available at <http://epa.gov/oppt/nano/nmsp-interim-report-final.pdf>.

into specific questions regarding nanotechnology safety or risks,²²⁸ clarify existing regulations and policies in light of nanotechnology,²²⁹ or create internal methods of categorizing nanotechnology developments or products within their purview,²³⁰ for the most part agencies are operating on a business as usual mode for nanotechnology.

Specifically, the EPA has published two notices in the Federal Register applicable to nanotechnology products. The first instructs that the EPA will regulate engineered carbon nanotubes under the Toxic Substances Control Act.²³¹ The second clarifies that the Federal Insecticide Fungicide and Rodenticide Act applies to product claims involving ion-generating silver pesticides.²³² This clarification notice for silver pesticides, while not specific to nanotechnology, was a response to petitions regarding Samsung's marketing claims that its silver ion-generating washing machine utilized nanotechnology in the form of germ-killing silver nanoparticles.²³³

The U.S. Patent and Trademark Office ("USPTO") has also taken steps to deal with the expanse of nanotechnology patent applications by creating a nanotechnology patent class. One source reports that the USPTO began issuing nanotechnology-related patents as early as 1976.²³⁴ In developing a nanotechnology classification system, the USPTO created a framework that attempts to advance uniformity in classifying nanopatents in an effort to standardize the terminology, create an effective system for disclosure and cross-referencing, assist inventors and examiners in identifying and reviewing

228. U.S. FOOD & DRUG ADMIN., *supra* note 203, at 20.

229. Toxic Substances Control Act Inventory Status of Carbon Nanotubes, 73 Fed. Reg. 64,946 (Oct. 31, 2008); Pesticide Registration; Clarification for Ion-Generating Equipment, 72 Fed. Reg. 54,039 (Sept. 21, 2007).

230. *See, e.g.*, MAPP 5015.9 REPORTING FORMAT, *supra* note 21, at 4-5; U.S. PATENT & TRADEMARK OFFICE, CLASSIFICATION DEFINITIONS: CLASS 977 NANOTECHNOLOGY (2010), available at <http://www.uspto.gov/web/patents/classification/uspc977/defs977.pdf> [hereinafter CLASS 977 DEFINITIONS].

231. Toxic Substances Control Act Inventory Status of Carbon Nanotubes, 73 Fed. Reg. at 64,946.

232. Pesticide Registration; Clarification for Ion-generating Equipment, 72 Fed. Reg. at 54,039.

233. Susan Morrissey, *Reclassifying Nanosilver: EPA Will Now Consider Nanosilver Used in Washing Machines as Pesticides*, CHEMICAL & ENG'G NEWS, Dec. 4, 2006, at 14, 14, available at <http://pubs.acs.org/cen/news/84/i49/8449notw7.html> (last visited Nov. 30, 2011).

234. Tyson Winarski & Elizabeth Stoker-Townsend, *Nanotechnology Thriving on Patents*, INTELL. PROP. TODAY, Apr. 2005, at 26, 26 (attributing information to the National Science Foundation). However, the first patent within the USPTO patent classification system was filed in September 1975 and issued in August 1978. *Injectable Compositions, Nanoparticles Useful Therein, and Process of Mfg. Same*, U.S. Patent No. 4,107,288 (filed Sept. 9, 1975).

relevant prior art, and decrease inadvertent patent infringement.²³⁵ As a result of the USPTO's efforts, there are currently over 7410 patents classified as nanotechnology-related inventions²³⁶ under five broadly delineated areas,²³⁷ divided into 263 subclasses.²³⁸ While suffering from numerous shortcomings,²³⁹ these actions by the USPTO serve as an example for other

235. Jordan Paradise, *Claiming Nanotechnology: Improving USPTO Efforts at Classification of Emerging Nano-Enabled Pharmaceutical Technologies*, 10 NW. J. TECH. & INTELL. PROP. 169, 184 (2012).

236. This number is based on the author's search of the USPTO website at <http://patft.uspto.gov/netahtml/PTO/search-adv.htm> using the "Advanced Search" function and the 977 classification as the single search term (enter `ccl/977/$` into the query box). An identical search of the published patent applications at <http://appft1.uspto.gov/netahtml/PTO/search-adv.html> identified 10,613 applications that fall into the 977 classification. Searches performed Nov. 30, 2011.

237. CLASS 977 DEFINITIONS, *supra* note 230. The five broad areas under the 977 class are: (1) nanostructures and chemical compositions; (2) devices that include at least one nanostructure; (3) mathematical algorithms; (4) methods or apparatuses for making, detecting, analyzing or treating nanostructure; (5) and specified uses of nanostructures. *Id.*

