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*Analyzing the Laws, Regulations, and Policies
Affecting FDA-Regulated Products*

Exploring Emerging Nanobiotechnology Drugs and Medical Devices

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I. INTRODUCTION

“Nanotechnology” expands across research domains, applications and products and remains a field with neither a single scientific definition nor a formal regulatory or statutory definition. This definitional question is an international challenge, with most developed countries actively contemplating whether this expansive technology requires additional regulation. As part of the National Nanotechnology Initiative (NNI) in the United States, 26 federal agencies, including the Food and Drug Administration (FDA), contributed to the development of a description for nanotechnology as: “1) Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1-100 nanometer range; 2) creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and 3) ability to control or manipulate at the atomic scale.”¹

This article provides a foundational look at the field of nanomedicine in order to highlight existing products and future applications now in research and development phases. We present existing oversight mechanisms for products in the drug and device realm; specifically examine nanodrugs and nanodevices approved by FDA; and highlight emerging nanoproducts that may pose a challenge for current regulatory schemes both in the United States and internationally. While we refer chiefly to U.S. developments, similar products and oversight questions confront relevant international regulatory systems. We purposely do not address the legal and regulatory issues in depth and recognize that this is a developing area with ongoing regulatory issues. Indeed, the subject of law, regulation, and policy relating to nanotechnology was the focus of the 1st Annual Conference on Nanotechnology Law, Regulation and Policy sponsored by the Food and Drug Law Institute, Arizona State University, and Burdock Group.

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¹ Environmental Protection Agency, *Nanotechnology: An EPA Research Perspective Factsheet* (June 2007), <http://es.epa.gov/ncer/nano/factsheet/nanofactsheetjune07.pdf>.

II. NANOTECHNOLOGY IN HEALTH AND MEDICAL APPLICATIONS

The ability to control atoms and molecules has significantly advanced medical science and has catalyzed the emerging field of nanomedicine. Nanomedicine is the application of nanotechnology to health and medicine, including nanoscale drugs and therapies, drug delivery systems (e.g., targeted drug delivery), *in vivo* imaging agents, biomaterials for enhanced tissue engineering, tools for *in vitro* diagnostics and multi-functioning medical devices.² Defining the exact scope of nanomedicine has proven as equally challenging as defining nanotechnology and remains the subject of debate. The National Institutes of Health refers to nanomedicine as the “application of nanotechnology for treatment, diagnosis, monitoring and control of biological systems.”³ Because of the medical nature of these applications, an inability to adequately regulate and monitor these technologies could have a substantial impact on public health. Likewise, excessive regulation may ultimately hamper the development of valuable or even life-saving products.

Nanotechnology promises to bring tremendous products to health and medical fields, but may also raise novel questions regarding oversight. In the United States, FDA, as the gatekeeper to clearance and approval of medical and healthcare products in the United States, will be largely responsible for the oversight of the clinical research, approval and marketing of nanotechnology products for human use. FDA is reviewing and has approved “nano” human drugs and medical devices using the established oversight paths for drugs and devices under the Federal Food, Drug, and Cosmetic Act (FDCA).⁴ Under this statute, regulatory distinction is drawn between the chemical action of drugs and the mechanical action of medical devices, where a device “does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and...is not dependent upon being metabolized for the achievement of its primary intended purposes.”⁵ New drugs are regulated through a pre-market evaluation and approval process and have to meet safety, efficacy and manufacturing standards. Lower risk medical devices can often be marketed if shown to be substantially equivalent to an already marketed device; higher risk devices must go through a pre-market application process showing that the device is safe and effective. How a product is classified for regulatory purposes ties directly to the information required by FDA and the ultimate cost to bring it to market.

FDA's approval of nanotechnology products using the established oversight framework has provoked debate, with some arguing that nanotechnology warrants its own oversight provisions.⁶ To investigate whether existing provisions continue to encourage development of safe, effective and innovative products using nanotechnology, FDA established a Nanotechnology Task Force comprised of authorities in FDA's major centers relevant to medical applications, including the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).⁷

² Volkner Wagner et al., *The Emerging Nanomedicine Landscape*, 24 NATURE BIOTECH. 1211, 1211 (2006), citing R. Duncan, *Nanomedicines in Action*, 273 PHARM. J. 485 (2004).

³ S. Moein Moghimi et al., *Nanomedicine: Current Status and Future Prospects*, 19 THE FASEB J. 311 (2005).

⁴ Federal Food, Drug & Cosmetic Act, 21 U.S.C. §§301-99 (2006).

⁵ Federal Food, Drug & Cosmetic Act, 21 U.S.C. §321(h) (2006).

⁶ See, e.g., Michael R. Taylor, REGULATING THE PRODUCTS OF NANOTECHNOLOGY: DOES FDA HAVE THE TOOLS IT NEEDS? (2006), available at http://www.nanotechproject.org/process/files/2705/110_pen5_fda.pdf.

⁷ Press Release, Food & Drug Admin., FDA Forms Internal Nanotechnology Task Force (August 9, 2006), available at <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-33->

In July 2007, they concluded that a new regulatory framework or special regulations for nanotechnology were not necessary at the current time, but that FDA must keep abreast of the science in order to appropriately apply regulations in the future.⁸ FDA has also begun to investigate specific aspects of nanomedicine products, including toxicological effects and interaction with biological and chemical pathways in the human body. The National Cancer Institute's Nanotechnology Characterization Laboratory, together with FDA and the National Institute of Standards and Technology, is conducting "preclinical efficacy and toxicity testing of nanoparticles" in an effort to identify appropriate standards for molecular-sized cancer drugs.⁹

One area of concern flagged by the Task Force is that of products combining aspects of drugs, device and biologics. FDA currently regulates combination products, those containing a drug-device, drug-biologic or device-biologic, according to the primary mode of action (PMOA), which refers to the mode of action providing the most important therapeutic action of the product.¹⁰ Depending on the determined PMOA, the products will be regulated either as a drug, device or biologic and subject to the relevant regulatory requirements.¹¹ The Task Force acknowledged the potential for highly integrated drug and device products to raise novel issues for regulation its recent report, stating:

