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BEYOND BIOTECHNOLOGY: FDA REGULATION OF NANOMEDICINE.

John Miller*

Nanotechnology, which involves investigating and manipulating matter at the atomic and molecular levels, may radically transform industry and society. Because nanotechnology could introduce whole new classes of materials and products, it could present an array of novel challenges to regulatory agencies. In this note, John Miller explores the regulatory challenges facing the Food and Drug Administration in regulating nanomedical products. First, the FDA will have trouble fitting such products into the agency's classification scheme. Second, it will be difficult for the FDA to maintain adequate scientific expertise in the field. He concludes that the FDA should consider implementing several reforms now to ensure that it is adequately prepared to regulate nanomedicine.

I. INTRODUCTION

While advances in biotechnology and the rise of the Internet dazzled investors and made headlines in the final years of the twentieth century, a quiet revolution was taking place in the field of nanotechnology. Advances in nanotechnology research, which involves investigating and manipulating matter at the atomic and molecular levels[1], may result in drastic changes in society. In medicine, nanotechnology could produce an array of new products, from novel drugs

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[1] One nanometer, which is one-billionth of a meter, spans 10 atoms. Consider this explanation of how small nano-sized objects are:

> How small do we mean by *nano*? Let's take a trip down the powers of ten: a dime is 1,000 microns thick, a human egg cell is a tenth of that, a red blood cell is a tenth of that, a nerve axon is a tenth thinner still, and you can fit ten viruses along that axon's diameter. Now we're down to 100 nanometers. A cell's membrane is a tenth as thick as that, a DNA strand is a fifth as thick as that, and an amino acid is a third of that. Now we're down to about one nanometer.

Stephan Herrera, *The Big Science of Nanomedicine*, Red Herring Mag., Oct. 30, 2000, at http://www.redherring.com/mag/issue84/mag-nano-84.html.

and devices to nanorobots that travel through the body finding and diagnosing illness. The emerging field of nanomedical research and development will present complex social and ethical issues as well as regulatory challenges. This note will primarily explore the regulatory problems that the Food and Drug Administration will encounter in regulating nanomedical products --- specifically, the problems of fitting such products into the agency's classification scheme and maintaining adequate scientific expertise in the field. Although the FDA has been relatively successful in preparing for these problems in regulating biotechnology, nanomedicine will present more difficult regulatory challenges. Thus far, the agency has done little to prepare for this burgeoning technology. This is unfortunate, because a failure to effectively regulate nanomedical products could be disastrous for public health, the emerging nanotechnology industry, and the FDA. The FDA must act now to prepare for nanomedicine.

Part two of this note will provide an overview of nanotechnology and a detailed description of the coming revolution in nanomedicine. Part three will sketch out the regulatory structure and current state of the FDA, and part four will discuss the consequences of the FDA's failure to effectively prepare for nanomedical products. Part five includes a detailed description of the regulatory challenges posed by nanomedicine, highlights what the FDA has done to address these issues in the context of other emerging technologies such as biotechnology, and explains why it will be more difficult to deal with these challenges in regulating nanomedicine. Finally, part six will propose several courses of action for the agency to effectively prepare for nanomedicine.

II. THE COMING REVOLUTION IN NANOMEDICINE

A. *General Introduction To Nanotechnology*

The dawn of nanotechnology can be traced back to 1959, when Caltech physicist Richard Feynman painted a vision of the future of science. In a talk titled "There's Plenty of Room at the Bottom", Feynman hypothesized that atoms and molecules could be manipulated like building blocks.[2] Soon thereafter, Hollywood provided the public with a glimpse of the future of nano-science with the release of the film Fantastic Voyage, which depicted a surgical team that was miniaturized and injected into a man to operate on a blood clot in his brain.[3]

Nanotechnology began to emerge as a realistic scientific endeavor during the 1980s. In 1982, IBM researchers introduced the scanning tunnelling microscope (STM), a microscope that could display individual atoms of gold.[4] Scientists' abilities to utilize advancing nano tools were highlighted in 1989 when IBM scientists manipulated thirty-five atoms of xenon to form the letters IBM.[5] The last decade has witnessed rapid technological advancements. Scientists have

[2] *Id.* (*quoting* Feynman: "Consider the possibility that we, too, can make a thing very small which does what we want -- that we can manufacture an object that maneuvers at that level!").

[3] Fantastic Voyage (1966), *available at* http://us.imdb.com/Title?0060397.

[4] Robert F. Service, *Atom-Scale Research Gets Real; Outlook For Nanotechnology*, 290 Sci. 1523, 1526 (2000) [herinafter *Outlook*].

[5] Carol Wright-Smith & Christopher M. Smith, *Atomic Force Microscopy*, 15 The Scientist 23, 23 (2001).

demonstrated their ability to "play" with molecules and atoms,[6] and nanostructures have already been incorporated into several commercial products.[7] Such capabilities to explore, manipulate, and build at the nano level will be greatly increased in the coming years.[8]

Nanotechnology could have a dramatic impact on society by significantly transforming industry. Research involving nanotubes, one area of nanotechnology, is likely to yield significant advances in electronics in the near future.[9] Nanotechnology will also have an immediate effect on materials science, optical networking, and medicine.[10] In the longer run, the field is expected to have a profound influence on almost every industry.[11] Richard Siegel, the director of the Rensselaer Nanotechnology Center, predicts that nanotechnology could "cause social and industrial rearrangements not unlike the industrial revolution."[12] Another analyst declares that the new technology "will change the way we live, the way we combat disease, the way we manufacture products, and even the way we explore the universe."[13] K. Eric Drexler, a leading authority on nanotechnology, predicts that nanomachines will allow scientists to prevent

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[6] For example, scientists from Osaka University have revealed a sculpture of a bull approximately the size of a single blood cell. The bulls, fashioned by computer controlled laser, are 10-millionths of a meter long and seven millionths high. 10 of the bull sculptures could stand nose to tail across the width of a single hair. *See* Richard Woods, *Small is Beautiful,* The Weekend Australian, Aug. 25, 2001, *available at* http://australianit.news.com.au/articles/0,7204,2678137%5E15306%5E%5Enbv%5E,00.html. Other scientists have displayed nano-sized guitars and automobiles. *See also* Alexandra Witze, *The Next Small Thing: In Realm of the Tiny, Newfangled 'Nanotech' Knows No Boundaries*, Dallas Morning News, Oct. 30, 2000.

[7] Mihail Roco, *A Frontier For Engineering: The Aim of Nanotechnology is To Build the Future, Molecule By Molecule*, 123 Mechanical Engineering 52, 54 (Jan. 2001), *available at* http://www.memagazine.org/backissues/jan01/features/frontier/frontier.html. According to Roco,

> IBM has developed magnetic sensors for hard disk heads; Eastman Kodak and 3M have produced nanostructured thin-film technologies; Mobil has synthesized nanostructured catalysts for chemical plants, and Merck has produced nanoparticle medicines. Toyota has fabricated nanoparticle reinforced polymeric materials for cars in Japan, and Samsung Electronics is working on a flat-panel display with carbon nanotubes in Korea.

Id.

[8] *Id*. at 53 ("There has been an explosion of discoveries in the last few years, and development is expected to accelerate in the next decade.").

[9] Some companies expect to be producing molecular-sized transistors that can be linked together into complex circuits in the next few years. *See* Robert Service, *Molecules Get Wire*d, 294 Sci. 2442, 2442 (2001) (noting that scientists assembling molecules into basic circuits was the "breakthrough of 2001").

[10] Akansha Atroley, *As Small As IT Can Get*, Computers Today, Aug. 31, 2001, *available at* http://www.india-today.com/ctoday/20010816/trends.html.

[11] Roco, *supra* note 7, at 53 ("Nanoscale science and engineering promise to restructure almost all industries toward the next industrial revolution[.]).

[12] *The Next Big Thing*, MX, Sept. 28, 2001; *see also* Roco, *supra* note 7, at 53 ("This technology will spawn a new kind of industrial revolution in the coming decades. Nanotechnology holds the promise of scientific breakthroughs in a wide range of fields, has an immense potential for industry and the overall economy, for better health care, and for a sustainable environment.").

[13] John Falciono, *Changing the Way We Live*, 123 Mechanical Engineering 4, 4 (Jan. 2001).

death by cellular repair, build spaceships, construct computers the size of credit cards that would be billions of times more powerful than existing computers, eliminate pollution, rebuild extinct plants and animals, and efficiently produce food to end hunger on the planet.[14]

The potential of nanotechnology to transform society has not gone unnoticed. In 2000, President Clinton launched a $422-million National Nanotechnology Initiative (NNI) to galvanize research and development in the field.[15] In 2002, federal funding for nanotechnology reached over $500 million.[16] Mihail Roco, chair of the National Science and Technology Council's subcommittee on Nanoscale Science, Engineering, and Technology, maintains that federal funding for nanotechnology gives "assurance to industry that this field will be developed much sooner."[17] States have also begun to channel funds toward nanotechnology research,[18] and universities are beginning to offer doctorates in nanotechnology.[19]

Federal and state funding for nanotechnology is complemented by private investment. Venture capitalists, disillusioned by the burst of the Internet bubble, have begun to target nanotechnology as a field ripe for investment.[20] Start-up companies are emerging,[21] and eager

[14] *See generally* K. Eric Drexler, Engines of Creation (1986); K. Eric Drexler, et. al., Unbounding the Future (1991).

[15] The Subcommittee on Nanoscale Science, Engineering, and Technology was established to implement the Nanotechnology Initiative. *See* Roco, *supra* note 7, at 55.

[16] *National Nanotechnology Initiative: Research and Development FY 200*2, *available at* http://www.nano.gov/2002budget.html. There are ten federal agencies funded by the program: Department of Defense, Department of Energy, Department of Justice, Environmental Protection Agency, Department of Transportation (FAA), National Aeronautics and Space Administration, National Institutes of Health, National Institutes of Standards and Technology, and the National Science Foundation, and the U.S. Department of Agriculture. *Id.* The National Science Foundation is making the largest investments by establishing university nanotechnology centers and sponsoring interdisciplinary research programs. The participating universities are: Columbia, Cornell, Rensselaer Polytechnic Institute in New York, Harvard, Northwestern, and Rice. *See* Scott Nance, *Six University Centers Funded As Part of Federal Initiative To Jumpstart Nanotechnology,* New Tech. Week, Oct. 1, 2001.

[17] *See* Roco, *supra* note 7, at 55.

[18] *See, e.g. Texas Nanotechnology Initiative Elects Board of Directors: Consortium Is Dedicated to Positioning Texas As Leader,* PR Newswire, Jan. 18, 2002 (quoting the President of the Texas Nanotechnology Initiative: "Texas has already begun establishing a nanotechnology community with roots in Austin, Dallas and Houston. TNI will focus on growing the academic, corporate, governmental, and investment infrastructure necessary to make Texas a hotbed for nanotechnology."); Kenneth Weiss, *Davis Awards Science Funds; Education: The Governor Selects Three Institutes, Including One Based at UCLA, to Receive $300 Million,* L.A. Times, Dec. 8, 2000 (noting that the university-based California Nanosystems Institute, with locations on several state university campuses, received millions in state funds); *Nanotech Hubs Spread All Over,* United Press International, July 11, 2001 (noting that the Pennsylvania Technology Investment Authority allocated $10.8 million to create a Nanotechnology Institute).

[19] In July 2001, the University of Washington launched the nation's first doctoral degree program in nanotechnology. Tom Paulson, *UW, Richland Join In Brave New World of Nano,* The Seattle Post-Intell., Sept. 10, 2001.

[20] Patrick Seitz, *Up and Atom With Latest: Nanotechnology,* Inv. Bus. Daily, Sept. 28, 2001.

[21] For example, Zyvex was established to develop a molecular assembler. Robert Freitas, *Say Ah! Nanorobots the Size of Bacteria Might One Day Roam People's Bodies, Rooting Out Disease Organisms and Repairing*

investors have started to attend conferences and read investment reports. [22] Corporations like HP, IBM, and 3M are allocating approximately one third of their research budgets to nanotechnology.[23] One New York venture capitalist observes that corporations are "actively shifting resources and appropriating R&D budgets to capture value and a distinct competitive advantage in what will be, as many agree, a high-growth, multi-billion dollar industry in just a few years."[24]

Other countries have also recognized the importance of investing in nanotechnology. Japan[25], South Korea[26], Canada[27], and the European Community[28] can all boast of programs in nanotechnology.

