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Industry Study

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Biotechnology Industry

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BIOTECHNOLOGY 2008

ABSTRACT

Defined broadly as the manipulation of genetic material in living organisms or the derivatives thereof, biotechnology represents a veritable gold mine of possibilities for improving the human condition. Society tends to focus on the glamorous; the success of the Human Genome Project and its modern miracle of unraveling the composition of human deoxyribonucleic acid (DNA). However, biotechnology is much more than genetics. It twines the developments in understanding the building blocks of life with their characteristics and uses in organic systems. In short, biotechnology is a multifaceted science that supports all manner of micro and macro interactions within the life sciences. This paper addresses three specific industries within the rubric of biotechnology - bio-fuels, agriculture, and medicine – and offers broad policy recommendations designed to foster discussion and debate among senior leadership in order to leverage the applications of biotechnology for the good of the nation. In addition, the paper provides the reader with three essays that provide greater depth and breadth on significant current biotechnology issues. Continued development and implementation of governmental policies and funding that aggressively promote continued scientific discovery and breakthroughs in this diverse industry offer unprecedented opportunities to increase mankind's quality of life by reducing dependence on fossil fuels, significantly reducing greenhouse gas emissions, increasing production and distribution of food, improving resistance to disease, and developing personalized medicine. The question is not if this will occur, but when and how to ensure that it takes place in an ethical, reasonable manner that benefits America and the rest of the world.

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PLACES VISITED

Domestic

Walter Reed Army Institute of Research, Silver Spring, MD
Armed Forces Institute of Pathology, Rockville, MD
U.S. Department of Agriculture Agricultural Research Service, Beltsville, MD
Centers for Disease Control and Prevention, Atlanta, GA
Applied Phytogenetics, Inc., Athens, GA
GTC Biotherapeutics, Framingham, MA
Harvard Stem Cell Institute, Boston, MA
Charles River Laboratories, Wilmington, MA
Broad Institute, Cambridge, MA
Massachusetts Institute of Technology, Department of Chemical Engineering, Cambridge, MA
Genzyme, Cambridge, MA
Massachusetts Biotechnology Council, Cambridge, MA
TEI Biosciences, Boston, MA
U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD

International - India

U.S. Embassy, New Delhi
Federation of Indian Chambers of Commerce and Industry, New Delhi
Government of India, Department of Biotechnology, New Delhi
Government of India, Ministry of Defence, Defence Research and Development Organization, New Delhi
National Institute for Plant Genome Research, New Delhi
International Centre for Genetic Engineering and Biotechnology, New Delhi
Indian Council of Agricultural Research, New Delhi
International Service for the Acquisition of Agric-Biotech Applications, New Delhi
Institute of Nuclear Medicine and Allied Sciences, New Delhi
Ranbaxy Laboratories Limited, Gurgaon
Lifecare Innovations, Gurgaon
Nicholas Piramal Research Centre, Mumbai
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Reliance Life Sciences, Dhirubhai Ambani Life Sciences Centre, Mumbai
Serum Institute of India Ltd., Pune
National Institute of Virology, Pune
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GUEST SPEAKERS

"Biotechnology Industry Overview"
Mr. Jim Greenwood, President and CEO, Biotechnology Industry Organization (BIO)
"Federal Government Regulation, Intellectual Property, Patent and Copyright Law"
Mr. Jason P. Fieger, Senior Associate, Booz Allen Hamilton
"U.S. Federal Government Support for Biotechnology: The Role of the National Science Foundation"
Dr. Maryanna Henkart, Director (ret.), Division of Molecular and Cellular Biosciences, Biological Sciences Directorate, National Science Foundation
"Agricultural Bioterrorism"
Ms. Candi Jones, Office of Intelligence and Analysis, Department of Homeland Security
"Perspectives on Energy Technologies: Biomass and Nanoscience"
Mr. Patrick Glynn, Office of Energy BioResearch Centers, Department of Energy
Mr. Altaf H. Carim, Office of Basic Energy Services, Department of Energy
"International Trade Issues – Genetically Modified Foods"
Mr. Jack Bobo, Trade Policy Advisor, U.S. Department of State
Mr. Wolf-Martin Maier, Counselor, Food Saftey, Heath and Consumer Affairs, European Commission Delegation, Washington, DC
"Federal Regulation of New Pharmaceuticals and Medical Devices"
Dr. Harry Dorsey, ICAF Faculty
"U.S. - India S&T Cooperation With a Focus on Biotechnology"
Dr. Kamal Kant Dwivedi, Counselor (S&T), Embassy of India

Introduction and Industry Definition

Since the dawn of humanity, people have utilized the principles of biotechnology in their intercourse with the environment. From discovering the uses of natural fertilizer to developing medicines from bacteria, biotechnology has improved the world in which we live, increasing food supplies and extending lives. Defined broadly as the manipulation of genetic material in living organisms or the derivatives thereof, biotechnology provides a veritable gold mine of possibilities for improving the human condition. However, as with all good things, caution must be exercised lest humanity go the way of Mary Shelley's monster. It is through careful and deliberate application of biotechnology that mankind may achieve the wonders implied by the science while maintaining our humanity and dignity.

During the Industry Study, it became apparent that biotechnology is an underlying science that supports many disciplines/industries. Society tends to focus on the glamorous; e.g., the success of the Human Genome Project and its modern miracle of unraveling the composition of human deoxyribonucleic acid (DNA). However, biotechnology is much more than genetics. It twines the developments in understanding the building blocks of life with their characteristics and uses in organic systems. In short, biotechnology is a multifaceted science, underpinning all manner of micro and macro interactions within the life sciences.

This report focuses on three specific industries that are supported by biotechnology: fuels, agriculture, and medicine. For each, the paper will define and assess the industry's current condition, detail challenges experienced by the industry, and provide an assessment of the industry's future prospects. At first blush, there may seem to be some overlap; however, the application of biotechnology is so varied in each industry, it is instructive to treat each separately so that the reader may form a more complete understanding of the science and its applications. In addition, the paper provides the reader with three essays that provide greater depth and breadth on significant biotechnology issues of the day. These essays relate to Bio-defense and Pandemics, Stem Cells Ethics and Policy, and Vaccines/Biologics. The first is an obvious topic of concern for national defense. The second and third essays examine issues that are of current concern to the U.S. and will likely gain more attention in the media as scientists and companies expand their efforts into these areas. These areas have the potential for significant breakthroughs within the next decade, thereby impacting society in ways only postulated in science fiction. It is an exciting time for biotechnology.

Finally, the paper will offer policy recommendations for each industry area explored. The intent is to foster discussion and debate among senior leadership in order to leverage the applications of biotechnology for the good of the nation. As with all interesting topics that have the potential to impact society, there is no clear path to the future. However, with proper debate and discussion, there exists a potential to increase in mankind's quality of life through greater access to food, resistance to disease, and personalized medicine.

Bio-Fuels

Current Condition

As a result of the oil shocks of 1973 and 1979, governments, businesses, and academics began to intensively study the use of bio-fuels to meet the nation's energy requirements. Interest waned in the mid-1980s when oil prices dropped below $20 a barrel but has returned to the forefront due to renewed congressional interest in the "use of bio-fuels as a means of reducing

the nation's reliance on foreign sources of oil and reducing greenhouse gas emissions, as well as stimulating agricultural production in rural America."[1] Fuels produced from biomass (bio-fuels) hold great promise as potentially cost-effective energy alternatives that simultaneously reverse the potentially disastrous effects of climate change created by the burning of fossil fuels. In his 2007 State of the Union Address, President Bush asked Congress to enact legislation to reduce dependence on foreign oil by reducing gasoline consumption by 20 percent over 10 years, a goal that would require the use of 35 billion gallons of renewable and alternative fuels by 2017, more than $1.6 billion of new funding over ten years for energy innovation, and $2 billion in loans for the construction of cellulosic ethanol plants.[2] Congress responded by passing major energy legislation at the end of its first session in 2007. The Energy Independence and Security Act of 2007 is designed to improve energy efficiency and increase the availability of renewable energy. In addition to the Energy Independence and Security Act, provisions in the Economic Stimulus Bill and Farm Bill would extend through 2009 tax incentives for energy efficiency and renewable energy that are set to expire in 2008 and extend or expand energy efficiency and renewable energy provisions of the Farm Security Act of 2002. "The Senate-passed farm bill contains provisions for renewable energy. There are several provisions for the production, blending, and use of bio-fuels (ethanol, biodiesel, renewable diesel). Also there are investment incentives for infrastructure (fueling stations) and for the development of production facilities."[3] These farm bill based government subsidies for bio-fuel production will make bio-fuels more competitive with oil and will likely lead many in the oil industry to abandon the construction of new refineries as well as encourage even the most reluctant to devise strategies that incorporate other forms of fuels into their portfolios. "Oil will still be the backbone of the energy industry's operations, but unless a major impediment to bio-fuel production develops, oil will no longer be the only significant component of vehicle fuel worldwide. Economic and regulatory circumstances could, for the first time, compel some oil super-majors to truly move beyond petroleum and into a more robust future."[4]

