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BREAKTRHOUGH BIOTECHNOLOGIES: CAN THE FDA KEEP UP WITH THE SPEED OF SCIENCE?

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BREAKTRHOUGH BIOTECHNOLOGIES: CAN THE FDA KEEP UP WITH THE SPEED OF SCIENCE? (2004 Third Year Paper)

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Abstract

Biotechnology advances have the potential to dramatically change the practice of medicine. Currently research is underway to find cures for diseases that were before untreatable, and many biotechnology products are already on the market improving the drugs and devices we use today. However, one important factor to ensure that the pace of biotechnology goes on unhindered is proper regulation. As the guardian of public health, the Food and Drug Administration has struggled to meet the demands of the rapidly growing field. In particular, the FDA has recognized three potential breakthrough areas of biotechnology that may need regulatory reform: cell and gene therapy, pharmacogenetics / pharmacogenomics, and novel drug delivery. This paper will examine the current state of these three technologies and the regulatory landscape surrounding them.

BREAKTRHOUGH BIOTECHNOLOGIES: CAN THE FDA KEEP UP WITH THE SPEED OF SCIENCE?

Kristy Hong

Third Year Paper
Food and Drug Law

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I.

Introduction

The drugs, techniques, and tools developed through biotechnology have the potential to dramatically change the health and quality of life of current and future generations. The field of biotechnology uses knowledge from almost every scientific discipline including chemistry, biology, engineering, computer science, and material science to improve current medicine and find innovative solutions to almost every medical condition. In only three decades the amount of biotechnology progress has been remarkable and continues to generate excitement across many audiences, including academics, pharmaceutical companies, investors, and the general public.[1]

As the pace of drugs discovered through traditional pharmaceutical approaches has been slowing,[2] many people are looking to biotechnology to both fuel the pipeline of drugs and make the process of drug development safer and more efficient. While the work by researchers and scientists is one essential element to getting these new technologies to market, another important aspect of introducing innovative medical technology to the public is a regulatory framework that will find the proper balance between speed and safety. The Food and Drug Administration (FDA) is the agency that has been charged by our government to ensure the safety and efficacy of all medical products sold to the public[3]. Any innovative drug or device must be approved by the FDA before it can be sold to the public. The FDA also imposes regulations on the way a medical product is developed and tested. After a product is introduced to the public, the FDA has continuing authority to

[1]See Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, 19 (2000). Genentech, Inc. was the first biotech company to go public in October 1980.

[2]See Overview of FDA Regulation of Human Medicinal Products Developed with Biotechnology, 718 PLI/Pat 979, 995-97 (2002) [herinafter Overview of FDA Regulation].

[3]Federal Food Drug and Cosmetic Act, 21 U.S.C. § 362. See also the FDA Mission Statement, "The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.", available at http://www.fda.gov/opacom/morechoices/mission.html.

ensure post-marketing safety.

While government regulation is necessary to ensure that only products that have a sufficient risk to benefit tradeoff are allowed to reach the public, the regulatory pathway that a product must go through to obtain FDA approval can often be a long and costly process. The total development time for a new drug is approximately ten to fifteen years[4], and estimates for the total cost of developing a new drug and bringing it to market is $500 million, which includes the costs for failed candidates[5]. The FDA requires products to go through a rigorous testing period conducted in multiple phases. After the candidate has completed the required clinical tests, an application is then submitted to the FDA for review. The time required to review the application can take approximately one to two years[6].

In recent years, the FDA has responded to criticisms of regulatory delay by embarking on several initiatives designed to accelerate the drug and device development process[7]. While these measures have resulted in significant improvements, the FDA faces a much larger challenge with the task of improving regulation of innovative biotechnology products. In a recent 2002 statement titled Improving Innovation in Medical Technology: Beyond 2002, the FDA acknowledged that its current framework for regulation of medical products was insufficient for some new areas of biotechnology.[8] In particular, the FDA focused on three areas of biotechnology with breakthrough potential, but high regulatory uncertainty and confusion: (1) cell and gene therapy, (2) pharmacogenomics/ pharmacogenetics, and (3) novel drug delivery systems.[9]

[4]Overview of FDA Regulation, supra note 2, at 997.

[5]Id.

[6]Id. at 1003.

[7]Most notable is the Prescription Drug User Fee Act of 1992, which enabled the FDA to charge a user fee to applicants. The user fees allowed the FDA to obtain the resources necessary to accelerate the review process.

[8]Available at http://www.fda.gov/bbs/topics/NEWS/2003/beyond2002/report.html. See also, FDA, Press Release: FDA Launches New Initiative to Improve the Development and Availability of Innovative Medical Products, Jan. 31, 2003, available at http://www.fda.gov/bbs/topics/NEWS/2003/NEW00867.html.

[9]Id.

This paper will examine these three areas of biotechnology and the regulatory landscape surrounding those technologies. Part I will describe the technologies and the science behind them. Current advances and challenges in the technology will be addressed, along with some of the possible applications. Part II will give a background on the FDA's regulation of medical products, and an overview of the FDA regulatory structure. Part III will focus on FDA regulation applied to the three breakthrough areas of biotechnology. Other relevant regulatory provisions and social issues will also be discussed. The regulatory challenges will be presented along with recommendations for improvements.

II.

A.

Cell and Gene Therapy

One of the most promising and exciting areas in biotechnology is not based on a drug or chemical, but instead focuses on altering our own tissues and cells at the most fundamental level. Cell and gene therapy uses the power inherent in living matter to treat disease and injury. Far from the traditional trial and error approach to finding new medicines, cell and gene therapy uses a strategic approach to curing disease by first understanding the underlying mechanisms of the disease and related physiological functions.

1.

Cell therapy

Cell therapy involves treating diseased tissues by adding to the body specific cells that have been selected or engineered to make local or systemic changes. While living cells have been used before to treat patients through procedures such as blood transfusions, organ transplants, and bone marrow transplants, cell therapy goes beyond typical transplantations by using various techniques to manipulate the cells, combine the cells with other drugs or devices, or stimulate cell activity[10]. Some examples of *ex vivo* (outside the body) manipulation include "propagation, expansion, selection, purification, or alteration of biological characteristics

[10]Food and Drug Administration, Guidance for Human Somatic Cell Therapy and Gene Therapy 3 (Mar. 1998). The FDA defines somatic cell therapy as "the administration to humans of autologous, allogeneic, or xenogeneic living non-germline cells, other than transfusable blood products, for therapeutic, diagnostic, or preventive purposes."

by pharmacological treatment irradiation, or other methods."[11]

Most cell therapies use somatic cells, as opposed to germ line cells, meaning the changes will affect only the current generation and not the reproductive cells. Somatic cell therapies have several dimensions of classification. One important distinction is the source of the cells. If cells used in the therapy are from the same patient, then the therapy is called autologous.[12] Allogenic treatment uses cells that come from a human donor other than the patient.[13] Finally, xenotransplantation uses cells derived from an animal source that are altered to be compatible with humans.[14] Autologous treatments are advantageous because they are less likely to induce an immune response, but require advance harvesting of the cells from the patient. Xenotransplantations offer the best option for large scale source of tissues and organs, yet present the most challenge in terms of compatibility and immune acceptance[15].

Somatic cell therapy can also be classified according to the function of the cells being implanted, which can be either structural or functional.[16] Structural cell therapy involves treating tissues such as cartilage, muscle, and skin. Autologous structural cell therapies are often referred to in the industry as manipulated autologous structural (MAS) therapies.[17] Some MAS products have already been approved and are currently being marketing in the United States. Carticel® is a product marketed by Genzyme for people with cartilage degradation in the knee joint.[18] A small biopsy of the patient's own cartilage cells are removed, grown in culture ex vivo, and then implanted back into the injured knee.[19] Apligraf and Dermagraft are examples of marked skin replacement products that use allogenic cells.[20] These skin grafts are used for patients with

[11]Shane M. Ward, Global Harmonization of Regulatory Requirements for Premarket Approval of Autologous Cell Therapies, 55 Food & Drug L.J. 225, 230 (2000).

[12]See id. at 226.

[13]Scott R. Burger, GTP/GMP Cell Engineering for Cell and Gene Therapies, BioProcessing Journal, 292 (Jan/Feb 2003).

[14]Id.

[15]See Elizabeth Pennisi, FDA OKs Baboon Marrow Transplants, 269 Science 293 (1995). Discussing critics fears of the increased dangers of infectious disease originating in primates.

[16]See Shane M. Ward, supra note 11, at 226.

[17]See id. at 230.

[18]See http://www.genzymebiosurgery.com/prod/cartilage/gzbx_p_pt_cartilage.asp.

[19]Id.

[20]See product websites at http://www.organogenesis.com/content/proddescrp.htm; http://wound.smith-nephew.com/US/Product.asp?NodeId=2550.

severe burns or chronic ulcers. Before these products, the only source fore treating these patients was to transplant their own skin from a different area or to use cadaverous tissue.[21]

Functional cell therapies encompass the use of all other cells that perform a function other than support. The most widely known form of functional cell therapy is stem cell therapy. Stem cells are the most primitive, undifferentiated form of a cell.[22] The primary function of stem cells is to produce other cells. They are the only cells in the body that have the ability for long term proliferation.[23] While most cells have a limited life span and then die off, stem cells have the ability to regenerate themselves as well as other cells.[24] Stem cells can turn into functional cells, such as blood, liver, heart and brain cell, through a process called differentiation.[25]

Bone marrow transplantation, which has been performed for 40 years, is one of the earliest forms of functional stem cell therapy.[26] Today, roughly 40,000 bone marrow transplants are performed each year[27]. Bone marrow is rich with stem cells, especially hematopoetic stem cells which generate blood cells.[28] Bone marrow transplants are often used in conjunction with cancer treatments to replenish stem cells after chemotherapy.[29] Bone marrow transplants are used for other indications such as metabolic disorders or autoimmune disease.[30]

In an adult, the primary sources of hematopoetic stem cells is the bone marrow or peripheral blood.[31]

[21] Id.

[22] See National Institutes of Health, Stem Cell Information, available at http://stemcells.nih.gov/infoCenter/stemCellBasics.asp (updated Sept. 2002).

[23] See Id.

[24] See Id.

[25] See Id.

[26] See Scott R. Burger, supra note 13, at 1.

[27] Id.

[28] See Jennifer Kulynych, Blood as a Biological Drug: Scientific, Legal, and Policy Issues in the Regulation of Placental, and Umbilical Cord Stem Cell Transplantation, 32 U. Rich. L. Rev. 407, 407-08 (1998).

[29] See Id.

[30] See Scott R. Burger, supra note 28, at 1.

[31] See National Bone Marrow Program, Sources of Stem Cells, at http://www.marrow.org/MEDICAL/sources_of_stem_cells.html [herinafeter Sources of Stem Cells]..