238. These Class 977 cross-reference art collection subclasses span sections 700–963. *Id.* at 977-10 to -40.

239. Despite the nascent state of patent litigation involving the scale or characteristics of nanotechnology in the realm of nanomedicine, the scholarly literature has identified several concerns that will emerge as patenting continues. The first major concern is overlapping claims that will occur as the result of broad claiming of early patents and the increased understanding of the properties and functioning at the nanoscale that were unknown in decades past. For example, early patent claims may conflate the macro, micro, and nanoscale in a manner that is problematic for later inventions that identify and harness something present at a range in the nanoscale and not at the micro or macro scale. Another concern is the convergence of technologies at the nanoscale, in that overlapping patents and claims may cross multiple technologies, with many issued before "nano" was a widespread word. Many of these concerns will abate given the USPTO's classification system as patenting moves forward, although questions will arise with regard to inventions submitted and patents issued prior to the development of the classification system. In performing the cross-listing classifications, the USPTO is merely putting issued patents into those 263 subclasses and not making determinations on claim scope and potential infringement from one patent to the next, except as part of the evaluation of prior art. For academic perspectives, see, for example, Indrani Barpujari, *The Patent Regime and Nanotechnology: Issues and Challenges*, 15 J. INTELL. PROP. RTS. 206 (2010); Diana M. Bowman & Graeme A. Hodge, *A Small Matter of Regulation: An International Review of Nanotechnology Regulation*, 8 COLUM. SCI. & TECH. L. REV. 1 (2007); K. Eric Drexler & Jason Wejnert, *Nanotechnology and Policy*, 45 JURIMETRICS J. 1 (2004); Fiedler & Reynolds, *supra* note 205; Ernest J. Getto et al., *Nanotechnology: Will Tiny Particles Create Large Legal Issues?*, SCITECH LAW., Summer 2009, at 6; Mark A. Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601 (2005); Thomas M. Mackey, *Nanobiotechnology, Synthetic Biology, and RNAi: Patent Portfolios for Maximal Near-Term Commercialization and Commons for Maximal Long-Term Medical Gain*, 13 MARQ. INTELL. PROP. L. REV. 123 (2009); Glenn Harlan Reynolds, *Nanotechnology and Regulatory Policy: Three Futures*, 17 HARV. J.L. & TECH. 179 (2003); Douglas J. Sylvester & Diana M. Bowman, *Navigating the Nanotechnology Patenting Landscape: English Garden or Tangled Grounds?*, in BIOMEDICAL NANOTECHNOLOGY 359 (Methods in Molecular Biology, No. 726,

federal agencies in terms of gathering information relevant to nanotechnology and categorizing nano-specific features that could be useful in the future as more becomes known about products, uses, and potential risks of nanotechnology. Utilization and effective linking of this information among agencies could serve as a mechanism to fill in the information gaps currently confronting other relevant agencies.

Aside from these actions by the EPA, the USPTO, and, as described below, the FDA, thus far federal executive agencies responsible for the oversight of the spectrum of nanotechnology products have utilized existing laws, regulations, policy, and institutional structures to govern these products. The authority of these agencies and the administrative tools available to them are diverse and vary greatly across domains. Basic administrative law concepts instruct that federal agencies operate within the authority vested in them by Congress under the enabling statute and subsequent statutes, and construed by the courts. Agencies are able to promulgate regulations or adjudicate individual instances within the bounds of this authority and mandate from Congress. Agency policy and procedures, public and internal guidance, advisory opinions, and a variety of other agency documents serve to clarify and interpret statutes and regulations; while not having the force of law, these documents all contribute to “oversight” in a broad sense.

This section has focused on a discussion of the creation and application of agency-promulgated regulations, the development of public and internal guidance, as well as methods of information gathering that agencies have initiated in the nanotechnology realm such as reporting mechanisms and internal classification schemes. Part III.C and Part IV will address the capacity of the current statutory and regulatory scheme to deal with nanotechnology. This Article urges that the FDA’s broad mandate from Congress and scope of authority with regard to drugs, medical devices, and biologics provide ample opportunity for the Agency to develop requirements for enhanced data and information from industry to inform its assessment of the characteristics and

Sarah J. Hurst ed. 2011); Georgios I. Zekos, *Patenting Abstract Ideas in Nanotechnology*, 9 J. WORLD INTELL. PROP. 113 (2006). For practitioner perspectives, see, for example, Laurie A. Axford, *Patent Drafting Considerations for Nanotechnology Inventions*, 3 NANOTECHNOLOGY L. & BUS. 305 (2006); Raj Bawa, *Nanotechnology Patenting in the US*, 1 NANOTECHNOLOGY L. & BUS. 31 (2004); Matthew J. Dowd et al., *KSR International Co. v. Teleflex Inc.: Another Small Issue for Nanotechnology?*, 4 NANOTECHNOLOGY L. & BUS. 293 (2007); Drew Harris et al., *Strategies for Resolving Patent Disputes Over Nanoparticle Drug Delivery Systems*, 1 NANOTECHNOLOGY L. & BUS. 372 (2004); Vivek Koppikar et al., *Current Trends in Nanotech Patents: A View From Inside the Patent Office*, 1 NANOTECHNOLOGY L. & BUS. 24 (2004) John Josef Molenda, *The Importance of Defining Novel Terms in Patenting Nanotechnology Inventions*, 1 NANOTECHNOLOGY L. & BUS. 174 (2004); Sean O’Neill et al., *Broad Claiming in Nanotechnology Patents: Is Litigation Inevitable?*, 4 NANOTECHNOLOGY L. & BUS. 29 (2007).

properties of nanotechnology products, as well as the assessment of both short and long-term public health effects.

C. *The Food and Drug Administration*

The FDA utilizes existing statutory provisions²⁴⁰ and regulatory pathways to review nanomedicine products falling within its oversight.²⁴¹ This has provoked debate from those that believe that nanotechnology warrants its own oversight provisions.²⁴² The FDA and other agencies struggle with a dearth of observed or reported health or safety issues traceable to any nano-characteristics of a product; this serves as the basis of the FDA's position that the current system thus far provides adequate assurances for safety and efficacy in the case of new drugs and high risk medical devices, bioequivalence in the case of generic drugs, and substantial equivalence in the case of lower risk medical devices.²⁴³