The very nature of nanoscale materials—their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications—may permit the development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for "combination products" may need to be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated combination products.¹²

Thus, a major challenge with nanodrug and nanodevice products regulated by FDA and similar federal agencies in other countries will be both the explicit linking of traditional drugs, devices and biologics into a single product and the blurring of the line between diagnostic and therapeutic and chemical and mechanical aspects of drugs, medical devices and biologics. Determining the appropriate regulatory route is by no means a new problem for FDA as cutting-edge technologies combining aspects of drugs, devices and biologics have existed for decades, such as drug-eluting stents and antimicrobial catheters. However, at the nanoscale the distinctions between chemical and mechanical action are not easily distinguishable.¹³ While not so critical in a scientific sense how a nanotechnology product works (chemically or mechanically), it becomes extremely important for law and regulatory purposes.

FDA-Nano%20FDA%20News%20release.pdf.

⁸ Food & Drug Admin., *NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE (2007)*, available at <http://www.fda.gov/nanotechnology/taskforce/report2007.pdf>.

⁹ See National Cancer Institute, Nanotechnology Characterization Lab, <http://ncl.cancer.gov/> (last visited Feb. 15, 2008).

¹⁰ Federal Food, Drug & Cosmetic Act, 21 CFR §3.2 (e) (2006).

¹¹ Food & Drug Admin., *Guidance for Industry and FDA Staff: How To Write a Request for Designation (RFD)*, (2005), available at <http://www.fda.gov/oc/combination/howtowrite.html>.

¹² Food & Drug Admin., *supra* note 8, at 20, 21.

¹³ Frederick A. Fielder & Glenn H. Reynolds, *Legal Problems of Nanotechnology: An Overview*, 3 S. CAL. INTERDISC. L. J. 593 (1994).

This question of regulation and oversight for nanotechnology has become an international issue, with major industrialized nations struggling to determine the most effective and rigorous way to oversee nanotechnology products in the health sector without stifling the research and development of useful and potentially life-saving treatments and diagnostics.¹⁴ There is increasing academic literature that tracks international activities in this area and overviews key issues that regulatory agencies will face as the technologies progress.¹⁵ Similar to the United States, no governing body internationally has enacted nano-specific regulations for products classified as drugs or medical devices but have used existing regulatory pathways.¹⁶ The issue of how to regulate these products has been discussed and debated both by individual governments and their respective regulatory agencies.

III. A LOOK AT EXISTING PRODUCTS

Enabled by rapid advances in the fields of chemistry, physics, materials science, engineering and biology, nanomedicine research and product development is burgeoning. Current research activity is dominated by development of drug delivery applications, accounting for about three quarters of the emerging market.¹⁷ Many nanodrug and nanodevice products are already on the market, in clinical testing phases, or under review by FDA. Using its established oversight paths, FDA has approved human drug products such as Abraxane¹⁸ and Doxil¹⁹ anticancer drugs, Rapamune immunosuppressant for prevention of organ rejection in renal transplant patients,²⁰ Epaxal Hepatitis A vaccine²¹ and Estasorb topical estrogen therapy for the treatment of hot flashes.²² Medical device nanoproducts that have entered the market include Vitoss bone graft substitute,²³ TiMesh tissue reinforcement and hernia repair,²⁴ EnSeal tissue sealing and hemostasis system for laparoscopic and open surgery²⁵ and CellTracks Analyzer II *in vitro* diagnostic device.²⁶ Below, we highlight a number of these products and their approval history. To inform our cat-

¹⁴ See, e.g., Thomas A. Faunce, *Nanotherapeutics: New Challenges for Safety and Cost-Effectiveness Regulation in Australia*, 186 MED. J. OF AUSTRALIA 189 (2007), available at http://www.mja.com.au/public/issues/186_04_190207/fau10553_fm.pdf; David B. Jeffreys, *An Overview of Recent Developments in the European Regulation of Medicines/Medical Device Combination Products*, 37 DRUG INFO. J. 39 (2003).

¹⁵ See, e.g., Diana M. Bowman & Graeme A. Hodge, *A Small Matter of Regulation: An International Review of Nanotechnology Regulation*, 8 COLUM. SCI. & TECH. REV. 1 (2007).

¹⁶ *Id.*, at 13.

¹⁷ Wagner et al., *supra* note 2.

¹⁸ See Abraxis Biosciences, Abraxane, <http://abraxane.com/index.aspx> (last visited Feb. 24, 2008).

¹⁹ See Ortho Biotech Products, LP, Doxil, <http://www.doxil.com/index.jsp> (last visited Feb. 24, 2008).

²⁰ See Wyeth Pharmaceuticals, Rapamune, [http://www.wyeth.com/products?product=wyeth_html/home/products/prescription/Rapamune%20%ae%20\(sirolimus\)/prescribinginfo.html](http://www.wyeth.com/products?product=wyeth_html/home/products/prescription/Rapamune%20%ae%20(sirolimus)/prescribinginfo.html) (last visited Feb. 24, 2008).

²¹ See Crucell-Berna Biotech, Epaxal, <http://www.crucell.com/Products-Epaxal> (last visited Feb. 24, 2008).

²² See Espirit-Pharma, Estrasorb, <http://www.estrarorb.com> (last visited Feb. 24, 2008).

²³ See Ortho Vita, Inc., Vitoss Product Description, <http://orthovitaportal.com/Vitoss%20Technical%20Information/default.aspx> (last visited Feb. 24, 2008).

²⁴ See GfE Medizintechnik, High Performance Metals and Materials (Germany), http://www.gfe.com/opencms2/opencms/en_gfe-online.de/GfE_Unternehmensprofil.html (last visited Feb. 24, 2008).

²⁵ See SurgRX, SurgRX EnSeal Tissue Sealing and Hemostasis System, <http://www.surgrx.com/product.html> (last visited Feb. 24, 2008).