However, getting tissue from the marrow can be an extremely painful and invasive process.[32] The bone marrow donation process consists of a one to two hour surgical procedure where the bone marrow is usually removed from the hip or back. Donors may have pain for several weeks after the procedure. The other source of hematopoetic stem cells in an adult is the peripheral blood.[33] However, the stems cells are found in a much lower concentration, and the donor blood must be filtered to get a concentrated sample.[34] Also, stem cells used in peripheral blood transplants are more likely to have adverse affects on the patient, such as chronic graft versus host disease.[35]

The other source for stem cells is umbilical cord blood from a newborn. The cord blood is collected at time of birth and causes no pain to the mother or child.[36] The blood is stored on a cord blood bank for future use. Cord blood has a lower incidence of rejection by the recipient and has a broader compatibility profile.[37] Also, scientists are currently working on developing special processes that can select for stem cells and then expand the number of those cells ex vivo, which could make autologous stem cell therapy a viable treatment option.

The most controversial source of stem cells is from a human embryo. Harvesting embryo cells requires combining a donor egg and sperm in vitro, and then the cell to reproduce.[38] The cells organize into an inner circle and outer circle of cells.[39] The cells in the inner circle have been found to be an extremely valuable type of stem cell that can generate many different types of tissue.[40] However, the major ethical debate surrounding the use of embryos questions whether it is a violation of human life to use embryos as a source

[32]See National Bone Marrow Program, Steps of Marrow and PBSC Donation at http://www.marrow.org/DONOR/steps_of_donation.html.
[33]See Sources of Stem Cells, supra note 31.
[34]See Jennifer Kulynuch, supra note 28, at 411.
[35]Id. at 413.
[36]Id.
[37]Id.
[38]See Stem Cell Information, supra note 31.
[39]Id.
[40]Id.

of medical treatment.[41]

An example of cell therapy using differentiated cells is transplantation of pancreatic islet cells for Type I diabetes, which is currently in clinical trials.[42] The current treatment options for Type I diabetics is either carefully monitoring of blood sugar levels with frequent insulin injections or a whole organ transplant of the pancreas and kidney.[43] Cell therapies using pancreatic islet cells, which are specifically responsible for producing insulin, offer many advantages over the traditional treatments. If successfully implanted, the cells would provide a long term source of insulin, instead of regular insulin injections.[44] Replacing only the cells instead of the entire organ faces less of a donor shortage problem because it requires only a sample of tissue rather than a whole organ donation, and the procedure for implanting the cells is less invasive and dangerous than whole organ replacement.[45]

Cell therapy is sometimes referred to in the broader context of a related field called tissue engineering. Tissue engineering is a term that encompasses cell therapy along with other non-cell based techniques such as bioinformatics and biomaterials that are synthetic and biocompatible. The term is a recent concept that was born in 1987.[46] The National Science Foundation's official definition of tissue engineering is the application of principles and methods of engineering and life sciences to obtain a fundamental understanding of structure-function relationships in novel and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve [tissue] function.[47] In 2002 over $600 million dollars

[41]The President's Council on Bioethics, Monitoring Stem Cell Research (Jan. 2004) available at http://www.bioethics.gov/reports/stemcell/index.html.

[42]FDA, Pancreatic Islet Transplantation to Treat Type I Diabetes (Sept. 10, 2003) available at http://www.fda.gov/cber/genetherapy/pancislet.htm.

[43]Id.

[44]Id.

[45]Id.

[46]Larry V. McIntire, Introduction, WTEC Panel Report on Tissue Engineering Research, Chapter 1, 1 (Jan. 2002).

[47]Other related terms that have significant overlap with tissue engineering are regenerative medicine and reparative biology. See id. (citing the definition introduced by Skalak and Fox at a 1998 National Science Foundation workshop on tissue

a year was spent on tissue engineering technologies by over 70 start-up biotechnology companies.[48]

One of the key applications of tissue engineering is organ replacement and repair. Currently when an organ is diseased or no longer functioning properly, the organ is repaired or replaced with either a completely synthetic device or transplanted with an organ from a donor. These traditional methods of organ replacement have significant costs and limitations. Synthetic devices are usually effective at prolonging the life of a patient, yet are still inferior to a naturally functioning organ. When a synthetic device is implanted permanently, the body eventually responds with an inflammatory reaction that is called a foreign body response.[49] This inflammation results in an undesirable layer of scar tissue that forms around the implant[50]. Through tissue engineering researchers are developing new biomaterials that would degrade over time and be assimilated and reabsorbed by the body, thus avoiding an inflammatory response.

Transplants from a human donor, while not synthetic, may still be rejected even though it is carefully matched with the patient's blood type and other biological factors[51]. The use of organ transplants as a reliable treatment is also severely limited by the shortage of organ donors. Currently thousands of people are on waiting lists for donor organs, many of whom will pass away before an organ becomes available.[52] Also, due to the strict tissue matching requirement this means that some minority groups may have a disproportionately long waiting period since there are few matching donors available[53].

engineering).

[48]See id. at 2.

[49]Linda G. Griffith, WTEC Panel Report on Tissue Engineering Research, Chapter 2: Biomaterials, 7 (Jan. 2002).

[50]Id.

[51]For example, in kidney transplants a test to match human leukocyte antigen is used to improve acceptance rates. See David W. Gjertson et al., National Allocation of Cadaveric Kidneys by HLA Matching: Projected Effect on Outcome and Costs, 324 New Eng. J. Med. 1032, 1034-35 (1991).

[52]See Cynthia Robbins-Roth, supra note 1, at 93. A 1993 study by researchers at MIT showed that each year 4,000 people on these waiting lists die and 100,000 die before even making it onto a waiting list.

[53]See, e.g., Steve Takemoto et al., Equitable Allocation of HLA-Compatible Kidneys for Local Pools and for Minorities, 331 New Eng. J. Med. 760, 762-64 (1994); Ian Ayres et al., Unequal Racial Access to Kidney Transplantation, 46 Vand. L. Rev. 805, 815-36, 849-53 (1993).

Tissue engineering could address these limitations by actually repairing or creating an organ that is equivalent to the patient's own original tissue. One way of achieving this is to use the patient's own tissue. [54] For example, a small sample of the patient's cells could be removed and then grown ex vivo and replanted inside the body.[55] Other technologies focus on creating structural grafts and implants that encourage the patient's organ to regenerate and repair itself inside the body.[56]

2.

Gene therapy

Gene therapy goes one level further than cell therapy by attacking the disease at the nerve center of the individual cell. The entire blueprint for our physical body is contained in the nucleus of each cell in molecules called deoxyribonucleic acid (DNA).[57] DNA is made up of genes, which control the production of proteins in our body.[58] Proteins are important because they are one of the structural foundations of the body and special proteins called enzymes control metabolic functions responsible for proper health.[59]

In 1972 scientists figured out how to take the DNA out of one cell and place it in another cell.[60] With this technique, genes from one organism could be cut and spliced into the DNA of another organism. This technique became to be known as recombinant DNA (rDNA).[61] The rDNA technology was first used to

[54] See Jennifer Kulynych, supra note 30, at 408.
[55] See Larry V. McIntire, supra note 46.
[56] See Id.
[57] See FDA, Human Gene Therapy and The Role of the Food and Drug Administration, available at http://www.fda.gov/cber/infosheets/genezn.htm.
[58] Id.
[59] Id.
[60] Joseph M. Rainsbury, Biotechnology and the RAC – FDA/NIH Regulation of Human Gene Therapy, 55 Food & Drug L.J. 575, 576 (2000)
[61] Id.

produce large quantities of a specific protein by implanting the gene for that protein in a bacterial plasmid.[62] This technology became the basis for a new class of therapeutic products called genetically engineered proteins.[63] Insulin was the first rDNA product developed with rDNA and approved by the FDA for marketing in 1982.[64] Now many other genetically engineered proteins are available to the public including erythropoietin and growth hormone.[65]

Gene therapy is the application of rDNA to human patients. Adding genes to human cells could be used to correct genetic mutations by introducing a functional gene into the cell to replace or correct a defective gene. After the desired gene is created through rDNA, the gene must be introduced into the patient's cell using a carrier molecule called a vector. Currently, the most common vector is a virus that has been stripped of its disease causing properties and instead holds the therapeutic gene[66]. Most commonly these viruses are adenoviruses or retroviruses[67]. Although viruses are capable of easily penetrating the cell, they may cause other complications such as an adverse immune response or the virus could disturb unintended functions in the cell and cause a new disease. Scientists are experimenting with other delivery techniques such as direct injection of DNA, lipid coated DNA, or linking DNA to molecules that would bind with specific cell receptors.[68] The process of gene transfer can either be conducted *ex vivo*, *in situ* (delivered locally into the body), or *in vivo* (delivered systemically).[69]

Diseases that were thought incurable now have hope for treatment and cure. The location and sequence for the genes responsible for cystic fibrosis, sickle cell disease, Tay-Sachs disease, fragile X syndrome and

[62] Linda R. Judge, Biotechnology: Highlight in the Science and Law Shaping the Industry, 20 Santa Clara Computer & High Tech. L.J. 79, 81 (2003).
[63] Id.
[64] Id.
[65] Id.
[66] Approximately 25-30% of the vectors used in gene therapy are adenoviruses. Judith A. Cregan, Biotechnology and the Law: Light, Fast, and Flexible: A New Approach to Regulation of Human Gene Therapy, 32 McGeorge L. Rev. 261, note 26 (2000).
[67] Id.
[68] Available at http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml#whatis.
[69] Judith A. Cregan, supra note 66, at 265-66.

myotonic dystrophy have already been discovered.[70] Besides diseases causes by a single gene mutations, the primary focus of gene therapy research has been cancer. Another promising application of gene therapy is in diseases associated with the brain and psychological function. Genes are ideal therapies because they are small enough to cross the blood-brain barrier. Gene therapy is currently being investigaged as a cure for Parkinson's disease[71].

Although much excitement has surrounded the possibilities of gene therapy, currently no gene therapies have been approved as a marketable therapy. Gene therapy is still an experimental science, with only 1% of current human trials in Phase III and the rest in early stage testing[72]. The first gene transfer clinical trial began in 1990 on a 4-year-old girl with severe combined immunodeficiency disease (SCID). However, although the child responded to the treatment, the therapy did not generate enough of a response for it to be therapeutic. The field hit its biggest and most public setback in 1999 when 18-year old Jesse Gelsinger died in a gene therapy clinical trial at the University of Pennsylvania, one of the leading gene transfer research centers.[73] He died of massive organ failure caused by an immune reaction to the adenovirus vector.[74] His death created alarm in the public, and the field was faced with intense scrutiny about the safety of the science.[75] The FDA responded by halting all gene transfer trials at the university and placed a clinical hold on all other researchers using the same type of virus.[76] At the NIH a working group was formed to review the regulatory framework and look into whether the NIH role in regulation needed to be changed.[77]

[70]Linda R. Judge, Biotechnology: Highlight in the Science and Law Shaping the Industry, 20 Santa Clara Computer & High Tech. L.J. 79, 81, 83 (2003).
[71]See Undercover Genes Slip Into the Brain at www.newscientist.com (March 20, 2003).
[72]Nancy M. P. King, RAC Oversight of Gene Transfer Research: A Model Worth Extending?, 30 J.L. Med. & Ethics 381, 382 (2002).
[73]Judith A. Cregan, supra note 66, at 267-68 (2000).
[74]Id.
[75]Id.
[76]Id.
[77]Advisory Committee to the Director Working Group on NIH Oversight of Clinical Gene Transfer Research, Enhancing the Protection of Human Subjects in Gene Transfer Research at the National Institutes of Health, July 12, 2000. From February to May, 2000, the Working Group, which was comprised of scientists, bioethicists, and representatives of the general public, met with various representatives from the OBA, NIH, FDA, Office for Human Research Protection, and RAC.