Nanotechnology-based research and development activity in medical and health applications is booming. While many nanotechnology-based medical device products are entering the market (such as *in vitro* diagnostics and imaging tools, dental products, bone repair systems, and tissue reinforcement products), nanomedicine is currently dominated by drugs and drug-delivery applications, accounting for about three-quarters of the emerging nanomedicine market.²⁴⁴ These rapidly developing applications in nanomedicine often integrate mechanical, chemical, electrical, and optical properties at the nanoscale.²⁴⁵ As discussed previously, unlike products at the macroscale and microscale, the distinction between chemical and mechanical action are not easily distinguishable or measurable at the nanoscale.²⁴⁶ While this distinction between chemical, electrical, mechanical, and optical properties is not critical for the science to evolve, it is extremely important in determining which regulatory pathway a company will need to pursue for any given product, as the dividing line between a drug and a device has traditionally been drawn in terms of whether it acts chemically (is metabolized by the body) or

240. Federal Food, Drug & Cosmetic Act, 21 U.S.C. §§ 301–99 (2006).

241. See *infra* Figures 1 & 2.

242. See, e.g., International Center for Technology Assessment et al., Citizen Petition, FDA Docket No. 2006P-0210, at 3–4, 22 (May 16, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/06p0210/06p-0210-cp00001-01-vol1.pdf>.

243. See U.S. FOOD & DRUG ADMIN., *supra* note 203, at 17–18, 22, 24, 32 (noting lack of appropriate testing specifically tailored to nano-scale, as opposed to larger, particles and outlining current testing and regulatory procedures). The Task Force report does not deal with biosimilars specifically as the report was issued three years before the legislation creating the biosimilars pathway. Implementation of those provisions is pending.

244. Wagner et al., *supra* note 42, at 1211.

245. See *infra* Part III.C.1.

246. Fiedler & Reynolds, *supra* note 205, at 608–09.

mechanically.²⁴⁷ This ties directly to categorization as a drug, device, or biologic, and whether abbreviated routes to market are available.

The FDA has taken the following steps with regard to nanotechnology: forming a multi-center task force, instituting a CDER-specific internal policy, publishing draft guidance for industry, soliciting public comments through public meetings, and partnerships with research institutions to examine particular aspects of nanotechnology.

1. Nanotechnology Task Force

An FDA Task Force was convened in response to several citizen petitions aimed at perceived gaps in oversight for consumer products containing nanoparticles.²⁴⁸ To investigate generally whether existing provisions continue to encourage development of safe, effective and innovative products using nanotechnology and also address specific issues raised in the petitions, the FDA established the Nanotechnology Task Force comprised of authorities in the CBER, CDER, and CDRH.²⁴⁹ In July 2007, the FDA's Nanotechnology Task Force issued a report indicating that no new regulatory categories were needed for drug, medical device, and food products that contained nanoparticles or nanomaterials or were manufactured using nanotechnology.²⁵⁰ However, the report also urged that the Agency must continuously monitor and understand the science in order to appropriately apply regulations in the future and suggested that Centers should consider issuing guidance for industry.²⁵¹ The report flagged combination products utilizing nanoscale materials as potentially problematic, acknowledging novel issues for regulation due to their dynamic quality based on size and "their potential for diverse applications."²⁵² Specifically, it provided:

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

247. *Id.*

248. Press Release, U.S. Food & Drug Admin., FDA Forms Internal Nanotechnology Task Force (Aug. 9, 2006), available at <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-33-FDA-Nano%20FDA%20News%20release.pdf>.

249. U.S. FOOD & DRUG ADMIN., *supra* note 203, at 5.

250. *Id.* at 30, 35.

251. *Id.* at 15, 33.

252. *Id.* at 20.

determinations of the most appropriate pathway for such highly integrated combination products.²⁵³

2. CDER Manual of Policies and Procedures

Specific to drugs, the FDA's CDER and the Research Office of Pharmaceutical Science issued an internal Manual of Policies and Procedures ("MaPP") in May 2010 that instructs drug reviewers to capture "relevant information about nanomaterial-containing drugs" that will be entered into a nanotechnology database.²⁵⁴ The MaPP states that "in order to develop guidance for industry, CDER needs to organize all the data submitted in support of nanotechnology-based drug applications,"²⁵⁵ gather all "relevant information about nanomaterial-containing drugs" and enter them into a nanotechnology database maintained by the Agency.²⁵⁶ Of interest for the synthesis of data at the nanoscale, the MaPP defines the terms nanomaterial/nanoscale material ("[a]ny materials with at least one dimension smaller than 1,000nm"); nanomedicine ("[t]he use of nanoscale materials for medical applications"); and characterization ("[p]hysicochemical evaluation of relevant drug properties").²⁵⁷

An important feature of the MaPP definitions is the range included in the CDER's conception of nanoscale as 1–1,000nm compared to the NNI definition extending from 1–100nm.²⁵⁸ This range suggests that the FDA has determined, as many scientists have argued for years,²⁵⁹ that nanotechnology cannot be fit precisely into a range under 100nm, as the size-dependent novel properties vary with the material, environment, and interactions. While this MaPP serves an internal information-gathering purpose and imposes no additional requirements on drug applicants, it signals recognition of the nascent state of understanding of the complex science of nanotechnology in human drugs.

The MaPP provides several attachments that drug reviewers are instructed to complete for each drug application falling into the nanoscale classification. The first is a list of nanotechnology product evaluation questions.²⁶⁰ These questions include identification of the type of nanoscale materials in the product, whether it is a reformulation of a previously-approved product,

253. *Id.* at 20–21 (footnote omitted).

254. MAPP 5015.9 REPORTING FORMAT, *supra* note 21, at 1.

255. *Id.* at 2.

256. *Id.* at 1.

257. *Id.* at 3.

258. *See supra* Part I.

259. *Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks on the Scientific Basis for the Definition of the Term 'Nanomaterial'*, at 13 (Dec. 8, 2010), available at http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf.