²⁶ See Immunicon, Celltracks Analyzer II, <http://www.immunicon.com/cms/Default.aspx?tabid=61> (last visited Feb. 24, 2008).

egorizations and descriptions of these products, we conducted targeted searches of the FDA product website and also searched the scientific and technology literature. These categories are not intended to be an exhaustive representation of all products and categories subject to the FDA approval process and on the market.

A. Nanotechnology and Human Drug Products

In exploring the breadth of nanotechnology products in human drugs, we have identified five general categories of nanodrugs either on the market or in the process of entering the market classified according to their basic nano-structure. Many of these are reformulations of existing drugs with new methods of delivery. The first three categories are similar, in that the size of the drug delivery vehicle is at the nanoscale.

1. Drugs Encapsulated and Delivered in Bilayer Vesicles

One of the most extensively studied drug delivery formulations that falls under this category is the liposome, a nanoscale closed vesicle composed of a lipid bilayer which surrounds an entrapped aqueous space. Hydrophilic drug molecules can be carried within this aqueous space, while hydrophobic drugs can be inserted into the liposome's lipid bilayer. As an alternative to lipids, bilayer vesicles can also be composed of polymers, resulting in polymersomes. Another characteristic of this class of drugs is their capacity for surface modification. Currently, polymers, such as polyethylene glycol, are used on the surface of a vesicle to confer "stealth" properties to the drug carrier, meaning that they create a steric barrier which prevents adsorption of blood plasma proteins to the vesicle surface.²⁷ This results in decreased removal of the drug carrier from the blood flow.²⁸ In effect, this increases the circulation time of the nanodrug in the body and therefore also its chances of finding the cancer tumor. In the future targeting ligands such as peptides²⁹ or antibodies may also be attached to the surface to enhance drug delivery by allowing the drug carrier to selectively accumulate at the desired sight of action.³⁰

An example is Doxil, used to treat ovarian cancer, breast cancer, and AIDS-related Kaposi's sarcoma. Doxil was originally approved by FDA in November 1995 through the accelerated review process (a review process for drugs that promise significant benefit for a serious or life-threatening disease) to treat AIDS-related Kaposi's sarcoma.³¹ Doxil is the liposomal formulation of doxorubicin (trade name Adriamycin), a drug used in various anti-cancer formulations since 1973.³² Sequus reformulated doxorubicin using STEALTH liposomes, encapsulating the doxorubicin to allow longer circulation time in the blood.³³ Sequus reports that the small

²⁷ S. Moein Moghimi & J. Szebeni, *Stealth Liposomes and Long Circulating Nanoparticles: Critical Issues in Pharmacokinetics, Opsonization and Protein-binding Properties*, 42 PROGRESS IN LIPID RES. 463 (2003).

²⁸ Moghimi et al., *supra* note 3.

²⁹ A. Garg et al, *Targeting Colon Cancer Cells Using PEGylated Liposomes Modified with a Fibronectin-Mimetic Peptide*. Submitted. (2008).

³⁰ Vladimir P. Torchilin, *Drug Targeting*, 11 EUR. J. OF PHARMACEUTICAL SCI. S81 (2000).

³¹ Food & Drug Admin, *FDA Oncology Tool, Approval Summary for Doxorubicin Liposomal for Accel. Approv., Treatment of AIDS-related Kaposi's Sarcoma*, available at <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=223>.

³² Food & Drug Admin., *FDA Oncology Tools Approval Summary for Doxorubicin*, available at <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=211>.

³³ See Daily Med: Current Medication Information, Doxorubicin Hydrochloride, § 12.1 Mechanism of Action, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2256#nml34067-9> (last visited Feb. 15, 2008).

size (approximately 100 nm) enables it to enter the tumor's cracked vasculature and deliver the cancer-fighting agent directly to the tumor.³⁴ As a condition of the accelerated approval of Doxil, Sequus completed a controlled study to verify clinical benefit in 2000 and Doxil was granted full approval status.³⁵ Subsequently, through supplemental drug applications, Doxil has received approval for use in the treatment of ovarian cancer and multiple myeloma.³⁶

DepoCyt is an alternative bilayer vesicle formulation used to treat lymphomatous meningitis (LM), a rare but often fatal complication of malignant cancers that affects the central nervous system.³⁷ The formulation of cytarabine into particles composed of a network of bilayer lipid membranes using DepoFoam technology³⁸ reportedly gives the injected drug a longer half-life in the body and reduces the necessary dose frequency through sustained drug release.³⁹ DepoCyt was approved in April 1999 for the treatment of LM through the FDA's accelerated approval process.⁴⁰ FDA granted full approval of DepoCyt in April 2007 after Skyepharma completed two controlled clinical trials that demonstrated effectiveness of the drug in treating LM.⁴¹ The drug reportedly reduced the number of treatments for those suffering from LM from several per week to one treatment every two weeks.⁴²

2. Drugs Delivered in Micellar Nanoparticles

Micellar nanoparticles are composed of a monolayer of amphiphilic molecules arranged in a sphere to create a hydrophobic core shielded from water by a mantle of hydrophilic groups. Various types of amphiphilic molecules can be used to create micelles, including lipids and surfactants, but the most frequently utilized molecules are amphiphilic block copolymers. Micellar nanoparticles can be used to deliver water-insoluble drugs by physically trapping the drug within the micelle's hydrophobic core, or by covalently linking the drug to molecules of the micelle.⁴³ This type of delivery system aids in the transport of the drug into the superficial layers of the skin by creating a "drug depot" from which the drug can continuously diffuse into the circulation.⁴⁴ Micellar nanoparticles are also capable of surface modification to increase circulation times and/or improve targeting.⁴⁵ The drug Estrasorb, a topical soy-based estrogen therapy lotion used to treat menopausal hot flashes,

³⁴ See *id.*

³⁵ Ramzi Dagher et al., *Accelerated Approval of Oncology Products: A Decade of Experience*, 96 J. NAT'L CANCER INST. 1500 (2004).

