Industrial College of the Armed Forces
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Biotechnology

Abstract

The biotechnology industry is critically important to the development of products that will improve health care, agriculture, industrial processes, environmental remediation and biological defense. Biotechnology has been responsible for medical breakthroughs benefiting millions of people worldwide through the development of vaccines, antibiotics, and other drugs, and to new varieties of pest-resistant crops. Biotechnology will continue to contribute to homeland defense and national security by providing tools needed to develop a new generation of vaccines, therapeutics, and diagnostics for defense against bioterrorism. Biotechnology contributes to the success of the United States as a global leader in research and development and international commerce and will be an important catalyst for creating more high-skilled jobs throughout the 21st century.[1]

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Introduction

The tremendous potential of the biotechnology industry to improve the quality of life met the harsh realities of a recession and a declining U.S. stock market over the past year. Significant events in the industry over the past year include: the emergence of bioterror defense to our national security; the arrival of fiscal constraints confronting biotech companies with rising research costs and competition for scarce venture capital; and the resurgence of ethical questions over cloning on the public agenda. The biotech industry has the potential to revolutionize life as we know it, but it brings ethical questions that may change the course of the industry's growth. Legislative debates in the Congress are in progress over the limits of acceptable biomedical research.

This paper will examine the biotechnology industry with emphasis on the changing conditions the industry is facing. The strong potential of biotechnology to change fundamentally health care and agriculture and to grow and profit as an industry depends on the fulfillment of its scientific promise. For the industry to continue to enjoy public and investor support, it must continue to innovate and translate "promise" into "products." Government must support basic research and foster the right market conditions to allow biotechnology to achieve its potential.

Industry Defined

Biotechnology – both as a scientific art and commercial entity – is less than 30 years old. But what is biotechnology? No consensus exists on its definition nor is there agreement that it can truly be called an industry. According to the United States Office of Technology Assessment, biotechnology is "any technique that uses a living organism, or parts of organisms, to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses."[2]

Biotechnology is clearly an interdisciplinary "industry" that includes medicine, biology, chemistry, basic sciences, information technology, and engineering. Another perspective is that biotechnology is not an industry but a field of science, similar to physics, which merges many scientific disciplines that will produce knowledge and will in turn support the development of many different industries. It is a set of techniques developed through decades of basic research that are now being focused on applied research and product development to produce new, improved, safer, and more effective products and processes.

Biotechnology began soon after humans changed from hunting and gathering as a way of life to an agrarian lifestyle. The human desire to produce plants and animals that had superior characteristics led to selective breeding. Some produced a greater yield; some were better tasting, while others were more resistant to adverse environmental conditions. By selecting seeds from these desirable plants, early farmers were able to produce more high

quality food. Similar practices led to the development of many breeds of domesticated animals.

Early examples of biotechnology involved manipulating entire organisms. Today it is possible to manipulate organisms at the molecular level. During the 1960s and ’70s scientists came to understand the smallest parts of organisms – their cells and molecules – in addition to using whole organisms. The biological molecules most often manipulated are nucleic acids, such as DNA (deoxyribonucleic acid), and their constituent proteins. Our concept of the gene has changed from that of particles or "unit characters" to that of segments of the DNA molecule, composed of unique chains of proteins.

A modern definition of biotechnology is the application of technologies, such as recombinant DNA techniques, biochemistry, molecular and cell biology, genetics and genetic engineering, and cell fusion techniques using living organisms or their products to manufacture industrial products including antibiotics, insulin, and interferon to improve plants or animals, to develop microorganisms for specific uses, to identify targets for pharmaceutical development, to transform biological systems into useful processes and products or to develop organisms for specific uses. In the modern definition, the focus of biotechnology is not the principle of using organisms to do things but the techniques for doing so, such as DNA sequencing, cloning genes, plants and animals.

Biotechnology: A Collection of Technologies

Biotechnology is a collection of technologies using cells and biological molecules. The following technologies are commonly included as parts of the biotechnology "industry":[3]

Fermentation: Early humans realized that the by-products from the breakdown of glucose in microbes (bacteria and yeast) could be used in a number of processes. The baking industry still uses yeast as a leavening agent. Yeast also produces alcohol during the production of wine and beer. Bacteria produce lactic acid for making yogurt and acetic acid for making vinegar. New fermentation processes are being used to produce a wide variety of products including antibiotics, hormones, and enzymes.