However, gene therapy had it's first successful treatment in humans in 2002 in a trial conducted in France.[78] The trial involved gene therapy for SCID. Fifteen children were successfully treated for the disease.[79] However, one boy who had been successfully treated developed a leukemia-like condition. The vector that had introduced the therapeutic gene was thought to have disturbed another part of the cell that was responsible for cancer suppression.[80] The FDA placed a temporary halt on all gene therapy in January 2003 as a result[81].

B.

Pharmacogenomics / Pharmacogenetics

Unlike most consumer products, drug manufacturers need not show absolute safety and efficacy of the product in order to gain approval. As long as the risks do not outweigh the benefits, the drug can be approved with ultimate determinations of safety and efficacy for a specific patient left to the physician. In fact, some drugs have been approved that have only shown effectiveness in less than half of the subjects in the clinical trials and many drugs are approved that have caused severe side effects in some subjects.[82] Some estimates say that the current costs from adverse reactions to drugs could be as high as $100 billion annually and more than 100,000 people die each year from an adverse reaction. [83] As many as 2.2 million other people suffer

[78]New Scientist, 'Miracle' gene therapy trial halted, Oct. 2, 2003 available at http://www.newscientist.com/news/news.jsp?id=ns99992878.

[79]Id.

[80]Office of Biological and Environmental Research, Human Genome Project Information, available at http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml#whatis.

[81]Id.

[82]Lars Noah, The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles, 43 Jurimetrics J. 1, 4 (2002). One study cites that almost one out of five approved new drugs cause serious side effects that were not even discovered until after the drug has been used widely in the market. See Maryann Napoli, Many Prescription Drugs Have Unexpected Harmful Effects, 5/1/02 HealthFacts, available at 2002 WL 10889054.

[83]Michael J. Malinowski, Law, Policy, and Market Implications of Genetic Profiling in Drug Development, 2002 Hous. J. Health L. & Pol'y 31, 39 (2002) [herinafter Genetic Profiling].

from other serious side effects, while many other people simply have no reaction at all to a drug.[84] Doctors and patients have had to live with the fact that different people will have very different reactions to the same drug. The variability in drug response has left physicians with a lot of guess work and experimenting with off-label uses.

Pharmacogenetics and pharmacogenomics are both terms that have been used to describe the science of using a person's genetic makeup to facilitate the development and tailoring drugs to the individual to increase the predictability of response and to reduce the possibility of adverse affects. While pharmacogenetics and pharmacogenomics have subtle differences in literal meaning[85], both terms tend to be used interchangeably to refer to the same science. The following discussion will use the term pharmacogenomics, with the intention to encompass both pharmacogenetics and pharmacogenomics to refer to the broad science of discovering the relation of between genes and drugs and the susceptibility to disease.

Pharmacogenomics combines both pharmacology and genetics to use our knowledge about genes to reduce the variability in response to drugs and discover new drug targets. It has long been known that factors such as race and gender can affect a person's susceptibility to disease and response to treatment[86]. Pharmacogenomics can use the power of modern genetic tests to gain similar information for genetic variances that may not by physically apparent.

Historically, the possibility of gene therapy began more than fifty years ago with the discovery of the double helix structure of DNA by Watson and Crick[87]. DNA is the structure in the cell that carries all of our genes.[88] Genes control the production of proteins, which is responsible for all life functions within the body.[89] The

[84]Id.

[85]'Genetics' means "the study of inheritance of specific traits". 'Genomics' means "the study of genes and their function." For a detailed explanation of the use of the two terms see Barbara Ann Binzak, How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process 58 Food & Drug L.J. 103, n. 10 (2003).

[86]See e.g., Dee Marlo E. Chico, Pharmacogenomics: A Brave New World in Designer Drugs, 5 Scholar 111, 117-18 (2002); Ron Winslow, Pharmacia Drug Holds Promise for Blacks with Hypertension, WALL ST. J., June 11, 2002, at D4.

[87]Dee Marlo E. Chico, supra note 86, at 114.

[88]Id.

[89]Id.

building blocks of DNA are four different nucleotide bases: adenine (A), cytosine (C), guanine (G), and thymine (T). The bases are linked up in long chains, and the order of the bases is what determines the identity and function of a gene. In 1990 the Human Genome Project began the ambitious task of determining the nucleotide sequence of all the genes in a human.[90] With the human genome comprised of approximately 30,000 genes and three billion nucleotides, this was a huge endeavor that took over a decade to complete with the collaboration of many parties in both the public and private sector.[91] The team announced on June 26, 2000 that they had completed a rough draft of the entire human genome sequence.[92]

Knowing the sequence of DNA is like finding the blueprint to the human body. The source of all individual traits and diseases are found in this sequence. The vast majority of the human genome is the same for everyone, with only 0.1% of the genome varying from person to person[93]. This 0.1% of the genome accounts for all of our individual differences. When a gene sequence deviates from the norm, this is referred to as a mutation.[94] Some mutations can be harmless and while others will be the cause of disease. If a genetic mutation is found in more than one percent of the population this is called a "polymorphism"[95]. A polymorphism that results from a difference in just one nucleotide pair is called a single nucleotide polymorphism (SNP).[96]

Particular attention has been given to SNPs linked to the metabolism, absorption, and excretion of drugs. A special enzyme in the liver known as cytochrome P450 has been discovered to have a prominent role in the oxidation of drugs.[97] Many researchers believe that studying the SNPs related to these enzymes will allow physicians to improve the selection of treatment and dosing on an individual level. For example, researchers

[90] Id.
[91] Michael J. Malinowski, Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities, and Lost Opportunities, 41 Jurimetrics 23 (2000) [hereinafter Snake Oil].
[92] Fracis S. Collins et al, A Vision for the Future of Genomics Research, 422 Nature, April 24, 2003.
[93] Snake Oil, supra note 91.
[94] Id.
[95] Id.
[96] Id.
[97] Lars Noah, supra note 82, at 7.

have discovered an SNP that occurs in 5% of the population results in a malfunction in the enzyme that metabolizes codeine[98]. Thus, people with that SNP will not get the same pain relief from regular doses of the drug. If doctors can test for this SNP, they will know to give these individuals an alternate pain relief medication. On a larger scale, an SNP consortium was founded in 1999 to discover all the SNPs in the entire human genome.[99]

Already scientists have discovered the location and sequence for many genes that cause hereditary diseases that result from a single gene mutation such as cystic fibrosis, Huntington's disease, and sickle cell anemia.[100] Even diseases that are caused by more complicated mechanisms can be detected with genetic tests. Tests are currently available that may tell a person if they have an increased chance of getting some types of cancers. [101] Although these tests show only an increased susceptibility to a certain disease, the genetic test would alert the individual and physician to take early precautions.[102] However, many scientists warn against treating genetic tests as a definitive or sole factor in making health decisions. The presence of genes in most cases is only one of many factors that can contribute to the individual's predisposition to a disease or reaction to a drug.[103]

The next stage of research is already under way to use pharmacogenomic data not only as a tool for using existing drugs, but also to discover new drugs targeted specifically at a specific gene type[104]. Current conventional drugs target about 500 out of the 30,000 protein coding genes[105]. Understanding the function of genes and the protein path it regulates can give scientists a targeted goal for developing new drugs.

[98]Id. See also, Soren H. Sindrup & Kim Brosen, The Pharmacogenetics of Codeine Hypoalgesia, 5 PHARMACOGENETICS 335, 343 (1995).
[99]Available at http://www.ncbi.nlm.nih.gov/SNP/.
[100]Id.
[101]Tests for the BRCA can show a increased risk for breast cancer. See Snake Oil, supra note 91.
[102]Id.
[103]Id.
[104]Andrew Pollack, Drug Developed from Gene Study Tested on People, N.Y. TIMES, Feb. 26, 2001, at C14.
[105]Francis S. Collins et al, supra note 92.

Some successful treatments have already been developed that target a specific genotype. For example, Genentech's Herceptin is a marketed breast cancer treatment developed for women only with the Her-2-neu gene[106], and Millenium Pharmaceuticals is developing a drug for leukemia targeting individuals with a specific genotype.[107] Also, in 2002 the FDA approved of a home genetic testing kit by Visible Genetics, now acquired by Bayer, that predicts which HIV treatments may be most effective.[108] FDA also has approved the use of genetic test information on drug labels. For example, Eli Lilly's drug Strattera for attention deficit disorder comes with labeling that states that a genetic test is available to determine whether an individual has a genetic profile that would result in slower processing of the drug, which would mean that person would require a lower dosage of the drug.[109]

The future progress for pharmacogenomics may be even more rapid as new technologies being developed related enabling technologies is allowing for rapid sequencing of genomes to the point that gene sequencing could be accomplished in days rather than years[110]. Enabling technologies such as biochips and microarrays are allowing scientists to sequence genes in bulk.[111] Advances in bioinformatics are making it possible to process the enormous amounts of data generated from gene sequences to make functional linkages and turn data into useful information about physiological function.

It was proposed that some pharmaceutical manufacturers might be wary of using pharmacogenomics approaches for fear of fragmenting patient populations thus reducing the possibility of "blockbuster" drug revenues.[112] However, many companies are embracing the new technology as a way to differentiate their

[106] Genetic Profiling, supra note 83, at 42.
[107] Id.
[108] Visible Genetics, Inc. News from The BioSpace Beat, FDA Clears New Software For Bayer's HIV Genotyping Test, Nov. 2002. available at http://www.biospace.com/b2/news_company.cfm?CompanyID=2857.
[109] Anna Wilde Mathews, FDA Will Issue Rules on New Era of 'Personalized Medicine', Wall St. J. B1 (Nov. 3, 2003).
[110] One company has already developed the genetic map for the entire population of Iceland. See http:\\www.decode.com.
[111] Charles Vorndran, Ph.D. & Robert L. Florence, Bioinformatics: Patenting the Bridge between Information Technology and the Life Sciences, 42 IDEA 93 (2002).
[112] See, e.g., Geeta Anand, Big Drug Makers Try to Postpone Custom Regimens, WALL ST. J., June 18, 2001, at B1.

product as superior, which could command a premium price.[113] Pharmaceutical companies could also get additional revenues from the sale of diagnostic genetic test kits. Furthermore, pharmacogenomics would allow many companies to "rescue" many failed drug candidates that showed promise in clinical trials, but were rejected do to adverse effects in some of the patients.

C.

Novel Drug Delivery

Even if a pharmaceutical company can invent a compound that is effective at treating a certain disease, the next challenge is getting the drug to the area of the body that needs treatment without disturbing other functions which could produce harms that outweigh the benefits of the treatment. Delivering drugs locally, meaning directly to the tissue, instead of systemically opens up the possibility of using compounds that were previously found effective, but considered too dangerous to deliver systemically.