260. MAPP 5015.9 REPORTING FORMAT, *supra* note 21, at 6.

whether it is soluble or insoluble in an aqueous environment, the range of the nanomaterial, the reported particle size, other reported properties, and methods used to characterize the nanomaterial.²⁶¹ Another attachment details the template for the format of the drug product database entry, including basic descriptions of the product (e.g., drug name, indication, route of administration, sponsor, approval date, Center division), particle size range, and technique for assessing the nanospecific properties.²⁶² The database entry also includes website links to quality reviews, clinical reviews, ClinPharm reviews, and PharmTox reviews.²⁶³ These last four database entries could be especially useful for ongoing evaluation of the toxicological effects and cross-linking of similar products either by FDA or outside experts or advisory committees if made publically available or available to a segment of specialists. A third attachment provides a product review flow chart, visualizing the series of questions posited in the first attachment questionnaire.²⁶⁴

While this internal procedure is in early stages, it has the potential to generate an abundance of nano-specific information in the context of drug products approved by the CDER. Other FDA Centers should implement similar procedures for products within their regulatory authority, using the CDER MaPP as a guide for structuring this information. This will be particularly illuminating for post-market tracking of combination nanotechnology products that are classified for oversight purposes by their PMOA; it may be that as information accumulates regarding patient use and potentially adverse events that the FDA may want to reassess the use of PMOA measures for nanotechnology-based nanomedicine products. For example, where a nano combination product is classified as a medical device based on its mechanical properties rather than a drug based on its chemical properties (which would mandate more extensive clinical trials to satisfy safety and efficacy measures), it may later become apparent through post-market studies or event reporting that the unique characteristics that make the product “nano” behave in a manner that necessitates a drug-like approval process instead to most adequately assure safety and efficacy.

3. Draft Guidance for Industry

On June 9, 2011, the FDA released draft guidance for industry laying out the Agency’s “current thinking on whether FDA-regulated products contain

261. *Id.*

262. *Id.* at 8. A subsequent attachment lays out the common techniques utilized for nanomaterial characterization, including abbreviations. *Id.* at 10.

263. *Id.* at 8.

264. *Id.* at 9.

nanomaterials or otherwise involve the application of nanotechnology.”²⁶⁵ The guidance urges that the document does not establish legally enforceable obligations, but should be viewed only as recommendations for the industry.²⁶⁶ It “does not establish any regulatory definitions” or “address the regulatory status of products,” but does state that future additional guidance may be issued for specific product or classes of products.²⁶⁷ Published concurrently with an announcement on policy principles for nanotechnology regulation from the Office of Science and Technology Policy (“OSTP”),²⁶⁸ the draft guidance exemplifies the ongoing battle by federal administrative agencies to quantify, categorize, and regulate nanotechnology. The deadline for written comments was August 15, 2011.

Framed as two general points to consider applicable to both new products and any manufacturing changes to FDA-approved and cleared products, the draft guidance provides both a dimensional aspect—“[w]hether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1nm to 100 nm)”—and a behavioral aspect—“[w]hether 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.”²⁶⁹ Notably, the second point expands the first dimensional aspect beyond the 100 nm range *if* the properties exhibited are tied directly to its dimensions up to one micrometer (also called a micron).²⁷⁰

Supporting its two points, the guidance also provides the Agency’s rationale for the elements contained within the points to consider. These largely recite the current state of knowledge of nanoscale properties and

265. *Draft Guidance for Industry*, *supra* note 24 (footnote omitted). For more information, see also *Q & As—Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm258391.htm> (last visited Jan. 22, 2012); Press Release, U.S. Food & Drug Admin., FDA Takes ‘First Step’ Toward Greater Regulatory Certainty around Nanotechnology (June 9, 2011), *available at* <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258377.htm>.

266. *Draft Guidance for Industry*, *supra* note 24.

267. *Id.*

268. OFFICE OF SCI. & TECH. POLICY ET AL., EXEC. OFFICE OF THE PRESIDENT, MEMORANDUM FOR THE HEADS OF EXECUTIVE DEPARTMENTS AND AGENCIES: POLICY PRINCIPLES FOR THE U.S. DECISION-MAKING CONCERNING REGULATION AND OVERSIGHT OF APPLICATIONS OF NANOTECHNOLOGY AND NANOMATERIALS (2011), *available at* <http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf>.

269. *Draft Guidance for Industry*, *supra* note 24.

270. *Id.*

phenomena as the underpinnings of the two points.²⁷¹ Specifically, the FDA distinguishes the “*deliberate* manipulation and control of particle size” of an engineered material or end product from the natural functioning at the nanoscale, identifies the traditional bounds of the nanoscale encompassing 1nm to 100nm as serving merely as “a first [dimensional] reference point” for industry, highlights the relationship between size and physical and chemical properties as important for questions of safety and efficacy, and explains the broadening of dimensions of “nanoscale” up to one micrometer as linking to the use of agglomerates and aggregates that may coat or functionalize a product.²⁷²

4. Public Input

The FDA has also utilized requests for public comments in order to gather information on the scientific aspects of nanotechnology. The FDA has held several public meetings: October 2006 to aid in developing the Nanotechnology Task Force Report;²⁷³ September 2008 to gather information to assist the Agency in implementing recommendations laid out in the Nanotechnology Task Force Report;²⁷⁴ and September 2010 to solicit data and information on biocompatibility assessment of diagnostics and devices that include nanomaterials.²⁷⁵ The FDA also maintains materials for the public on its web page regarding nanotechnology.²⁷⁶

5. Research Efforts

The FDA as an agency does not see much investment for basic research;²⁷⁷ however, the FDA is encouraging nanotechnology research in a number of areas in order to inform agency decisions. The FDA is collaborating with the NIH as part of the National Toxicology Program to address specific product

271. *Id.*

272. *Id.* (emphasis added).