Challenges and Outlook

Ethanol. Corn derived ethanol is currently the only renewable fuel being produced in the United States in significant quantity and is aggressively promoted by its supporters as a key element in obtaining energy security for the United States. It faces several significant hurdles in its competition with gasoline. It is more expensive to produce and several studies indicate that it requires more energy to process corn into ethanol than the fuel produces. The shift of corn from its use in the food chain to use in the energy chain is unprecedented in agricultural history and is having a profound impact on prices for consumers, livestock growers and food processors.[5]

In an effort to reduce greenhouse emissions, a small amount of ethanol is added to approximately 30 percent of the gasoline sold in the United States, and most U.S. automobiles can burn "E-10" gasoline that contains 10 percent ethanol. More than six million flexible fuel vehicles (FFV) have been produced that can run on "E-85," a blend of 85 percent ethanol and 15 percent gasoline.[6] Despite this capability and nearly $3.5 billion dollars spent to date in federal subsidies to refiners, oil companies are slow to adopt the higher mix due to significant costs of separate pumps, trucks, and storage tanks. As of mid-2006, only 800 of the 170,000 service stations in the United States sold "E-85." In addition, many drivers who tried "E-85" once report reverting to regular unleaded gasoline due to a loss of up to 25 percent in fuel economy.[7]

As a result of steadily increasing gasoline prices that ensure sustained profitability, the U.S. ethanol industry has grown to an annualized production rate of more than 7.8 billion

gallons. Upon completion of new bio-refineries under construction over the next decade, more than 13 billion gallons will be supplied, nearly 10 percent of the nation's current gasoline consumption. Expanding the marketplace for ethanol requires significant infrastructure development to transport, store, blend, and dispense the product, all of which is rapidly coming on line.[8] The Energy Independence and Security Act of 2007 sets an annual production goal of 36 billion gallons of ethanol by 2022, 21 billion gallons of which is to come from cellulosic and other advanced bio-fuel production sources.[9] Cellulosic ethanol is produced from the structural material of plants found in agricultural and forestry wastes and rapidly growing, abundantly available crops such as switchgrass. Less energy is utilized in its production than corn-derived ethanol, resulting in lower greenhouse gas emissions. Unfortunately, it is also more difficult to break cellulose down into simple sugars required to make ethanol than to break down corn.[10]

Two objectives must be achieved in order to produce a viable cellulosic ethanol industry in the United States: "…commercializing the technology to produce large quantities of ethanol from cellulose, and creating an infrastructure that can deliver large quantities of new cellulosic materials to those new production plants."[11] Up to this point, the federal government has focused almost exclusively on the first objective—commercializing cellulosic technologies. The cellulosic goal established in the Energy Independence and Security Act of 2007 creates a market that will accommodate perhaps five to ten competitors. On the other hand, Congress and the administration are only now beginning to fund development of the infrastructure to enable cellulosic cultivation and delivery. "In the U.S., the Department of Energy has selected six proposed new cellulosic ethanol refineries to receive a total of $385 million in federal funding. When completed, these six refineries are expected to produce 130 million gallons of ethanol yearly."[12] Putting this infrastructure in place is a necessary condition to achieving production capability of 250 million gallons of cellulosic ethanol by 2013, a mandate contained in the Energy Policy Act of 2005.[13]

Biodiesel. The annual production of biodiesel in the United States increased 7500 percent from 1999 to 2005—from less than 1 million gallons in 1990 to nearly 75 million gallons in 2005, the vast majority from soybeans.[14] In 2007, the United States produced nearly 450 million gallons of biodiesel, an 80 percent increase in production from 2006. "Today there are more than 650 biodiesel fueling stations and hundreds of fleet operators use biodiesel to fuel their trucks. Every year more Americans are realizing the benefits of biodiesel, which can produce fuel from soybeans and other vegetable oils, including waste products like recycled cooking grease."[15] Government supports mirror those for ethanol, including a production tax credit of $1 per gallon blended with petroleum-based diesel fuel. In spite of this phenomenal growth, the outlook for the industry remains unclear. Although the production tax credit is extended beyond its 2008 expiration in both Senate and House versions of the 2007 Farm Bill, vegetable oil feed stocks such as soybeans, sunflower, and rapeseed are far less plentiful than ethanol sources. That being said, higher fuel prices along with the aforementioned government incentives are making the industry increasingly more profitable and raising questions concerning the production of agricultural products to meet the demand. A "hypothetical federal mandate that biodiesel make up 1 percent of current vehicle diesel fuel use would exhaust most available vegetable oils and animal fats and require manufacturers to find an additional 1.3 billion pounds of oil."[16]

Algae. The feedstock exhibiting the most promising potential for bio-fuel production is algae. Research at the Colorado State University (CSU) Engines and Energy Conservation Laboratory

and the University of New Hampshire (UNH) suggests, "…algae could supply enough fuel to meet all of America's transportation needs in the form of biodiesel. While it would require twice the land area of the United States to produce enough soybeans to meet current U.S. heating and transportation needs, enough algae can be grown to replace all transportation fuels in the United States on 15,000 square miles or 4.5 million acres of land, a landmass roughly the size of Maryland."[17] The UNH report posits that the more efficient a plant is at converting solar energy into chemical energy the better it is from a bio-fuels perspective. Algae perform this task so well that "up to 50 percent of its body weight can be fat, or the oil needed to make biodiesel. That makes algae the highest yielding feedstock for biodiesel, producing 24 times more oil per acre, on average, than the next leading feedstock – palm oil at 635 gallons/acre/year."[18]

On February 24, 2008, Virgin Atlantic became the first airline to fly with bio-fuel. One of its Boeing 747-400 aircraft flew from London to Amsterdam carrying a 20 percent mix of bio-fuel derived from coconut and babassu oil in one of its four fuel tanks. Commenting on the flight in the March 19, 2008 edition of The Guardian, Virgin CEO Richard Branson stated, "Two years ago the skeptics said that bio-fuel freezes at 15,000 feet and it would be impossible to fly an aircraft using bio-fuel. Our recent flight demonstrated that a Boeing 747 can fly at high altitude using bio-fuel. We will share the lessons from this historic flight with our visionary industry partners and go on looking for a renewable fuel source, such as algae, that could unlock our reliance on traditional kerosene."[19] This technology holds great promise for the U.S. Department of Defense which is seeking to both reduce dependence on foreign energy sources and contain costs as part of the Secretary of Defense's Assured Fuels Initiative. "Total Pentagon fuel consumption is roughly four percent of total U.S. consumption, and nearly three quarters of that is aviation fuel."[20]

Patents

For the most part, case law and moral issues concerning bio-fuels are not controversial. As researchers such as Craig Venter move into synthetic biotechnology, it can be expected that there may be increased legal or moral issues concerning the use of these synthetic organisms. The bio-fuels patent field consists of over 850 patents spread across 285 different companies.[21] Bio-fuels are represented in three distinct areas of patent law: feedstock; refining; and micro-organisms.