Research in novel drug delivery techniques seeks to maximize the effectiveness, safety, and ease of using existing drugs. When most people think about how drugs are administered to the human body, only a limited number of options probably come to mind. For example, drugs in the form of pill must first get metabolized and be absorbed systemically. Insulin must be administered by injection directly into the bloodstream because the digestive process would destroy the protein.

However, new advances in drug delivery technology are making extreme advances in our delivery options. Advances in drug delivery could allow for new modes where drugs could be inhaled, transmitted through

[113]Genetic Profiling, supra note 83, at 31.

the skin, or even implanted inside the body. Furthermore, the precision with which the drug dosage is administered could be vastly improved. Some day it may be possible to have implanted devices that would periodically dispense medicines like insulin or morphine.[114]

Recognizing the importance of drug delivery techniques, the National Institutes of Health recently published a Request for Applications (RFA) to encourage research in this area.[115] The NIH described several areas where drug delivery research would provide vast improvements in public health. Drug delivery technology to improve the accuracy and convenience of drug dosing and administration. Some of the problems and side effects of many drugs can be eliminated by having a more precise dosage of drug. Drug delivery can also make delivery of drugs more convenient and less painful to administer. New techniques that sustain the level of drug for a longer period of time can result in reduced.

Drug delivery also addresses many problems of how to get the drug into the patient's bloodstream in the least invasive way. Some drugs, for example insulin, cannot be taken orally because the digestive system would destroy the activity of the drug. Therefore, many people must take their insulin treatments through painful injections that must be administered several times a day. Novel techniques in drug delivery are now looking at alternative methods of insulin delivery – either through transdermal or ....

Drug delivery research is also being done to improve the effectiveness of devices. This has been especially effective for cardiovascular devices. Companies like Boston Scientific, Corp. and Johnson & Johnson have developed drug coated stents to improve the success rate after a cardiac surgery.[116] In a typical procedure, a angioplasty balloon is inserted into the artery to clear the blockage, and then a metal stent is permanently

[114] John Miller, 2002-2003 Beyond Biotechnology: FDA Regulation of Nanomedicine, 4 Colum. Sci. & Tech. L. Rev. 1, 3 (2003).

[115] National Institute of Biomedical Imaging and Bioengineering, Development of Novel Drug and Gene Delivery Systems and Devices, RFA: EB-03-011 (December 30, 2002).

[116] See Marilyn Alva, The Battle over Stents is Picking up Steam, Investor's Business Daily, Sept. 11, 2003 at A07.

implanted into the artery to support the artery and prevent it from collapsing.[117] However, after a stent is placed inside the artery, the presence of the foreign object often causes the blood around the area to clot and block the artery shortly after the surgery.[118] Coating the stent with a drug that would prevent the clotting a proliferation of scar tissue has dramatically improved the success of these surgeries.

Drug delivery is also a concern in gene therapy. Researchers are currently working on the challenge of getting the desired gene into the cell. The current technique of using viral vectors is less than optimal as it creates undesirable immune responses and can have unintended effects on the cell. New techniques in delivering genes using nanotechnology or synthetic systems could eliminate these adverse effects.[119] Scientists have even developed a way to administer a gene to the brain, which is particularly difficult be because of the "blood-brain barrier".

III.

[117] Id.
[118] Id.
[119] John Miller, supra note 114.

A.

History and Evolution of the FDA

Official government regulation of food and drugs in the United States has existed for roughly a century. The enactment of the Pure Food and Drug Act in 1906 marked the first statute dedicated to the safety of food and drugs.[120] The Food Drug and Cosmetics Act was passed in 1938 and marked a dramatic increase in the regulatory power of the FDA.[121] FDA gained authority to require premarket approval of drugs to ensure its safety before being sold to the public.[122] With the 1962 Kefauver-Harris Amendments, the FDA increased its scope of regulatory power by adding to its premarket requirements that the drug not only be safe, but also effective for its intended use.[123]

The FDA did not gain responsibility over biologics until 1972, even though the Biologics Act was first promulgated in 1902.[124] The Hygienic Laboratory, which later became the National Institutes of Health (NIH), was responsible for enforcing the Biologics Act.[125] The main purpose of the Biologics Act was to prevent contamination and the spread of disease.[126] The main biologic products at that time were crude human and animal extracts, with little to no technology for purification or testing, the main focus of regulation was on the manufacturing process.[127] In 1944 the Public Health Service Act reenacted the Biologics Act and

[120] See FDA History, available at http://www.fda.gov/oc/history/default.htm.
[121] Id.
[122] Id.
[123] Id.
[124] See Gary E. Gamerman, Regulation of Biologics Manufacturing: Questioning the Premise, 49 Food & Drug L.J. 213, 215-19 (1994)
[125] Id.
[126] Id.
[127] Id.

added that biologics regulation had to be consistent with the FDCA, thereby imposing product licensing requirements for the first time.[128] A move toward more stringent biologics regulations was prompted by a tragedy in 1955 when some children were infected by polio after receiving a vaccination.[129] This prompted the formation of the Division of Biological Standards in the NIH and a new focus on tightening regulations. Congress eventually transferred DBS to the FDA in 1972, which then became the Center for Biologic Evaluation and Research (CBER).[130]

FDA regulation of medical devices has also been fairly recent. Medical devices did not come into the scope of FDA's responsibilities until the FDCA of 1938.[131] However, the FDA was only given authority to regulate the product after it had entered the market.[132] The first statute providing for premarket approvals of medical devices was enacted in 1976 with the Medical Device Amendments.[133] With this amendment, the FDA's distinct and separate regulation of medical devices was promulgated. Unlike pharmaceuticals, medical devices can include a broader range of products posing different risk profiles.[134] Medical devices can include tongue depressors and bedpans, on one hand, all the way to pacemakers and brain scanning machines.[135] Therefore, the center at the FDA responsible for devices, the Center for Devices and Radiological Health (CDRH) established a risk-based approach to medical devices, with three classes of devices with varying levels of regulatory controls. The Safe Medical Devices Act of 1990 (SDMA) was the next statutory addition to medical device regulation, largely responding to complaints about delays in device classification inadequate adverse event reporting.

[128] Id.
[129] Id. at 220.
[130] Id.
[131] Rodney R. Munsey, Trends and Events in FDA Regulation of Medical Devices Over the Last Fifty Years, 50 Food & Drug L.J. 163, 163 (1995)
[132] Id.
[133] Id..
[134] Id.
[135] Id.

B.

Current State of the FDA

In 1997 the FDA enacted the Food and Drug Administration Modernization Act, the most wide sweeping amendments to the FDCA since the 1962 Amendments.

In recent decades, the biggest criticism of the FDA was the long approval times after an application was submitted. In the 1980's review times averaged around two years.[136] The pressure to accelerate drug approvals came from a variety of sources including industry groups, patient rights advocates, and Congress. In 1992, the FDA responded with the Prescription Drug User Fee Act (PDUFA). PDUFA introduced a user fee system where a drug sponsor had to submit a fee with each new drug application. With the fees generated from PDUFA, the FDA could hire additional resources to dedicate to application reviews, but in return the FDA had to commit to certain performance standards. The PDUFA was drafted to automatically expire in five years, so the FDA had incentive to meet the performance standards that would signal Congress to renew the user fee provisions. The user fees were a success with a 50% improvement in approval times.[137] Thus, the user fee program was renewed in 1997 (PDUFA II) and again in 2002 (PDUFA III). While at first, the user fee program applied only to drugs and biologics, the Food and Drug Modernization Act of 2002 finally extended the user fee programs to medical devices as well. Currently all standard applications to the FDA fall under a user fee requirement, unless the application is eligible for one of the statutory exceptions.

While user fees have successfully reduced review times, some critics warned against possible conflicts of interest and industry capture at the FDA. In 2002 user fees brought in $137.7 million to the FDA budget,

[136]Mary K. Olson, How Haver User Fees Affected the FDA?, Regulation April 1, 2002.
[137]Id.

which is almost half of FDA's total spending on review activities.[138] Another fear is that with the increasing reliance on industry funds, Congress may decrease FDA's allocation of funding even further, thus jeopardizing FDA's other funding.[139]

Recent product withdrawals and an increase in adverse events is also pulling the FDA toward to opposite direction of increased caution. High profile recalls of drugs such as Redux (phen-fen), Baycol, Propulsid, and Rezulin have raised questions of whether FDA is letting some products through the gate that should never have been approved.[140] Serious side effects have also increased a dramatic 89% from 1993 to 2000.[141] While the FDA would like to be able to use some of the user fees towards post-marketing surveillance, the industry has been opposed.[142]

Even with the user fee programs and increase in adverse events, the FDA is still being pressured to improve its review times. In recent years, the FDA has been under increased scrutiny as the average review time has increased and the number of new application is at a low point since the user fee program has been enacted.[143] In 2002 the FDA reaffirmed its goal toward speed and efficiency summarized in "Improving Innovation in Medical Technology: Beyond 2002".[144] FDA Commissioner Mark B. McClellan was in part responding to the decreased number of drug approvals in the recent years. In order to facilitate development, the Commissioner pointed to several strategies to reduce review times. The first initiative focuses on reducing multiple review cycles by improving early stage communications with the sponsor.[145] As part of this program the FDA will give advice to product developers early in the development process to ensure the studies and trials are designed in a way that avoids some of the major mistakes that can delay approval. Second, the FDA

[138] See Overview of FDA Regulation, supra note 2, at 987.
[139] See Mary K. Olson, supra note 136.
[140] See Overview of FDA Regulation, supra note 2, at 1001.
[141] Overview of FDA Regulation, supra note 2, at 999.
[142] Id. at 1002.
[143] See supra note 8.
[144] Id.
[145] Id.

proposed to conduct a root cause analysis to see what the primary sources of delay in the cycle were.[146] The FDA also plans to publish a Good Review Management Principles (GRMPs) as a guidance document for reviewers.[147]

C.

The Regulatory Lifecycle

The FDA is involved from the very formative stages of the development process. The development process is divided into several stages: pre-clinical, Phase I, Phase II, and Phase III studies.[148] Pre-clinical research involves all the laboratory and animal studies done prior to tests on human subjects.[149] Before the FDA allows testing on humans to begin, the sponsor must show that the drug or device is not toxic in at least two different animal models.[150] During these animal studies, a pharmacologic profile of the drug or device is developed. Parameters such as toxicity, absorption, and mechanism of metabolism are measured.[151] After the preclinical research is finished, a sponsor can then file either an investigational new drug (IND) for new drugs and biologics or investigational device exemption (IDE) for devices to the FDA. A sponsor must get FDA approval before starting any human studies, since it is illegal under the FDCA to use any medical products in humans before they are approved for marketing.