B. *Nanomedicine*

One of the most promising applications of nanotechnology is in the context of medicine. Indeed, a whole new field of "nanomedicine" is emerging. Nanomedicine has been defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures.[29] Almost every drug company in the world has begun to engage in nanotechnology research.[30] The National Cancer Institute and the National Aeronautics & Space Administration are working to develop nano-sized technologies that can detect, diagnose, and treat disease.[31] Researchers in the field are "confident that they are

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Damaged Tissue, The Sciences 26, 29 (July / Aug. 2000)**.** Carbon Nanotechnologies was established to produce carbon nanotubes. *See* Peter Fairley, *The Start of Something Big*, Chem. Week, Dec. 12, 2001.

[22] For example, the NanoBusiness Alliance has sponsored several "workshops" in 2002 and 2003 relating to nanotechnology investment. *See generally* http://www.nanobusiness.org. LuxCapital has recently release the *Nanotech Report,* at http://luxcapital.com/index2.htm.

[23] *First Definitive Study On Nanotechnology Released By Lux Capital; 'The Nanotech Report' Highlights Investment Implications Major Themes and Leaders in Nanotechnology,* PR Newswire, Aug. 29, 2001.

[24] *Id.*

[25] Woods, *supra* note 6 (noting that Prime Minister Junichiro Koizumi earmarked $162.5 million for nanotechnology research at state universities).

[26] South Korea announced in August 2001 that it would be "pouring hundreds of millions of dollars" into the industry during the next ten years. Woods, *supra* note 6.

[27] Peter Calamai, *Forget Those Sci-Fi Tales, the Nano-Truth is Awesome,* Toronto Star, Aug. 26, 2001. (noting that Jean Chretien, Canada's Prime Minister, has "declared … that nanotechnology is today's equivalent of the Industrial Revolution").

[28] Service, *Outlook*, *supra* note 4, at 1525.

[29] Robert Freitas, Nanomedicine 2, (1999), *available at* http://www.foresight.org/Nanomedicine.

[30] Herrera, *supra* note 1.

[31] *See* Andrew Lawler, *Plans For Mars Unite Cancer, Space Agencies*, 288 Sci. 415, 415 (2000) (noting that NASA and the NCI "announced that each intends to spend $ 10 million a year for the next 5 years in a coordinated

going to turn healthcare inside out."[32] Richard Smalley, a Nobel Prize-winning chemist at Rice University, described to Congress the potential of nanotechnology to transform medicine:

> [T]wenty years from now … nanotechnology will have given us specially engineered drugs … that specifically [target] just the mutant cancer cells in the human body, and [leave] everything else blissfully alone … Cancer … will be a thing of the past.[33]

Current applications of nanotechnology in medicine range from research involving diagnostic devices and drug delivery vehicles to robots that can enter the body and perform specific tasks. In the near future, applications of nanomedicine will involve engineered molecules to develop drugs, drug delivery techniques, diagnostics, medical devices and enhanced gene therapy and tissue engineering procedures**.** However, sophisticated nanorobots that can function in the body will not be practical for many years, if ever.

1. Drugs

Researchers have already begun to develop novel drugs using nanotechnology. Three examples of this class of nanomedical products include engineered cyclic peptides that kill bacteria, a molecular nanogenerator that targets and destroys cancer cells, and drugs based on the fullerene molecule. A group of researchers report that they have created a class of biological polymers, known as peptide nanotubes, that can effectively combat deadly bacteria.[34] The amino acids that comprise cyclic peptides are altered so that they target bacteria and insert themselves into the bacterial membrane where they spontaneously self-assemble into nanostructures.[35] The normal functioning of the cell is disrupted, and the bacteria die.

Researchers are also developing a "nanogenerator" that can target cancer cells and destroy them.[36] The product is comprised of a molecular cage that uses a chemical ring to grab and hold a single radioactive atom, actinium-255.[37] The cage is attached to an antibody that targets cancer cells. When a cancer cell is reached, the radioactive atom is inserted into the cell. Once inside the cancer cell, the actinium-255 atom breaks down, high energy alpha particles are

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effort to develop devices that could both speed detection of cancer on Earth and keep astronauts healthy during long sojourns from home.").

[32] Ian Sample, *Small Visions, Grand Designs,* New Scientist, Oct. 6, 2001, at 30.

[33] Robert Freitas, *supra* note 29, at 26 (quoting Smalley in testimony before a congressional subcommittee about the promise of nanotechnology).

[34] M. Reza Ghadiri et. al., Antibacterial Agents Based on the Cyclic D, Lpeptide Architecture, 412 Nature 451, 452--455 (July 26, 2001).

[35] *Id* at 452.

[36] David A Scheinberg et. al., *Tumor Therapy With Targeted Atomic Nanogenerators*, 294 Sci. 1537, 1537 (2001).

[37] *Id* at 1537--1538.

released, and the cell is destroyed.[38] Tests on mice with prostate cancer and widespread lymphoma have been highly successful, and researchers plan to file an application with the FDA to begin clinical trials in the near future.[39]

Finally, researchers are investigating the use of the fullerene molecule, a hollow sphere made up of 60 carbon atoms, to develop new drugs. Fullerene can interact with cells, proteins, and viruses, and can be altered to perform specific tasks.[40] C Sixty, a Canadian company, has already begun to apply to the FDA for clinical trials on a drug that will target HIV.[41] The fullerene molecule binds to and inhibits the normal functioning of an enzyme which is essential for survival of HIV.[42]

2. Drug Delivery

Nanomedical research has also focused on creating mechanisms to more effectively deliver drugs. The most basic drug delivery systems based on nanotechnology enhance the effectiveness of drugs by targeting certain types of cells[43], speeding up delivery time[44], and preventing digestive enzymes from breaking down the medication.[45]

Researchers are also investigating advanced drug delivery mechanisms. For example, James Baker is experimenting with polymer dendrimers, tree-shaped synthetic molecules.[46] Dendrimers have surface properties that allow them to attach to other molecules, and they can carry molecules internally. Baker believes that his research will ultimately produce a drug delivery device that can "infiltrate cells and detect pre-malignant and cancerous changes", release a chemical substance to kill the cells, and verify destruction of the cells.[47]

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[38] *Id* at 1537--1540.

[39] Phone conversation with Memorial Sloan Kettering Cancer Institute in New York (Jan. 6, 2002).

[40] *C Sixty Brings in New Investors Funding Moves Buckyball Based Drugs Toward Clinical Trials*, Internet Wire, Dec. 11, 2001.

[41] *Id.*

[42] http://www.csixty.com/learn.htm.

[43] Yoshihisa Suzuki of Kyoto University in Japan has developed a novel drug molecule that can release antibiotics only when it is near an infection. *See* Freitas, Nanomedicine, *supra* note 29, at 27.

[44] Elan Pharmaceutical Technologies claims that by using "Nanocrystals", they can enhance the solubility and speed the delivery time of a drug. *See Nanocrystals: Nanoparticulate Drug Delivery Technology*, *available at* http://atlas.pharmalicensing.com/licensing/displicopp/65.

[45] Ferrari is developing a nano-engineered pill that will allow people to take drugs orally that typically require intravascular injection. The surface of Ferrari's pill prevents digestive enzymes from breaking down the drug in the stomach. Sample, *supra* note 32, at 35.

[46] David Voss, *Nanomedicine Nears The Clinic*, 103 Tech. Rev. 60, 62 (2000).

[47] *Id.* at 65.

Other researchers are developing implantable devices that can periodically dispense medicines, such as insulin or morphine.[48] These devices, composed of copolymer-nanoshell composites, are capable of holding medicine. When the nanoshells are exposed to infrared light, the drug is released into the surrounding tissue.[49]

3. Diagnostics

Nanotechnology could significantly improve diagnostic capabilities. First, nanomedicine will increase the efficiency and accuracy of diagnosis from samples of body fluids. For example, some companies are attempting to develop microchips that use electrodes to identify the dielectric properties of cancerous cells, viruses, and bacteria in body fluids.[50]

Second, nanomedicine could result in non-invasive devices that can enter the body to determine glucose levels, distinguish between normal and cancerous tissue, and provide genetic screening for multiple diseases. For example, researchers are working with a nanoscale needle that can probe cells for carcinogenic chemicals.[51] Ultimately, research in this area could yield a tiny pill that will travel through the body and provide a comprehensive diagnosis of the patient's health.[52] There are even some who suggest that tiny devices could be implanted to constantly monitor health. As one reporter speculated, a person in the future may look at her watch, and it will read: "Slow down . . . your pulse is too high, and you are about to have a heart attack."[53]

4. Devices

[48] *See* Valerie Coffey, *Gold Nanoshells May Deliver Drugs*, *Detect HIV*, Laser Focus World, July 1, 2001, at 46.

[49] *Id.*

[50] Allen E. Menezes et. al., *Within A Nanometer of Your Life: Advances in Semiconductor Manufacturing Techniques Are Bringing Medicine Closer to Cures and Treatments That Have Eluded Researchers Working On The Macro Level*, 123 Mechanical Engineering 54, 56 (Aug. 2001) (noting that researchers at the University of Wales have developed a microchip technology that can diagnose diseased or damaged cells in body fluids and that Aura Oncology has been established to commercialize the technology); *see also* Woods, *supra* note 6 (noting that, in August 2001, a British biotech company revealed a handheld device that gave an analysis of a drop of blood in a matter of seconds); Daithi O' hAnluain, *Cancer Fight Dips Into Microchips,* Wired News, Oct. 15, 2001, *available at* http://www.wired.com/news/medtech/0,1286,47500,00.html (noting that researchers are developing a microchip that offers instant detection of cancerous cells).

[51] The nano-needle, a 50 nm-diameter silver-coated optical fiber carrying a helium-cadmium laser beam, is attached to monoclonal antibodies. The antibodies bind to BPT, a product of a chemical reaction between cellular DNA and a cancer-causing pollutant. The laser light causes the antibody-BPT complex to fluoresce, and the fluorescent light travels up the fiber to an optical detector. *See* Menezes, *supra* note 50, at 57.

[52] For example, researchers from Scottish Universities of Glasgow, Edinburgh, and Strathclyde are working on project "Robodoc", a capsule that will travel through the body finding and diagnosing illnesses. Woods, *supra* note 6.

[53] Woods, *supra* note 6.

Nanomedical research could result in an array of new medical devices. In the short run, surgical tools will be enhanced by nanotechnology. For example, nanotechnology has resulted in a surgical scalpel based on a nanostructured diamond that slices more neatly into eyeballs.[54]

Nanotechnology could also result in miniature devices that can be implanted to correct auditory, visual, and sensory impairment.[55] According to one scientist, "[v]isual image-enhancement or processing implants may be feasible within a decade."[56]

5. Gene Therapy

Human gene therapy involves introducing a gene into the body to treat or cure a disease or abnormal medical condition.[57] Although the FDA has not granted marketing approval to a gene therapy product, scientists have hope that gene therapy products could treat a range of medical conditions including cancer, cystic fibrosis, heart disease, hemophilia, and infectious diseases such as HIV.[58] The primary problem researchers have encountered is finding a vehicle to deliver the gene to the nucleus of the cell without eliciting an immune response. Thus far, researchers have primarily experimented with delivery vehicles that involve wrapping genes in genetically engineered viruses or coatings of fat.[59]

Nano devices could be used to make gene therapy safer and more effective. Baker is experimenting with polymer dendrimers as vehicles for gene therapy.[60] The relevant gene is attached to the dendrimer molecule, and the unique properties of the synthetic molecule allow the gene to be inserted into the targeted cell without provoking an immune reaction. Animal trials have demonstrated that dendrimers can transfer DNA into the nucleus of the cell without triggering a harmful immune reaction, and Baker is hopeful that human trials could begin in less than two years.[61]

6. Cell Therapy / Tissue Engineering

Tissue engineering and cell therapy involve the use of living cells and other natural or synthetic compounds to develop implantable parts for the restoration, maintenance, or

[54] *The Smaller the Better*, The Econ., June 23, 2001.

[55] V. Vogel, *Societal Impacts of Nanotechnology in Education and Medicine*, *in* Societal Implications Of Nanoscience and Nanotechnology, 143, 146 (Mihail C. Roco & William Sims Bainbridge eds., March 2001).

[56] *Id.*

[57] *Gene Therapy*, at http://www.fda.gov/cber/gene.htm.