³⁶ Food & Drug Admin., *FDA Oncology Tools Approval Summary for Doxorubicin Liposomal for Accel. Approval, Treatment of Metastatic Carcinoma*, available at <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=225>.

³⁷ Surasak Phuphanich et al., *A Pharmacokinetic Study on Intra-CSF Administered Encapsulated Cytarabine (DepoCyt) for the Treatment of Neoplastic Meningitis in Patients with Leukemia, Lymphoma, or Solid Tumors as Part of a Phase III Study*, 81 J. NEUROONCOL. 201 (2007).

³⁸ Skye Pharmaceuticals, Depofoam Technology, http://www.skyepharma.com/injectables_depofoam.html (last visited Feb. 24, 2008).

³⁹ Pacira Pharmaceuticals, DepoCyt Product Description, <http://www.pacira.com/html/products-depocyt.html> (last visited Feb. 24, 2008).

⁴⁰ Food & Drug Admin., *FDA Oncology Tools Approval Summary for Cytarabine Liposomal for Accel. Approval*, available at <http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=193>.

⁴¹ Center for Drug Evaluation and Research (CDER) Off. Mem. to Skyepharma Inc. (April 19, 2007), available at http://www.fda.gov/cder/foi/applletter/2007/021041s018_LTR.pdf.

⁴² Pacira Pharmaceuticals, DepoCyt, Product Description, <http://www.pacira.com/html/products-depocyt.html> (last visited Feb. 15, 2008).

⁴³ Moghimi et al., *supra* note 3.

⁴⁴ *Id.*

⁴⁵ Vladimir P. Torchilin, *Micellar Nanocarriers: Pharmaceutical Perspectives*, 24 PHARM. RES. 1 (2007).

is formulated with micellar nanoparticles.⁴⁶ FDA approved Esprit Pharma's new drug application for Estrasorb in October 2003.⁴⁷

3. *Drugs Delivered in Nanospheres*

These particles are spherical matrices ranging from tens to hundreds of nanometers in size, composed of synthetic or natural polymers (proteins) such as collagen or albumin. The drug is dispersed within this matrix through dissolution, entrapment or physical attachment to the constituent molecules of the nanosphere such that the drug is uniformly distributed throughout the particle.⁴⁸ An example of this category is Abraxane, which is a formulation of paclitaxel, a cancer-fighting agent which has been used in FDA-approved drugs such as Taxol, approved in 1992.⁴⁹ The nanosphere matrix is composed of albumin proteins that are physically attached to the paclitaxel drug molecules. The nanosphere is injected into the body and then undergoes a concentration dependent dissociation into individual drug-bound albumin molecules. Because albumin also preferentially accumulates in tumors, Abraxane is able to deliver the cancer-fighting agent directly to the tumor.⁵⁰ Abraxane received accelerated approval as a treatment for breast cancer in January 2005 through a new drug application submitted to FDA by American Bioscience.⁵¹ In clinical trials, Abraxane proved to be more effective than the non-nano formula, showing a response rate of 21.5 percent compared to 11.1 percent for the unencapsulated version.⁵²

4. *Drugs Formulated as Stable Dispersions Containing Nanometer-Sized Drug Crystals*

High-shear media milling is used to turn a large mixture of crude drug, water and stabilizer (a molecule which is added to prevent aggregation of the drug crystals) into a nanometer-sized dispersion. The resulting drug particles have an average diameter under 200 nm⁵³ (note that anything over 100 nm is larger than typically thought of as "nano" by scientists, but may be marketed as nano nonetheless).⁵⁴ This technique is reported to increase the solubility of poorly-water-soluble drugs. Additionally, these stable formulations may be post-processed into finished dosage forms for all routes of administration.⁵⁵ An example is Rapamune, a formulation of the drug sirolimus,

⁴⁶ Estrasorb® (estradiol topical emulsion), Prescribing Information, available at <http://www.estrasorb.com/EstrasorbBrief.pdf> (last visited Mar. 19, 2008).

⁴⁷ Food & Drug Admin., *CDER NDA Approvals for Calendar Year 2003*, available at <http://www.fda.gov/cder/rdmt/ndaaps03cy.htm>.

⁴⁸ Sanjeeb K. Sahoo & Vinod Labhasetwar, *Nanotech Approaches to Drug Delivery and Imaging*, 8 *DRUG DISCOVERY TODAY* 1112 (2003).

⁴⁹ Susan M. Cruzan, *Taxol Approved for Breast Cancer*, available at <http://www.fda.gov/bbs/topics/ANSWERS/ANS00577.html>.

⁵⁰ See Abraxis BioScience, available at <http://abraxane.com/> (last visited Feb. 15, 2008).

⁵¹ Food & Drug Admin., *CDER Fast Track Products Approved Since 1998 through 3/31/07*, available at <http://www.fda.gov/cder/rdmt/internetftp.htm>.

⁵² Food & Drug Admin., *ABRAXANE Label* (2007), available at <http://www.fda.gov/cder/foi/label/2007/021660s010lbl.pdf>.

⁵³ Elaine Merisko-Liversidge Et al., *Nanosizing: A Formulation Approach for Poorly-Water-Soluble Compounds*, 18 *EUR. J. PHARM. SCI.* 113 (2003).

⁵⁴ There are no nano-specific restrictions on the labeling and marketing of nanoproducts. In fact, the FDA Task recommended that no additional labeling be required for products using or containing nanoscale materials, but that FDA should assess appropriate labeling on a case-by-case basis. See Food & Drug Admin., *supra* note 8, at 35.