Throughout clinical trials a local institutional review board (IRB) must oversee and approve of all protocols

[146] Id.
[147] Id.
[148] See generally FDA, Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products (Mar. 2004).
[149] Id.
[150] These studies typically range from a few weeks to three months. Barbara Ann Binzak, How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process 58 Food & Drug L.J. 103, 114 (2003).
[151] See supra note 142.

for human research.[152] Human clinical studies conducted with government funding are also subject to federal law protecting human research subjects referred to as the "Common Rule"[153]. Human research protection focuses mainly on issues of safety, informed consent, patient selection, and patient confidentiality[154].

Clinical tests in human is conducted in three phases. Phase I involves the smallest number of subjects (20 to 80) and tests for basic safety, typically in healthy subjects.[155] Phase II then expands the study and starts to gather additional safety data as well as evaluate efficacy.[156] Phase III is a large scale study, ranging from several hundred to several thousand subjects, to confirm safety and to validate efficacy and proper dosing levels.[157] After the completion of the Phase III study, the sponsor submits its final application to the FDA for review in hopes of gaining marketing approval.

The sponsor usually meets several times with the FDA in the development process. The most common meeting times are after Phase II, to get FDA's input on how to design the Phase III trials, and right before submitting the final application to clarify what data and information the FDA will need to have[158].

Within 60 days of submission the FDA must decide to accept the application for review or deny a review all together because missing information or tests. If accepted, the FDA then reviews the application thoroughly and issues an "action letter" which notifies the sponsor of their decision which is either "approved", "approvable", or "not approvable". An "approved" drug or device can then be marketed to the public. An "approvable" product will likely be approved, but requires additional data or changes to the labeling. A

[152]Id.
[153]Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003 (June 18, 1991).
[154]45 C.F.R. §46.111 (2004).
[155]See FDA, The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective, FDA Consumer Magazine (July-Aug. 2002).
[156]Id.
[157]Id.
[158]Id.

"not approvable" drug has been determined to have serious deficiencies, and will probably not be approved in the future. After marketing approval, FDA may also require Phase IV studies to measure post-marketing safety.[159] FDA also imposes manufacturing and labeling guidelines that must be met before approval is granted.

D.

Structure of Regulation

The FDA regulates all products under three basic categories: drug, device, or biologic. The FDA is organizationally structured around these three categories with the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER). Each center is a discrete unit with its own regulatory processes and requirements for approval.

1.

Regulation of Drugs.

Section 201(g)(1) of the FDCA defines a "drug" as anything "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" or "intended to affect the structure or any

[159] Id.

function of the body of man or other animals".[160] The CDER has several categories of NDA submissions according to its type and indication.[161] If the drug is a novel compound that has never before been approved for marketing, it is called a new molecular entity (NME). Otherwise, the application could be for a new formulation of an already approved drug, a combination of two or more approved drugs, or a new indication for an already approved drug.[162]

If the NDA is an application for a product that is a significant advance over existing treatments, the FDA may give the application a priority status. Otherwise, the NDA goes through the standard review process. The FDA has committed to review times of 10 months for standard NDA's and 6 months for priority NDA's under PDUFA III.[163]

2.

Regulation of Biologics

Section 351(a) of the Public Health Service Act (PHSA) defines "biologic" 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"[164]. "Analogous product" includes "attenuated viruses, whole blood or plasma, blood and plasma derivatives, product acting through

[160] 21 U.S.C. 321(g)(1) (1994).
[161] For a listing of all seven categorizations, see http://www.fda.gov/cder/handbook/ndabox.htm.
[162] Id.
[163] Product Development: FDA Launches Initiative to Speed Innovative Medical Technologies to Market, Medical Letter on CDC & FDA (Mar. 2, 2003).
[164] 42 U.S.C. 262(i) (1994).

an immune response."[165]

Biologics, like drugs, are also therapeutic agents, yet historically have been subjected to more rigorous regulations.[166] In addition to regulation by the FDA, biologics were also required to comply with requirements under the Public Health Services Act (PHSA).

Until passage of the FDAMA, biologics sponsors had to submit a product license application (PLA) and an establishment license application (ELA) to the CBER. This dual licensing was thought of as unnecessary and outdated.[167] While the biological products historically were crude and hard to control for quality, new biological products such as recombinant proteins are produced with the precision and purity of most traditional pharmaceuticals. The ELA requirements were particularly burdensome because it required the product used in Phase III studies be produced in a full-scale manufacturing facility.[168] This deprived the company of any manufacturing flexibility, and requires costly upfront investments before the biologic has been approved for marketing.

Harmonization efforts between the CBER and CDER began in the 1990's. In an effort to make CBER and CDER regulation more consistent, the CBER has replaced the two license requirement with a single application called a Biologics Licensing Application (BLA). [169] A biologics license may be granted if the biologic is determined to be "safe, pure, and potent" as defined in § 351 of the PHSA.[170] A BLA may be filed with either the CBER or CDER.[171] The BLA covers both product quality and manufacturing compliance of GMP.[172] The FDAMA also lessened the burden of the GMP requirements by allowing the product used

[165]Id.
[166]Edward L. Korwek, Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000, 50 Food & Drug L.J. 123, 132 (1995).
[167]See, e.g., Gary E. Gamerman, supra note 124.
[168]Id.
[169]Section 123 of FDAMA amending PHSA § 351.
[170]See David Smith, Legal and Regulatory Issues, WTEC Panel Report on Tissue Engineering Research, Chapter 8, 88 (Jan. 2002).
[171]Id.
[172]Id.

in clinical trials to be produced in a small scale or pilot plant.[173]

Currently, the CBER regulates five different categories of biologics: blood, vaccines, cellular/gene therapy, tissues, and devices.[174] The CBER is responsible for ensuring the integrity of blood and blood components. The main concern is controlling the spread of infectious diseases such as HIV. The FDA imposes rigorous donor screening procedures and conducts inspections of blood establishments at least every two years. Also, the Blood Action Plan was release in 1997, as a measure to ensure better compliance with the Public Health Service.[175] Vaccines are regulated to ensure safety and efficacy, and CBER jointly monitors adverse events with the Centers for Disease Control & Prevention.[176] Regulation of devices includes products used for the collection of blood, blood components, and cells. CBER also regulates HIV test kits for blood. The regulation of cell and gene therapy and tissues will be discussed further in Part III.

3.

Regulation of Devices

Section 201(h) of the FDCA defines the category of "device" broadly as any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory" but it must 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

[173]Section 124 of FDAMA amending FDCA § 505(c).
[174]See FDA website for the CBER at http://www.fda.gov/cber/index.html.
[175]See http://www.fda.gov/cber/blood.htm.
[176]See http://www.fda.gov/cber/vaccines.htm.

for the achievement of its primary intended purposes."[177]

Devices are divided into three classes of increasing risk and complexity.[178] Class I devices pose the least risk and subject only to general controls.[179] Tongue depressors are an example of a Class I device. Class II devices, such as hearing aids, are subject to special controls.[180] Class III pose the most risk and are thought of as any device that is implanted into the body or used to sustain or support life and has novel uses, indications, or technology.[181] Class III devices must go through a premarket approval process, which requires clinical trials similar to the drug approval process to demonstrate safety and efficacy.

Class III devices pose the highest risk and therefore must be approved by the FDA before being marketing. Premarketing approval consists of submitting extensive data summarizing preclinical and clinical tests in humans. In order to begin clinical studies, the sponsor must file an Investigational Device Exemption (IDE), which is the device equivalent of an IND.[182] The IND is subject to a 30 day review by the FDA. Premarketing approval can be obtained either through a traditional premarket approval process (PMA) or through alternate premarket approval mechanisms called the Modular PMA, Streamlined PMA, or a Product Development Protocol (PDP).[183] All premarket applications require the device to go through preclinical and clinical test to demonstrate safety[184] and efficacy[185]. The PMA is the more common and traditional approach. The average review time for PMA's is 180 days. The FDA approves roughly 40 PMAs per year.[186]

[177] 21 U.S.C. 321(h) (1994).
[178] 21 U.S.C.A 360c.
[179] Id.
[180] Id.
[181] 21 C.F.R. § 860.93; 21 U.S.C. § 360c(c)(2)(C).
[182] 21 C.F.R. Part 812.
[183] FDA, Device Advice: Application Methods, available at http://www.fda.gov/cdrh/devadvice/pma/app_methods.html.
[184] A device is defined to be "safe" when "it can be determined... that the probable benefits to health from use of the device for its intended uses and conditions of use... outweigh any probable risks." 21 C.F.R. § 860.7(d).
[185] A device is defined to be "effective" when "it can be determined... that in a significant portion of the target population, the use of the device for its intended uses and conditions of use... will provide clinically significant results." Id.
[186] C. Stephen Lawrence & Randy J. Prebula, Successfully Navigating the Regulatory Environment: Overview of FDA Regulation-Drugs, Biologics, and Medical Devices, 718 PLI/Pat 935, 955 (2002).

A modular PMA is similar to a PMA except that instead of submitting all of the required PMA data at one time, the sponsor can submit to the FDA specific portions of the PMA as they are ready.[187] The sponsor must first meet with the FDA to develop a PMA Shell that outlines the submission plan and schedule.[188] The FDA will review each module independently as they are submitted. This reduces the time the FDA will need to review the application after the clinical trials are complete, and it gives the sponsor the ability to get feedback earlier on in the trials.

The Streamlined PMA is a pilot program within the Division of Clinical Laboratory Devices.[189] This regulatory pathway is available for devices where FDA guidance exists, FDA has significant experience dealing with similar devices, or the sponsor and FDA jointly develop the protocol. These applications would receive faster reviews as a result of better coordination with the FDA in the protocol design.