Since feedstocks are plant varieties, the legal and moral issues are similar to those in bio-agriculture. The one major difference concerns the use of the world's food supply for energy purposes. Bio-energy refining is similar to other refining industries and patent protection is granted for the machines and processes. The legal basis for these patents dates back to 1937, when George Chavanne patented the procedures for creating fuel from vegetable oil in Belgium.[22] Finally, the legal basis for patenting of micro-organisms used to produce bio-energy was established in the seminal 1980 U.S. Supreme Court case *Diamond v. Chakrabarty*, in which the court held that live human-made organisms, in this case genetically engineered bacteria to clean up an oil spill, were a product of human ingenuity and could be patented.[23]

Agriculture

Current Condition

Agricultural biotechnology is a collection of scientific techniques, including genetic engineering, that are used to create, improve, or modify plants, animals, and micro-organisms.

Genetic engineering techniques allow a precise alteration of a plant's traits (facilitating the development of characteristics not possible through traditional plant breeding), and permit targeting of a single plant trait (decreasing the number of unintended characteristics that may occur with traditional breeding).[24]

The initial objective for developing genetically engineered (GE) crops was to improve protection against diseases. Biologists were following similar life science techniques as implemented in the scientific 'trial and error' search for disease cures in humans. The GE crops currently on the market are mainly aimed at increasing the level of crop protection through introduction of resistance against plant diseases caused by insects or viruses or through increase tolerance towards herbicides. In addition to the benefits of protecting crops against diseases and weeds, farmers and agribusiness were striving to achieve greater yields (economies of scale per acre planted), reduce environmental scarring (decrease fertilizers and herbicides), and increase efficiency (time management). Insect resistance is achieved by incorporating into the food plant the gene for toxin production from the bacterium Bacillus Thuringiensis (BT). This toxin is currently used as a conventional insecticide in agriculture and is safe for human consumption. GE crops that permanently produce this toxin have been shown to require lower quantities of insecticides. Herbicide tolerance (HT) is achieved through the introduction of a gene from a bacterium conveying resistance to some herbicides. Use of these GE crops, referred to as "Roundup Ready" because they are engineered to resist Monsanto's glyphosate herbicide, has resulted in a reduction in the quantity of the herbicide used.[25]

The first generation of agricultural biotechnology involves traits that affect crop production – herbicide or pest resistance. Biotechnology's second generation involves crops with enhanced output characteristics, such as high oil content or other specialized features. It has been predicted that the next wave of biotechnology products on the market will be GE crops to target the needs of the end-user or consumer, such as foods with altered nutritional qualities, crops with improved processing characteristics, or plants that produce specialty chemicals or pharmaceuticals.[26] In 2005, GE crops were planted on an estimated 222 million acres worldwide. The total number of countries growing such crops reached 21 in 2005, but most of the acreage was highly concentrated among four crops (soybeans, corn, cotton, and canola) and five countries. The United States had 55% of global acreage, Argentina had 19%, Brazil (10%), Canada (7%), and China (4%) constituted the nations with the largest shares.[27] The principal (and principled) argument that the producers offer to justify the use of GE crops is the increased yield from GEs could end malnutrition in the world. The United Nations Food and Agriculture Organization rebuttal to this argument is that the world currently produces a sufficient amount of food to eliminate malnutrition. The problems associated with malnutrition are poverty and a lack of access to the available food.[28]

Challenges and Outlook

The European Union leads the world in opposition to GE crops or genetically modified organisms (GMOs). The principal focus of their opposition is safety. Several governments and groups in the European Union do not believe that GE crops are safe for consumption by their citizens. In the U.S., the process that is used by the FDA is a determination that the modified (enhanced) plant is "generally recognized as safe."[29] It simply acknowledges that the genetically modified plant is probably not dangerous to humans or animals. The U.S. Food and Drug Administration (FDA) does not actually approve GE crops for use in the United States or anywhere else in the world. In Europe, the review process is referred to as "substantial

equivalence." This process does not approve or validate a GE crop. These designations are accepted by the World Health Organization and Office (WHO) and organization for Economic Cooperation and Development.[30]

The general perception is that GE crops are widely accepted by residents of the Americas and nearly universally rejected by Europeans. After all, GE crops are ingredients in nearly every food product in a grocery store. Over 60% of the foods found in grocery stores contain GE products.[31] Because so many products in the U.S. are genetically modified, the obvious conclusion is that GE crops must be widely accepted by Americans. In reality, 61% of American women say that they are "unlikely" to try a food that is genetically modified. Men in America are less opposed to the idea of eating genetically modified foods. Only 46% of men say they are "unlikely" to eat foods containing GE crops.[32] Most Americans are not aware of the presence of GE crops in food products because the U.S. does not have a requirement to label foods which contain GE crops.

American business has become extremely sensitive to these preferences of American men and women saying they are unlikely to eat genetically modified foods. Anheuser Busch, the largest purchaser of rice in the U.S., announced that it would not purchase rice from any grower in the state of Missouri if the state allowed the introduction of genetically modified rice in any field in the state.[33] The beer maker's concern was in regards to the possibility of consumer rejection of its products - once the public learned that any of its products contained ingredients which had been genetically modified. Other American food producers have rejected the use of genetically modified ingredients. Meat producers, such as Dean Foods and Smithfield Farms, have publicly stated they will not include animal products produced from cloned livestock or their offspring in their products. This announcement came days after the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) announced that food derived from the offspring of cloned cows, pigs and goats to be safe for human consumption.[34] The issue with meat products is slightly more complicated because animals are often fed animal feed containing GE crop products. These companies distinguish between the use of cloned animal products and animal feed containing GE crop products.

The European media presents a different perspective concerning acceptance of GE crops. Clearly, the media presents an image of a populace who rejects food products containing GE crops. In some cases, national legislation supports this image. In Switzerland (a non-EU country), the citizens voted to support a five year ban on the importation of GE products with 55.7 percent of the population voting in favor of the exclusion.[35] Six EU countries imposed bans on GE crops.[36] The EU has held numerous referenda at the ministerial level concerning GE crops. In general, the EU has been unable to achieve consensus on the safety of GE or an agreement to exclude GE products imported from outside of Europe.[37] A consumer experiment recently conducted in Britain determined that there is price sensitivity in the choice between GE and non-GE food. Consumers were willing to buy GE food if the price of non-GE food was higher. Eventually 74.5% of consumers were willing to buy GE food.[38] Surveys in other European countries achieved similar results. Similar to the American study, Europeans consumers express a clear gender preference against GE foods. European women are far more likely to prefer non-GE foods than men.[39] An experimental study found that the presence of a label indicating the presence of GE crop products in food did not significantly affect a consumer's decision to purchase the food in general.

In May 2003, the United States, Canada, and Argentina initiated a complaint before the World Trade Organization (WTO) dispute panel regarding the EU's de facto moratorium on

approval of new GE crops. U.S. agricultural interests contended that the moratorium not only blocked exports such as corn and other products to the EU, but also as fueling unwarranted concerns about the safety of agricultural biotechnology throughout the world. The United States and its allies further argued that the EU moratorium was violating WTO rules stating that a country's actions to protect health and the environment must be scientifically based. Although the EU effectively lifted the moratorium in May 2004 by approving a genetically engineered corn variety, the three complainants pursued the case, in part because a number of EU member states have continued to block approved biotech products. In November 2006, the WTO's Dispute Settlement Body (DSB) adopted the dispute panel's report, which ruled that a moratorium had existed and six EU member states violated WTO rules. U.S. officials contend that the EU moratorium threatens U.S. agricultural exports to other parts of the world. Industry estimates suggest that the moratorium costs U.S. corn growers $300 million in exports to the EU annually.[40]

Medical Biotechnology

Current Condition

The field of medical biotechnology runs the gamut from traditional pharmaceutical manufacturing, to vaccines, to experimental stem cell therapies, to personalized medicine. It provides a dizzying array of possibilities from curing cancer to extending human lifespan. The common factor among all of these applications is the science of biotechnology. The ability to understand and directly control genes has led to a revolution in the field of medicine. Because the field of medical biotechnology is so diverse, it is difficult to judge its past performance as a whole. One method of assessing the sectors is by the number of drugs and vaccines approved by the FDA per year. According to the national biotechnology trade organization, BIO, the number of new biotech therapies has risen significantly since the early 1990s. (Figure 1)