[58] *Id.*

[59] Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology 87 (2000).

[60] Voss, *supra* note 46, at 62. *See also* Herrera, *supra* note 1 ("These beautiful creations seem capable of sneaking into diseased cells without sending the immune system on the warpath. It is the advantage of the purely artificial device.").

[61] Voss, *supra* note 46, at 62.

replacement of the body's tissues and organs.[62] Nanotechnology research in the field of tissue engineering has primarily focused on reducing the risk of immune reaction. For example, to treat patients with pancreatic cells that do not produce enough insulin, researchers have experimented with implanting insulin-producing cells from a pig. [63] However, the primary problem associated with such a procedure is that the immune system attacks the foreign pig cells.[64] Researchers are conducting clinical trials using a silicon capsule with nano-sized pores that prevents the immune system from identifying the foreign cells.[65] The pores, which are only a few nanometers wide, are small enough to screen out the antibodies employed by the immune system while large enough to allow insulin molecules to exit into the bloodstream.[66] Nanoporous fabrication technology could also be used to direct the growth of tissue[67] and facilitate the integration of synthetic materials into the human body.[68]

In the long run, nanomedical research could lead to the development of artificial cells that can be implanted in the brain. Complex networks of neurons are responsible for intelligence, motor control, and sensing. Researchers have made significant breakthroughs in constructing nanotechnology-based transistors that act like individual neurons[69] and are hopeful that they can

[62] The fields of tissue engineering and cell therapy are usually distinguished. However, for purposes of this brief description, the entire field will be referred to as "tissue engineering."

[63] *See* Menezes, *supra* note 50, at 58; Voss *supra* note 49, at 63--65; Sample, *supra* note 32, at 32; Kristen Philipkoski, *Tiny Capsules Float Downstream*, Wired News, Oct. 29, 2001, at http://www.wired.com/news/technology/0,1282,47934,00.html.

[64] Philipkoski, *supra* note 63.

[65] *Id.*

[66] *Id.*

[67] Tissue reconstruction efforts have involved the use of a scaffold to grow tissue. However, researchers have encountered difficulty in directing organized tissue growth. By dotting the surface of the scaffold with nano-pores, researchers believe that they will be able to "shape and weave" the tissue. Research involving a "smart bandage" composed of biodegradable plastic with nano-sized grooves aids in healing severed tendons illustrates this concept. Traditionally, operations on severed tendons have been highly ineffective, because the regenerating natural tissue sheathing attaches itself to the tendon, precluding mobility The nano pores on the bandage allow macrophages to grow into the grooves of the bandage separated from the sheathing and promote adhesion of the tendon to the rest of the tissue. Although researchers at Glasgow University have only recently begun clinical trials, it is believed that this technique will allow researchers to direct the growth of any pattern of tissue. *See* Menezes, *supra* note 50, at 57.

[68] Nanomedical products can facilitate the integration of synthetic materials into the body. For example, researchers are experimenting with a biomaterial containing nano-sized pores to treat spinal disc deterioration. When the material is fused with vertebrae, the porous structure allows the bone to gradually infiltrate into and throughout the device. The natural and artificial materials join together resulting in spinal reconstruction and less nerve compression and pain than traditional therapies. Menezes, *supra* note 50, at 55.

[69] See Bai, Q., K.D. Wise, and D.J. Anderson, *A High-Yield Microassembly Structure For Three-Dimensional Microelectrode Arrays*, 47 IEEE Trans. Biomed. Eng. 281, 281--89 (2000). *See also* Vogel, *supra* note 55, at 146 (noting that "major progress has already been made in recording from single neurons and their stimulation, and culturing nerve cells on microelectronic devices").

develop a neurobiochip that contains many transistors and can act as a group of brain neurons.[70] The chip could be implanted in patients with damaged or malfunctioning brain circuitry.

7. Nanorobots

Some researchers are attempting to construct complex nanorobots that can travel throughout the human body using molecular motors and computers, store and transport molecules, perform operations, and communicate with physicians. Robert Freitas has written extensively about the technical details, specific requirements, and physical limitations of nanorobots.[71] He paints the picture of how nanorobots will transform medicine by describing how a future doctor might treat a bacterial infection:

> There will be no need for antihistamines, cough drops and a weeklong course of antibiotics. The physician keeps several generic classes of nanorobots in her office for just such a circumstance. She types the name of the offending bacterium into a computer. Following the computer's instructions, she programs billions of nanorobots to find, recognize and destroy the particular microbial strain. The nanorobots are suspended in an aerosolized carrier fluid, which the patient inhales. . . . [T]he nanorobots march down the patient's throat, moving by way of legs, screw drives, flagella or another form of autonomous locomotion. The robots follow a search pattern, and they destroy any harmful microorganisms they encounter. The patient feels nothing: nanorobots are the size of bacteria, which constantly crawl on and inside the body without being noticed. . . .With an acoustic homing device [the physician] guides the nanorobots back into the patient's mouth, where she retrieves them through a collection port on the tip of the homing device.[72]

Not only will nanorobots treat pathogens, but Freitas and others think that they will be able to eliminate cancer and HIV as life-threatening conditions, reverse trauma and injury from burns and accidents, enhance mental capabilities and physical abilities, and slow down aging.[73]

Different researchers have described different medical nanorobots. Examples of nanorobots are "microbivores" and "pharmacy in a cell". "Microbivores," a concept designed by Freitas, are nano-sized devices that bind to targeted bacteria. The bacteria are transported to a

[70] Menezes, *supra* note 49, at 56 (noting that the "neurochip would be a prosthetic device for the brain, much like an artificial heart, prosthetic hip, or knee"); *see also* Vogel, *supra* note 55, at 146 (concluding that it is likely that brain implants will eventually be able to enhance or compensate for lost brain function).

[71] Freitas, Nanomedicine, *supra* note 29.

[72] Freitas, Nanomedicine, *supra* note 29, at 28.

[73] Menezes, *supra* note 50, at 58 ("Biomedical nanotechnology will make it possible to build nanorobots having cellular dimensions with the ability to eliminate infections, unclog arteries, and a range of other applications. . . . Who can say? Biomedical nanotechnology's future may one day eliminate old age, or at least its symptons."); Robert Freitas, *What Would Be The Biggest Benefit To Be Gained For Human Society From Nanomedicine?,* at http://www.foresight.org/Nanomedicine/NanoMedFAQ.html#FAQ19.

chamber where they are digested by a sequence of 40 engineered enzymes.[74] The remains are then harmlessly discharged into the bloodstream.[75]

Carlo Montemagno is attempting to construct a nanorobot that acts like a "pharmacy in a cell."[76] This nanorobot enters a cell, grabs proteins produced by the cell that will not be used, and stores them until they are later needed by the patient. The nanorobot consists of a nickel drum attached to a biological motor. The drum is coated with antibodies that pick up molecules, and an electric field pulls the molecules to a storage chamber and holds them in place. The motor would be powered by ATP.

In recent years, researchers have made significant progress in building the robots and motors that will power them. Scientists have made strides using two different methods to build sophisticated nanorobots. Some have used miniature robots or microscopic tweezers to build nanorobots molecule by molecule.[77] Other scientists have made impressive breakthroughs in researching self-assembly, where nano-parts are thrown together and spontaneously assemble.[78] They have also made progress in developing nano-sized springs, cogwheels, levers, and bearings[79] as well as a "glue" to join nanostructures.[80] Montemagno has built a nanomotor comprised of a genetically modified ATPase protein attached to a tiny propeller.[81] The production and breakdown of ATP by the protein, caused by electrochemical reactions with each of the molecule's three proton channels, causes the protein to rotate and the propeller to turn. Other researchers are experimenting with motors powered by different sources.[82]

However, despite the pace at which research is progressing and the excitement generated by the prospect of nanorobots, it could be many years before nanorobots are tested in humans.

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[74] Robert Freitas, *Nanomedicine Art Gallery,* at http://www.foresight.org/Nanomedicine/Gallery/Species/Microbivores.html.

[75] *Id.*

[76] *See generally* Sample, *supra* note 32, at 34--35*;* Paul Sharke, *hybrid NEMS*, 123 Mechanical Engineering 42, Feb. 2001, at 42, *available at* http://www.memagazine.org/backissues/feb01/features/nems/nems.html.

[77] Freitas, Nanomedicine, *supra* note 29, at 26. This process is known as positional assembly; Zyvex LLC was established to build a "molecular assembler."

[78] *Id.* "Sticky" molecules, such as a carboxylate group, have been used to connect nano-sized rods and connectors. Because DNA is made up of two complementary strands of nucleotides that bind together, researchers have also experimented with using genetic material to induce self-assembly.

[79] Witze, *supra* note 6.

[80] *See* Fiona Harvey, *Scientists Find a New Way to Glue Technology*, Fin. Times, Nov. 1, 2001, at 17. (noting that researchers believe that resin-gas injection assisted bonding can be used to join nanostructures).

[81] Carlo D. Montemagno, et. al, *Powering an Inorganic Nanodevice with a Biomolecular Motor*, 290 Sci. 1555, 1555 (Nov. 24, 2000); Voss, *supra* note 49, at 65.

[82] Japanese scientists have designed "spinning screws" that could be steered around the body magnetically. The "spinning screws" are made of cylindrical magnets. *See* Ian Sample, *Twist and Scout*, New Scientist, June 13, 2001, at 2020. Other researchers have attempted to develop a biological fuel cell that uses glucose and oxygen in the blood to produce electricity. For example, Adam Heller at UT Austin is working on a fuel cell comprised of two carbon fibers coated with the enzymes glucose oxidase and laccase. *See* Sample, *supra* note 32, at 35.

Steven Block, a biophysicist, argues that there is still "a lot of basic science work that needs to be done" and that scientists still "don't know how to design … complex macromolecules that work."[83] Even Richard Smalley, a believer in the potential of nanotechnology to transform medicine, has doubts about nanorobots: "What they talk about doing with nanorobots is beyond even my own considerable imagination. . . Turn on the lights everybody; it ain't gonna happen like that."[84] Critics argue that precise manipulation of atoms is extremely difficult. Even if individual nanorobots could be assembled, it may be impossible to produce billions of nanorobots necessary for commercial applications.

Nevertheless, there is reason to believe that nanorobots will have some impact on medicine in the next 30 years. Montemagno maintains that within two years, he will be able to demonstrate the uses of his biological motor[85], and Freitas avows that most of the work in designing and constructing nanorobots "should be complete within the next 20 to 30 years."[86] Rapid advancements in the last few years demonstrate that nanotechnology "can go from fiction to reality in 10 years."[87] Ultimately, only time will tell if nanorobots are more science fiction than reality.

III. THE FDA

A. *Overview of the FDA's Regulatory Framework*

The FDA is the agency responsible for regulating the safety and effectiveness of most food products, human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products, cosmetics, and animal feed.[88] The agency, which operates under the Department of Health and Human Services, has a budget of $1.294 billion and 9,100 employees.[89] The FDA is organized into several centers that specialize in regulating particular types of products: the Center for Food Safety and Applied Nutrition (CFSAN); the Center for Drug Evaluation and Research (CDER); the Center for Biologics Evaluation and Research (CBER); and the Center for Devices and Radiological Health (CDRH). CDER, CDRH, and CBER, which regulate drugs, devices, and biologics respectively, will primarily be responsible for regulating nanomedical products.

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[83] Patrick McGee, *Sizing Up Nanotechnology*, Wired News, June 26, 2000, at http://www.wired.com/news/technology/0,1282,37217,00.html.

[84] Herrera, *supra* note 1.

[85] Sample *supra* note 32, at 37.

[86] Freitas, Nanomedicine, *supra* note 29, at 17.

[87] Sample *supra* note 32, at 32 (quoting Gary Sayler, a microbiologist at the University of Tennessee).

[88] *The Food and Drug Administration: An Overview*, at http://www.fda.gov/oc/history/historyoffda/default.htm (adapted from George Kurian, ed., *A Historical Guide to the U.S. Government* (1988).

[89] See John P. Swann, *History of the FDA*, at http://www.fda.gov/oc/history/historyoffda/default.htm.