The authority for PDP was created in the 1976 Medical Device Amendments as a faster alternative to the PMA adding Section 515(f) to the FDCA.[190] The PDP functions like a contract between the FDA and sponsor. The PDP contains all the relevant information about the device, detailed protocols for the clinical tests, data to be submitted, and performance standards for the tests.[191] The FDA must approve the PDP. Once the sponsor has submitted all the information described in the PDP within the specified performance and safety standards, the device is considered approved.[192]

A "substantially equivalent" exception to a PMA was introduced with the 510(k) notification procedure. If a device was determined to be "substantially equivalent" to a device that has already been approved for marketing, the manufacturer was allowed to file a 510(k) Premarket Notification (PMN) which is substantially

[187] See Device Advice, supra note.
[188] Id.
[189] See FDA, Letter to IVD Manufacturers on Streamlined PMA (1997) available at http://www.fda.gov/cdrh/pmapilot.pdf.
[190] David Smith, supra note 170, at 87.
[191] For detailed description of what a PDP entails see http://www.fda.gov/cdrh/pdp/420.html.
[192] Id.

less detailed that a PMA and does not require clinical testing.[193] "Substantial equivalence" is shown by demonstrating the device has the same intended use and does not raise any new safety or effectiveness issues compared to the original device.[194]

The FDAMA clarified that "substantial equivalence" will be determined from the uses proposed on the labeling, however, if there is a likelihood that the device is intended for a use not on the label.[195] The average FDA review time for a 510(k) is 110 days.[196] The FDAMA also added a new provision allowing qualified third parties to review 510(k) notifications and give a recommendation to the FDA for final approval.[197] After reviewing the PMA, the FDA may request from clinical data if the device presents any new concerns or risks.[198]

The FDAMA introduced two new exceptions to filing a 510(k) PMN. Section 206(a) added a new section 510(l) to the FDCA that exempts most Class I devices from notification.[199] Section 206(m) includes a list of Class II devices that the FDA has exempted from a 510(k) notification. [200]

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) made three significant changes to the regulation of medical devices.[201] First and foremost, it authorized the FDA to collect user fees for certain medical device applications.[202] Through the user fees, the CDRH aims to collect $25,125,000 in 2003 and increasing to $35,000,000 by 2007.[203] The standard fee in 2003 was $154,000.[204] Small business applicants

[193]Rodney R. Munsey**,** supra note 131, at 168-70.
[194]Id.
[195]Section 205(b) of the FDAMA amending 21 U.S.C. 513(i).
[196]C. Stephen Lawrence & Randy J. Prebula, supra note 186, at 954.
[197]Section 210 of FDAMA adding 21 U.S.C. § 532.
[198]Id..
[199]21 U.S.C. § 510(l).
[200]21 U.S.C. § 510(m).
[201]Food and Drug Administration, Summary of the Medical Device User Fee and Modernization Act of 2002 (Nov. 7, 2002).
[202]Id. at 1.
[203]Id. at 10. These amounts will be adjusted for inflation, workload, and shortfalls in revenue.
[204]Id. at 5.

can pay a lower fee of only 38% of the standard fee.[205] A small business must have revenues of less than $30 million to qualify.[206] Second, it allowed establishment inspections to be conducted by qualified third parties. Third, it introduced the "premarket report", a new type of premarket submission for class III reprocessed single-use devices that previously required a PMA.[207] FDA has committed to certain performance goals in MDUFMA which will be phased in until 2007.[208] The MDUFMA contains a sunset provision providing for automatic expiration on October 1, 2007.

The MDUFMA also includes a "Bundling Policy" which allows multiple devices to be submitted in one application.[209] Bundling is especially advantageous with the new user fee policy, as well as streamlining some of the logistical process. Bundling can also occur for device biologic combinations submitting a BLA.[210] Bundling would be appropriate if the review of the devices would be most efficient in a single review.[211] Factors that would support a single review include similar data and the similarity of the devices or applications.[212]

IV.

[205]Id.
[206]Id.
[207]Id.
[208]Id. at 7-9.
[209]Food and Drug Administration, Bundling Multiple Devices or Multiple Indications in a Single Submission, Guidance for Industry and FDA Staff (Nov. 26, 2003).
[210]Id. at 3.
[211]Id. at 4.
[212]Id. at 5.

Regulation of New Biotechnologies

In the mid-1980's the Office of Science and Technology Policy officially addressed the question of how the federal government should regulate biotechnology in a public notice title "Coordinated Framework for the Regulation of Biotechnology"[213]. After two years of public comment and discussion among several agencies, including the FDA, NIH, and the National Science Foundation, the conclusion was that the existing framework was adequate to regulate the emerging field. In the final policy statement the FDA announced:

> Although there are no statutory provisions or regulations that address biotechnology specifically, the laws and regulations under which the agency approves products places the burden of proof of safety as well as effectiveness of products on the manufacturer. The agency possesses extensive experience with theses regulatory mechanisms and applies them to the products of biotechnological processes. In this notice, FDA proposes no new procedures or requirement for regulated industry or individuals. Rather, the administrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis.[214]

The problem was that often these innovative products were not easily categorized into the three existing categories. This case-by-case approach proved to be confusing and arbitrary.[215] Biotechnology soon became more sophisticated than the simple categories of drug, device, or biologic. The newest technologies often involved a combination of two or more of these components. Other fields such as genomics and proteomics may technically fit into the biologic category, yet introduce complexity that was never imagined when the category of biologic was first conceived.

However, rather than completely changing its infrastructure and approach completely, the FDA approached the problem by trying to fit these new categories into its existing framework. To help guide industry, the

[213]49 Fed. Reg. 50,856 (Dec. 31, 1984). The final policy statement was released in 1996. 51 Fed. Reg. 23,302 (June 26, 1986).

[215]For example, some recombinant proteins were classified as drugs, while others were biologics. See Martha J. Carter, The Ability of Current Biologics Law to Accommodate Emerging Technologies, 51 Food & Drug L.J. 375, 376 (1996).

FDA periodically published documents called "Points to Consider" to try and make specific recommendations.[216] It created a new type of product called combination product, but these products are eventually regulated primarily by one of the existing three centers and issues outside that center's expertise are handled through consultations with other centers.[217] Furthermore, the regulatory model is further complicated by the additional oversight of other government agencies such as the NIH in the case of gene transfer. As a result, it leaves many in the biotechnology industry confused or overwhelmed by the complexity of the constantly changing regulatory schemes. Although an Office of Biotechnology was established in 1990 in the FDA[218] to serve as a liaison between the FDA and the biotechnology community, it was closed in 1994. [219] The following discussion will review the regulatory structure surrounding the three novel areas of biotechnology introduced previously. The discussion will also highlight the regulatory and ethical challenges raised by the technologies, and recommendations for possible improvements.

A.

Cell and Gene Therapy Regulation

The FDA recently announced that many biotech products currently under the regulation of CBER would move to the CDER. On October 1, 2003, roughly 200 CBER staff was transferred to the CDER.[220] The products that will move to the CDER include "Monoclonal antibodies for in-vivo use; Cytokines, growth

[216]Id.
[217]Id.
[218]55 Fed. Reg. 12,283 (1990).
[219]Sandra H. Cutter, The Food and Drug Administration's Regulation of Genetically Engineered Human Drugs, 1 J. Pharmacy & Law 191, 210 (1992).
[220]Jill Wechsler, The big shift: FDA explains its plan for moving most biologics under the authority of CDER, Biopharm International, Mar. 1, 2003, at 16.

factors, enzymes, immunomodulators, and thrombolytics; Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); Other non-vaccine therapeutic immunotherapies."[221]

Within the CBER, a new office has been established to oversee cel and gene research, the Office of Cellular, Tissue and Gene Therapies (OCTGT).[222] This and vaccines are the only therapeutics that will remain at the CBER.[223]

1.

Cell Therapy

Cell therapy and tissue engineered products were initially regulated as either a biologic or device. However, neither regulatory structure seemed to be appropriately addressing the new complexities of regulating the new category of biologics. In 1997 the FDA was directed to reexamine the CBER regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps).[224] The result of this initiative was summarized in two documents: "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products"[225] and "Reinventing the Regulation of Human Tissues".[226] In these documents, the FDA introduced a new risk based regulatory scheme that would address the new sophisticated cell therapy and tissue engineering

[221]Id.
[222]Id.
[223]Id.
[224]President Clinton and Vice President Gore launched a campaign called "Reinventing the Regulation of Human Tissue" in February of 1997. See Shane M. Ward, supra note 11, at 232.
[225]62 Fed. Reg. 9721 (Mar. 4, 1997).
[226]Available at http://www.fda.gov/cber/tissue/rego.htm.

technologies, while imposing minimal regulation on less sophisticated biologics.[227] The Tissue Action Plan (TAP) was instituted in March 1998 to execute the framework described in those two documents.[228] The goals of the new tissue regulation approach were state as 1) control the spread of infectious disease, 2) prevent handling or processing that may damage the tissue product, and 3) ensure safety and efficacy of products that posed a higher risk.[229]

The new framework allows "minimally manipulated" [230] HCT/Ps to be regulated solely by § 361 of the PHSA to control communicable diseases.[231] Minimal manipulation includes procedures such as cell selection or separation, sterilization, cryopreservation, freezing, cutting, and grinding.[232]

An HCT/P must go through the full premarket approval process of a drug, device, or biologic if any one of the following conditions apply:

- The HCT/P is more than minimally manipulated;
- The HCT/P is intended for a nonhomologous[233] use, meaning the HCT/P is being used for a function different from its original function;

[227] See Shane M. Ward, supra note 11, at 234.
[228] The core team for TAP meets monthly and has eleven working groups. See http://www.fda.gov/cber/tissue/tapfyrpts.htm.
[229] Martha A. Wells, Overview of FDA Regulation of Human Cellular and Tissue-Based Products, 52 Food & Drug L.J. 401, 406 (1997).
[230] "Minimal Manipulation" is statutorily defined as "(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3.
[231] 21 CFR § 1271.10.
[232] FDA, Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5457 (2001).

- The manufacture of the HCT/P involves the combination of the cell or tissue component with a drug or a device (does not include minimal contact with nonbiologic for sterilizing, preserving, or storing purposing) or

- The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function.

HCT/Ps explicitly excused from premarket approval include HCT/Ps that have a system effect or depend on metabolic activity, but is for autologous use, is for allogeneic use in a first or second-degree blood relative, or is for reproductive use.

All HCT/Ps are subject to comply with Good Tissue Practices (GTPs). These GTP's are contained in the following documents:

- Final Rule – Human Cellular And Tissue-Based Products; Establishment Registration and Listing[234];

- Proposed Rule – Suitability Determination For Donors of Human Cellular And Tissue-Based Products[235]; and

- Proposed Rule –Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement.[236]

The Final Rule requires that all HCT/P establishments register with the FDA and all HCT/P products must also be listed with the FDA. Some HCT/Ps are excused from the registration and listing requirement

[236]66 Fed. Reg. 1508 (Jan. 8, 2000).

include tissues transplanted in the same individual during the same surgical procedure and establishments that collect only reproductive cells and transfer them immediately to the donor's partner, e.g. in vitro fertilization clinics.[237]

Some HCT/P's fall outside the FDA regulatory framework but are subject to other regulations in addition the PHSA. Bone marrow and whole organ transplantation that do not involve more than minimal manipulation of the tissue is regulated by the Health Resource Services Administration (HRSA).[238] Within HRSA, the National Marrow Donor Program has specific standards for bone marrow.

Also, the CBER has recently issued detailed guidance on cell therapy using xenotransplantation[239]. The guidelines build upon the PHS Guideline on Infectious Disease Issues in Xenotransplantation issued in 2001[240]. In the guidance, the FDA defines xenotransplantation broadly any procedure using nonhuman cell, tissues, or organs and also any procedure that involves human cell, tissues, or organs coming into ex vivo contact with an animal product.[241]

Some conflict has occurred over biologic/device combination products. The Tissue Reference Group within TAP was formed in 1998 to resolve jurisdictional conflicts for tissue engineering and cell therapy products.[242] The CBER also started a Device Action Plan in 1999 and established a Device Management Team to oversee regulation of devices within CBER.[243]

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[237] 21 C.F.R. § 1271.15.
[238] SR Burger, Current Regulatory Issues in Cell and Tissue Therapy, 5 Cytotherapy 289, 290 (2003).
[239] FDA CBER, Guidance for Industry: Source Animal, Product, Preclinical,and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (April 2003).
[240] Available at http://www.fda.gov/cber/gdlns/xenophs0101.htm.
[241] Id.
[242] John Miller, supra note 114, at 9.
[243] Id.

2.