Genetic Modification or recombinant DNA technology: Genetic modification technology is often referred to as recombinant DNA technology. In genetic modification, single genes whose functions are known are moved from one organism to another using recombinant DNA technology. Techniques used in recombinant DNA include gene isolation and amplification, site-directed mutagenesis, viral infection and plasmid construction. Currently, genetic modifications are used to produce high-yield and disease- and pest-resistant varieties of crops and new and safer vaccines and drugs.

Genetic Engineering Technology: The integration of genetic material from two different organisms or genetic recombination occurs naturally as part of reproduction. When humans started selective breeding, they manipulated the genetic material of parents to produce superior offspring in an effort to produce more desirable species. This practice was previously restricted to closely related species. Today, a single gene with a known function can be removed from one organism and transferred to a totally different organism. This

introduces new genetic instructions that cause the cells to produce needed chemicals, carry out useful processes, or give the organism some new desired characteristics.

Protein Engineering Technology: Genetic modifications are used to improve existing proteins, usually enzymes, to provide proteins lacking in individuals because of genetic defects, and to create proteins not found in nature. These new and improved proteins can encourage the development of ecologically sustainable industrial processes because they are renewable and biodegradable resources. The chemical, textiles, pharmaceutical, pulp and paper, food and feed, metal and minerals and energy industries have all benefited from cleaner, more energy-efficient production made possible by incorporating biocatalysts into their production processes.

Antisense Technology: Antisense technology is the process of creating synthetic segments of DNA or RNA, called oligonucleotides.[4] Antisense molecules are designed to interact with mRNA before it can be translated into the amino acids which make up proteins. In this way, disease-associated proteins can be prevented from even forming. These molecules are called antisense because they are the opposite of the "sense" of the original RNA or DNA. Therapeutic intervention using antisense compounds is visualized as an approach to treat diseases whose causative agents or targets have been characterized at the DNA level. Antisense technoloy has potential for protein function analysis as well as for validation of therapeutic drug targets. Areas of applications include control of viral diseases, inhibition of inflammation and other diseases, slowing of food spoilage etc.

Monoclonal Antibody Technology: One type of cell in the immune system produces proteins called antibodies. Antibodies exhibit specificity that makes them powerful tools for locating substances that occur in minuscule amounts and measuring them with great accuracy. A monoclonal antibody is a type of antibody produced from a single cell. All antibodies produced by a given cell are identical and bind to the same specific target in the same way. Monoclonal antibody technology uses the specificity of antibodies in a variety of ways, including treating various diseases and detecting the presence of drugs, bacteria, viruses, abnormal cells, food contaminants and environmental pollutants.

Biosensor Technology: Biosensor technology couples biological method with microelectronics. A biosensor is composed of a biological component, such as a cell or antibody, linked to a tiny transducer. Biosensors are detecting devices that rely on the specificity of cells and molecules to identify and measure substances at extremely low concentrations. When the substance of interest collides with the biological component, the transducer produces a digital electronic signal proportional to the concentration of the substance. Biosensors can be used to measure many blood components, safety of food and level of environmental pollutants.

Nanotechnology: Nanoscience centers on the study of physical, electromagnetic, and biological principles, systems, or occurrences at the nanometer (10^{-9}) scale to develop applications in a range of microscopic venues. A full-fledged technological discipline is still a few years away, given that much of what is being worked on in this field is still in basic

research. Nanotechnology will likely affect vast sectors of the economy, from biotechnology and health care to electronics and energy.

Bioremediation: Bioremediation is the treatment of soil or water to enhance the microbial degradation of contaminants. Composting is a traditional type of bioremediation where organic agents are added to promote biodegradation and reduce contaminants. It is one of the oldest examples of environmental biotechnology. Modern environmental biotechnology makes use of microorganisms and enzymes to clean up oil spills and toxic waste sites, and to purify sewage.

Bioinformatics: Bioinformatics joins information technology and biotechnology. It encompasses the study of information itself, including integrated hardware, software, and network systems; experimental design; and parallel, high-throughput data capture and analysis. The intent is to use computers to store, organize, link, retrieve, analyze, share and visualize complex and enormous sets of genomic, chemical, and biological data and convert it into meaningful knowledge.