The Center for Drug Evaluation and Research is responsible for regulating drugs under the Federal Food, Drug, and Cosmetic Act of 1938 and its amendments. [90] In order to manufacture and market a new drug, a manufacturer must first file an Investigational New Drug (IND) application to get approval for human subjects research.[91] CDER must approve and monitor the clinical trials. Upon completion of clinical trials that test the product's safety, effectiveness, and dosage, CDER may approve a New Drug Application (NDA) if the benefits of the drug outweigh the risks.[92] The manufacturer must comply with labeling requirements and a set of manufacturing regulations called the current Good Manufacturing Practices (GMPs).[93] CDER can levy a "user fee" on manufacturers for reviewing a new drug application.[94] The revenue generated from user fees must be used to make approval more efficient.

CDRH is responsible for regulating medical devices under the Federal Food, Drug, and Cosmetic Act and its amendment.[95] Devices are classified into three different categories: Class I, Class II, or Class III. Class I devices present the lowest risk and are subject to "general controls."[96] Class II devices are subject to "special controls,"[97] and Class III devices present the greatest risk and are subject to review for safety and effectiveness. In order to obtain FDA approval for clinical trials, a manufacturer must submit an Investigation Device Exception (IDE). In order to market the device, a manufacturer must submit a Premarket Approval Application (PMA), which imposes strict conditions on the manufacturing and labeling of the device. A new

[90] The 1906 Food and Drugs Act, empowered the FDA to regulate drugs that were adulterated (unsanitary or unsafe) or misbranded. The 1906 Act limited the effectiveness of FDA regulation in two significant ways: the FDA could not regulate drugs before they were sold, and the FDA had to prove that the seller knew its claims were false. The 1938 Federal Drug and Cosmetic Act enabled the FDA to require premarket notification. The manufacturer could market a drug within 180 days of notifying the FDA unless the FDA challenged its safety. The tragic births associated with Thalidomide in the 1950s resulted in the Congress enacting amendments in 1962. The amendments required the FDA to confirm the effectiveness and safety of the drug before marketing could take place. The FDA was also given greater authority in designing and supervising clinical trials. *See generally* Peter Barton Hutt & Richard A. Merrill, Food and Drug Law: Cases and Materials 4--6 (2d ed. 1992); Richard A. Merrill, *Symposium on Regulating Medical Innovation: The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753 (1996).

[91] *See* James T. O'Reilly, Food and Drug Administration § 13.11 (2d ed. 1995).

[92] *Id.*

[93] *Id.*

[94] 21 U.S.C. §§ 379g--379h (1994).

[95] Prior to 1938, medical devices were not subject to federal regulation. The 1938 Federal Drug and Cosmetic Act authorized the FDA to regulate medical devices. However, regulatory authority was limited to adulterated or misbranded products, and the FDA was primarily focused on drugs. In 1976, Congress amended the act to substantially increase FDA regulation of medical devices. *See* Merrill, *supra* note 93, at 1800--12.

[96] "General controls" include: (1) regulations against adulteration or misbranding; (2) regulations requiring establishment regulation and product listing; (3) premarket notification; and (4) compliance with good manufacturing practices. *See* James T. O'Reilly, Food and Drug Administration § 18.05 (2d ed. 1995).

[97] "Special controls" include: (1) some performance standards; (2) requirements for patient registries; and (3) post-market surveillance of the device. *See* 21 U.S.C. §360c(a)(1)(B)(2000); O'Reilly, *supra* note 96, at § 18.06.

device that is "substantially equivalent" to a device already being marketed is not subject to review as a Class III device if the manufacturer obtains 510(k) approval.[98]

While drugs and devices are regulated under the Food, Drug, and Cosmetic Act, biologics are regulated by CBER primarily under the Public Health Service Act.[99] CBER is responsible for regulating a wide variety of "biologics": "blood and blood components, devices, allergenic extracts, vaccines, tissues, somatic cell and gene therapies, biotech derived therapeutics, and xenotransplantation."[100] CBER's responsibilities in regulating biologics are similar to CDER's responsibilities in regulating drugs. Approval must be granted for clinical testing of new biological products. In order to obtain a license to market, the agency must determine that a biological product is "safe, pure, potent, and manufactured accordingly".[101]

B. *Current State of the FDA*

In the mid 1990s, the FDA came under attack for unnecessary delays in availability of new drugs, biologics, and medical devices.[102] Congress passed the FDA Modernization Act (FDAMA) of 1997 to improve the efficiency and effectiveness of FDA regulation.[103] The legislation included provisions focusing on regulation of drugs and biologics[104] and medical

[98] The FDA can treat as "substantially equivalent" devices that have the same intended use and the same technology as an existing device or differ in design or technology from a predicate device but perform the same function and are shown to be as safe and effective. O'Reilly, *supra* note 96, at § 18.07.

[99] Ch. 288, 37 Stat. 309 (1912) (codified at 42 U.S.C. §§ 201 et seq. (1994)).

[100] Lorrie Harrison McNeill, *CBER Update - Spring 2001*, Update 2001 (Spring 2001) at http://www.fdli.org/pubs/Update/2001/Issue4/McNeill/print.html.

[101] O'Reilly, *supra* note 96, at § 13.22.

[102] Thomas M. Lenard & Brian Mannix, *The Future of Medical Innovation: Reaping the Benefits of the Knowledge Revolution* (1995) (arguing that "Americans receive the benefits of fewer new drugs and medical devices later than they should.").

[103] Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 301 et seq. (1994)).

[104] The most significant initiative to enhance the efficiency of drug regulation was the reauthorization of "user fees" on drug manufacturers. § 101--107. The legislation also attempted to increase patient access to experimental drugs through the fast-track process and increase the similarities between regulations on drugs and biologics and streamline the approval process for clinical research on drugs and biologics. § 112, § 123(f) states:

> The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).

In an attempt to streamline the approval process for clinical research on drugs and biologics, FDAMA enables clinical investigations to begin 30 days after the manufacturer provides the FDA with a submission containing required information. § 117. A manufacturer can request to meet with the FDA to collaborate in designing clinical trials for NDA's and BLA's. § 119. The legislation also intended to increase the use of scientific advisory panels and simplify the approval process for drug and biological manufacturing changes. § 120, § 116.

devices[105] as well as several broad policies intended to improve the overrall effectiveness of the FDA.[106] The FDAMA was initially haled as a success in improving regulation. The late 1990s witnessed the FDA significantly decrease review times for drugs, biologics, and devices despite increasing applications for sophisticated products.[107] However, the agency will face several regulatory challenges in the coming years. First, clinical research continues to skyrocket[108], and there is evidence that review times will lengthen in the near future.[109] Second, the terrorist attacks of September 11 have put additional pressures on the FDA. Since the FDA regulates products that could be utilized by terrorists, there have been calls for the agency to assume a more prominent role in combating terrorism.[110] Third, the agency has also come under attack after being forced to make several high profile withdrawals such as Rezulin[111] and the publicized death of a patient in clinical trials.[112] As a result, the FDA is approving fewer products.[113]

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[105] Congress authorized the FDA to allow third party review of low-risk 510(k)'s and put a higher priority on FDA review of life-saving devices. § 210, § 202. The act directed the FDA to institute "early meetings" with product sponsors. § 201, § 205. Finally, the act mandated that the FDA consider the "least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval." § 205.

[106] First, the legislation introduced a process for dispute resolution when a scientific controversy arises between the manufacturer and the agency. § 404. Second, the legislation placed a strong emphasis on consultation and cooperation with domestic and international entities. The Act notes that the FDA should "participate. . .with representatives in other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements;" and "carry out [its mission] in consultation with experts . . . and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products." § 406. Under § 414, the FDA was directed to implement programs and policies to enhance collaboration with the NIH and other science-based Federal agencies, and under § 415, the FDA was encouraged to enter into contracts with organizations or individuals to enhance product evaluation. The agency was also directed to establish a system for recognizing national and international standards in product review. § 410.

[107] *See generally FDA's Drug Review and Approval Times,* at http://www.fda.gov/cder/reports/reviewtimes/default.htm.

[108] Industry research for new drugs and devices increased by 150% during the 1990s. The NIH research increased by 50%. Alan Slobodin*, New FDA Commissioner Must Rapidly Adapt FDA To New Security Role*, 16 Legal Backgrounder 45 (October 19, 2001).

[109] In 1999, the median time between submission and approval for new drugs and biologics was 12 months for regular product applications and 6 months for priority applications. *FDA's Drug Review and Approval Times,* at http://www.fda.gov/cder/reports/reviewtimes/default.htm. However, in 2000, the median time lengthened to approximately 16 months. Slobodin*, supra* note 108. In 2000, review times for 510(k) applications were approximately two months and review times for PMA applications were approximately 8 months. Lewin Group, Outlook for Medical Technology Innovation: Will Patients Get The Care They Need? Report 4: The Impact of Regulation and Market Dynamics on Innovation 12--13, (4th Report 2001). However, the FDA predicts that device times will increase based on current resource projections. Slobodin, *supra* note 108.

[110] *See* Slobodin, *supra* note 108 (noting that "[m]anagement control, policy making, and policy implementation at the FDA must reflect the Administration's counter-terrorism priority and policies")

[111] Kim Dixon, *FDA More Cautious In Approving Drugs*, The Record (Bergen County), Sept. 9, 2001.

[112] Jesse Gelsinger died in September 1999 as a result of immune complications associated with a gene therapy procedure. *See* Tim Friend, *Gene-therapy Patient Died of the Procedure,* U.S.A. Today, Dec. 2, 1999.

Despite these additional pressures and responsibilities, the agency's budget has remained constant.[114]

IV. WHAT'S AT STAKE IN FDA REGULATION OF NANOMEDICINE

FDA regulation of nanomedicine, like FDA regulation of other novel technologies, requires the FDA to engage in a careful balancing act. The agency must attempt to promote timely patient access and foster innovation while also protecting public health by guarding against unsafe technologies. A failure to adequately prepare for reviewing products based on nanomedicine could have significant ramifications for public health, the FDA, and the emerging nanotechnology industry.

First, public health could be jeopardized in two distinct ways if the FDA is not prepared to regulate nanomedical products.[115] If a lack of agency preparation results in hasty approval of dangerous therapies and a failure to effectively monitor clinical research, patients could be exposed to a significant risk of harm during clinical trials. The death of Jesse Gelsinger in September 1999 as a result of complications associated with an experimental gene therapy procedure demonstrates the safety risks associated with the failure to effectively monitor clinical trials.[116]

Alternatively, a lack of agency preparation could take the form of unnecessary delays in patient access. Inadequate resources combined with a growing caseload, an inefficient regulatory structure, a lack of expertise, or FDA reviewers exercising extreme caution could all result in the FDA taking excessive amounts of time to review new technologies. Unnecessary delays could result in patients being denied access to potentially life-saving and health-enhancing medical devices.

Second, ineffective regulation could have a substantial impact on nanomedical research and development. If a poor regulatory decision results in a publicized casualty, clinical research in the nanomedical sector could be brought to a halt. Researchers already fear that it will be difficult to recruit patients for clinical trials involving nanomedical products.[117] If a research

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[113] The number of approvals dropped significantly in 2001. There were several high profile rejections such as Zelnorm for irritable bowel syndrome. *See* Dixon, *supra* note 111.

[114] Slobodin, *supra* note 108.

[115] Larry Thompson, *Science at FDA: The Key to Making the Right Decision*, FDA Consumer Magazine, March-April 2000, at http://www.fda.gov/fdac/features/2000/200_sci.html. ("Given the breadth of the scientific information used by the agency, FDA's scientists and managers must work to remain current lest they miss something and put the country's public health in jeopardy. . . . The consequences may be nothing less than life and death.").

[116] *See* Friend, *supra* note 112.

[117] Michael Brooks, *Thanks But No Thanks,* New Scientist, Oct. 6, 2001, at 33.

> ([I]t still isn't clear whether anyone actually wants to be a nanomedicine guinea pig. It's all very well to dream up and develop cell-repair machines, but what if the prospect of rampaging nanorobots or unexpected immune reactions means that no one is prepared to have the technology implanted?. . . The fate of trial subjects in similar endeavors might make saying no to nanomedicine not seem like such an extreme reaction.).

subject were to perish as the result of an experimental procedure involving a nano-product, it would become nearly impossible to recruit patients willing to engage in human subjects research. Without the volunteers necessary to conduct large-scale trials, the industry would be unable to secure FDA approval for marketing. Start-ups would be severely crippled, and investors could lose confidence in the field.[118]

Other emerging medical technologies as well as the entire nanotechnology industry would also be impacted by a high profile injury or death. FDA reviewers always fear that approval of a dangerous product will result in an embarrassing interrogation before Congress;[119] the reluctance to approve any new clinical trial or product would be significantly magnified in the aftermath of a tragedy. Furthermore, such an incident involving a nanomedical product would be utilized by opponents of nanotechnology to bolster their case for a legislative ban on all nanotechnology research.