⁵⁵ See Elan Corporation, Nanocrystal Technology, http://www.elan.com/EDT/nanocrystal_technology (last visited Feb. 24, 2008).

an immunosuppressant used for the prevention of organ rejection in renal transplant recipients.⁵⁶ Rapamune incorporates a version of nano-sizing technology developed and marketed by the Elan Corporation, called NanoCrystal technology. Rapamune was originally approved as a new molecular entity and as a priority review drug in September 1999 as an immunosuppressant used to resist organ rejection in kidney transplant patients.⁵⁷ The nano-formulation, facilitated by Elan's NanoCrystal Technology, allows Rapamune to be administered as a tablet rather than through the originally approved refrigerated solution.⁵⁸ The tablet formulation was approved as a new formulation through the new drug approval process on August 25, 2000.⁵⁹

5. *Nanocarriers as the Drug Itself*

Unlike the first three categories in which a nano-sized carrier with no inherent therapeutic activity is synthesized and used to deliver a pre-existing, active drug molecule (thus creating a "nanodrug") the constituents of this category function simultaneously as both the drug and the carrier. Separate components which individually may be incapable of therapeutic action are brought together to create a new nanoscale entity with therapeutic benefit. Currently this technique is used with vaccines, where nanoparticles are made to mimic viruses. Similar to the first two categories, these so called "virosome" particles are composed of a lipid envelope and then undergo surface modification. However, unlike the surface modification of vesicles and micelles, these nanoparticles are functionalized with the surface proteins of a virus such as influenza; this confers therapeutic activity to the nanoparticles by allowing them to fuse with target cells and stimulate an immune response.⁶⁰ Though the virosomes as described here are hollow inside the lipid envelope, this is not a necessity of the design, as no drug is encapsulated in this space. An example of this type of vaccine is Epaxal, an aluminum-free vaccine for Hepatitis-A, an infection causing acute inflammation of the liver.⁶¹ Crucell Incorporated, the manufacturer of Epaxal, is currently working with FDA towards approval of the vaccine.⁶²

B. *Nanotechnology and Medical Device Products*

Most nanodevice products we identified were cleared by FDA as being substantially equivalent to a predicate device through the Class II "510(k)" clearance route. This is a determination by FDA that the device is "substantially equivalent" to an existing device and requires only premarket notification to FDA. Marketed medical device categories we identified included anti-microbial coatings used on wound dressings and implantable medical devices, tissue repair and reinforcement

⁵⁶ See Rapamune (sirolimus) Oral solution and Tablets Prescribing Information, available at <http://www.wyeth.com/content/ShowLabeling.asp?id=139> (last visited Mar. 19, 2008).

⁵⁷ Food & Drug Admin., *CDER Priority NDA Approvals in Calendar Year 1999*, available at <http://www.fda.gov/cder/rdmt/NDAPriority99.htm>.

⁵⁸ See Elan Drug Technologies NanoCrystal Technology, *Commercialized Products*, http://www.elan.com/EDT/nanocrystal_technology/Commercialized_Products.asp.

⁵⁹ Food & Drug Admin., Renata Albrecht, NDA 21-110/S-003, Letter to Wyeth Pharmaceuticals, available at <http://www.fda.gov/cder/foi/appletter/2002/21110scf003ltr.pdf>.

⁶⁰ Anke Huckriede et al., *The Virosome Concept for Influenza Vaccines*, 23 *VACCINE* S26 (2005).

⁶¹ Crucell, Epaxal®, <http://www.crucell.com/Products-Epaxal> (last visited Feb. 15, 2008).

⁶² *Crucell Presents Update on Products and Programs at New York Analyst Meeting*, WEBWIRE, Nov. 16, 2006, <http://www.webwire.com/ViewPressRel.asp?aId=23777>.

materials, surgical instruments for tissue and vessel sealing, *in vitro* diagnostic devices, immunoassays and bonding agents for dental work.

1. *Anti-Microbial Nanocoatings*

These were used in a variety of products, such as wound dressings and implantable devices, including stents, catheters and orthopedic implants. For example, Smith & Nephew manufactures a product called Acticoat Moisture Control Dressing with Silcryst nanocrystals that serves as an anti-microbial wound dressing for burns, graft sites and ulcers. Silcryst is licensed to Smith & Nephew by NuCryst.⁶³ FDA cleared this device in April 2005. The company describes it as having 3 layers: an outer polyurethane film layer, a middle polyurethane foam layer and an inner nanocrystalline silver coated polyurethane film layer that has contact with the wound site.⁶⁴ The corporate website provides that the Silcryst silver nanocrystals release silver ions faster than normal silver, have increased anti-microbial activity and have an increased proportion of surface atoms as compared with internal atoms.⁶⁵ We found five similar FDA cleared Acticoat products: Acticoat Dressings Foam (listed as the predicate device), the Acticoat Moisture Control, the Acticoat 7 Dressing, the Acticoat Alginate-Absorbent and the Acticoat Primary-Burn.⁶⁶ In July 2007, NuCryst received clearance for its own Silcryst Silver Antimicrobial Wound Cream, listing an Acticoat product as a predicate device.⁶⁷

Similarly, Acrymed, Inc. manufactures AcryDerm Silver Antimicrobial Wound Gel (marketed as SilvaGard technology), a polyurethane adhesive wound and burn dressing containing silver ions for use in securing devices to the skin following general and plastic surgery.⁶⁸ This was cleared through the 510(k) process in October 2006⁶⁹ and an over the counter version cleared in July 2007.⁷⁰ The i-Flow Corporation markets an On-Q Silver Soaker Antimicrobial Catheter (cleared through the 510(k) process in November 2005), an implantable medication delivery catheter treated with SilvaGard for its antimicrobial effect.⁷¹

2. *Products for Tissue or Bone Repair and Restoration*

These include OrthoVita, Inc.'s Vitoss to promote new bone growth using beta-tricalcium phosphate nanoparticles (β -TCP),⁷² cleared via 510(k) in December 2003,

⁶³ See NUCRYST Pharmaceuticals, Acticoat Licensing Agreement, available at http://www.nucryst.com/partners_sil.htm. *The Virosome Concept for Influenza Vaccines*

⁶⁴ Food & Drug Admin., K050030 510k Summary of Safety and Effectiveness at 2 (Apr. 21, 2005), available at <http://www.fda.gov/cdrh/pdf5/K050030.pdf>.

⁶⁵ See Smith & Nephew, Acticoat, <http://www.acticoat.com/> (last visited Feb. 24, 2008).