Current Condition

The following chart provides a financial and structural summary of the biotechnology industry from 1995 through 2001. The biotechnology industry doubled in size between 1993 and 1999.[3] After receiving a steady flow of investment capital throughout the second half of the 1990's, the industry absorbed a $32.7 billion[4] infusion in 2000, which exceeded the previous five years combined. This constituted approximately 86% of the total industry financing ($38.0 billion) for 2000. This chart also shows the substantial cumulative and annual growth rates for four of the key indicators. The approximately 30% increase in the number of publicly traded firms over the six-year period should be noted.

Year	**2001**	**2000**	**1999**	**1998**	**1997**	**1996**	**1995**
Sales*	$18.1	$16.1	$14.5	$13	$10.8	$9.3	$7.7
Revenues*	$25	$22.3	$20.2	$17.4	$14.6	$12.7	$11.2
R&D Expense*	$13.8	$10.7	$10.6	$9	$7.9	$7.7	$7
Net Loss*	$5.8	$5.6	$4.4	$4.1	$4.5	$4.6	$4.1
Market Capitalization*	$330.8	$353.5	$137.9	$93	$83	$52	$41
Number of Public Companies	339	300	316	317	294	260	265
Number of Companies	1,379	1,273	1,311	1,274	1,287	1,308	1,311
Employees	174,000	162,000	155,000	141,000	118,000	108,000	103,000

Table 1: Biotechnology Industry Statistics * = billions of U.S. dollars
Source: http://www.bio.org

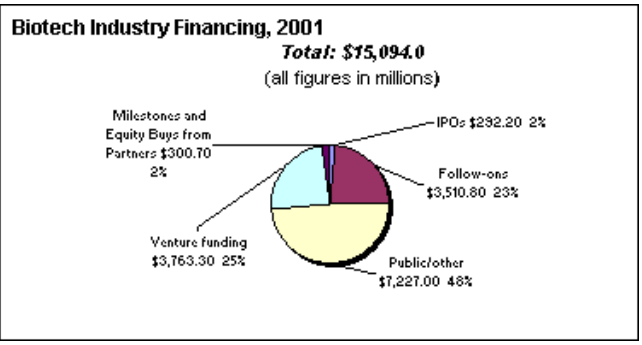


Figure 1:Biotech Industry Financing
Source: BioWorld Financial Watch
Public/other is defined as financing of public companies, including loans, bridge financings, exercises of warrants, etc.

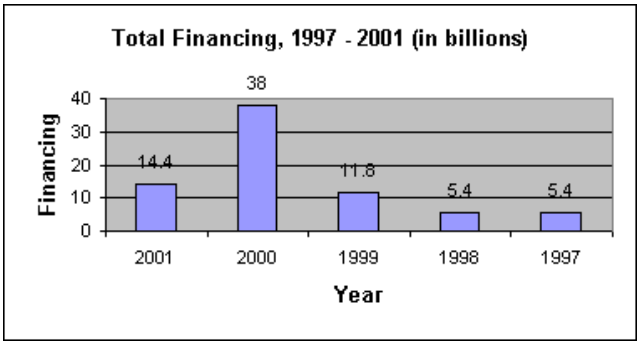


Figure 2: Venture Capital Invested in Biotech
Source: BioWorld Financial Watch

Importance of Drug Discovery to Biotech Industry

Resource allocation decisions in the biotech and pharmaceutical industries strive to achieve "speed to market" for new drug discoveries. The success of a biotech drug company depends on its ability to translate basic scientific research into drugs that can be manufactured and sold at sufficient margin to recoup the enormous investments in this high-risk endeavor. Government policies can help speed the process of Food and Drug Administration (FDA) approval for biotech drugs, and thereby help harness the great promise of biotechnology to improve the quality of human life. The following graph shows why it takes from 10-15 years to get a new biotech drug discovery to market:

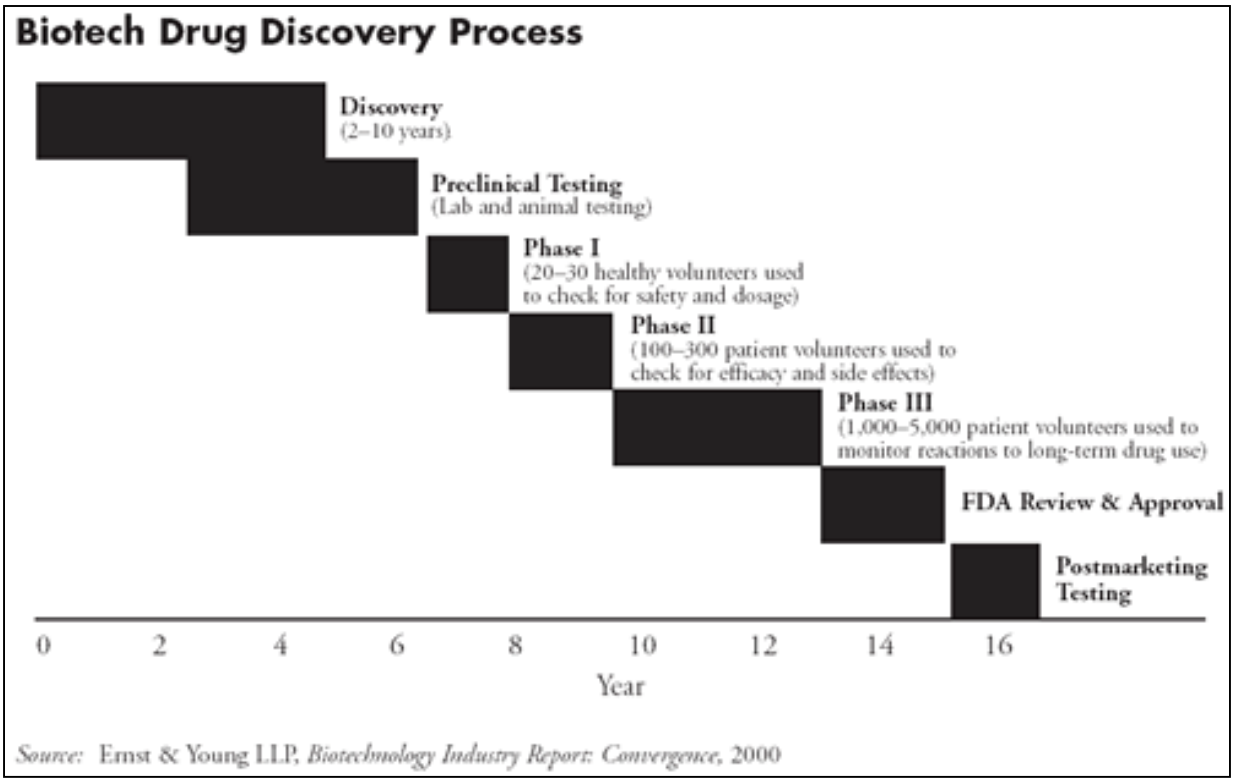


Figure 3: Biotech Drug Discovery Process

"[The biotech industry] is a lot like the entertainment business," says Kevin Sharer, CEO of Amgen, a large biotech firm. "Very few products turn out to be blockbusters, and you have to maximize the performance of the ones that do in order to be able to afford the high-risk investments needed to create new ones."[5]

The U.S. Patent and Trademark Office (PTO) awards patents for the protection of inventions.[6] Patents give the owner the right to exclude others from producing the protected invention for twenty years from the date of application – essentially, a legal monopoly to encourage innovation.[7] A patent does not, however, provide the right to produce, or market products, nor does it require an inventor to bring the product to market.[8]The 1994 Uruguay Round Agreements Act, which implemented the agreements creating the World Trade Organization, provided the basis of extending U.S. patents from 17 to 20 years in 1994.[9] The lengthy product development pipeline timeline eats up much of the current patent term, thus reducing the timeframe available to recover R&D expenses.

The federal agencies primarily responsible for regulating biotechnology in the United States are the United States Department of Agriculture (USDA), Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). Specific divisions and offices within each agency provide oversight and have legal authority to determine safety standards and approve conditions for marketing of products manufactured using biotech-patented organisms. Products are regulated according to their intended use, with some products being regulated by more than one agency.[10] For example, the development of a food crop resistant to a particular virus would require safety review by large number of government agencies. The USDA would review the safety of the plant for cultivation; the EPA would review for environmental safety: and the FDA would review whether it is safe for people to eat. Before commercialization, genetically engineered plants and organisms must conform with standards set by state and federal marketing statutes such as state seed certification laws, the federal Food, Drug, and Cosmetic Act (FFDCA), the federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), and the federal Plant Pest Act.[11]