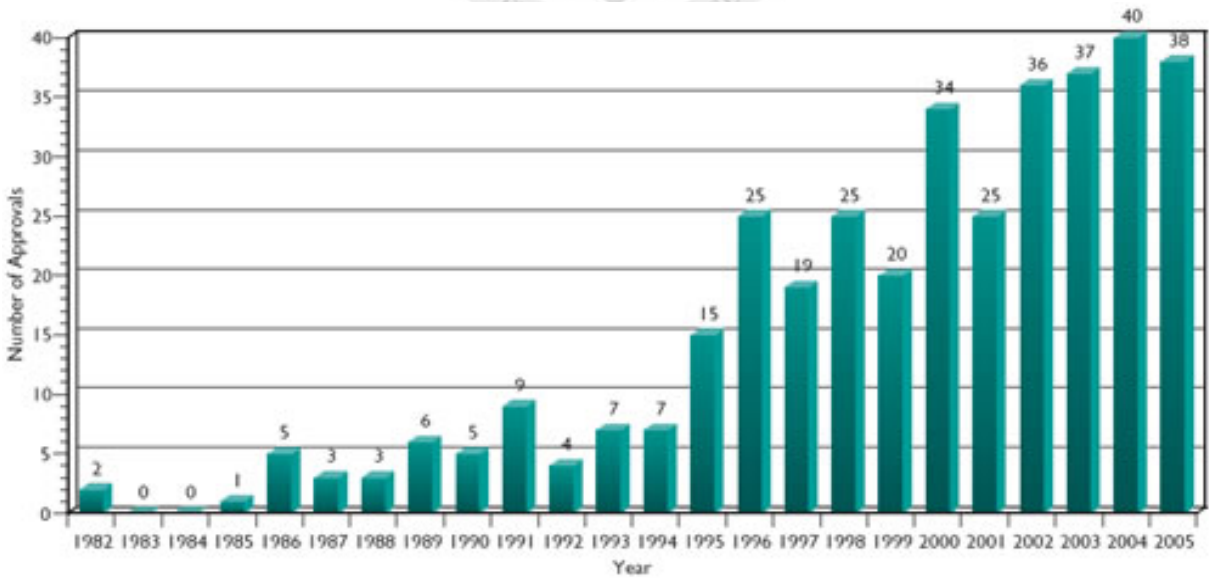

Figure 1. New Biotech Drug and Vaccine FDA Approvals[41]

The medical biotech field has produced more than 200 therapies to treat such illnesses as cancer, diabetes, HIV/AIDS and autoimmune disorders. The field is responsible for medical diagnostic tests that keep the blood supply safe from the AIDS virus and detect other conditions early

enough to be successfully treated. Employment in the medical biotech field grew approximately 8% from 2001 to 2006.[42] Two major advances in medical biotechnology include personalized medicine and longevity research.

Personalized medicine is a broad field involving predictive, preventive, personalized, and participatory medicine.[43] Personalized medicine is the tailoring of treatments to an individual's genetic profile, and in the future, its primary role will be to prevent rather than treat disease.[44] More specifically, an individual will be treated by knowing how the medication will react to an individual's genomic structure, and perhaps, the sequence of the disease. The decoding of the human genome in 2000 sparked hopes that a new era of tailored medicine was just around the corner. However, uncovering the genetic differences that determine how a person responds to a drug and developing tests or biomarkers, for those differences has proved to be more difficult than initially thought and continues to be a challenge.[45] The challenge is linking genome technology to biology.[46] Technology is available to sequence the genome of every human being, but researchers are still working on identifying the genetic causes of a disease and therapies to treat diseases.[47] Medicines will be personalized by drug companies to customize a drug to a particular patient population, diagnostic and therapeutic, or it can even be designed for a patient population based on gene type or DNA.[48] The applications of personalized medicine are still mainly in the realm of promises though there are applications now. New technologies are continuing to be developed for sequencing which will make personalized medicine increasingly more important over the next five to ten years.[49]

Another advancing area of research is in human longevity. Over the last decade, there have been numerous examples of increasing lifespan in laboratory worms, flies, and mice. Improvements of up to 40% disease-free lifespan have already been demonstrated in laboratory animals.[50] As of 2006, several forms of worm have been created with either enhanced or suppressed genes that demonstrated remarkable longevity. Scientists are continuing to conduct assays of gene expression to determine which genes influence longevity. In 2007, 25 new human longevity enhancing genes were found in various studies.[51] While the potential for increased human lifespan exists, it is unclear when it these therapies can be realized. It is instructive to consider three future scenarios: 1) Scientists eliminate major causes of early death (cancer, Alzheimer's, and coronary diseases) 2) Novel techniques come on line that expand current human lifespan to its theoretical maximum (stem cell regeneration, caloric restriction mimetics, etc) and 3) New biological techniques emerge that take people past the current human lifespan. In the first scenario, demographers have estimated that the elimination of major diseases would result in an increase in average life expectancy to only 85.[52] This is a result of continuing systemic decline in the body due to aging. In the second scenario, life expectancy would increase to the current maximum of about 120 years. This would require actions to slow the systemic decline related to aging. In the final scenario, life expectancy would increase past the theoretical maximum through repeated repairs of age related damage. One noted longevity researcher, Dr. Aubrey de Gray, suggests that given repeated repairs, a person may end up achieving 'escape velocity' where healthcare improves life expectancy at a rate faster than we age. Dr. de Gray has proposed that the result of this technological improvement means that the first person to reach 150 is likely alive today and the first 1000 year old will be born in the next 20 years.[53]

Challenges and Outlook

Two key issues facing medical biotechnology are the increasing cost of healthcare in the United States and the world wide regulation of Intellectual Property. These are pressing policy issues that concern the national security of the United States.

The cost of healthcare is currently the number one issue facing the U.S. medical industry today. Mandatory spending programs are linked with life expectancy and the current expected changes in demographics will result in significant future budget deficits. An aging population accounts for 25% of the projected cost growth through 2030, while rising health care costs accounts for 75%.[54] However, this analysis is based on projected life expectancies of 81, up from 78 in 2007. Should life expectancies increase, the aging population portion of the cost growth may increase significantly. Advances in medical biotechnology may challenge the budget through increasing Social Security costs and health costs. The key to addressing these issues is two fold; increasing the health of the aging population and then expanding the workforce with older adults. An effective means to deal with this challenge is to focus federal funding on an effort to increase life expectancy and healthy life span.

The second key issue is the protection of intellectual property. In the area of patents the issue can be broken into two parts: the patenting of genes and the stifling of innovation. There is considerable concern that the US Patent and Trademark Office has been granting gene patents on the basis of "trivial, dubious, or even fraudulent utility claims."[55] These allegations against the US Patent and Trademark Office are being upheld by the Supreme Court. Most recently, in *KSR v. Teleflex*, the court invalidated a patent because it failed the obviousness test.[56] The important distinction is that it is legal to patent the specific use of a gene so long as the patent satisfies the criteria for novelty, utility, and clarity. To date, almost 2,000 genes have been patented and a recent study claims that well over half of the patents are problematic in meeting the legal criteria.[57] A bad application of legal standards which leads to bad patents is not good public policy. The issue of whether patenting genes chokes off scientific research is interesting. The science of biotechnology emerged during the 1980's at the same time as the Bayh-Dole Act. Prior to this time, basic research was funded by the government and considered a public good that was available in the public domain, excluding none from its use. However, there was a concern that the research was not being commercialized fast enough and that government funding was no longer sufficient. So, as a matter of public policy, the Congress passed the Bayh-Dole Act to essentially privatize basic science and research.[58] Many credit this act with the innovation explosion that has occurred in the field of biotechnology. To claim, as many now do, that allowing for this privatization to occur may be choking off innovation does not take into account the tremendous gains of privatization. To reverse this trend and make the information part of the public domain, would require increased government expenditures and alternative methods of incentives to encourage innovation at the same pace as has occurred in the past thirty years. It is important to remember that the patent is for only twenty years, so the ability to exclude its use will eventually expire. Other challenges include that of vaccine development and generic biologics manufacturing, addressed in a separate essay in this report.