If ineffective regulation takes the form of regulatory delays rather than hasty approval, the industry will also be crippled. Increased delays in approval for clinical research and marketing result in increased difficulties for start-up companies attempting to secure financing.[120] Increased delays also decrease the likelihood of larger companies devoting resources toward novel research and development.[121]

A failure to prepare for nanomedicine could also impair the efficacy of the FDA. The American public has historically maintained high confidence in the FDA. Indeed, the FDA takes great pride in its "proud tradition" that allows the public to live with "peace of mind."[122] Severe injuries or death during clinical trials and product recalls could reduce the public's confidence in the FDA. At the same time, regulatory delays that result in patient suffering or deaths could also shatter public support. A distrusting public would undermine the effectiveness of the FDA. Recruitment efforts would be hampered and the spirit of managers and employees would be dampened. The agency acknowledges the importance of public support: "[I]n order to keep

[118] Bogdan Dziurzynski, *FDA Regulatory Review and Approval Process: A Delphi Inquiry*, 51 Food and Drug L.J. 143, 144 (1996), (noting that manufacturer's "inability to establish a consistent track record of success further complicated the ability of companies to raise capital").

[119] *Id*. at 145 (noting that "FDA reviewers do all they can to avoid being publicly criticized for a purported lack of regulatory oversight" and that this has caused the agency to become "one of the most conservative government health protection agencies in the world").

[120] *See id.* at 144 ("Trade press reports on the complexities of drug development and the failure of some biotechnology companies to successfully navigate the regulatory waters jaded analysts and made investors apprehensive.").

[121] Lewin Group, *supra* note 109, at 11 (noting that "[t]o the extent that new technology raises this form of regulatory uncertainty or otherwise challenges the readiness of the agency to manage regulation in a timely and predictable manner, companies may be discouraged from attempting to develop some of these more innovative technologies").

[122] *FDA's Growing Responsibilities For the Year 2001 and Beyond,* http://www.fda.gov/oc/opacom/budgetbro/budgetbro.html ("This peace of mind is an important contribution to the special quality of life, confidence and vitality that makes the United States the envy of the world --- and it is a part of FDA's proud tradition [.]").

fulfilling the public's expectations and maintaining its confidence, FDA needs the public's support."[123]

V. CHALLENGES POSED BY NANOMEDICINE

The FDA will face an explosion of applications for novel therapies in the coming years, and a substantial portion of these new therapies will be based on nanomedicine. Indeed, the FDA itself has identified nanotechnology as a burgeoning arena of science that the agency must prepare for. At a Science Board meeting in November 2000, Elizabeth Jacobson, the Senior Advisor for Science, noted that "[n]anotechnology is no longer science fiction."[124] The centers have recognized that they will encounter nano-products in the near future.[125] Jane Henney, the former FDA Commissioner, noted that nanorobots that can enter the circulatory system to deliver genes and drugs are on the "near horizon."[126] As nanomedicine come closer to fruition, it will present complex social and ethical issues as well as regulatory issues.

A. *Social and Ethical Issues*

Nanomedicine will generate social and ethical debates regarding issues such as whether implantable nano-devices that can constantly monitor for illness compromise privacy rights and risk abuse; whether neurobiochips that stimulate brain function give humans machine-like qualities and steer society on a path toward mental manipulation through implantable devices in the brain; and whether technology that makes bones stronger, enhances speed, and improves longevity is socially desirable.[127] Appalling visions of a future world dominated by nanorobots have already caused some to call for a prohibition on all nanotechnology research. For example, Bill Joy of Sun Microsystems has argued that abuse of nanotechnology could pose a threat to

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[123] *Id.*

[124] Elizabeth Jacobson, 2000 FDA Science Board Meeting, Nov. 17, 2000, at 26. Jacobson further explains:

> In April, NASA and NCI announced a Memo of Understanding to develop nano explorers, their term, for the human body in the form of injectable nano robots or nanobots that will roam the body to detect, diagnose, and treat disease. . . . These little nano bots would be biosensors, and probably drug use delivery systems as well.

[125] CDRH has noted that it will be challenged to resolve complex issues connected with emerging technological developments such as nanotechnology. *See Better Health Care With Quality Medical Devices: FDA on the Cutting Edge of Device Technology,* at http://www.fda.gov/opacom/factsheets/justthefacts/5cdrh.html. CBER acknowledges nanotechnology could be the delivery vehicle for gene therapy in the near future. *See Human Gene Therapy and The Role of the Food and Drug Administration*, Sept. 2000, at http://www.fda.gov/cber/infosheets/genezn.htm.

[126] Jane Henney, *Jane Henney Delivers Remarks at the National Press Club*, FDCH Political Transcripts, Dec. 12, 2000.

[127] For a detailed analysis of the complex social and ethical issues associated with nanomedicine and nanotechnology, *see* Societal Implications Of Nanoscience and Nanotechnology (Mihail C. Roco & William Sims Bainbridge eds., March 2001).

humanity.[128] Nanotechnology could result in a devastating plague or be used to create weapons of mass destruction.[129] Even Drexler has predicted the ways in which this technology might be harmful. His writings discuss the "grey goo" problem: nanomachines self-replicating out of control and demolishing everything in their path.[130]

Proponents have responded to calls for the prohibition of nanotechnology research and development in several ways. First, a group of nanotechnology advocates promulgated the Foresight guidelines in June 2000.[131] Identifying the potential ways in which nanotechnology might be abused, the document outlined measures to encourage responsible use and governmental supervision. Second, proponents have argued that the fears expounded by Joy and others are hyperbolized or simply wrong.[132] Finally, proponents note that, because development of nanotechnology is inevitable, society should embrace it and begin to prepare for it. [133]

While these ethical and social discussions should take place, the FDA maintains that these issues should be fleshed out in Congress and not by a regulatory agency.[134] There are currently no laws regulating nanotechnology, and Congress is unlikely to pass legislation addressing nanotechnology in the near future.[135] Without congressional action, it is likely that the FDA will regulate nanomedical products within the framework provided by current statutes[136]; thus, review will focus on the safety and efficacy of individual products.

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[128] Bill Joy, *Why The Future Doesn't Need Us*, Wired Mag., Apr. 2000, at http://www.wired.com/wired/archive/8.04/joy.html.

[129] *See generally* John Heilemann, *Second Coming - The PC May Have Sparked The Information Age, But Tomorrow's Computing Power Will Ignite Extraordinary Revolutions That Will Transform Our World - For Better of For Worse*, PC Magazine, Sept. 4, 2001; Chris Evans-Pughe, *Monster Technology*, Electronics Weekly, June 6, 2001; Raymond Kurzweil, *Promise and Peril - The Deeply Intertwined Poles of the 21st Century Technology: Technology Information*, Communications of the ACM, March 1, 2001.

[130] Drexler, Engines of Creation, *supra* note 14, at 172--173.

[131] *See* Foresight Institute, *Foresight Guidelines on Molecular Nanotechnology* (Revised Draft Version 3.7 June 4, 2000), at http://www.foresight.org/guidelines/current.html.

[132] Service, *Outlook*, *supra* note 4, at 1524 (noting that nanoscience researchers have begun to fight back).

[133] Gina Kolata, *Scientists Debate What to Do When Findings Aid an Enemy*, N.Y. Times, Sept. 25, 2001 (quoting Professor Reynolds of the Foresight Institute: "Barring some new scientific law that makes nanotechnology infeasible, you're going to have it sooner or later.").

[134] The FDA has indicated that it will regulate nanomedical products based on considerations of safety and efficacy and not policy considerations. *See* Jacobson, *supra* note 124, at 27 (noting that "[w]e don't claim to be as envisionary as that or to be worried about that aspect of things, but robotic applications and medicine are here today and we need to be able to assure their safe and effective use").

[135] Kelly Hearn, *Feature: Nanotech Laws Unlikely, Say Experts*, United Press International, Feb. 24, 2001 (noting that because there is still so little public understanding of these new technologies, it is "unlikely lawmakers will regulate in the immediate future").

[136] However, fierce public opposition could force the agency to take ethical and social issues into account in regulating nanomedicine. With regard to cloning, the FDA has asserted jurisdiction and argued that it will attempt to prohibit all cloning based on safety and ethical considerations. *See* Bernard Schwetz, *Remarks of the Acting Principal Deputy Commissioner of Food and Drugs,* 56 Food Drug L.J. 123, 127 (2001). Schwetz states:

B. *Regulatory Issues*

There are two primary regulatory problems posed by nanomedicine: classification difficulties and a lack of scientific expertise. Although the FDA has taken substantial steps to address these problems in the context of other emerging technologies, it has not taken substantive steps to prepare for these problems in the context of nanomedicine.

1. The Classification Problem

The first significant regulatory dilemma posed by products based on nanotechnology is that of classification. Although the current classification system has been applied to other emerging technologies, the miniaturization of medical products will compound problems associated with regulating combination products and blur the distinction between the different categories of products to a greater degree than ever before.

a. The Classification System: Drug, Device, Biologic, or Combination Product – The FDA classifies medical products for regulatory purposes as drugs, devices, biologics, or combination products. A drug is defined as:

> (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnostics, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure of any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)….[137]

> FDA considers the use of cloning technology to clone a human being as a serious public health issue. There are many unresolved safety concerns with this technology . . . FDA has the authority to regulate human cloning technology, and no investigators have the approval to use the technology at this time. As recognized by the National Bioethics Advisory Commission there are, of course, broader social and ethical implications of using cloning technology to clone a human being. As Dr. Kathyrn Zoon recently testified before a congressional committee, FDA is opposed unequivocally to the cloning of human beings because of moral, ethical, and scientific issues.

Id. Indeed, the FDA may be able to creatively employ statutory tools to prohibit nanomedical research. *See* Frederick Degnan, *Emerging Technologies and Their Implications: Where Policy, Science, and Law Intersect,* 53 Food & Drug L.J. 593, 594 (1998). According to Degnan,

> Agencies can be adept at imposing such requirements, even under statutory provisions that do not call specifically for such requirements. Courts generally uphold such agency actions in deference to the overriding public-health mission that these agencies are charged to carry out. . . . Fortunately, there are any number of precedential examples where a forward-looking agency policy has relied on statutory provision and interpreted it in light of new scientific or technological developments, and, in effect, changed if not revolutionized how the agency has regulated a given area.

Id.

[137] 21 U.S.C.S. § 321(g)(1) (2001).

A device is defined as:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -
> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
> (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, 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 any of its primary intended purposes.[138]

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.[139]

If a product combines a drug and biologic, a drug and device, or a biologic and device, it is a combination product. The product's primary mode of action determines which center has primary jurisdiction over the product.[140] The center chosen to regulate a combination product must apply the appropriate regulatory requirements to each part of the product. For example, if a product incorporates a biologic and a drug, and the primary mode of action is the biologic, CBER would regulate the product using applicable biologic and drug regulations.

A manufacturer can submit a request to have the product characterized as a drug, biologic, device, or combination product[141], and the intent of the manufacturer is often evaluated

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[138] 21 U.S.C.S. § 321(h) (2001).

[139] Food and Drug Modernization Act of 1997 § 123(d)(1), 21 U.S.C. §301 (2003).

[140] Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511, 4526 (codified as amended at 21 U.S.C. § 353 (1994)).