Since patent protection extends for only twenty years from the date a company applies – before even submitting a drug for FDA approval -- delays in obtaining that approval can reduce potential profits for a biotech company. The following graph provides the history of biotech drugs receiving FDA approval since 1982. Industry-wide biotech companies are demanding quicker drug approvals from the FDA. In 2001, the time it took the FDA to review biotech drugs increased by 40%![12]

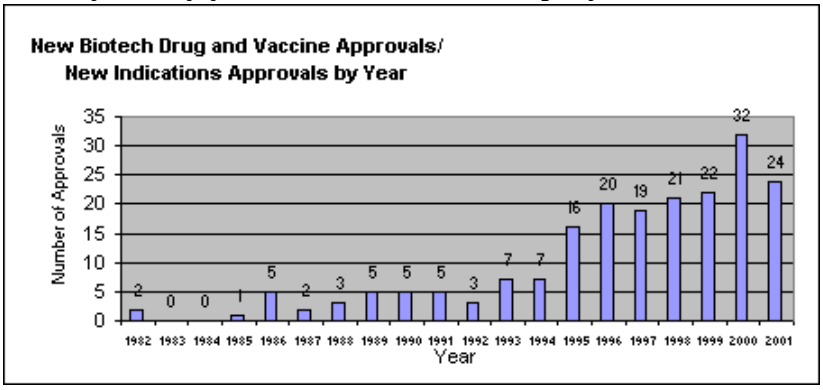


Figure 4: FDA New Biotech Drug Approvals since 1982

The biotech industry wants the renewal of Prescription Drug User Fee Act (PDUFA) to achieve the needed throughput in FDA drug approvals. This law imposes a fee on applicants for FDA approval of new drugs; total revenue from the fees received is sufficient to hire several thousand FDA employees. With over 350 drugs in late-stage clinical trials, there is a concern in the biotech industry that the FDA will not be able to keep pace.

Manufacturing Biotech Drugs

"While there have been big advances in biotech discovery technologies, there has not been a corresponding increase in [manufacturing] development capacity," says Peter B. Davis, chief financial officer of Berkeley (Calif.) biotech firm Xoma Ltd. "Now, the worry is less whether [the industry] can find a molecule than what to do with the molecule it finds."[13] Hence, the biotech industry's Catch-22: The more successful the product, the worse the production bottleneck.

Biotech drugs are far more complex, built from fragile molecules meant to mimic natural disease-fighting proteins found in the body. Because these protein-based drugs are too big to be absorbed through the stomach, they must be injected directly into the bloodstream, not swallowed as pills. That's unfortunate, because pills, which are chemical entities, are pretty straightforward. “If you can make one, you can make millions just like it without much worry. Biologics are made from living cells or bacteria, and are inherently harder to control. What we [in the biotech industry] need to do,” observes Kevin Sharer, Amgen CEO, “is transition from a company that has had products in relatively uncompetitive markets to one that must be a fully effective commercial competitor. That’s a tremendous challenge. The future [for biotech companies] looks very promising. But you have to deliver.”[14] To sustain success in the long term, the U.S. biotech industry will have to deploy capital assets for cutting-edge computational and diagnostic tools to interpret gene and protein data and move products through clinical trials. Companies also need to expand research and development capabilities and collaborate to stay on the cutting edge.

Relationship of Academia and Biotech industry

Biotechnology is one of the most research-intensive industries in the world by a two to one margin (R&D to sales ratio) over the next closest industry – electronics.[15] Basic research is crucial to advancements in biotechnology, and the university-industry model in the U.S. is the envy of Europe and Japan.[16] Universities contribute to the biotechnology industry in several ways: 85% of all industry research was done with at least half or greater collaboration with universities[17]; universities and advanced public research institutes employ twice as many PhDs and post-doctoral students as private for-profit industry does;[18] and the Bayh-Dole Act (1980) provides monetary incentives for universities and their professors to market products that were developed with federal grants.[19] Examples of the tremendous synergy with which industry and academia collaborate and support each other can be found in Research Triangle Park, North Carolina, Cambridge, Massachusetts and La Jolla, California.