Gene Therapy

Gene therapy is unique in its regulation because both the FDA and the NIH have significant oversight over the clinical trials. The NIH established its involvement with the regulation of rDNA research. In 1974 researchers at Stanford University proposed to transplant DNA from a cancer causing virus into the E.coli bacteria that is found commonly in the human intestine[244]. This caused alarm in the scientific community and the researchers were asked to postpone the research until the risks around the research could be explored. The NIH took primary responsibility for determining the future of rDNA research.

The NIH is an agency whose principal purpose is to support and fund medical research for the nation[245]. The NIH does not have regulatory power per se, but rather holds power by controlling the use of government research funding. Therefore, although NIH guidelines apply only to institutions receiving NIH funding, almost all current research is conducted with some affiliation to government funding or an institution receiving government funding[246]. Even if the research is completely privately funded, most researchers will voluntarily comply with NIH Guidelines.

Recognizing the importance of the new technology, the NIH established the Recombinant DNA Advisory Committee (RAC).[247] A few years later the RAC developed strict guidelines govern rDNA research[248]. The guidelines established that all protocols involving rDNA must be registered with the NIH.[249] In 1984 the RAC established a working group to begin developing guidelines for gene transfer studies that would be done

[244]Id.
[245]See The NIH Almanac, available at http://www.nih.gov/about/almanac/index.html (describing the mission statement of the NIH).
[246]NIH Guidelines for Research Involving Recombinant DNA Molecules (May 1998) § I.C.1.a.
[247]Joseph M. Rainsbury, supra note 60, at 576.
[248]Judith A. Cregan, supra note 66, at 273.
[249]Id.

in humans[250]. The working group completed the guidelines for human studies in 1985, in a document called Points to Consider[251].

The first human gene transfer trial came five years later in 1990 and was reviewed 14 times before it was approved.[252] At that point the Points to Consider for gene transfer was officially added the NIH Guidelines as Appendix M.[253] Since then the regulation imposed on gene research has been amended several times and involves a complicated network of players, including the FDA, NIH, IRB, IBC, and local oversight mechanisms.

In 1991 the FDA issued its own guidance called "Points to Consider in Human Somatic Cell Therapy and Gene Therapy"[254]. To affirm its regulatory role even further, the FDA release a statement in the 1993 Federal Register stating that the FDA's authority provided in the FDCA and PHSA was broad enough to cover cell and gene therapy.[255] In the years following, RAC's authority over gene therapy continued to decline. In 1995, RAC approval was limited to only those protocols that were determined to be novel. [256] The process was referred to as "consolidated review" in an effort to eliminate what was thought of as double review by both the NIH and FDA.[257]

RAC's regulatory authority over gene transfer protocols was relinquished to the FDA completely in October 1997, and RAC approval was no longer needed for any gene transfer protocols[258]. The only exception is if three members of the RAC decide that a particular protocol is so novel and controversial that it warrants public debate[259]. The CBER at the FDA took over as primary regulatory authority over protocol approvals

[250]Nancy M. P. King, supra note 72, at 381.
[251]Id.
[252]Edward L. Korwek, supra note 166, at n.203.
[253]Nancy M. P. King, supra note 72, at 381.
[254]Joseph M. Rainsbury, supra note 60, at 581.
[255]Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. at 53,248 (Oct. 14, 1993).
[256]See 60 Fed. Reg. 20,726 (1995).
[257]Edward L. Korwek, supra note 166, at146.
[258]62 Fed. Reg. 59,032 (1997).
[259]62 Fed. Reg. at 4783.

through the IND process. However, research that receives NIH funding or is associated with an institute receiving NIH funding must still comply with the NIH Guidelines, register the protocol with the OBA, and receive IRB and Institutional Biosafety Committee (IBC) approval. The IRB and IBC serve as the local oversight bodies. The IRB focuses on patient safety and the IBC is charged with other scientific aspects such as laboratory and environmental safety. With the loss of approval power over clinical protocols, some have wondered whether the RAC has lost some respect within the biomedical community.[260] Although the RAC has long been well respected, the future role of the RAC remains unclear. The RAC is a long standing and respected institution, and should be. The RAC should still serve as the liaison to public debate and is the proper forum for looking at the ethical and social issues gene therapy raises.

The question remains whether the current system can adequately protect the public health without unduly hindering the progress of breakthrough research. Currently the FDA does not conduct inspections of clinical trials in gene therapy. It has added a new provision requiring the investigator to hire an independent third party to conduct random inspections[261]. A Gene Transfer Safety Symposium has been recommended by Senator Edward Kennedy[262].

Informed consent is another issue that was brought to the forefront in the Jesse Gelsinger death. Both the FDA and NIH have requirements for informed consent. However, do to some information deficiencies, neither the FDA or NIH can be sure that informed consent forms contain all the relevant information that a patient would need to make the most informed decisions.[263]

The FDA and NIH recently jointly launched a new database Genetic Modification Clinical Research Infor-

[260] Joseph M. Rainsbury, supra note 60, at 592.
[261] FDA to Crack Down on Monitoring Patients Undergoing Gene Therapy, TRANSPLANT NEWS, Mar. 13, 2000, available in LEXIS, News Library.
[262] Aaron Zitner, Kennedy's Bill Would Create Gene Therapy Oversight Panel: Clinton Administration Also Seeks New Rules for Tests, BOSTON GLOBE, Mar. 7, 2000, at E5.
[263] See Judith A. Cregan, supra note 66, at 281.

mation System (GeMCRIS) - a Web-accessible database of human gene transfer trials that the two agencies developed collaboratively.[264]

Some reports have emerged of interagency rivalry that may be harming the regulatory framework[265]. One commentator at a Senate hearing stated, "on several critical matters, there's been a lack of appropriate cooperation between the FDA and the NIH.[266]

For example while both the FDA and NIH require adverse event reporting, inconsistent reporting requirements for adverse events for the NIH and FDA has caused confusion with researchers[267]. First, FDA requires life threatening or unexpected adverse events to be reported as soon as possible, but no later than seven days after the event. All other serious adverse events must be reported within 15 days. The NIH simply required immediate reporting of all adverse events, yet provides to definition for a serious adverse event. Data confidentiality was also inconsistent between the FDA and NIH. While the FDA is statutorily bound to keep all information submitted in the IND confidential, the NIH's position is to make any and all information available to the public. Furthermore, after the death of Jesse Gelsinger, investigation into all the current clinical trials using a similar adenovirus vector revealed that out of 691 adverse events that had occurred, 39 were promptly reported to the NIH.[268]

The NIH recently made a significant effort to harmonize its regulation with the FDA.[269] This statement was released in 2001 and harmonized the adverse event reporting timelines and assured the industry that

[264]See http://www.gemcris.od.nih.gov/

[265]Judith A. Cregan, supra note 66, at 282; Gregory A. Jaffe, Inadequacies in the Federal Regulation of Biotechnology, 11 HARV. ENVTL. L. REV. 491, note 12 (1987).

[266]Judith A. Cregan, supra note 66, at 282 (2000) (quoting Dr. Walters from 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. 76 (2000)).

[267]NIH Gene Therapy AE Reporting Standards Less Clear Than FDA, BLUE SHEET, Mar. 22, 2000, available in 2000 WL 8519047.

[268]Wilder J. Leavitt, Regulating Human Gene Therapy: Legislative Overreaction to Human Subject Protection Failures, 53 Admin. L. Rev. 315, 330 (2001).

[269]NIH, Recombinant DNA Research: Actions Under the NIH Guidelines, 66 Fed. Reg. 57970, Nov. 19, 2001.

proprietary or trade secret information in the adverse event report would be kept confidential.[270]

B.

Pharmacogenomics Regulation

The regulation of pharmacogenomics industry is bifurcated into two pathways with drugs and its related genetic tests being regulated by the FDA[271] and stand alone predictive genetic tests conducted in laboratories falling under the responsibility of the Centers for Disease Control and the Human Health Services[272]. Pharmacogenomics and genetic testing raises several social and ethical issues such as confidentiality and exacerbating the orphan drug problem[273].

1.

Pharmacogenomic Drugs

Drugs that are made targeted to a specific gene, the manufacturer must present all relevant genomic data to the FDA in the PMA. However, when the genetic information is used as only one factor in the drug's safety or dosing, the FDA's pharmacogenomic data submission requirements have been less clear. Manufacturers

[270]Id.
[271]See 62 Fed. Reg. 62,243, 62,259-60 (Nov. 21, 1997)
[272]See Clinical Laboratory Improvement Amendments of 1988, 42 U.S.C. § 263a (2000); 65 Fed. Reg. 25,928 (May 4, 2000).
[273]See, e.g., Legal Liabilities at the Frontier of Genetic Testing, 41 JURIMETRICS J. 1 (2000); Michael J. Malinowski & Robin J.R. Blatt, Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards, 71 TUL. L. REV. 1211 (1997).

of drugs have been reluctant to submit to pharmacogenomic data to the FDA because of the uncertainty around how the data should be submitted and fears over what affect the data would have on the drug's approval.[274] The FDA made an effort to clarify their policy and encourage data submissions with a recently published a guidance document for industry.[275]

The FDA clarified that it will not be mandating genetic tests with the development new drugs.[276] However, if the sponsor conducts genetic tests in connection with drug development, then under certain circumstances, the sponsor will be required to include that data with the IND, NDA, or BLA.

The FDA outlines guidelines for when pharmacogenomic data will be required and when submission is only voluntary. If a pharmacogenomic test was a deciding factor in aspects of the study relating to safety, effectiveness, or dosing, then the sponsor must submit the data to the FDA.[277] If the drug labeling includes genetic information on the labeling, then the application must include the complete genetic data that supports such labeling. Furthermore, the sponsor is also required to submit the data if the test is considered a valid biomarker.[278] If the test is a valid biomarker, but not related to the drug's safety, effectiveness, or dosing, data submission is still required, but may be submitted in an abbreviated report. The FDA considers a pharmacogenomic test to be a valid biomarker if "(1) it is measured in an analytical test system with well established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results."[279] For example, a well established genetic test for variances in the gene that encodes the drug

[274]Id.
[275]Food and Drug Administration, Guidance for Industry: Pharmacogenomic Data Submissions, 23 Biotechnology L. Rep. 68 (2004).
[276]Id.
[277]Food and Drug Administration, Guidance for Industry: Pharmacogenomic Data Submissions, 23 Biotechnology L. Rep. 68, 74 (2004).
[278]Id.
[279]See generally Food and Drug Administration, Guidance for Industry: Pharmacogenomic Data Submissions, 23 Biotechnology L. Rep. 68 (2004).

metabolizing enzyme cytochrome P450 would be considered a valid biomarker.[280]

If the pharmacogenomic tests were purely exploratory, e.g. looking at general gene expression, or if the test are not considered a valid biomarker, then submission of the data is purely voluntary.[281] These Voluntary Genomic Data Submissions (VGDS) are highly encouraged by the FDA because they would allow the FDA to stay educated on the latest advances in genetic tests.[282] In order to minimize the burden of submitting the voluntary information, the FDA has no stringent format requirements for data submissions.[283] With some guidelines for content, a sponsor could even submit an article that was submitted to scientific journal as their data submission.[284] FDA further clarified that any voluntary submission of data would not affect the decision making process for the approval of the drug.[285]

Required pharmacogenomic data will affect regulatory decisions as one of the many factors of drug safety and efficacy.[286] As a result, the FDA may recommend as part of approval that the sponsor add the genetic risk factors to the drug labeling. Also, if the sponsor tested the drug in a population with a specific genotype, then the FDA would require that the corresponding pharmacogenomic diagnostic test be developed in conjunction with the drug as a condition of approval.