⁶⁶ Food & Drug Admin., K050030 510k Summary of Safety and Effectiveness at 3 (Apr. 21, 2005), available at <http://www.fda.gov/cdrh/pdf5/K050030.pdf>.

⁶⁷ See Food & Drug Admin., K063805 Section 5-510(K) Summary (July 13, 2007), available at <http://www.fda.gov/cdrh/pdf6/K063805.pdf>.

⁶⁸ See Acrymed, Inc., Medical Device Infection Control, <http://www.acrymed.com/medical.html> (last visited Feb. 15, 2008).

⁶⁹ Food & Drug Admin., K061232 510(K) Summary (July 13, 2007), available at <http://www.fda.gov/cdrh/pdf6/K063805.pdf>.

⁷⁰ Food & Drug Admin., K070333 510(K) Summary (July 10, 2007) available at <http://www.fda.gov/cdrh/pdf7/K070333.pdf>.

⁷¹ See i-Flow Corporation, ON-Q PainBuster Post-Op Pain Relief System, http://www.iflo.com/prod_painbuster.php (last visited Feb. 24, 2008).

⁷² See OrthoVita, Inc., Vitoss Product Description, <http://orthovitaportal.com/Vitoss%20Technical%20Information/default.aspx> (last visited Feb. 24, 2008).

and GfE Medizintechnik's TiMesh, a titanized soft tissue reinforcement implant cleared via 510(k) in September 2003.⁷³ Vitoss utilizes particles approximately 100 nm in size that create highly porous, 3-dimensional β -TCP scaffolds (pores ranging from 1 to 1000 micrometers (μm) in size). The company claims although similar in architecture and chemical composition to natural bone mineral, these nano-sized particles with a higher surface area enhance resorption and new bone growth.⁷⁴ The TiMesh surgery implants have a covalent bonded titanium layer of 30 nm as a coating that allows more flexibility than previous materials.⁷⁵

3. *Surgical Instruments for Tissue and Vessel Sealing*

SurgRx markets the EnSeal Tissue Sealing and Hemostatis System, described as "nanometer sized conductive particles embedded in a temperature-sensitive [polymer] material" that regulate the heat passing into the tissue for maximal sealing.⁷⁶ This was cleared through the 510(k) process in July 2003.⁷⁷ Using millions of nanometer sized conductive carbon particles, the five millimeter diameter EnSeal instrument seals vessels during laparoscopic and open surgery. Reportedly the sealed vessel walls can withstand over seven times normal systolic pressure.⁷⁸

4. *Diagnostic Test Kits and Immunoassays*

A variety of diagnostic test kits and immunoassays using nanotechnology have also been cleared by FDA, including Immunicon Corporation's Celltracks Analyzer II, an *in vitro* diagnostic device containing ferrofluid nanoparticles to detect tumor cells,⁷⁹ cleared via 510(k) in March 2006,⁸⁰ Nano-Ditech Corporation's Nano-Check Ami 3 in 1 Cardiac Marker Test,⁸¹ cleared via 510(k) in March 2006 using gold colloidal particles to bind to plasma or blood samples for detection of Acute Myocardial Infarction,⁸² and Nano-Check Dat 5 Multi Drug Screening,⁸³ cleared via 510(k) in March 2005 using gold colloidal particles to bind to urine samples for detection of five common drugs of abuse.⁸⁴

⁷³ Food & Drug Admin., K031225 510(K) Summary (Sept. 29, 2003) <http://www.fda.gov/cdrh/pdf3/K031225.pdf>.

⁷⁴ See OrthoVita, Inc., Vitoss Product Description, <http://orthovitaportal.com/Vitoss%20Technical%20Information/default.aspx> (last visited Feb. 24, 2008).

⁷⁵ See GfE Medizintechnik, TiMesh (Germany), <http://www.pfmmedical.com/main.htm> (last visited Feb. 24, 2008).

⁷⁶ See SurgRX, Vessel Sealing with Smart Electrode Technology and Nanoscale RF Control, <http://www.surgrx.com/technology.html> (last visited Feb. 24, 2008).

⁷⁷ Food & Drug Admin., K031133 510(K) Summary (July 3, 2003), available at <http://www.fda.gov/cdrh/pdf3/K031133.pdf>.

⁷⁸ See SurgRX, Inc., SurgRx, <http://www.surgrx.com/index.html> (last visited Feb. 24, 2008).

⁷⁹ See Immunicon, Celltracks Analyzer II, <http://www.immunicon.com/cms/Default.aspx?tabid=61> (last visited Feb. 24, 2008).

⁸⁰ Food & Drug Admin., K060110 510(K) Summary (Jan. 12, 2006), available at <http://www.fda.gov/cdrh/pdf6/K060110.pdf>.

⁸¹ See Nano-Ditech Corporation, Nanocheck DOA, <http://www.nanoditech.com/product/product.htm#b> (last visited Feb. 24, 2008).

⁸² Food & Drug Admin., K050975 510(K) Summary (May 2, 2006), available at <http://www.fda.gov/cdrh/pdf5/K050975.pdf>.

⁸³ See Nano-Ditech Corporation, Nanocheck DOA, <http://www.nanoditech.com/product/product.htm#b> (last visited Feb. 24, 2008).

⁸⁴ Food & Drug Admin., K050594 510(K) Summary (May 25, 2005), available at <http://www.fda.gov/cdrh/pdf5/K050594.pdf>.