273. Food and Drug Administration-Regulated Products Containing Nanotechnology Materials; Public Meeting, 71 Fed. Reg. 46,232 (Aug. 11, 2006).

274. Consideration of FDA-Regulated Products That May Contain Nanoscale Materials; Public Meeting, 73 Fed. Reg. 46,022 (Aug. 7, 2008).

275. Public Workshop on Medical Devices and Nanotechnology: Manufacturing, Characterization, and Biocompatibility Considerations, 75 Fed. Reg. 51,829 (Aug. 23, 2010).

276. *Nanotechnology*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm> (last updated Sept. 28, 2011).

277. The FDA does support research and development for Orphan Products, but does not itself conduct nanoresearch aside from some research within the individual centers on characteristics of nanomaterials and processes. *FDA Nanotechnology Regulatory Science Research Categories*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm196697.htm> (last visited Jan. 22, 2012).

concerns.²⁷⁸ The National Cancer Institute's Nanotechnology Characterization Laboratory, together with the FDA and the National Institute of Standards and Technology, is conducting "preclinical efficacy and toxicity testing of nanoparticles" in an effort to identify appropriate standards for molecular-sized cancer drugs.²⁷⁹ The FDA has identified its areas of interest, such as risk characterization based on physical and chemical properties, *in vitro* and *in vivo* models to assist in predictions of human response to exposure, quantification methods, measures of adsorption and transport in the human body, and relationships between nanomaterial properties and the human body in terms of uptake via the skin, lungs, and gastrointestinal tract.²⁸⁰

The FDA also boasts several public-private partnerships, including a partnership with Johns Hopkins University and the Houston-based Alliance for NanoHealth ("ANH"). The objectives of the collaboration with Johns Hopkins are laid out as development of relationships for training and outreach and development of collaboration among government and academia.²⁸¹ The ANH collaboration aims to "help speed development of safe and effective medical products in the emerging field of nanotechnology," which entails the FDA and the ANH "work[ing] to expand knowledge of how nanoparticles behave and affect biologic systems, and to facilitate the development of tests and processes that might mitigate the risk associated with nanoengineered products."²⁸²

While only an initial foray into oversight of nanotechnology by the FDA, these moves reflect an incremental and coordinated effort among various FDA Centers, including the CDER, CBER, CDRH, and the Center for Food Safety and Nutrition ("CFSAN") on issues with nanotechnology products.

IV. MOVING FORWARD—ASSESSING OVERSIGHT OPTIONS FOR EMERGING NANOTECHNOLOGY COMBINATION PRODUCTS

The previous two sections illustrate the growing importance of nanotechnology in the spectrum of drug, device, and biological applications reviewed by the FDA. They also highlight the current uncertainty surrounding how to appropriately regulate these products. As previously discussed, the FDA first categorizes such products as a drug, device, or biologic and only then applies safety and efficacy requirements.²⁸³ This categorization

278. See *Partnerships: Federal*, NAT'L TOXICOLOGY PROGRAM, <http://ntp.niehs.nih.gov/go/219> (last updated Nov. 3, 2004).

279. See *Nanotechnology Characterization Lab*, NAT'L CANCER INST., <http://ncl.cancer.gov/> (last visited Nov. 30, 2011).

280. *FDA Nanotechnology Regulatory Science Research Categories*, *supra* note 277.

281. *Nanotechnology Partnerships at FDA*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm208110.htm> (last visited Jan. 22, 2012).

282. *Id.*

283. See *supra* Part II.

determines whether the product will be subject to the most rigorous safety and efficacy measures (NDAs for new drugs, PMAs for highest risk medical devices, and BLAs for biologics) or whether it will be subject only to measures of bioequivalence, substantial equivalence, or biosimilarity. As previously noted, it appears most nanodrugs are entering the market through the premarket approval process requiring safety and efficacy (although some have proceeded to market on an accelerated basis based on promise for treatment of life-saving or serious diseases), while most nanomedical devices have been cleared through the less rigorous 510(k) process requiring only a showing of substantial equivalence to a predicate device.²⁸⁴ Biologics have been subject to safety and efficacy testing as set out in the PHSA; as described in Parts II.C and D, it remains to be seen how the biosimilars pathway will unfold. The regulatory pathways are becoming troublingly Byzantine. As is described above, the discontinuities and silo effects in the current system pose real concerns for long-term safety.

This section urges that the FDA utilize increased data gathering, monitoring and tracking of nano-specific features and outcomes, as well as strengthened collaborative approaches within the Agency, to bolster its treatment of nanotechnology. While not urging application of the precautionary principle, this Article does argue that the FDA can, and should, be doing more to address the uncertainties and safety concerns. This section classifies suggestions for change into several areas: first, implementing general coordination among agencies at the federal level; second, the possibility of organizational restructuring within the FDA; and third, necessary regulatory and policy changes within the FDA to address issues of safety and monitoring of approved nanoproducts.