[141] Food and Drug Modernization Act § 416, 21 U.S.C § 360bbb-2 (2003).

as evidence of how the product should be classified.[142] Ultimately, the FDA is accorded substantial deference in making this determination.[143]

A manufacturer may prefer that the product be characterized in a particular way for a number of reasons. First, the FDAMA aimed to make the regulatory requirements for biologics and drugs similar,[144] but there are significant differences between the approval process for devices and the approval process for drugs and biologics. There are statutory differences in approval times,[145] and there may be a greater likelihood of securing approval for a product if it is designated as a device.[146] Second, in the case of a combination product, a manufacturer may prefer that a particular center have primary jurisdiction over the product for several reasons. A manufacturer may be more familiar with a particular center or a manufacturer may want to target a particular center for its tendency to evaluate certain types of evidence[147] or the fact that it does not charge user fees.[148]

b. Classification of Other Emerging Technologies – The original classification system, which designated products as either drugs, devices, or biologics, was adequate as long as products clearly fell into a particular category. Advancing medical technologies that appeared to combine drugs, devices, and biologics led Congress to create the fourth category for combination products in 1990. In 1991, agreements were formed between CDER and CBER[149], CDRH and CDER[150],

[142] United States v. Articles of Drug, 633 F. Supp. 316, 326 n. 1 (D Neb. 1986), *aff'd in pertinent part,* 825 F.2d 1238 (8th Cir. 1987). *See also* S. Rep. No. 361-74, 4 (1st Sess. 1935); Jay M. Zitter*, What is a 'Device' Within Meaning of Federal Food, Drug, and Cosmetic Act*, 129 ALR Fed 343 (1996).

[143] *See* Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 653 (1973); Biotics Research Corp. v. Heckler, 710 F.2d 1375, 1377 (9th Cir. 1983); Action on Smoking & Health v. Harris, 655 F.2d 236, 237--38 (D.C. Cir. 1980).

[144] FDAMA § 123(f) ("The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).").

[145] For example, CDRH must review a PMA within 180 days and a 510(k) within 90 days. CDER has 360 days to review an NDA for standard drugs and 180 days to review an NDA for priority drugs. Lewin Group, *supra* note 109, at 30--31.

[146] Ellen Flannery, 6 B.U. J. Sci. & Tech. L. 5, 5 (Spring 2000) (noting that "medical device regulation traditionally was deemed to be a shorter and easier route to market than regulation as a pharmaceutical product or a biological product").

[147] The Centers employ different evidence standards. CDER places more emphasis on methodological aspects such as randomized controlled trials than CBER and CDRH. Lewin Group, *supra* note 109, at 30.

[148] Drugs and biologics are subject to user fees while devices are not.

[149] FDA Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (Oct. 31, 1991), *reprinted in* FDLI, 3 Food & Drug L Rep. No. 2, at 29 (Supp. Feb. 1992).

[150] FDA Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991), *reprinted in* FDLI, 3 Food & Drug L Rep. No. 2, at 44 (Supp. Feb. 1992).

and CDRH and CBER[151] establishing guidelines for determining which center has primary jurisdiction over a combination product.

Throughout the 1990s, the agency and manufacturers were generally able to determine if a product was a drug, biologic, device, or combination product. However, there have been two regulatory problems associated with combination products. First, there have been disputes over which center should have primary jurisdiction as determined by the primary mode of action of the product. Not only have manufacturers quarreled with the FDA, but there have been arguments between the centers. Even with the standards set forth in the intercenter agreements, the appropriate jurisdictional designation can be "difficult and time-consuming to determine."[152] Second, even when a combination product is efficiently directed to a particular center, the center does not always apply the appropriate regulations to all components of the product. For example, under the 1991 agreement between CDRH and CBER, CBER has been responsible for regulating the medical devices associated with blood collection and processing as well as cellular therapies. Although CBER maintains that it regulates devices according to "the appropriate medical device laws and regulations", the standards used to evaluate device components are more like CBER's licensing requirements than the standards employed by CDRH.[153]

The FDA initiated reforms in the late 1990's to address these problems. First, to eliminate jurisdictional confusions, CBER and CDRH established a Tissue Reference Group in 1998 to determine which center has primary authority over products based on tissue engineering and cell therapy.[154] Comprised of three representatives from each center, the group determines which center should maintain jurisdiction over particular products, clarifies regulations, and writes guidance documents. Second, to make CBER's review of the device component of a combination product more consistent with how review would take place under CDRH, CBER launched the Device Action Plan in 1999.[155] A Device Management Team was established to supervise the regulation of Devices at CBER and enhance cooperation between CBER and CDRH.

c. The Classification Problems Created By Nanotechnology – As medical products become smaller, classification will become increasingly difficult and confusing for two reasons. First, the ability to operate at the nano level will increasingly enable manufacturers to combine different types of components in producing a single therapy. Second, in the long run, sophisticated nanomedical products will blur the distinction between "mechanical", "chemical", and "biological" and make it difficult to determine if a product is a drug, device, biologic, or combination product.

[151] FDA Intercenter Agreement between the Center Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991), *reprinted in* FDLI, 3 Food & Drug L Rep. No. 2, at 17 (Supp. Feb. 1992).

[152] Lewin Group, *supra* note 109, at 29.

[153] Lewin Group, *supra* note 109, at 30.

[154] Memorandum from Jerome Davis, CBER, to Director, Division of Emergency and Investigational Operations, Tissue Products Regulated by CBER and CDRH (Dec. 17, 1998) (on file with author).

[155] *Id.*

The miniaturization of medical products will result in an increase in combination products. Because it will be difficult to characterize the primary mode of action of these products, there will be jurisdictional confusion and disputes. For example, it is unclear how the novel drug delivery devices, such as polymer dendrimers that deliver drugs to cancer cells or nanoshell composites that periodically dispense drugs, should be regulated. The 1991 Intercenter Agreement between CDRH and CDER, which is the primary source of guidance, cannot be unequivocally applied to novel drug delivery systems. The Agreement states that a device "with the primary purpose of delivering or aiding in the delivery of a drug and distributed containing a drug", such as a prefilled syringe, is a combination product with CDER maintaining primary jurisdiction.[156] However, it later states that a device used "concomitantly with a drug to directly activate or to augment drug effectiveness", such as laser activation of oxsoralen for psoriasis, is regulated by CDRH as a separate entity.[157] Assuming the dendrimers or nanoshells are activated by infrared light, it is unclear exactly how the delivery system would be regulated. FDA officials responsible for classification have acknowledged the "many shades of gray" involved in classifying novel drug delivery products.[158]

Another example of how nanomedical products that combine components can result in confusing jurisdiction authority is regulation of the molecular nanogenerator.[159] The FDA and researchers have both indicated that the product would probably be regulated by CDER in consultation with CBER and CDRH as a radioactive drug.[160] Yet Corixa filed a BLA with CBER in September 2000 for a similar product comprised of a monoclonal antibody combined with a radioisotope.[161] Although it might be possible to distinguish Corixa's product from the nanogenerator in that the antibody plays a more active role in inhibiting tumor cells in Corixa's product while the antibody is primarily a steering device in the nanogenerator, the example illustrates how determinations of primary jurisdiction for combination products can be arbitrary and confusing.

Thus, in the near future, where nanomedicine will enable manufacturers to combine products, regulators and industry will be able to use current guidelines to determine if a product is a drug, device, biologic, or combination product. However, without updated guidelines governing novel combination products such as drug delivery systems and drugs combined with monoclonal antibodies, there could be an increasing number of jurisdictional disputes. The time-intensive process associated with determining primary jurisdiction will result in increased regulatory delay for nanomedical products.

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[156] FDA Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, *supra* note 150.

[157] *Id* at 52.

[158] Email sent from CSO/Jurisdiction & Device Status Expert to the author (Jan. 17, 2002) (on file with author).

[159] *See supra* Part II.B.1 (providing a basic description of nano-generator).

[160] Email sent from unnamed FDA official to the author (Jan. 8, 2002) (on file with author). Phone conversation with the Memorial Sloan Kettering Cancer Institute (Jan. 6, 2002) (on file with author).

[161] *Corixa Provides Bexxar Regulatory Update* (Jan. 9, 2002), at http://www.corixa.com/default.asp?pid=release_detail&id=138&year=2002.

In the long run, nanomedicine will produce a whole new class of products that will defy easy classification as drugs, devices, biologics, or combination products. The current distinctions between "chemical", "mechanical", and "biological" activity will be rendered useless. First, at the atomic and molecular level, the distinction between drugs and biologics disappears. Since biological organisms are comprised of chemical elements, primarily carbon, oxygen, hyrdrogen, and nitrogen, biological interactions can be characterized as chemical interactions. Second, at the atomic level, the distinction between drugs and devices is worn away. At the macro level, a "mechanical interaction", which conjures images of machinery or tools, can be conceptualized as a change in force and matter but not a change in the chemical composition of the substance. However, when the focus is on atoms being rearranged, it makes no sense to distinguish between chemical and physical forces. Thus, the distinction between drugs, device, biologics, and combination products is only tenable to the extent future nanomedical products are arbitrarily assigned to a particular category. Without guidelines specifically identifying and categorizing different nanomedical products, these products could be characterized as "mechanical" or "chemical" or "biological" depending on the framing devices used to depict the product.

Attempting to categorize nanorobots illustrates this classification dilemma. "Microbivores" are nanorobots that would enter the body, destroy pathogens, and exit the body intact.[162] The microbivore destroys the pathogens by using genetically engineered enzymes. It could be argued that the microbivore functions primarily through chemical, mechanical, or biological means. First, it can be argued that the microbivore, comprised of "ports", "chambers", and "sensors", mechanically destroys the pathogen. Unlike a drug, which is metabolized by the body, microbivores exit the body without being fundamentally altered. Indeed, Freitas has described the product as an "artificial mechanical phagocyte", a "device", and a "machine."[163] However, it is arguable that the microbivore engages in a chemical interaction by using enzymes to chemically alter the pathogens. In this respect, it is like an antibiotic or any other drug. Although it is not metabolized like a typical drug, metabolization can be understood as the incorporation of the therapy into the body's bloodstream and the therapy's use of the body's energy as a source of fuel. Finally, since the enzymes used to destroy the pathogens are genetically altered proteins, a careful reading of the Intercenter Agreement between CBER and CDER would appear to support classifying at least part of the product as a biologic.[164]

Ultimately, any determination that the microbivore functions primarily through chemical, mechanical, or biological means would be somewhat arbitrary. A scientific breakdown of how an enzyme operates reveals that both mechanical and chemical methods are used to produce molecular changes.[165] Mechanical forces involving proton configuration are responsible for the

[162] *See supra* Part II.B.7 (providing a basic description of microbivore function).

[163] Freitas, Nanomedicine, *supra* note 29.

[164] CBER is responsible for regulating the following classes of products: (f) protein, peptide, or carbohydrate products produced by cell culture excepting antibiotics, hormones, antibiotics as defined by Section 507(a) of the FD&C Act, regardless of the method of manufacture, , and products previously derived from human or animal tissue and regulated as approved drugs. FDA Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, *supra* note 149.

[165] *See* Ralph J. Fessenden & Joan S. Fessenden, Organic Chemistry 991--93 (4th ed. 1990); *see also* Frederick A. Fielder & Glenn H. Reynolds, *Legal Problems of Nanotechnology: An Overview,* 3 S. Cal. Interdisc. L.J. 593, 609 (1994).

enzyme engaging in chemical reactions involving the production and breakdown of ATP. Biochemists and molecular biologists have been unable to classify an enzyme's activity as either chemical or mechanical.[166]

Difficulties associated with classifying "pharmacy in a cell" further illustrate the categorization problems created by major advances in nanomedicine. Classification turns on the characterization of the process by which the proteins in the cell are picked up, placed in storage, and then released as needed. It could be argued that this process results in a chemical change or simply the physical movement of matter. The classification is further complicated in two ways. First, antibodies, which are regulated as biologics, play a major role in moving the molecules. Second, the ATPase motor, which will propel the pharmacy in a cell, is based on an enzyme, which uses both mechanical and chemical methods to effect molecular changes.[167]

2. The Problem Of Scientific Expertise

The second regulatory dilemma posed by nanomedical products is maintaining scientific expertise at the FDA. Although the agency has taken steps to acquire the technical abilities necessary for effective regulation of other emerging technologies, the FDA will face unique problems in obtaining the aptitude to effectively regulate nanomedical products.

a. Scientific Expertise Is Critical To Effective Regulation – Effective regulation requires that the FDA maintain expertise in cutting edge technologies and scientific advances. The FDA has recognized the importance of a strong science base in its 2001 performance plan: "The pace of technology innovation in this country and around the world requires the Center's cadre of scientists to keep up with the latest technology and scientific advances, in both the development of medical technology and scientific methodologies."[168] Jane Henney, the former FDA Commissioner, explained the need for the FDA to obtain the scientific expertise to regulate nanomedical products:

> The ability to miniaturize has brought nanotechnology. . . . [p]roducts on the near horizon [that] will no doubt meld all three: nanorobots that can enter the circulatory system, delivering just the right amount of drug or gene product to the right place. Those who make decisions at the FDA about such traditional or complex and high-tech products must be scientifically equal to the intellectual cognitive development that has invented these advanced technologies as we judge which products are ready for the marketplace. If we are not scientifically strong, our decision-making will become risk-averse or, what is worse, simply wrong.[169]

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[166] *See* Reynolds, *supra* note 165, at 593.