5. Dental Bond Agents

Products currently on the market utilizing nanotechnology for restorative dental work include Dentsply International's Prime & Bond NT,⁸⁵ cleared via 510(k) in February 2005, Nano-Write Corporation's Nano-Tricrown,⁸⁶ cleared via 510(k) in June 2003,⁸⁷ and Pentron Laboratory's Sculpture Plus Nano-Hybrid Composite,⁸⁸ cleared via 510(k) in January 2003.⁸⁹

The Prime & BondNt is a one coat bonding agent with a seven nanometer diameter filler. The nanometer size filler is able to penetrate channels to provide added "nano retention and allows it to be evenly distributed in the resin matrix, adding strength to the adhesive layer."⁹⁰ Nano-TiCrown is a nanostructured titanium/titanium nitride (Ti/TiN) material having a wall thickness of 10 um.⁹¹

C. Emerging Products that May Challenge Existing Regulatory Classifications

Increasingly, products have been combining drugs, devices and biologics into a single product.⁹² It was originally unclear how these "combination products" should be regulated. The Office of Combination Products (OCP) at FDA was created by Congress in December 2002 to more effectively manage products combining drugs, medical devices and biologics as required by the 2002 Medical Device User Fee and Modernization Act (MDUFA).⁹³ OCP was given responsibilities spanning the regulatory life of drug-device, drug-biologic and device-biologic products, with primary regulatory responsibilities and oversight of combination products still residing with the CDER, CBER and CDRH. A product is assigned to CDER, CBER, or

⁸⁵ See Dentsply International, Prime & Bond NT, http://www.caulk.com/assets/pdfs/products/Prime&Bond_NT2_English.pdf (last visited Feb. 24, 2008).

⁸⁶ See Nano-Write Corporation, <http://www.nanowrite.com/> (last visited Feb. 24, 2008).

⁸⁷ Food & Drug Admin., K031627 510(K) Summary (June 11, 2003), available at <http://www.fda.gov/cdrh/pdf3/K031627.pdf>.

⁸⁸ See Pentron Laboratory, Simile Nano-Hybrid Composite, <http://www.pentron.com/pentron/ClinicalSubcategoryDetail.cfm?id=132&cat=30> (last visited Feb. 24, 2008).

⁸⁹ Food & Drug Admin., K023792 150(K) Summary (Jan. 17, 2003), available at <http://www.fda.gov/cdrh/pdf2/K023742.pdf>.

⁹⁰ See Dentsply International, Prime & Bond NT, http://www.caulk.com/assets/pdfs/products/Prime&Bond_NT2_English.pdf (last visited Feb. 24, 2008).

⁹¹ See Nano-Write Corporation, <http://www.nanowrite.com/> (last visited Feb. 24, 2008).

⁹² "Combination product includes: 1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; 2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; 3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or 4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect." Federal Food, Drug, and Cosmetic Act, 21 CFR 3.2(e).

⁹³ Food & Drug Admin., *Overview of the Office of Combination Products*, <http://www.fda.gov/oc/combination/overview.html> (last visited Feb. 24, 2008).

CDRH based on its PMOA.⁹⁴ The Final Rule defining PMOA of a combination product is in the *Federal Register*⁹⁵ and also available on the OCP website, defining PMOA as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.”⁹⁶

Historically, classification of new products using existing definitions has been a struggle for FDA.⁹⁷ The creation of the OCP has resulted in a more collaborative approach to regulating emerging medical products crossing traditional boundaries between drugs, medical devices and biologics. However, rapidly developing applications in nanomedicine at the convergence of mechanical, chemical, electrical and optical properties at the nanoscale will likely add another layer to the classification challenge for the OCP. Classification of a product according to its PMOA has meant that any product having a chemical action as its PMOA would be regulated as a drug; one having a mechanical action as its PMOA would be regulated as a medical device. Highly integrated nanotechnology products will pose a challenge to existing regulatory frameworks in the future because of potentially multiple modes of action that blur chemical, mechanical and other distinctions. We describe several applications in research and development stages that may pose new questions for FDA depending on how they are integrated into a consumer health or medical product.

Various research groups are developing “nanoshells” that can potentially combine imaging capabilities with selective binding to cancer cells to kill them via heat or light and/or targeted drug delivery using temperature sensitivity.⁹⁸ The variance in the size ratio between the core and the wall of the shell allows precise tuning to

⁹⁴ Federal Food, Drug, and Cosmetic Act §503(g).

⁹⁵ Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49848 (August 25, 2005).

⁹⁶ Food & Drug Admin., *Final Rule: Definition of a Primary Mode of Action for a Combination Product*, available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm> (last visited Sep. 28, 2006). The FDCA defines it as: “Primary mode of action is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.” Federal Food, Drug, and Cosmetic Act, 21 CFR 3.2(m). The FDCA defines “mode of action” as “the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition, ‘therapeutic’ action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body. When making assignments of combination products under this part, the agency will consider three types of mode of action: The actions provided by a biological product, a device and a drug. Because combination products are comprised of more than one type of regulated article (biological product, device, or drug), and each constituent part contributes a biological product, device, or drug mode of action, combination products will typically have more than one identifiable mode of action.” “1) A constituent part has a biological product mode of action if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings, as described in section 351(i) of the Public Health Service Act. 2) A constituent part has a device mode of action if it meets the definition of device contained in section 201(h)(1) to (h)(3) of the act, it does not have a biological product mode of action, and it does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes. 3) A constituent part has a drug mode of action if it meets the definition of drug contained in section 201(g)(1) of the act and it does not have a biological product or device mode of action.” Federal Food, Drug, and Cosmetic Act, 21 CFR 3.2(k)(1)-(3).

⁹⁷ Susan Bartlett Foote & Robert J. Berlin, *Can Regulation be as Innovative as Science & Technology?*, 6(2) MINN. J. LAW, SCI. & TECH. 619, 639 (2005).

⁹⁸ See, e.g., Tarek M. Fahmy et al., *Nanosystems for Simultaneous Imaging and Drug Delivery to Cells*, 9AAPS J. E171 (2007).

effectuate absorbance or scattering of specific light wavelengths into heat.⁹⁹ Some research applications utilize light absorbance for imaging and photothermal ablation to target cells, suggesting that these will be regulated as medical devices given the mechanical action. For example, one research lab has developed nanoshells made of a dielectric silica core covered by a thin gold shell. The imaging function comes from the ability of the nanoshells to scatter near infrared (NIR) light. The nanoshells, conjugated to antibodies specific to human epidermal growth factor receptor-2 (HER2) expressing cancer cells, absorb NIR light and mediate photothermal ablation of the cancer cells. Tested *in vitro*, the nanoshells were shown to effectively image and kill specifically targeted cells.¹⁰⁰ Similarly, an article in *Nano Letters* recently described nanoshells with both absorption and scattering characteristics in the NIR light range. Resonance is utilized to increase optical contrast in tumors for optical coherence tomography (OCT) imaging and then absorbance is used in photothermal ablation.¹⁰¹ However, one can imagine an application where the ablation action is chiefly chemical in nature partnered with the mechanical imaging. Here, what will be considered the PMOA?