A. *The Need for a Strong Nanotechnology Coordinating Entity*

In order for any collaborative model to succeed, a strong coordinating entity must be created to facilitate efforts at assessing and adapting oversight of nanotechnology among federal, state, and local agencies. The presence of a well-funded national coordinating entity for contemplation of nanotechnology oversight would assist in synthesizing and applying the emerging findings regarding nanotechnology characterization, measurements, and risk assessment and would lead a more unified, and unifying, approach to development of mechanisms of oversight for emerging nanotechnologies. This is not to suggest, as some esteemed scholars have, that in order to effectively deal with nanotechnology Congress needs to set up a singular federal agency to regulate

284. *See supra* Part II.B.

all nanotechnology products.²⁸⁵ This vision merely urges more collaboration among agencies wrestling with oversight generally, and regulation and policy specifically, in the area of nanotechnology.

The most promising entity within the federal government to serve this role is the NNI. Created in 2000, and situated within the framework of the National Science and Technology Council as a national coordinating entity for nanotechnology research, development and education, the NNI has been the federal vehicle for extensive mobilization and allotment of nanotechnology funding.²⁸⁶ The NNI, which serves as coordinating entity for agencies dealing with nanotechnology, does not have a specific mission or aim involving legal and policy coordination. Although it fosters collaborative efforts in research and education among the agencies, none of the almost ten billion dollars spent on the NNI from 2001–2009²⁸⁷ has been devoted to tackling perhaps the most challenging problem facing these regulatory agencies: how to regulate and oversee the products resulting from this massive national investment.

The NNI does currently have a Nanotech Environmental and Health Implications Working Group that “provides a forum for focused interagency collaborations on EHS [environmental, health, and safety implications] and leadership in establishing . . . the EHS research agenda, in addition to communicating EHS information between NNI agencies and to the public.”²⁸⁸ Likewise, the National Nanotechnology Initiative Amendments of 2009²⁸⁹ provide multiple subgroups under the OSTP for research coordination regarding environment, health and safety, and public engagement.²⁹⁰ Either a separate oversight-specific subgroup could be created or these existing subgroups could be more effectively utilized to address oversight and policy questions.

Unfortunately, Congress and the NNI missed the opportunity to institute such an oversight-contemplating arm as part of the ten-year renewal of the initiative. The NNI recently asked for public comment on its Strategic Plan for

285. J. CLARENCE DAVIES, WOODROW WILSON INT’L CTR. FOR SCHOLARS, OVERSIGHT OF NEXT GENERATION NANOTECHNOLOGY 25 (Project on Emerging Nanotechnologies, PEN 18, 2009), available at www.nanotechproject.org/process/assets/files/7316/pen-18.pdf.

286. *What is the NNI?*, NAT’L NANOTECHNOLOGY INITIATIVE, <http://www.nano.gov/about-nni/what> (last visited Nov. 30, 2011).

287. SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., NAT’L SCI. & TECH. COUNCIL, THE NATIONAL NANOTECHNOLOGY INITIATIVE: RESEARCH AND DEVELOPMENT LEADING TO A REVOLUTION IN TECHNOLOGY AND INDUSTRY: SUPPLEMENT TO THE PRESIDENT’S 2009 BUDGET 7 (2008).

288. SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., *supra* note 60, at 35.

289. S. 1482, 111th Cong. (2009).

290. Gurumurthy Ramachandran et al., *Recommendations for Oversight of Nanobiotechnology: Dynamic Oversight for Complex and Convergent Technology*, 13 J. NANOPARTICLE RES. 1345, 1360 (2011).

the 2011 fiscal year, including targeted aims of “foster[ing] the transfer of new technologies into products for commercial and public benefit” and “responsibly translating . . . knowledge [of the fundamental scientific science] into practical applications.”²⁹¹ In February, the NNI published its 2011 Strategic Plan, highlighting four goals: advancing a world-class nanotechnology research and development program; fostering the transfer of new technologies into products for commercial and public benefit; developing and sustaining educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and supporting the responsible development of nanotechnology.²⁹² While the NNI’s fourth goal alludes generally to public health and the ethical, legal, and social implications of nanotechnology development, it does not include the development of collaborative structures to wrestle with questions of oversight raised by nanotechnology and the importance of partnering evolving scientific information into regulatory decisions and frameworks of the federal agencies.²⁹³

However, as is typically the case with emerging technologies where federal agencies are faced with scientific uncertainty and a lack of assessment measures, large-scale coordination is often cumbersome due to differences in statutory authority, regulatory missions, resources, priorities, and various other factors. Feasibility is a limiting factor for such coordination.

B. Restructuring the FDA

Congress and the FDA have endured long-standing complaints that the categorical statutory and regulatory approach has caused a silo effect among product areas depending largely on definition through amendments to the FDCA spurred by reactions to large-scale events threatening public health and safety.²⁹⁴ While Congress could contemplate the creation of a nanotechnology specific Center or Office within the FDA, this would exacerbate the silo effect by further segregating products based on definitional and categorical aspects. A more workable model would be adjustments within the FDA by the Commissioner to foster increased collaboration among the CDER, CBER, and CDRH perhaps drawing on the established multi-center Nanotechnology Task

291. NNI Strategic Plan 2010; Request for Information, 75 Fed. Reg. 38,850, 38,850 (July 6, 2010).

292. SUBCOMM. ON NANOSCALE SCI., ENG’G, & TECH., *supra* note 60, at 23–32.

293. *Id.* at 30–32. One scholar has specifically urged President Obama to strengthen the oversight role of the NNI and separate it from the promotional role of the NNI in his assessment of the current status of oversight relevant to nanotechnology. See J. CLARENCE DAVIES, WOODROW WILSON INT’L CTR. FOR SCHOLARS, NANOTECHNOLOGY OVERSIGHT: AN AGENDA FOR THE NEW ADMINISTRATION 8–9 (Project on Emerging Nanotechnologies, PEN 13, 2008), available at www.nanotechproject.org/process/assets/files/6709/pen13.pdf.