Bio-defense Essay

"The greatest threat facing our nation in the 21st century is the danger of terrorist networks or terrorist states armed with weapons of mass destruction. We're taking decisive action at home and abroad to defend our people from this danger. …. We will ensure that you have the tools necessary to do the solemn duty of protecting the American people from harm."[59]

President George W. Bush

Speech to NDU Students at the National Defense University
October 23, 2007

Recognizing and Acknowledging the Threat

The threat of an adversary using weapons of mass destruction is not new. In fact, for the past several decades, the topic has been one of immense importance to our nation's security and future prosperity. Yet, in the last several years, the invincible superpower mentality that lulled our nation into a dangerous state of security complacency has been replaced by a shocked public awareness and renewed sense of urgency to develop anti-terrorist safeguards. President George W. Bush has been unwaveringly consistent with the language he has used to describe the WMD threat in the National Security Strategies of 2002 and 2006. The United States, in conjunction with its allies, has fortified its previous response to terrorism and reevaluated the direct threat of a terrorist attack which could potentially involve chemical, biological, radiological, or nuclear (CBRN) agents as weapons of mass destruction.

Along with the growing threat in the past decade, the technology of weapons of mass destruction has proliferated at an alarming level as both the information and capabilities for developing these deadly agents have become more accessible. Both state and non-state adversaries continually desire the means to challenge the power and influence of the United States and its democratic allies. The catalyst for the growing threat of weapons of mass destruction is the terrorists' inability to meet the extensive cost of research, development, and procurement of their own high technology weapons. Neither can they sustain the requirements for large standing military forces. In short, terrorists are unable to fight or challenge the U.S. in a conventional confrontation and use of asymmetric violent attacks, including use of weapons of mass destruction, are far more cost effective.[60]

Defining the Threat

Why is the threat from weapons of mass destruction so important today? Former Chairman Joint Chiefs of Staff, General Colin Powell admitted in 1993, *"The one thing that scares me to death, perhaps even more so than tactical nuclear weapons, and the one that we have the least capability against is biological weapons."*[61] Despite the 20th and early 21st century's astronomical advances in medical technology, biological warfare (BW) still poses extremely difficult and seemingly insurmountable problems for the U.S. and its allies. For decades, the U.S. has readily relied upon the Department of Defense to provide the nation's sole protection from WMD threats. From the mid 1970s until post-1992 Operation Desert Storm, the Department of Defense persisted in putting BW defense (more so than chemical or nuclear weapons readiness and training) in the "too-hard-to-do box" because commanders and intelligence advisors perceived that the threat of use was miniscule compared to the effort required to defend against it. During the later part of the twentieth century (1979), two circumstances gave renewed impetus to a number of defensive measures. First, the former Soviet Union disclosed its advanced biological weapons development program (in gross violation of their signatory restrictions via the Biological Weapons Convention), through their limited biological weapons use during the Soviet Union - Afghanistan War and; secondly, Iraq threatened the potential to use BW during the 1991 Gulf War.

News-making discoveries in microbiology and genetic engineering have increased the public's understanding of the implications of ungoverned biotechnology. General Powell's concerns are now echoed around the world. Scenarios, which are not reported by the news, are cropping up as vignettes in other forms of entertainment media such as books, movies, and

television. Books and movies by the score have perpetuated the fears of terrorist and catastrophic weapons of mass destruction (WMD) consequences. Fear may be good if it shakes the complacent into action; BW can be defeated, but only if confronted.

Though accredited to advanced technology, the threat is not new. Military exploitation of living organisms to cause enemy casualties is as old as warfare itself. From biblical times, water holes have been poisoned, infected corpses fired across enemy lines, and diseased prisoners returned to infect their colleagues. More recently, in the 19th century, unscrupulous traders distributed blankets contaminated with smallpox among the American Indians. Decimated by epidemics against which they had no immunity, the Native Americans were easy prey for their conquerors.[62] In the 21st century, both science and technology allow the development of new more deadly BW agents in the laboratory.

Today, scientists can engineer organisms to exhibit specific traits and resistant characteristics. Additionally, organisms have been artificially mutated to give more specific, more intense, and quicker pathogenic effects. They have even been modified to survive longer and take advantage of different vectors or natural carrier organisms such as rats, fleas, ticks, mosquitoes, birds, and even beef, poultry and fish.

There have also been natural changes in diseases which affect mankind, some caused by mutations in viruses and others which allow them to cross the species barrier from animals to man. The cross-species transfer has been helped by some appalling errors made by man himself. The advent of bovine spongiform encephalopathy (BSE), or "mad cow disease" in cattle and the resultant potential for an epidemic of the human variant, Kreutzfeldt-Jacob Disease, is one example.[63] Other diseases, such as Human Immunodeficiency Virus (HIV) and Escherichia coli (E Coli), have jumped the human – animal gap for other reasons or have come to prominence because of lifestyle and culture.

The emergence of Ebola virus and the extremely rapid tissue deterioration caused by Necrotizing Fasciitis, or flesh-eating bacteria, have also turned the world's attention to the microbiologist for understanding the ways these diseases are transmitted and acquired and, ultimately, for ways to gain protection from their virulence. Revelations of the depth and breath of U.S. vulnerabilities sparked public awareness and support for better detection, surveillance, and responses specifically including medical prophylactic and treatment measures. Since then great advances have occurred (though much more is needed) in the medical response areas especially in the areas of vaccine development - almost keeping pace with the most likely advancing BW threats. However, methods for rapid, reliable point and standoff detection, identification, warning and reporting procedures, and critically needed planning and resourcing of response units remains a challenge even today and are only beginning to be properly addressed across the Federal Government and the Department of Defense (DoD).

Biological agents may have escaped from offensive research facilities and, even worse, they have been the subjects of clandestine trials among the public. For example, in April 1979 at the Soviet Biological Research Facility located in Sverdlovsk, Russia, an accidental release of trace amounts of anthrax spore aerosol resulted in the cumulative deaths of over 800 residents of the local community.[64] The BW hazard remains a strategic threat today.

Conclusions

The U.S. is not alone in developing measures to improve its defense and response against bioterrorism or in detecting bioterrorist threats. The fact remains, however, that no other country in the world has approached the U.S. level of effort. Inevitably this has led to a debate within the

US in which some Americans question how well the money allocated to the U.S. effort is being spent, while others feel the spending is still inadequate. We offer that the consequences of not preparing for this threat would be unfathomably catastrophic. We cannot afford not to continue these efforts and, though we have made tremendous positive progress, we still have much more to do.

Pandemics Essay

A pandemic is an occurrence of a specified virus covering a vast geographic area. Merriam Webster defines pandemic as "occurring over a wide geographic area and affecting an exceptionally high proportion of the population." Influenza pandemic has the potential to affect more than 100 million people with over 7 million deaths and have a direct economic impact of more than $280 billion dollars in the United States alone.

Recorded history dates the first probable influenza diagnosis at 412 B.C. by Hippocrates[65] and similar descriptions followed by Livy in ancient Rome and Lord Randolph at Edinburgh in 1562. In 1793, a Philadelphia physician, Dr. Robert Johnson first described the symptomatic indications of influenza and is generally credited with discovering the epidemic's viral cause. Influenza can prove to be very pathogenic (high probability of serious illness or death). The influenza pandemic of 1918 killed more people globally than all World War I deaths combined.

Influenza

Influenza, more commonly referred to as the flu, develops from viruses. Though a virus is not categorized as living or non-living, the virus infects a victim, both human and animal, by bonding to the host and implanting the virus's genetic material into the host's cell. The host's genetic code is then "hacked" and forced to replicate the virus's genetic material as viable viruses that, then, serve as carrier genes to the host cells.

The influenza does not contain DNA (deoxyribonucleic acid), unlike all other living things, but rather contains RNA (ribonucleic acid) as its basic genetic building block. There are three types of influenza virus[66] (A, B and C) based on variations of its internal proteins. Type A can be transmitted by birds and mammals and has a high mutating factor, while type B is confined to humans. Types A and B are readily capable of producing severe illness and death in humans. Type C has not proven capable of infecting humans.

Viruses exist because of their ability to thrive within some animals without demonstrating any symptoms and they have the ability to escape destruction by the host animal's immune system. A person's immune response generates antibodies that help to reject, or destroy, the virus. A virus stays viable by staying ahead of the body's ability to generate the antibodies. This occurs by a process known as antigen variation – a spontaneous genetic mutation polarizes the antibodies thus avoiding destruction or rejection.[67] A virus will grow to pandemic proportions when the antigen variations are so successful that our immune system has no effect on the virus.