[280] Id.
[281] Id.
[282] Id.
[283] Id.
[284] Id. at 78.
[285] Id.
[286] Id. at 79.

2.

Genetic Tests

Genetic testing has raised concerns over discrimination that could result from the information, especially by employers or insurance companies. In 2000, President Clinton issued an executive order prohibiting the use of genetic information in the hiring, promoting, discharging, and all employment decisions[287]. The Equal Employment Opportunity Commission takes a similar stance against using genetic information for employment decisions[288]. Besides risks with the use of information, genetic tests may result in some dangerous results. First, is the phychological damage that could occur if a person is falsely diagnosed to have a fatal disease.

Predictive gene testing that is given as a service and not linked to a product is not subject to the safety and efficacy requirements of the FDA. Rather regulation falls under the Clinical Laboratory Improvements Act and Amendments (CLIA)[289]. CLIA oversight of laboratories is sporadic and unsufficient, with more than 150,000 CLIA certified laboratories that need oversight and frequent reporting deficiencies and infrequent laboratory inspections[290]. In a recent survey of 245 laboratories offering genetic testing, 15 percent of the labs received a quality score of less than 70 percent.[291] The quality and reliability of some genetic tests have been questioned, with one woman in 1999 who almost mistakenly had her ovaries removed based on an erroneous genetic test for a cancer gene.[292]

[287]Executive Order to Prohibit Discrimination in Federal Employment Based on Genetic Information, Exec. Order No. 13,145 (Feb. 8, 2000), 65 Fed. Reg. 6,877.
[288]EEOC Compliance Manual § 902.8 (1995).
[289]Pub. L. No. 100-578, 102 Stat. 2903 (1994).
[290]Snake Oil, supra note 91.
[291]Judy Peres, Genetic Testing Can Save Lives – But Errors Leave Scars, Chi. Trib. Sept. 26, 1999, at 1.
[292]See Genetic Testing's Human Toll: In Unregulated Field, Erros can Upend Lives and Mean Unneeded Surgery, Wash. Post, July 21, 1999, at A01.

Due to the lack of regulation of some genetic tests, both the public and industry has suffered. The public may become victim to misleading or false genetic tests that could lead them to receive unnecessary or dangerous treatments. Manufacturers genetic tests in general suffer from lack of regulation as well as the public loses confidence and trust in this emerging field of technology because there is no reliable way to distinguish between valid tests and those with no merit.[293]

Given the lack of CLIA to ensure product quality, the FDA is the best positioned, both from an infrastructure and experience standpoint, to take responsibility for oversight of stand alone predictive genetic testing. The FDA is already familiar with the technology as it already reviews diagnostic genetic test kits used in combination with drugs. The Advisory Committee at the Centers for Disease Control has published recommendations for quality assurance programs for laboratory genetic testing that the FDA could use as a resource for crafting their regulations[294].

C.

Novel Drug Delivery Regulation

Almost all novel drug delivery devices will be a combination product, and thus must interact with more than one FDA center to gain approval. The combination products approach has had its limitations. It has been noted that "manufacturers dread combination products because of the inherent difficulties of dealing with more than one FDA Center." The FDA took a step forward by developing the Office of Combination

[293]See Snake Oil, supra note 91(discussing how the lack of regulation has "demonized" the technology in both the medial community and general public).

[294]Eugene C. Cole, Centers for Disease Control & Prevention, Contract No. 200-98-0011, General Recommendations for Quality Assurance Programs for Laboratory Molecular Genetic Tests (Aug. 31, 1999), available at http://www.phppo.cdc.gov/DLS/pdf/genetics/dyncor.pdf.

Products to address some of the complaints, however problems still plague the system.

Combination products were first officially recognized in a statute in 1990 in the Safe Medical Devices Act of 1990. The act added § 503(g) to the FDCA prescribed how regulation of combination should be handled by the FDA. One of the FDA's centers - CDER, CBER, or CDRH - would be assigned as a primary reviewer based on the combination drug's "primary mode of action".[295] Past regulation of combination products has been criticized for being lengthy and inconsistent.[296]

The "primary mode of action" is a difficult test to apply to many biotechnology products where the mechanism of action is not always known. Looking at the past jurisdiction of some combination products, the determination of which center takes lead is not always intuitive. The "cultured skin" products were regulated by the CDRH, although the FDA questioned whether jurisdiction should be transferred to the CBER.[297] The to alleviate some of the jurisdictional conflict, three intercenter agreements were drafted between each of the FDA centers.[298] However, the intercenter agreements were not clear as to the basis of assignment for a particular product.[299] Also, in some cases it has taken up to 13 months just to determine which center has primary jurisdiction.[300]

The MDUFMA introduced a new Office of Combination Products under the Commissioner's Office to try and address some of these issues of efficiency and timeliness.[301] The office was established on December 24, 2002.[302] The OCP has been tasked with addressing several of the problems described. An internal working

[295] 21 U.S.C. 353(g)(1).
[296] John R. Manthei et al, Changing the Landscape for Device Manufacturers: Medical Device User Fee and Modernization Act of 2002, 15 NO. 2 Health Law. 10, 12 (2002).
[297] FDA, Notice of Public Hearing: Combination Products Containing Live Cellular Components, 67 Fed. Reg. 94 (May 15, 2002).
[298] See Edward L. Korwek, supra note 166, at 144.
[299] See Id.
[300] AdvaMed, The Lewin Group, Preparing FDA for the Revolution in Medical Technology, available at www.advamed.org.
[301] 68 Fed. Reg. 37075 (2003).
[302] Id. at 37076.

group has been charged with the task of defining "primary mode of action". The Office also committed to making decisions on an RFD within 60 days of receipt. The centers have created nine combination product categories:

(1) convenience kit of package

(2) prefilled drug delivery device/system
(3) prefilled biologic delivery device/system

(4) device coated/impregnated/otherwise combined with drug
(5) device coated or otherwise combined with biologic
(6) drug/biologic combination

(7) separate products requiring mutually conforming labeling

(8) possible combination based on mutally conforming labeling of separate products

(9) other type of combination product

A recent report summarizing FDA employee perspectives on the regulation of combination products revealed several shortcomings of the current system.[303] One area of improvement that was identified was for earlier identification of a combination product issue. Sometimes, other centers were not brought into consultation until after the clinical trials were completed.[304] The earlier the relevant centers are involved, the better guidance the sponsor can receive. Even when a sponsor chooses to submit an official Request for Designation (RFD), complaints of arbitrariness and lack of communication have been reported.[305] Some of the limitations of the Combination Products Program is also cultural. Some employees reported a reluctance to engage another center, even when their input would be appropriate.[306]

Although the objective for all three centers is the ensure the safety and efficacy of approved products, each center has its own distinct and separate process and procedures this is requires an applicant to follow.

[303]See Combination Products Program, Regulation of Combination Products: FDA Employee Perspectives (October 2002).
[304]See Id.
[305]See Id.
[306]See Id.

These differences are significant in that it means difference data or testing requirements. For example, a combination drug-device would be subject to both the Quality Systems Regulation for the device component and Good Manufacturing Practices for the drug component.[307]

Some manufacturers have complained of inconsistency in the application requirements or some device manufacturers might not have the capabilities or systems in place to meet the GMP standards. Similar complaints with the adverse reporting system have also been reported. A combination product manufacturer would have to report the same adverse event to multiple centers in different formats which is inefficient and duplicative. While the CBER and CDER have been working to harmonize their regulations, similar progress has not been make to incorporate the CDRH, and some representatives at CDRH reported that after an adverse event "considerable 'fumbling around' sometimes occurs in determining jurisdiction and/or engaging a consultant from CBER or CDER when a combination product issue emerges."[308].

Another problem with the combination products program is the lack of information management systems to support consultations. Although each center has electronic data tracking systems, the systems are not on the same platform and not integrated with each other to share information.[309] Furthermore, none of tracking systems identify whether a product is a combination or the status of a consultation.[310]

[307]Id.
[308]Combination Products Program, Regulation of Combination Products: FDA Employee Perspectives, 12 (October 2002).
[309]Id.
[310]Id. at 13.

V.

Conclusion

Now that the FDA has realized that new biotechnology does not easily fit into its traditional regulatory framework, it should continue to work to match the pace of the rapidly changing industry. At one time it may have made sense to simply try and fit some of the new biotechnology into existing categories, but as complex combination products become the standard medical products instead of the exception, it may no longer be efficient to hold steadfastly to the old structure.

One overall improvement to biotechnology regulation would be to make the Office of Combination Products a new Biotechnology Center, with the reviewing agents located in one center, instead of merely acting as a jurisdictional liaison. This would avoid the need for cumbersome intercenter agreements and potential for miscommunication and turf wars. Having a center dedicated to biotechnology would also address some of the problems of agency workload and expertise.

Already, the agency staff within the three centers are being diverted to contribute to consultations. Consolidating the reviews into one center would be a more efficient use of reviewers time. Furthermore, the biotechnology center could be divided into functional practice groups, such gene transfer, pharmacogenomics, and drug delivery. This would allow staff the ability to focus and build expertise in one area, while giving industry a clearer idea of who would be responsible for the reviews.

While this type of reorganization would be a dramatic departure from the current structure, it is clear that biotechnology is not just a passing trend, but it is here to stay, and may hold the future for where medicine is heading.

Also, just as the 501(k)'s have been outsourced to qualified third parties, the FDA should continue to look

for non-core areas and functions that would allow the FDA to concentrate on activities that make the best use of its time and resources.

Several industry surveys have stated that the industry feels that the FDA lacks the technical expertise and that is contributing to regulatory delays.[311] The FDA should continue its trend of looking to outside sources of advice and support. The FDA must keep training and retention of its staff as a top priority. As the FDA staff is pressured to continue to speed review times, they may have less opportunity for training and development. FDA collaborations with other agencies such as the NIH, National Science Foundation, and National Cancer Institute will be essential for the FDA to stay abreast on the most current scientific issues. While the new frontier of biotechnology raises several challenging regulatory issues, it also brings an opportunity to build a new regulatory structure that is more responsive and flexible to rapid advances in technology. Already, the science is advancing at remarkable speeds. Genes and DNA are no longer the smallest building blocks that medical science is targeting. The new area of nanotechnology is now looking for solutions at the molecular level[312]. The next advances in biotechnology are sure to bring about unforeseen complexities spanning scientific, regulatory, social, and ethical issues. The FDA can best serve as the guardian of public health by being prepared for the unexpected and remaining open to the possibility of change within its own organization.

[311] See John Miller, supra note 114, at n.199.
[312] Id.