US and European Industry Trends

Unlike the U.S., biotechnology in Europe developed in the 1980's primarily with large companies. While biotechnology grew faster (as a percentage) in Europe than in the U.S. from 1997 through 2001, and the number of dedicated biotech firms in Europe surpassed the U.S. in 2000 (1300 to 1275), the U.S. retains a sizeable advantage over Europe. For example, U.S. biotech industry exceeds its European counterpart in revenue (3.3:1) and employment (3:1). An average U.S. firm in 2001 had 127 employees and took in $18.2 million in revenue, while a European firm had 39 employees and took in $4.8 million in revenue.[20] The dominance of the U.S. in biotechnology can be expected to continue.[21]

Changes to the Biotech Industry in 2001-2002

Five major trends and events characterized the biotechnology industry in 2001-2002. The first, and most obvious, was that following the attacks of September 11 and the October anthrax scares, biotechnology – specifically, defense against bioterrorism – became a central element of national policy in the United States. The response to these attacks has not been considered thoroughly, and when it is, the sudden infusion of federal funds is likely to reorder the priorities of a financially fragile industry.

The biotechnology industry is willing and eager to support the nation in providing its expertise in the fight against bioterrorism. The Biotechnology Industry Organization (BIO – an association representing more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 states and 33 nations) has publicly stated its strong support for the use of biotechnology to promote the research, development, and commercialization of products and services to detect, diagnose, protect, and treat people against harmful biological agents.[22]

The first case of anthrax was reported in Florida on October 4; the next six weeks brought 18 more confirmed cases and five suspected cases in Florida, New York, New Jersey, Connecticut and the District of Columbia. Five people died of anthrax. Letters mailed to prominent legislators closed Senate office buildings for months; cleanup of those buildings and the postal facilities where the letters were processed cost continues to grow.

On November 21, the CDC released its six-part *Interim Smallpox Response Plan and Guidelines*, adapted from a 1972 plan. While the Interim Plan is tailored towards smallpox, its guidance could be readily tailored to respond to other pathogens. The plan noted the importance of communication between federal government officials and local healthcare professionals, and the flow of pertinent information to the public. Critical to this discussion is the fact that half of the 3,000 local public health departments in America are not even connected to the Internet. Most are not staffed at night or on weekends when critical reports of epidemics might begin.[23]

The Administration and Congress responded to the anthrax attacks by substantially increasing the budgets of agencies with biotechnology expertise. The President submitted a supplemental budget request to the Congress that included, for example, an additional $1.7

billion for the National Institutes of Health for research into bioterror pathogens and responses to them. Even more strikingly, on January 2, 2002, the President signed a supplemental appropriation containing an additional $2.1 billion for the Centers for Disease Control. The tremendous increase in funding dedicated to bioterror defense highlights the new importance of biotechnology to national defense; however, it remains to be seen if these funds will be spent effectively. The absence of a national strategy for bioterror defense may hinder the allocation of these newly appropriated funds.

Second, 2001-2002 saw the commercial elements of the industry face significant new challenges, including a national economic recession. Amgen and Genentech became big enough and financially stable enough to begin to challenge "big Pharma" – the established traditional pharmaceutical firms – for investment funds and market share for new drugs. Other large firms, however, suffered setbacks as new drugs failed to pass thorough clinical trials.[24] Investors are beginning to doubt the ability of genomics to deliver breakthrough drugs in the near term. The financial picture of the industry is decidedly mixed: one industry analyst suggests that while the pharmaceutical industry as a whole will grow seven to eight percent over the next five years, biotech will likely grow by as much as 15 percent a year. However, declining investor confidence in the biotech industry brought down stock prices and market capitalization by more than 40 percent in the first few months of 2002. Investment in the industry in the U.S. dropped from the record $33 billion in 2000 to an estimated $12 billion in 2001, according to a report prepared for BIO, the industry's trade organization, by the accounting firm Ernst & Young. We can expect to see more mergers of stronger companies and bankruptcies of weaker ones over the next year as the industry continues to work through its first major shakeout. Others may survive as the basic research arm of the pharmaceutical industry, isolating the proteins (which are components of genes) associated with specific diseases, then patenting them and licensing them to the established firms that will develop the medicines to block the pathogenic activity of those proteins.