In most pandemics, the host immune system has no indigenous antibodies because there has been no previous exposure. The virus has "jumped" species and the new hosts have no defense. H5N1, avian flu, poses this problem for humans.

A pandemic will likely present itself in the human population when the four following conditions have been met:

- A virus pathogen for humans establishes a global presence in animal host

- A new flu virus subtype to which the population is immunologically naïve

- The new virus infects people, and they get seriously ill
- The virus is easily spread from person to person[68]

Simply put, a pandemic occurs when a new virus is efficiently transmitted from host to victim, on a global scale. At the point of pandemic, the virus is not contained and travels across geographic boundaries.

The Avian Flu

The newest influenza flu virus subtype, also known as avian flu, has presented itself in Asia and has the potential to progress into a pandemic. Avian flu is type A subtype H5N1. To this point, is has not migrated to human beings in epidemic or pandemic levels. However, as President George W. Bush stated in the preface to the *2005 National Strategy for Pandemic Influenza* document:

> "Nature presents us with the daunting challenge: the possibility of an influenza pandemic. A new strain of influenza virus has been found in birds in Asia, and has shown that it can infect humans. If this virus undergoes further change, it could very well result in the next human pandemic."

The disease has, however, progressed from animal-to-animal transmission to animal-to-human infection and very limited human-to-human transmission. The first known case of human infection occurred in Hong Kong in 1997 with subsequent infections raising the total number of casualties at 18 cases with six ending in death. The flu was contained through aggressive containment and extermination of the poultry industry in Hong Kong.

The avian flu was contained from 1998 until 2003. Then two additional cases were reported in Hong Kong in 2003. The World Health Organization (WHO) has documented a total of 318 cases of Avian Flu infection and 192 deaths[69] in 12 different countries. While efficient human-to-human transmission has not evolved, the H5N1 virus subtype represents the greatest known risk for an active pandemic among the human population.

As recently as 2003, the virus subtype mutated into a strain with heightened pathogenicity, or capacity for disease. This new strain, labeled the "Z strain" has surfaced in Thailand, China, Vietnam, Turkey, Germany and other Asian and Eastern European countries in various animals to include, but not limited to, fowl and poultry. This strain has presented itself in mammals, such as domestic cats in Germany in 2006,[70] and has a greater resistance to standard antiviral drugs.

As referenced earlier, multiple elements must converge for a pandemic to begin. Those elements include:

- Emergence of a new influenza Type A virus from genetic mutation or evolution
- Pathogenicity of the virus to cause serious illness and death
- Susceptible population with little or no immunity
- Efficient human-to-human transmission of the virus

While the first three elements are established with the avian flu, the lack of efficient transmission restricts the potential as a pandemic. Constant monitoring will indicate when the current H5N1 strain mutates to a human virus signaling the culminating element of a pandemic. The continuity of transmissions of this virus in Asia, and its indication of spreading to Europe, raises great concern that the mutations will occur in the near future.

The high potentiality of an H5N1 pandemic necessitates that international and federal agencies establish protocols for responding effectively when early indications present themselves.

U.S. Strategy for Pandemic Influenza

While the World Health Organization is the international agency mandated to address global health issues, the United States government has a multi-faceted strategy to mitigate the effects of any emerging infectious diseases consistent with the WHO's preparedness efforts. In 1996 President Bill Clinton issued a Presidential Directive providing a more focused effort to address infectious diseases. A January 2000 National Intelligence Estimate, *The Global Infectious Disease Threat and Its Implications for the United States,* emphasized the importance of a sound, well-formulated strategy for combating the spread of infectious diseases, to include influenza sub-type viruses.

In response to President Clinton's directive, the Department of Health and Human Services, in concert with the Department of Homeland Security after 2001, developed a comprehensive strategy for the federal, state and local governments' integrated planning efforts. It also incorporated the role of the civilian health care system. The National Strategy for Pandemic Influenza (NSPI) guides our preparedness and response to an influenza pandemic, with the intent of:

- Stopping, slowing or otherwise limiting the spread of a pandemic to the U.S.;
- Limiting the domestic spread of a pandemic, and mitigating disease; and
- Sustaining infrastructure and lessening impact to economy and functioning society[71]

The NSPI will leverage all instruments of national power and serve as the framework for a multi-pronged effort. The pillars of the NSPI are; preparedness and communication; surveillance and detection; and response and containment. Each of these key elements are crucial to the success of early intervention or possible prevention of wide spread transmission of the attacking virus.

The NSPI will coordinate all planning efforts with multilateral agencies such as the WHO, World Organization for Animal Health, Global Outbreak Alert and Response Network (GOARN), International Partnership on Avian and Pandemic Influenza (IPAPI), United Nations and the International Red Cross as well as regional agencies critical to the containment of influenza type viruses such as the Asian-Pacific Economic Cooperation (APEC) forum. Such coordination efforts will:

- ***Support the creation and exercising of avian and pandemic response plans***
- ***Educate populations, domestic and abroad, about high-risk practices***
- ***Expand in-country medical, veterinary and scientific capacity to respond to an outbreak***

Conclusion

The United States faces an influenza outbreak every year. Despite annual vaccinations and well-funded scientific research, more than 30,000 deaths and 200,000 hospitalizations at a cost of $10 billion occur annually.[72] An influenza virus pandemic could affect more than 100 million people with over 7 million deaths and have a direct economic impact of more than $280 billion dollars.[73]

Pandemics will disrupt every aspect of our daily life. Only a small portion of the total population affected seeks treatment and are treated within the hospital system; and, yet an actual pandemic would overwhelm the entire in-patient hospital capacity of this country. Panic would effectively disrupt the education system for many weeks and would cause many millions of people to avoid their workplace. Lost productivity would have a crippling effect on the economic viability of this country and the rest of the industrialized world. Only through education, communication and preparation can future pandemics be minimized or averted with minimal loss of life, health and economic impact.

Stem Cells Ethics and Policy Essay

There are more than 200 different cell types in the human body that are differentiated from each other in terms of their specific function. Once such cells have differentiated into their specialized function – whether a nerve, muscle, skin, blood bone, or other specialized form – they can only give rise to their own cell type. Unlike these specialized adult cells, the embryonic stem cells are said to be pluripotent; they have the unique capability to self-replicate and develop into any other type of cell. Exploring their characteristics in laboratories for the purpose of regenerative medicine, scientists are hoping to create cells that will replace human tissue lost to aging, disease, or injury.

Embryonic stem cells originate in the three to five day old embryo known as a blastocyst. Because the blastocyst has the potential to develop into a mature human being, many people believe that the embryo should be considered a human being and possesses a right to life. The creation of an embryo for research purposes that results in the ultimate death of this embryo, consequently, is considered unethical. Others do not deny that human life commences at fertilization, but deny that the blastocyst itself is a person or human being in the full sense of that term. Further, such scientists hold that it is because the blastocyst potentially could become a human that it should be studied rather than the embryos of other mammals.

In order to bridge the gap between the ethical issue over embryonic stem cells on one hand and scientific research needs on the other, many different techniques have been developed for producing embryonic stem cells that are providing some promising results. Using the nuclear transfer technique (NT) or therapeutic cloning of embryo and pre-implantation genetic diagnosis technique (PGD) for harvesting the embryonic stem cells, scientists succeeded in isolating an embryonic stem cell from a blastocyst that does not have the potential to become a human being or does not appear to harm the embryo. Nevertheless, controversy remains.[74] The most advanced technique of converting an adult cell into an embryonic stem cell by "adding four new genes to ordinary adult skin cells" holds some promise, but it's still too early to say that it is a silver bullet that cures a major prevailing problem.[75]

Many Americans support the view that embryos should not be considered human beings. Some polls show that almost 60 per cent of Americans support stem cell research, indicating an understanding of the complexity of the issue. They have balanced ethical concerns with medical necessity and support the research on embryonic stem cells that benefits humanity.