294. Foote & Berlin, *supra* note 11, at 623.

Force. Such reorganization will be difficult given the current docket in front of the FDA, but the Agency should nonetheless pursue changes in policy that are within its mandate and authority from Congress. Although feasibility of a national coordinating body for nanotechnology legal and regulatory issues and FDA restructuring suffer from inevitable hurdles, the following two subsections suggest a variety of actions that the FDA could implement to initiate the process for improved information-gathering regarding nanomedicine products at the individual product review and approval stage.

C. *Uniform Information-Gathering Frameworks*

Perhaps the most critical steps to address nanotechnology involve the reassessment of concepts and measurements of safety utilizing the existing statutory and regulatory toolkit available. Nanotechnology invariably raises new questions for the FDA's risk versus benefit quantification and assessments due to lack of information regarding risk and public health effects. As discussed in Part I.B, large-scale scientific uncertainty remains regarding short and long-term effects, including toxicity, effect of various exposure routes and routes of administration, possible unintended effects on non-target areas given the ability of nanoparticles to cross the blood-brain barrier, and interaction of various nanoparticles and nanomaterials within the human body. Faced with a dearth of information regarding whether nanoparticles and nanomaterials have novel toxicological effects and would thus demand different measures to assure safety, the FDA has chosen to proceed to regulate based on existing frameworks, taking some small initial steps to gather drug-specific information via the internal MaPP detailed in Part III.C.2 and presenting considerations for industry as detailed in Part III.C.3.

The existing statutory and regulatory scheme under which the FDA operates provides it with sufficient authority over nanomedicine products falling into the categories of drugs, medical devices, and biologics to develop nano-specific rules and regulations according to established administrative procedures.²⁹⁵ The problem turns on determining whether and to what extent nanoproducts warrant additional nano-specific rules or regulations. In order to inform this determination, the FDA needs to gather and assess more information. While several modifications to the process would enhance the FDA's oversight and serve to gather much-needed information to allow the FDA to make such determinations, core concerns remain regarding the expertise necessary to assess safety and efficacy data, how to balance potential novel risks and benefits, and how to monitor possible short-term and long-term effects of nanomedicine products directly attributable to the nanoscale

295. Initial suggestions to improve FDA oversight of nanotechnology are presented by the author in Ramachandran et al., *supra* note 290.

properties. Although the FDA has broad statutory authority to require pre-market and post-market data submission for these three product areas,²⁹⁶ the FDA currently lacks the research budget and personnel to initially identify the amount and type of information to request and subsequently how to assess that data.²⁹⁷ The nascent state of understanding of properties and characterization of nanomaterials and nanoparticles, particularly within the human body, poses a major problem for the FDA.

1. Full-Scale Safety and Efficacy Requirements

As a threshold matter, the FDA should set forth regulations or policy indicating that nanotechnology products are subject to full-scale safety and efficacy requirements for the requisite product categories (i.e., drug, medical device, biologic) until there have been considerable research studies undertaken that examine the range of uncertainties and unknowns. Where subject to the less rigorous approval pathways, there is concern that nanomedicine products may not satisfy traditional measures of equivalence (or similarity) that the FDA employs to deem one product as having the same safety profile because of the unique characteristics and properties exhibited at the nanoscale. This approach is akin to the OCP's decisions involving innovations that raise novel questions for regulation in the realm of combination products and sponsor requests for designation.²⁹⁸ This also responds to current controversy regarding the inadequacy of the 510(k) clearance process for medical devices and the successful completion of Phase IV studies for drugs approved via the Fast Track or accelerated process based on promise for treatment of life-threatening or serious diseases.

Once the FDA has amassed a significant amount of information pursuant to the suggestions in Section IV.C.2 below, conclusions about continuance of such a nano-specific channeling into the most rigorous approval pathway can be based on robust scientific and technical information. The FDA should use the nano-specific information gathered across the three Centers in joint considerations of whether to continue to require the full extent of safety and efficacy data by requiring a nano generic version of a non-nano pioneer drug to go through full NDA process (or a nano follow-on biologic of a pioneer to require a full BLA process), or at least require nano-specific information to be gathered in post-market studies; not allowing medical device products incorporating nanomaterials to be substantially equivalent to a predicate device unless that predicate device has substantially equivalent nanomaterials or nanoproperties (this goes to the scope of the "different technological

296. See *supra* Part II.A–C.

297. TAYLOR, REGULATING THE PRODUCTS OF NANOTECHNOLOGY, *supra* note 212, at 45–47.

298. 21 C.F.R. §§ 3.1, 3.7 (2010).

characteristics” that nonetheless pose no additional threat to safety or efficacy phrase within the statute); and requiring all nanoproducts to proceed through the BLA process rather than allowing measures of biosimilarity or interchangeability to factor into the process.

2. Information-Gathering Mechanisms

Even if the FDA does not implement policy requiring full-scale safety and efficacy for nanoproducts, the FDA should implement specific uniform information-gathering mechanisms. The FDA should proceed in a parallel manner among all Centers pertaining to nanomedicine products—CDER, CBER, and CDRH. Memoranda of Understanding among these Centers would help memorialize these parallel efforts, define key roles, interactions, and ultimate coordination processes for nanomedicine. Information-gathering efforts should be installed that are uniform for NDAs (drugs), BLAs (biological products), and PMAs (medical devices). Within the scope of its authority, the FDA should also mandate that the industry supply the nano-specific information so the burden of information collection does not lie entirely with the FDA. The FDA can use the CDER’s recent MaPP to develop language for other Center policies and procedures of tracking that information, as well as to help identify the information to be required by industry. The FDA should consider whether the information reported to clinical trial online databases should include nano-specific information. In appropriate circumstances, the FDA should utilize relevant regulations and statutory provisions to request post-market studies directed toward the nanoparticle or property of the product, such as REMS and new safety information provisions discussed in Section II.A.