[167] *See* Reynolds, *supra* note 165, at 609.

[168] Lewin Group, *supra* note 109, at 26 (citing the FDA FY 2001 Congressional Budget Request).

[169] Jane Henney, *Jane Henny Delivers Remarks at the National Press Club* (Dec. 12, 2000), in FDCH Political Transcripts.

b. Scientific Preparation For Regulation of Other Emerging Technologies – The FDA has done an adequate job of preparing for novel technologies in the past. The FDA's experience in regulating products based on early biotechnology, artificial intelligence, and the advanced biotechnology products developed in the late 1990s demonstrate that the agency is able to acquire the scientific expertise necessary for effective regulation.

The FDA was able to equip itself for effective regulation of early biotechnology products. The biotechnology revolution was launched in 1976 when a human protein was expressed from recombinant DNA in *E coli.*[170] Recombinant DNA technologies resulted in products such as synthetic insulin to treat diabetes and interferon to treat leukemia, and the biotechnology industry began to take flight in the 1980's. The FDA responded to the emerging industry in several ways. First, the FDA decided not to create a new center for biotechnology, but to incorporate biotechnology products into the current regulatory structure.[171] Each product was regulated on a case-by-case basis for safety and efficacy. The Office of Biologics Research and Review became the FDA's "expert" in biotechnology review. OBRR hired specialists in molecular biology, protein chemistry, and immunology, and almost all biotechnology products, including drugs and devices, were sent to OBRR for review.[172] The agency also began to draft documents called "Points to Consider" in the early 1980's.[173] Although not regulations or guidelines, they were intended to facilitate dialogue and understanding between the FDA and the emerging industry.[174] The FDA has continued to promulgate "Points to Consider" as the industry has advanced,[175] and they are now considered "dogma in the field of biotechnology."[176] Biotechnology advancements also led the agency to establish the Office of Biotechnology in 1990. The purpose of the Office was to "to enable [the] FDA to meet the new challenges presented by advances in the area of biotechnology."[177] The Office advised the Commissioner and other FDA officials on biotechnology science and policy, directed agency research and training, attempted to recruit and retain scientists with needed expertise, and represented the FDA on biotech matters to other agencies, industry, academia, and Congress.[178] The

[170] James D. Watson, et. al., Recombinant DNA (2d ed. 1991).

[171] Kathryn Zoon, *The Impact of New Biotechnology on the Regulation of Drugs and Biologics*, 41 Food Drug Cosm. L.J. 429, 430 (1986).

[172] David T. Bonk, *FDA Regulation of Biotechnology*, 43 Food Drug Cosm. L.J. 67, 77 (1988).

[173] The first "Points to Consider" concerned interferon, products derived from r-DNA technology, monoclonal antibody products, and cell lines used to produce biologicals. *See* Zoon, *supra* note 171, at 431.

[174] *Id*.

[175] For example, in 1991, the FDA published a Points to Consider document on human somatic cell and gene therapies. In 1995, the FDA published a Points to Consider document on therapeutic products derived from transgenic animals. Martha J. Carter, *The Ability of Current Biologics Law to Accommodate Emerging Technologies*, 51 Food & Drug L.J. 375, 376 (1996).

[176] *Id.*

[177] 55 Fed. Reg. 12,284 (1990).

[178] *Id*.

establishment of the Office was lauded as effective in putting the FDA "at the forefront of recent advances in the industry."[179] Having served its purpose of equipping the agency with the ability to effectively regulate biotechnology, the Office of Biotechnology was abolished in 1994.[180]

The FDA also took steps to enhance its science base in preparation for technology based on artificial intelligence. Scientists at CDRH began studying artificial intelligence and preparing for review long before they were presented with any applications. Neural networks, which use biological systems to process information, are now being used to create "smart" devices such as automatic Pap smear readers to do repetitive pattern recognition analysis. As one FDA official explains, "Our scientists saw that the use of artificial intelligence in medical devices was on the horizon and that we needed to have expertise in the area. As a result of our investment in this area, when the first application came in the door, we were ready for it."[181]

In the late 1990's and early 2000's, the FDA was faced with a wave of advanced biotechnology products. Breakthroughs in genomics, proteomics, gene therapy, and tissue engineering resulted in a significant increase in applications for clinical testing of novel technologies. In attempting to keep pace with the explosion of new technologies, the FDA has initiated several policies to improve the agency's effectiveness.

First, former FDA Commissioner Jane Henney promulgated several initiatives to improve the quality of the FDA workforce. She contracted with an outside group to work with the scientific staff and the office of human resources to determine the necessary composition of the scientific workforce in the near future.[182] The contractor was also directed to investigate ways to improve recruitment and retention at the agency. As a result, FDA attrition rates have decreased slightly in recent years.[183]

Second, the FDA has made efforts to improve internal training. For example, the centers put on monthly training sessions; the agency has established an alumni program to keep former

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[179] Sandra H. Cuttler, *The Food and Drug Administration's Regulation of Genetically Engineered Human Drugs*, 1 J. Pharmacy & L. 191, 210 (1992); *see also* David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA*, Chemical & Engineering News, Jan. 27, 1992, at 28--29.

[180] *FDA Dumps Office of Biotechnology: Miller to Stanford as Visiting Scholar*, Biotechnology Newswatch, Jan. 17, 1994. According to an FDA spokesman

> Abolishing the office is "no signal that biotechnology is less important", an FDA spokesman said. "The agency looks at that office as one established when biotechnology was an emerging technology," he said. It is no longer "emerging", the spokesman pointed out. "These days, most decisions regarding biotechnology are being made at the Center for Biologics Evaluation and Research rather than at the commissioner's level," he said.

Id.

[181] Thompson, *supra* note 115.

[182] Jane Henney, *Science and the FDA* (Feb. 14, 2000), at http://www.fda.gov/oc/speeches/2000/scienceforum.html.

[183] Agency-wide attrition rates were 7.2 percent in 1995 and 5.8 percent in 1999. However, the attrition rates for 5 of 9 scientific categories has increased slightly. Attrition rates in biology, pharmacology, math statistics, computer science, and microbiology have increased, while attrition rates in chemistry and engineering have decreased. Jacobson, *supra* note 124, at 30--31.

staff involved in consulting and training efforts, and there have also been efforts to cross-train staff through a scientific exchange program.[184]

Third, the FDA has pursued an aggressive leveraging program involving FDA collaboration with outside experts. There have been numerous "joint training" sessions with industry, where FDA staff tour manufacturing sites to learn about cutting edge research.[185] There are also various Cooperative Research and Development Agreements (CRADA's) between the FDA and different companies,[186] and CBER and CDRH have established "vendor days" to allow manufacturers to provide information about their products and research to FDA staff. The FDA has also pursued partnerships with universities[187] and fostered its relationships with other public health service agencies,[188] existing advisory panels and consultants, professional societies,[189] and domestic and international standards organizations.[190]

Fourth, the agency has taken steps to improve its regulatory science. Research activities allow the FDA to obtain independent laboratory information in reviewing applications, set standards for regulatory assessment, establish test methods, monitor products, and study emerging risks.[191] The FDA highlights the success of its Tissue Proteomics Program as evidence of its ability to engage in cutting edge regulatory science.[192] The research, which involves

[184] Lewin Group, *supra* note 109, at 28.

[185] In a speech made in February 2000, Henney highlighted FDA personnel travelling to Merck's manufacturing site to learn about developments in barrier isolation technology as an example of joint training. Other examples of joint training session topics include: new ELISA technologies in food inspections, microarray technology, nucleic acid amplification testing, and new trends in sterilization. *See* Gary Dykstra, *FDA & Industry Partnerships for Emerging Technology Training*, 2001 FDA Science Forum - "Science Across The Boundaries", at http://vm.cfsan.fda.gov/~frf/forum01/abst01sp.html.

[186] *See* Bernard Schwetz, Susan A. Homire, and James T. MacGregor, *Science at the FDA: Improving the Scientific Basis of Regulation Through Collaboration With "Stakeholders"*, at http://www.fda.gov/oc/oha/fdascience.htm. Examples of CRADA's include: (1) CDER and MULTICASE working together to develop software strategies for predicting drug toxicities; (2) CDER and Boehringer-Ingelheim Pharmaceuticals developing a model of carcinogenic potential of chemicals.

[187] *See id.* For example, JIFSAN, a partnership between the FDA and the University of Maryland, was designed to explore risk assessment and the Food Safety Initiative. There is a similar agreement involving food safety issues between the FDA and the Illinois Institute of Technology Research Institute. *Id.*

[188] For example, FDA is working with the Department of Health and Human Services, NIH, CDC, the Department of Defense, USDA, and EPA. FDA and EPA are collaborating to research endocrine disruptors. *Id.*

[189] *See id.* For example, PQRI is a nonprofit foundation formed under the umbrella of the American Association of Pharmaceutical Scientists. Its purpose is to facilitate FDA, university, and industry collaboration to address critical issues in pharmaceutical product quality. *Id.*

[190] *See* Schwetz, *supra* note 186. For example, the ICH(2) conference between regulatory bodies and global industry organizations resulted in a worldwide set of uniform recommendations for approval of new drugs.

[191] Office of Science and Technology, Annual Report: Fiscal Year 2000, at http://www.fda.gov/CDRH/ANNUAL/FY2000/OST/OST-ANNUALREPORT2000.HTML.

[192] *See* Bernard Schwetz, *Testimony Agriculture, Rural Development and Related Agencies*, May 10, 2001, FDCH Congressional Testimony.

collaboration with the NIH, focuses on developing proteomic tools for the early detection of cancer and other diseases.[193] The FDA can also boast of cutting edge laboratory research in other areas.[194]

There is evidence to suggest that these reforms and initiatives have been moderately successful in enabling the FDA to regulate advanced biotechnology products. The agency has been able to spend some time developing a regulatory framework for genetic testing[195], tissue engineering[196], gene therapy[197], and other novel technologies. Not only has the FDA worked diligently to establish regulations, notices, and guidelines regarding testing and manufacturing

[193] *Id.* According to Schwetz,

> [t]he project's accomplishments include the development of methods for early disease detection, the identification of new therapeutic targets and the discovery of new biomarkers for drug-induced patient toxicity. This bench-to-bedside model has resulted in a first-of-its kind clinical trial that incorporates a 'proteomic portrait' of the disease in human tissue that could lead to customized, patient tailored therapeutics. Currently, this research has identified over 150 proteins that are aberrantly expressed in human prostate, lung, breast, ovary, esophageal, and colon cancer.

Id.

[194] Other examples of cutting edge laboratory research conducted by FDA scientists include research into the mechanisms by which organ replacement technology interacts with the body, the testing procedures available for evaluating potential adverse effects of biomaterials on the immune system, a standardized screening assay for measurement of mutation induction in the p53 gene for studying cancer risk associated with technologies, tissue engineering, computational modeling, and genetic testing. *See Emerging Issues 2000: Genetic Technologies,* Office of Science and Technology, Annual Report: Fiscal Year 2000, at *http://www.fda.gov/CDRH/ANNUAL/FY2000/OST/OST-ANNUALREPORT2000.HTML#_Toc516621955.*

[195] The FDA has taken numerous steps to adequately prepare for the regulation of genetic testing devices in the near future. OST scientists have served as members of scientific advisory committees for other FDA Centers reviewing genetic devices, have taught courses on biocompatibility to update review staff, and have been involved in laboratory research projects. Information sessions, including presentations by developers of genetic and genomic technologies, have been organized by ODE's Division of Clinical Laboratory Devices. A Genomics / Proteomics working group has been formed to develop priorities for action related to FDA readiness in assessing new genetic technologies. *See* OST Annual Report, *supra* note 194.

[196] The Tissue Action Plan was formalized in March 1998 "to develop on a timely basis the policies, regulations, and guidance needed to implement FDA's February 1997 Proposed Approach to the Regulation of Cellular and Tissue Based Therapies." *See CBER Update*, Update 2001, Spring 2001, at http://www.fdli.org/pubs/Update/2001/Issue4/McNeill/print.html. *See also* Darin Weber, Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Congressional Hearing Transcripts, March 20, 2000 ("FDA's regulatory framework for cell and tissue-based products wasn't formulated overnight. It has been evolving for most of the last century and is continuing to evolve today[.]").