A Chinese research team has developed nanoparticles made of chitosan that encapsulate superparamagnetic iron oxide (Fe_3O_4) nanoparticles, fluorescent cadmium telluride quantum dots (CdTe QDs) and pharmaceutical drugs. The magnetic properties allow for guidance of the administered drug using a magnetic field and the fluorescence enables real-time monitoring of the particles as they deliver drugs.¹⁰² Here, the action is both mechanical (magnetic guidance and continued monitoring) and chemical drug delivery directly by the nanoparticles. Because the nanoparticle is subject to continuous monitoring in order to mediate the delivery of the drug, what is the primary therapeutic mode of action in this case? Do the nanoscale properties make this unique from other applications that serve an imaging and drug delivery purpose?

Tumor-targeted drug-carrying nanoparticles called “nanobubbles,” composed of biodegradable diblock copolymers, are also in research phases. These nanobubbles coalesce in tumors due to the enhanced permeability and retention (EPR) effect and form “microbubbles.” The microbubbles “produce strong echo in ultrasound imaging” and release encapsulated drug (doxorubicin) upon therapeutic ultrasound which causes “inertial cavitation.” The system allows for specific delivery of drugs only to irradiated sites.¹⁰³ In this case, the initial nanobubbles collect in tumors, form larger bubbles serving to create an echo for imaging purposes, and ultimately release a drug directly into the tumor. Hence, it is a drug, a drug carrier, and a diagnostic tool all at the same time. Again, does the size of the original nanoparticle make a difference in its combined functions in a regulatory sense? Which is the PMOA?

Similarly, other research suggests that nanoparticles may be used to assess the severity of a disease. Nanoparticles have been used to diagnose asymptomatic

⁹⁹ Max Sherman, *Exploring the World of Nano Medical Devices*, Medical Device & Diagnostic Industry, May 2006, available at <http://www.devicelink.com/mddi/archive/06/05/008.html> (last visited Feb. 25, 2008).

¹⁰⁰ Christopher Loo et al., *Immunotargeted Nanoshells for Integrated Cancer Imaging and Therapy*, 5 *NANO LETTERS* 709 (2005).

¹⁰¹ André M. Gobin et al., *Near-Infrared Resonant Nanoshells for Combined Optical Imaging and Photothermal Cancer Therapy*, 7 *NANO LETTERS* 1929 (2007).

¹⁰² Linlin Li et al., *Magnetic and Fluorescent Multifunctional Chitosan Nanoparticles as a Smart Drug Delivery System*, 18 *NANOTECHNOLOGY* 405102 (2007).

¹⁰³ Natalya Rapoport et al., *Multifunctional Nanoparticles for Combining Ultrasonic Tumor Imaging and Targeted Chemotherapy*, 99 *J. NAT'L CANCER INST.* 1095 (2007).

patients at high-risk of atherosclerotic disease by detecting the development of plaque, which reveals lesion activity and vulnerability to rupture. In addition to these diagnostic capabilities, the nanoparticles can also locally deliver antiangiogenic therapy (statin), which may slow down plaque progression and allow effective and aggressive therapy.¹⁰⁴ How should an application be classified when it allows for a continuous monitoring of plaque development while triggering the amount of drug therapy in parallel?

Currently in research phases, Bio-silicon is being developed for controlled release drug delivery, with the potential for targeted cancer therapy such as localized chemotherapy. Bio-silicon is a “nanostructured form of elemental silicon, engineered to create a ‘honeycomb’ structure of pores, allowing silicon to biodegrade while also allowing the retention of various drugs and vaccines[.]”¹⁰⁵ Bio-silicon has been reported to dissolve into common silicic acid in body fluids as it delivers drugs or vaccines.¹⁰⁶ The company leading this research claims that they have created a unique biomaterial having potential to serve both as a medical device and a novel drug delivery system.¹⁰⁷ What implications for classification are there if the nanostructure dissolves over time as it delivers drugs? Is the PMOA the drug delivery, or the unique structure of the matrix that allows it to degrade over time?

IV. CONCLUSION

The rising interest in nanomedicine in general and nanodrugs and nanodevices specifically, as well as the growing market impact of these technologies in healthcare and medicine underscore the need for examining existing regulatory systems in terms of their applicability to nanoproducts. At the present time, if regulated at all, nanotechnology products are assessed on a case by cases basis using existing regulatory systems. The future challenge for FDA and similar federal regulatory agencies internationally will be determining whether certain types of nanotechnology products in the drug and device realm warrant additional regulations or whether current oversight can be adapted to the newly emerging capabilities and characteristics of nanobiotechnology. Questions include whether a distinct regulatory definition for nanotechnology can and should be developed for drug and medical device products; how this definition will vary from applications in other technical fields regulated by other federal agencies; and specifically whether distinctions between “chemical” and “mechanical” action need to be reassessed at the nanoscale.

Adapting existing regulations to fit a new technology and products is not a new challenge for regulatory agencies, nor for FDA specifically; there is typically a lag between the development of a technology and the generation of law to oversee it. However, questions about the suitability of the century-old definitions for classifying product as a drug, device or biologic may be ill-equipped to handle the convergence of properties at the nanoscale.

¹⁰⁴ Gregory Lanza et al., *Nanomedicine Opportunities in Cardiology*, 1080 ANN. N.Y. ACAD. SCI. 451 (2006).

¹⁰⁵ See pSivida, available at <http://www.pshivida.com/about/biosilicon.asp> (last visited Feb. 25, 2008).

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*