Conclusions and Policy Recommendations

While the ethical and moral issues over stem cell research have not been resolved and remain the subject of national debate, current U.S. policy on this issue is deeply flawed. U.S. government regulations on stem cell research restrict the use of government funds for research involving stem cells harvested from human embryos. The White House, favoring mostly adult stem cell research, restricted funding of research to sixty human embryonic stem cell lines created prior to August 2001, most of which have been destroyed.[76] This current ethical position in U.S. policy could harm stem cell science in the United States; it will slow the pace of science by focusing on one area of research and excluding another, and will cause many scientists and researchers to leave the United States to continue their work in other countries that support comprehensive embryonic stem cell research.

Proponents of stem cell research highlight the considerable potential of embryonic stem cells and opponents speak of ethical issues and immorality of using human cells for this purpose.

Promising medical research on both embryonic and adult stem cells provide strong argument for continuing this work. Current U.S. government policy hampers American research and places American science in an unfavorable position to compete with stem cell research elsewhere in the world. Alternatively, a decision not to use stem cells as a treatment for disease and to give up stem cell research altogether is not an acceptable scientific option. Thus U.S. government policy should be more flexible, adopting the Stem Cell Research Enhancement Act, which would allow federal funding of stem cell research on lines derived from discarded human embryos created for fertility treatments.

The U.S. Government should continue to financially support scientific work on new techniques that allow the creation of alternatives to embryonic stem cells. These alternatives are proving to be less controversial and promise at least the same results. Such policies might decrease the risk of losing economic benefits resulting from new discoveries and also decrease the attractiveness of U.S. scientists looking overseas for collaborators or going to countries with more flexible stem cell policies.

Vaccines and Biologics Essay

Vaccines have eradicated deadly disease, saved millions of lives, and significantly contributed to our nation's health. For decades the U.S. vaccine market has been mired in challenges, but recent shifts in policy have revitalized the sector. New niche markets, emerging science and technology, and updated government policies for vaccines have conspired to improve conditions so that the potential for a vibrant U.S. vaccine market is within reach.

Background

Since Edward Jenner first used cowpox to protect against the deadly smallpox disease, the development of increasingly better vaccines led to today's prevention of over 20 infectious diseases through routine vaccinations. As of 2006, the Food and Drug Administration (FDA), which regulates vaccine licensing and production, had licensed 51 vaccine products for nearly two dozen infectious diseases, and many more are actively being developed around the world.[77] A vaccine is defined as a "preparation of a weakened or killed pathogen, such as a bacterium or virus, or a portion of the pathogen's structure that upon administration (injection into a human) stimulates antibody production or cellular immunity against the pathogen, but is incapable of causing severe infection."[78]

As recently as 1967, 37 separate companies produced vaccines in the U.S. In the last quarter of the 20th century, declining profitability, unfavorable pricing policies and increased regulation led to a number of manufacturers exiting the market. In 2004, only four manufacturers produced vaccines in this country, and single manufacturers produced several childhood immunizations.[79] The U.S. Centers for Disease Control (CDC) found that the limited number of manufacturers, coupled with production suspension and delays, resulted in numerous shortages of multiple vaccines in recent years. In fact, from 1998 to 2004, three-fourths of childhood vaccines were intermittently in short supply.[80]

Historically, vaccines represented only a fraction, 1.5% in 2002, of the entire pharmaceutical market.[81] Because vaccine products are administered to individuals according to recommended schedules identified by the CDC, there is no opportunity to expand the market through repeat purchasing. The FDA and other regulators erect high barriers to entry even before research and development costs are considered. Similarly, the federal government's

practice of establishing discount prices has disadvantaged manufacturers.[82] Despite these challenges, advances in biotechnology knowledge are changing the market with the application of biologics to vaccine production and the emergence of new, non-infectious disease markets for vaccines.

Future Niche Growth

The future looks bright. The first vaccine to reach $1 billion in annual sales was Prevar, a vaccine introduced in 2000 to treat a form of pneumonia. Its sales were nearly $2 billion in 2006. Last year, global sales of vaccines were expected to exceed $10 billion. With a strong pipeline, 450 vaccine products in early 2007, and developing niche markets, the stumbling vaccine market of the late 20th century appears to be headed toward a revival.[83] Emerging opportunities exist in expanding the vaccine market beyond childhood and bioterror-related infectious disease prevention. With improved government funding, a significant increase in private-public partnerships, and expanded humanitarian/philanthropic investment, vaccine development for third world diseases has greatly expanded.[84] Additionally, U.S. firms have been drawn back to the vaccine market in the hope of creating new niches for adolescent and adult products with high profit potential. Technology has enabled the development of vaccines at a rate of approximately one per year in the past 25 years-up from one every five years previously. With shorter development timelines, manufacturers are now venturing beyond treating deadly infectious diseases to creating therapeutic vaccines targeting diagnosed diseases such as chronic infections or cancers. After years of stagnant growth, vaccines are expected to grow at a rate 50% greater than the overall pharmaceutical market.[85]

Emerging Science and Technology

Many vaccines are biologics: large, complex, genetically engineered living cells (proteins) that are living matter rather than earlier pharmaceuticals which were merely chemical compounds. Because of their complexity, laboratory tests cannot substantiate that a generic follow-on biologic will perform in humans in the same manner as the original patented drug, which underwent years of clinical trials to determine its efficacy and safety. These biologics are vastly different from the chemical drug compounds developed in the 1980s and 1990s. By 2010, half of all drugs will be biologics, with over 400 biologics currently under development- a market of $67 billion.[86]

After a drug's patent expires, competing pharmaceutical companies produce generic drugs of the same quality and safety as the original patented drug. Resulting, lower cost generic biologics present an opportunity to manage drug/vaccine costs. Since the federal Government, through Medicare, Medicaid, and other social programs, is the largest buyer of pharmaceuticals, their regulation and encouragement is appealing. However, since biologics are so markedly different from chemical drugs (one biologic requires 310 discrete manufacturing steps) and the efficacy and safety of generic biologics is controversial, the FDA is at a crossroads of how to approve generic or "follow-on" biologics.

Government Policies

The FDA's actions have hampered the evolution of the specific vaccine and larger biologics' pharmaceutical industries. The vaccine market of the late 1990s was negatively impacted by the FDA's poor communications of evolving standards, and the combined effects of increased regulation, infrastructure improvement costs, and government price controls for many

vaccines drove several manufacturers from the market. More recently, while the FDA has stated that they have the capability to review and approve safe generic "follow-on" biologics, they have made conflicting statements. In discussions with the World Health Organization in the fall of 2006, the FDA stated that they (FDA) have not "determined how interchangeability can be established for complex proteins." In essence, the FDA is stating that it is not able to determine that a 'similar' biologics (a complex protein) can be determined safe for consumers.[87] Alternately, in April 2007, the FDA Commissioner stated that the FDA has the "expertise and experience" to determine the degree of clinical trials necessary to produce a safe drug.[88]

Since it is the process rather than the product that can readily be measured in biologics' development, the focus of FDA compliance is on design and validating a "well defined production process."[89] Biologics' manufacturers must apply for both a manufacturing facility and a product license. The FDA's Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA) share joint responsibility for regulating vaccines. In addition to ensuring safety and efficacy standards for each lot of a vaccine product, the CBER/ORA partnership, also known as Team Biologics, inspects manufacturing facilities as part of its establishment validation both before and after granting vaccine approval.[90] Biologics, however, present unique production issues for regulators. Since biologics are manufactured with genetically engineered DNA coded to produce a specific biological protein, not only is the genetic coding a trade secret so too is the manufacturing process. Therefore, it appears unlikely that a generic pharmaceutical firm could develop like-manufacturing-processes of the biologics' original developer.[91] Both the drug composition and the manufacturing process are intellectual property and public law must preserve intellectual property rights.