To assist in this endeavor, the FDA needs to utilize its scientific advisory network of experts; request information from scientists and the public in the form of announcements in the Federal Register, public meetings, forums, and other opportunities to identify relevant issues; and develop mechanisms to collect, analyze, characterize, and mine this information. The FDA has begun to do this, having sponsored several public meetings, urging research into characterization and measurement methods, and initiating an internal process in the CDER to begin tracking nanodrugs.²⁹⁹ However, this approach has been piecemeal, with little coordination yet even among Centers within the FDA, let alone collaboration with other federal agencies. It also fails to take advantage of the FDA’s authority to request specific information about a product prior to approval, or clearance of that product.

For those nanomedicine products already approved or cleared that were not subject to the most rigorous pre-approval processes, the FDA should also

299. *See supra* Part III.

request additional information from the manufacturer or sponsor in order to track and assess those nanospecific properties and characteristics. Efforts should also loop into other FDA Centers as well, including the CFSAN (regulating foods, dietary supplements, and cosmetics) and the Center for Veterinary Medicine.

CONCLUSION

The FDA engages in a delicate balance between protecting the public health and safety and promoting advancements in medicine and health care. Technological innovation often outpaces oversight by specialized scientific federal agencies tasked with regulating the resulting products and processes. Nowhere is this lag between innovation and regulatory response more prevalent than the realm of nanotechnology, a spectrum of disciplines and applications that integrates unique and novel properties. Relevant specifically to the FDA is nanobiotechnology and nanomedicine, blending chemical, mechanical, and biological properties in a way that stretches existing oversight frameworks for drugs, medical devices, and biologics. While nanotechnology raises problems for oversight, this Article has suggested several approaches for the FDA to begin assessing and responding to the challenges. These encompass a variety of coordinating and collaborative efforts coupled with the use of authority in the context of increased information gathering from industry and post-market monitoring.

FIGURE 1: EXAMPLES OF FDA-APPROVED DRUGS UTILIZING NANOSCALE PROPERTIES OR MATERIALS³⁰⁰

Product	Indications	Company	Formulation Description	Original Approval
Doxil	Ovarian cancer, breast cancer, and AIDS-related Kaposi's sarcoma	OrthoBiotech Products, LP	Liposomal doxorubicin	NDA November 1995 (<i>accelerated approval</i>)
DepoCyt	Lymphomatous meningitis	Pacira	Liposomal cytarabine	NDA April 1999 (<i>accelerated approval</i>)
Rapamune	Immunosuppressant for prevention of organ rejection in renal transplant patients (13 & older)	Wyeth	Nanocrystalline sirolimus	NDA September 1999
Emend (Aprepitant)	Prevents nausea and vomiting induced by chemotherapy	Merck & Co.	Nanocrystalline aprepitant	NDA March 2003
Estrasorb	Topical soy-based estrogen therapy for treatment of menopausal hot flashes	Graceway	Estradiol in micellar nanoparticles	NDA October 2003
Abraxane	Breast cancer	Abraxis Bioscience	Albumin-bound paclitaxel	NDA January 2005
Emend (Fosaprepitant Dimeglumine)	Prevents nausea and vomiting induced by chemotherapy	Merck & Co.	Lyophilized fosaprepitant dimeglumine	NDA January 2008

300. Information adapted from Paradise et al., *supra* note 14, at 410–17; Paradise, *supra* note 235, at 203–207.

FIGURE 2: EXAMPLES OF FDA-APPROVED MEDICAL DEVICES UTILIZING NANOSCALE PROPERTIES OR MATERIALS³⁰¹

Product	Indications	Company	Formulation Description	Original Approval Information
Simile Nano-Hybrid Composite	Dental material	Pentron Laboratory	Silica-zirconia nanoparticle filler	510(k) January 2003
Nano-Ticrown	Dental material	Nano-Write Corporation	Nanostructured titanium/titanium nitride material	510(k) June 2003
TiMesh	Tissue reinforcement and hernia repair	GfE Meizintechnik	Titanium nanomaterial	510(k) September 2003
Vitoss	Bone graft substitute	Ortho Vita, Inc.	Nanoparticles	510(k) December 2003
Prime & Bond NT	Dental bonding agent	Dentsply International	Nanometer sized bonding agent	510(k) February 2005
ACTICOAT	Antimicrobial wound dressing for burns, graft sites, and ulcers	Smith & Nephew	Utilizes Silcryst silver nanocrystals technology (licensed from NuCryst)	510(k) April 2005
On-Q Silver Soaker	Antimicrobial catheter	i-Flow Corporation	Treated with SilvaGard (licensed from Acrymed)	510(k) November 2005
AcryDerm	Antimicrobial wound gel	Acrymed, Inc.	Polyurethane adhesive using SilvaGard silver nanoparticle technology	510(k) October 2006
Silcryst	Antimicrobial wound cream	NuCryst	Nanocrystalline silver cream	510(k) July 2007
ASAP Wound Dressing	Topical cream	American Biotech Labs	Coated with nanosilver	510(k) April 2009

301. Paradise et al., *supra* note 14, at 415–17; Press Release, American Biotech Labs, American Biotech Labs(R) Obtains FDA Approval for New Wound Care Gel Product (Apr. 14, 2009), available at <http://www.reuters.com/article/2009/04/14/idUS215860+14-Apr-2009+PRN20090414>.