[197] The FDA has spent a great deal of time and resources recruiting and training staff to regulate gene therapy. *See Human Gene Therapy and the Role of The Food and Drug Administration,* Sept. 2000, at http://www.fda.gov/cber/infosheets/genezn.htm. In 2000, the FDA announced that it would increase its inspections of gene therapy studies. It also announced the Gene Therapy Clinical Trial Monitoring Plan, under which the sponsors of gene therapy trials must routinely submit monitoring plans to the FDA.
See Edward Korwek and Mark D. Learn, *Biologics Update*, Update 2001, at
http://www.fdli.org/pubs/Update/2001/Issue2/Korwek_Learn/print.html.

procedures, but there is evidence that it has been able to more efficiently review applications and better monitor clinical trials and manufacturing.[198]

However, despite its best efforts to keep pace with advancing medical technologies, the FDA may begin to experience difficulties in maintaining expertise. A greater number of companies are beginning to complain of a lack of technical expertise by FDA reviewers.[199] FDA officials have also begun to raise concerns that a lack of expertise may impair effective approval and monitoring of sophisticated clinical research.[200] Indeed, maintaining technical expertise in the coming years will be "a difficult task in the face of rapid technological change, staff turnover, and the broader context of high employment and movement of knowledge workers."[201]

c. The FDA Will Face Unique Problems In Attempting To Acquire Scientific Expertise In Nanotechnology – While the FDA has taken steps to acquire the scientific expertise necessary for effective regulation of other emerging technologies, the agency has done little to prepare for the advent of nanomedicine. A careful review reveals that there have been no conferences, forums, working groups, leveraging activities, or regulatory science projects aimed at increasing agency expertise in nanomedicine. The agency's failure to begin preparing for the nano trend is evidenced by the absence of any topic dealing with nanomedicine at the 2002 FDA Science Forum.[202] The agency concedes that, in the context of nanomedicine, there are "now serious gaps between what the agency needs to do and what it can do."[203]

The FDA will be confronted with complex scientific issues in regulating nanomedical products that are at least as complicated as those raised by the most sophisticated applications of

[198] Joseph Scodari, *Testimony October 7, 1998: Joseph C. Scodari President and Chief Operating Officer Biotechnology Industry Organization; House Commerce; Implementation of FDA Modernization*, FDCH Congressional Testimony, Oct. 7, 1998 ("Our experience and those of other BIO member companies points to numerous examples where both clinical development and complex manufacturing issues were speedily resolved because of the scientific expertise within the Center for Biologics Evaluation and Research (CBER)."); *see also* Lewin Group, *supra* note 109 at 12 ("Regulation of the medical device industry by FDA has improved in recent years. . . . Improvements in FDA regulation are attributable to such main factors as the agency's reengineering efforts, collaboration with industry, and a commitment to the implementation of the FDA Modernization Act of 1997 (FDAMA).").

[199] *FDA Makes Drug Approval An Easier Pill to Swallow*, Biotechnology Newswatch, April 3, 2000, at 34 (noting that 27% of companies surveyed stated that lack of technical knowledge by reviewers interfered with efficient product approval, compared to 18% in 1995); *see also* Lewin Group, *supra* note 109, at 27 (noting that one company blames a lack of technical expertise for approval of its gene amplification product being delayed).

[200] *Gene Therapy: Is there Oversight for Patient Safety: Hearings Before the Subcomm. on Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 39 (2000) (Statement of Dr. J.P. Siegel).

[201] Lewin Group, *supra* note 109, at 26.

[202] The 2002 Science Forum, held in February 2002, is intended to focus on the importance of the FDA's many scientific and regulatory disciplines to the Agency's decision-making process. Topics include: bioengineering of plants and animals, tissue engineered combination products, children's health issues, genomics, bioterrorism, antibiotic resistance, botanicals, and bovine spongiform encephalopathy. *See* 2002 FDA Science Forum, at http://www.fda.gov/oc/meetings/2002sciforum.html.

[203] *FDA's Growing Responsibilities for the Year 2001 and Beyond,* at http://www.fda.gov/oc/opacom/budgetbro/budgetbro.html.

biotechnology. In the short run, the agency will be forced to struggle with immunological complications raised by inserting nanostructures into the human body. The immune system can react to structures the size of amino acids,[204] and researchers in the field, who are primarily chemists, physicists, and engineers, are less familiar with immune reactions.[205] The agency will also be forced to determine how to ensure that large-scale manufacturing at the molecular level is performed in a consistent and safe manner. In the long run, the introduction of nanorobots will present tremendous scientific uncertainties. The FDA will be forced to evaluate the risks associated with "old nanorobots" being left in the body if they fail, *in vivo* replication, and untested interactions between different nanorobots or nanorobots and drugs. The agency will have to promulgate guidelines regarding the ability of doctors to "pull the plug" in case nanorobots do not function properly. There will also be complicated manufacturing issues associated with positional assembly as well as self-assembly techniques. For example, the FDA must ensure that the quality assurance within the manufacturing process is adequate to reduce the possibility of dysfunctional nanorobots as well as the environmental risks associated with nanorobots. As Freitas notes, "A true glitch will come from some direction that nobody anticipated."[206]

There are several reasons why it will be more difficult for the FDA to maintain scientific expertise in nanomedical research than past and other emerging technologies. First, nanomedicine represents a unique technology in that it will touch virtually every aspect of modern medicine. As one scholar put it, "[T]he difference between nanotechnologists and biotechnologists is that the former do not restrict themselves to biological limitations of the latter, and they are much more ambitious about the kinds of accomplishments that they want to achieve."[207] Unlike other past and emerging trends in medical products, nanomedical products will be evaluated by every center at the FDA; often different centers will be forced to review similar products. For example, CBER will be primarily responsible for evaluating the efficacy and safety of dendrimers in gene therapy while CDER and CDRH will review dendrimers as drug delivery vehicles. This is different from other emerging technologies where a particular center could establish expertise in a particular area of research. Because CBER was handed the responsibility of regulating nearly all biotechnology products, it was able to develop an expertise in the area and develop a working relationship with the biotechnology industry. Staff became intimately familiar with products, ongoing research, and industry players while manufacturers became acquainted with the reviewers, procedures, and requirements of CBER. Division of responsibility to enhance expertise will not be possible with nanomedicine, where every center will be faced with review of nano-products.

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[204] Michael Brooks, *Thanks But No Thanks,* New Scientist, Oct. 6, 2001, at 33 (quoting David Williams, a biomaterials researcher at Liverpool University, as saying that "[t]he human body is best designed to repel or attack things the size of a cell").

[205] James Baker, a leader in the nanomedical field, notes: "Most of the people proposing this stuff are not biologists and they think they can stick anything in the body if it's small enough." *Id*. at 33.

[206] Robert Freitas, *What Could Go Wrong During a Nanomedical Procedure*, at http://www.foresight.org/Nanomedicine/NanoMedFAQ.html#FAQ18.

[207] Freitas, Nanomedicine, *supra* note 29, at 31 (quoting Gregory M. Fahy *in Molecular Nanotechnology and its Possible Pharmaceutical Implications*, 2020 Visions: Health Care Information Standards and Technologies, U.S. Pharmacopeial Convention, Inc., Rockville MD, 1993, p. 152--59).

Second, it will be more difficult for the FDA to acquire staff with an expertise in nanomedicine than other past and emerging technologies. Universities have recently established nanotech centers and begun to offer doctorates in nanotechnology, but there are still relatively few experts in this burgeoning field. Although the FDA can rely on experts working together with backgrounds in chemistry, physics, and materials research,[208] it will be increasingly difficult for the FDA to obtain scientists with backgrounds in the physical sciences for several reasons. First, there are fewer people entering doctorate programs in the physical sciences.[209] Second, a large number of FDA staff will retire in the near future. Approximately 50% of FDA staff will become eligible for retirement in the next five years, and agency statistics indicate that a large number of staff retire within a short time of becoming eligible.[210] Third, as nanotechnology begins to take root in the near future, the most qualified scientists in the physical sciences will be lured away by the higher salaries and stock options offered by industry.

Finally, the FDA will be forced to address the scientific issues generated by nanomedicine in the midst of other technological changes and a stagnant budget. Attempting to keep pace with the rapid rate of technological change has already stretched the agency's resources and capabilities. Futhermore, the FDA is facing additional pressures to more thoroughly review products in the aftermath of several high-profile recalls and assume a more prominent role in national security.[211] From drafting guidance documents to hiring appropriate personnel to acquiring the equipment and facilities needed to analyze nanostructures, adequately preparing for nanomedicine will require a great deal of focus and substantial monetary investment. Nevertheless, the last six years have witnessed the FDA experience budget shortfalls. Budgetary shortfalls, combined with the need to maintain expertise in other areas of technological advancement, will make it difficult for the agency to appropriate the funding necessary to prepare for nanomedicine.

VI. RECOMMENDATIONS

The FDA can take several steps to prepare for the coming revolution in nanomedicine. First, it should sponsor conferences and workshops focused on identifying and fleshing out the issues associated with nanomedicine. The 2003 Science Forum would provide an opportune moment to put nanomedicine in the spotlight. The fruit of these efforts should be the promulgation of "Points To Consider" Documents that initiate a dialogue between the agency and the emerging nanomedical industry.

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[208] J.L. Merz, *Technological and Educational Implications of Nanotechnology - Infrastructure and Educational Needs*, *in* Societal Implications Of Nanoscience and Nanotechnology, 148, 152 (Mihail C. Roco & William Sims Bainbridge eds., March 2001).

[209] *Id.* (noting that it is becoming increasingly difficult to attract the best graduate students to the physical sciences and engineering and quoting Richard Smalley as stating that few students "are electing to go into these areas in graduate schools throughout the U.S.").

[210] 25% of those eligible to retire do so within 14 months of becoming eligible and 50% do so within three years. *See* Alan Slobodin, *supra* note 109.

[211] *See supra* Part III.B.

Second, the FDA should consider establishing an Office of Nanotechnology. Like the former Office of Biotechnology, the Office would advise the Commissioner and other FDA officials on nanotechnology science and policy, represent the FDA on nanotechnology matters to other agencies, industry, academia, and the Congress, direct agency research and training, and attempt to recruit and retain scientists with needed expertise.

Third, in addressing the categorization problems posed by nanomedical products, the FDA should attempt to identify in advance what Centers will have primary jurisdiction over combination products resulting from nanomedicine. The Tissue Reference Group could be used as a model for an initiative that provides guidance for different types of products. For example, clearer guidelines for drug delivery products are needed in the short run. If nanorobots ever do become a reality, guidelines governing jurisdictional authority over nanorobots will be absolutely essential.

Fourth, in addressing the problem of maintaining scientific expertise, the agency must make efforts to acquire personnel with expertise in nanotechnogy and more scientists with backgrounds in the physical sciences. But even if the FDA could employ a sufficient number of qualified scientists, it is impractical to expect that the FDA staff will be able to keep abreast of the rapid changes in this dynamic field. The FDA must utilize other knowledge bases to increase its expertise by building on its programs and initiatives launched in the context of regulating advanced biotechnology products. Internal training efforts and continued collaboration with industry and academia to enhance nanotechnology expertise will be critical. The FDA should also pursue collaboration with the NIH, a major player in cutting edge nanomedical research. The agency should also begin to engage in laboratory research involving nanomedicine. The initial focus of research efforts should be on increasing the agency's understanding of immunological complications associated with placing nano-sized structures in the human body.

Finally, the most important component of the FDA's strategy for preparing for nanomedicine should be securing additional resources. The agency appears to be aware of the need to prepare for nanomedicine, and it has proven that it harbors the capability to keep pace with emerging technologies in the past. Thus, the primary impediment to the agency's efforts to prepare will be insufficient resources. The agency must actively persuade the Congress that increased funding is necessary to regulate the coming revolution in medicine.

VII. CONCLUSION

The health care revolution brought about by nanomedicine could dwarf all other trends in the history of medical technology. Although the FDA should be relatively prepared for some of the earliest and most basic applications of nanomedicine in areas such as gene therapy and tissue engineering, more advanced applications of nanomedicine will pose unique challenges in terms of classification and maintaining scientific expertise. The agency should begin to prepare now for the coming revolution in nanomedicine.