Law

Currently, there are no laws permitting the introduction to market of a generic follow-on biologic, although a few generic biologics have been approved. While the Hatch-Waxman Act authorized the manufacture and sales of generic drugs, it did not amend the Public Health Service Act which applies specifically to biological products.[92] Pharmaceutical firms argue that generic biologics may be approved by the FDA; however, current law clearly does not support this conclusion. Both the Senate and the House of Representatives have been working to craft a new law to regulate the sale of generic biologic drugs. The safety of follow-on biologics must be balanced against high drug costs. Various proposals would grant the FDA authority to approve generic biologics based on procedures to be developed by the FDA and include an "exclusivities" clause which would provide 12 years data exclusivity to a brand biologic, forbidding the introduction and sale of bio-similar products following patent expiration.[93]

The President's 2009 Budget Proposal

President Bush's 2009 Budget Request proposes to allow the FDA, in collaboration with Congress, to develop procedures for approval of generic biologics and authorizes the FDA to charge user fees to finance the additional workload. The budget proposal expects the FDA's new generic biologics review and approval procedures to support the introduction of follow-on biologics and not require extensive drug testing (i.e., clinical trials) to determine the generic biologics' safety. In an attempt to recognize the substantial investment in biologics research and development, while the budget contends that safety and drug effectiveness would be ensured in the new procedures, it also requires "adequate intellectual property protections" to support continued biologics research. Exclusive data or drug marketing rights were not specially

addressed in the budget proposal. Granting exclusive marketing rights is already an option available for the FDA for generic drugs, but it seems doubtful the FDA would use this option for follow-on biologics given the industry and political furor associated with generic biologics, absent directive language from Congress.[94]

Conclusions

Despite a late 20th century decline in the number of U.S. vaccine manufacturers, current advances in science and technology, coupled with new niche markets and more favorable policies, have reinvigorated the vaccine market. While biologics are extremely expensive considering the life cycle costs of research and development, the FDA's approval of generic biologics would reduce the cost of these drugs. The debate and pending legislation regarding follow-on biologics must balance safety concerns for new market entrants with exclusivity rights of drug developers. New law is needed, and is forthcoming, as many biologics come to the end of their patent protection. Both Congress and the Bush Administration are addressing these emerging issues. Whether a new generic biologics law will adequately protect developer's intellectual property and trade secrets, entice the bio-technology industry to continue to invest in biologics research and development, and at the same time offer less expensive drug alternatives remains to be seen.

Policy Recommendations

Biofuels

-- Transform the fuel supply by requiring oil companies to retrofit gas station pumps to dispense ethanol, increasing support for cellulosic ethanol, adjusting the ethanol subsidy as oil prices rise and fall, phasing out the ethanol import tariff for producers that meet social and environmental standards, and supporting lower prices for off-peak electricity.

-- Continue the funding of research to develop the enzymes and bacteria necessary to produce cellulosic ethanol from non-food crops and crop residue.

-- Fund ongoing research on to develop algae as a renewable source of aviation fuel in order to reduce the industry's current near total reliance on kerosene.

Agriculture

-- Establish an education plan developed in coordination with other governments and NGOs presenting the pros and cons of GE crops. The education material should be made available first to Americans and then to the world wide audience through an internet site and other forms of free media public notifications. The American public and citizens from other countries could decide to review or ignore the information individually.

-- Foods containing GE crops should be labeled to indicate the presence of GE organisms. American consumers would be able to make an informed choice. Market pressures may cause a differentiation in price between foods containing GE crops and those that do not. Additionally, the presence of a label would meet EU requirements opening new markets for the industry. After all, free markets and capitalism are the American way.

-- The agriculture biotechnology industry should press forward with continued research and development of advanced GE crops that will meet the needs of all food markets. In the future this may include increased yields, improved nutritional content or specialized needs for particular markets. As advanced GE crops are institutionalized in developing countries, local

citizens will benefit from improved nutrition and increasing yields should enhance developing economies to flourish with the enhanced productivity from GE food products.

Medical Biotechnology

-- In order to ensure that personalized medicine advances to its fullest potential, individuals must be protected against genetic discrimination by employers and insurers. The Genetic Information Nondiscrimination Act of 2008 (H.R. 493/S. 358) signed into law by President Bush on May 21, 2008 addresses this requirement. The main policy issues include defining genetic information; physically separating genetic information from other medical information; unintended disparities between "genetic" and "non-genetic" diseases; and the effect of legislation on participation in genetic research, on uptake of genetic technology and on the delivery of high quality health care.[95]

-- Longevity benefits can only be realized with focused policy actions. One such idea, called the Longevity Dividend, seeks to increase life expectancy by seven years. Proposed by Dr. Jay Olshansky, this Longevity Dividend calls for the redirection of $3B per year of the National Institute of Health (NIH) budget to combat age related decline.[96] Through the Longevity Dividend "people would remain in the labor force longer, personal income and savings would increase, age-entitlement programs would face less pressure from shifting demographics, and there is reason to believe that national economies would flourish."[97] The economic benefit from expanding health has already been demonstrated. From 1970 to 2000, the heathspan (that period of healthy activity in lifespan) increased approximately five years resulting in $3.2 trillion per year in national wealth.[98] It is clear that redirecting the current budget is the most flexible policy option available and offers the benefit of a sound financial return.

Conclusion

While the 1900s are characterized by many historians as the Information Technology Era, the 2000s may be dubbed the Biotechnology Era due to rapid advances that will completely revolutionize many aspects of life. Although the field of biotechnology has achieved notable breakthroughs in the past few decades, the industry can trace its birth back to the beginning of civilization when men discovered the ability to ferment grains to make alcoholic beverages and learned of the usefulness of cross-pollinating crops in order to create new hybrid strains—the earliest form of genetic engineering.[99]

Today the industry is a vibrant, vital contributor to the U.S. and world economy. According to U.S. Government estimates, prescription drug purchases in the U.S. grew from $40 billion in 1970 to approximately $229 billion during 2007, about $760 per capita. Government estimates project American drug purchases reaching $497 billion by 2016, primarily due to a rapidly aging U.S. population, inflation and the continued introduction of expensive new drugs. Biotech-related drugs accounted for perhaps $44 billion or 20 percent of the U.S. market in 2007. Generic drugs have grown from 33 percent of total U.S. drug expenditures in 1990 to 58 percent in 2007.[100] Agricultural biotechnology has revolutionized farming, boosting production of food crops and enhancing nutritional qualities. BT cotton has been enormously successful in the United States and India, significantly reducing water, pesticide, and fertilizer requirements while greatly increasing crop yields. Although currently surrounded by controversy, most of it unscientifically based and without merit, genetically engineered food crops represent significant promise to meeting the world's rapidly growing food needs. Spurred by soaring gasoline prices

and effective lobbying by agricultural and industrial interests, the Bush administration has placed renewed emphasis on reducing reliance on imported oil through increased production of bio-fuels, primarily ethanol. Currently, corn is the near-exclusive source of ethanol in America. This represents an unprecedented shift of a crop from its use in the food chain to use in the energy chain, and combined with rapidly rising petroleum prices, has resulted resulting in increased prices for consumers, livestock growers, and food processors. In reaction, governments and business are increasingly funding research by biotechnology firms worldwide to develop the genetically engineered bacteria and "super-enzymes" necessary to facilitate the conversion of agricultural waste and non-food crops into cellulosic ethanol and bio-diesel fuels.

As an industry, biotechnology requires large numbers of innovative scientists and technicians to "push the envelope" in research and development; numbers that are not being produced either in the United States or worldwide. This unfortunate trend must be reversed if the advances achieved in recent years are to be maintained. Coupled with the persistent shortage of qualified personnel, another significant challenge is the length of time and enormous costs involved in developing a new drug and getting it to market. According to a study released by the Tufts Center for the Study of Drug Development, these costs averaged $802 million in 2001, up from about $500 million in 1996.[101] Expanding on the study to include post-approval research (Phase IV clinical studies), Tufts subsequently estimated the average cost to develop a new biologic at $1.2 billion in 2006. The typical time elapsed from the synthesis of a new chemical compound to its introduction to the market remains 12 to 20 years. As a result of these costs and the lengthy time-to-market, emerging biotech companies encounter a harsh financial reality that commercial profits take many years to emerge from promising beginnings in the laboratory.[102]

All of these challenges must be met and overcome if the industry is to continue to grow and realize its full potential. Scientific discovery and breakthroughs offer unprecedented opportunities to increase mankind's quality of life by reducing greenhouse gas emissions, increasing access to food, improving resistance to disease, and developing personalized medicine. The question is not if this will occur, but when and how to ensure that it takes place in an ethical, reasonable manner that benefits America and the rest of the world.

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