Third, the industry is beginning to shift its focus from research to product development. Celera, one of the private-sector leaders in the human genome research project, shifted direction from being a genetic research company to being a pharmaceutical development company. Other biotech companies over the next 12 to 18 months could launch 10 products with potential annual sales of $500 million to $1 billion each. The agricultural side of the industry continued to expand in 2001, with an estimated 125 million acres planted in genetically enhanced crops worldwide.[25] The vast majority of this growth in Genetically Modified Organism (GMO) crop production, however, is in the United States and Canada. Europe and the major South American agricultural producers, as well as Japan, continue to resist genetically enhanced crops, and are very reluctant to accept even their imports for use as animal feed. The current round of World Trade Organization negotiations will address the differences in positions, but widespread acceptance in Europe and Japan probably is years away.

Fourth, the research elements of the industry continue to demonstrate that it has the potential to change our lives in ways we are only beginning to appreciate. Researchers now understand that cancers begin as the mutation of a single gene; exploring the paths of the onward development of cancers has the potential to enable us to end this disease. The

sequencing of the human genome, completed in broad outline in 2000, is nearing completion in detail. Perhaps equally important, scientists are working on the genetic sequences of hundreds of other organisms, ranging from single-cell pathogens to large mammals. The rice genome was just completed in April 2002. The uses to which this work can be put are scarcely known yet, but the possibilities are exciting. For example, a gene known to control a particular function or characteristic in one organism may appear in another, suggesting similar ways of controlling widely different pathogens or of controlling single-gene diseases.

Finally, the continued expansion of research frontiers has refocused attention on the ethical and social policy issues inherent in genetic biotechnology. In the summer of 2001, the United States had a serious national debate about the use of human embryonic "stem cells" in research. These cells, which form the core of a human embryo in early stages of development (16 cells), later differentiate into all the types of cells in the body. Cell biologists can manipulate the stem cells to produce a number of cell types useful in studying a variety of genetic diseases, but this results in the destruction of human embryos. Religious and social conservatives argue that this destruction of human embryos is immoral and should not be allowed in federally funded research. More liberal views argue that the vast majority of embryos will be destroyed eventually, and that failure to use the cells to help advance medical science is as unethical as destroying the embryos.

Several members of Congress called for legislation banning all use of stem cells in research. On August 9, 2001, President Bush forestalled Congressional action by announcing an Administration policy that restricts federal funding to projects using cells from five dozen "lines" – cells cloned from original embryos – already in existence for scientific use. Federal funds cannot be used in any research using other stem cells, but the President did not seek any limitation on privately funded research. The President also appointed an advisory Council on Bioethics, chaired by Professor Leon M. Kass of the University of Chicago and the American Enterprise Institute. The Council has met approximately monthly in 2002 and has produced a series of seven working papers. Social and religious conservatives applauded the conservative composition of the Council, while researchers and liberals cautioned that the Administration's policy would not slow research using stem cells, and could lead to "defections" of prominent U.S. researchers moving overseas to work in policy environments more conducive to such work.

Two more events focused attention on the ethical and social policy implications of biotechnology. On January 4, 2002, Professor Ian Wilmut of the Roslin Institute outside Edinburgh announced that Dolly, the sheep cloned in 1996, had prematurely developed arthritis in her left hind leg, at age 5½ years. Though Dr. Wilmut emphasized that there was no demonstrated linkage between Dolly's cloned origin and the disease, animal rights activists and cautious scientists stressed that the announcement showed the continued risks of cloning. Then on February 15, researchers at Texas A&M University announced that they had cloned a cat – the only one of 87 cloned embryos implanted in eight female cats to survive. The announcement was the result of ancillary research of the "Missyplicity Project," a privately financed effort by "Genetic Savings and Clone," a fund created by John Sperling seeking to clone his pet dog. The announcement led to widespread public questions

on the propriety of cloning of animals just to satisfy human emotions when there are millions of unwanted cats and dogs in the world.[26]

The future of the biotechnology industry is more difficult to predict than that of most industries. It is, of course, subject to the same economic forces. In addition, it has the research and regulatory uncertainties of the pharmaceutical industry. Uniquely, it brings a host of ethical and social policy issues that mean continuous public debate; its future will be significantly determined in the voting booth as well as in the marketplace.

Challenges

The biotech industry faces a diverse spectrum of challenges. There are legal, diplomatic, investments, ethical, and privacy issues, and concerns about GMOs, fairness in medical practice, transfer of technology to terrorism, and public confidence. Of these, we believe economic, bioterror, educational, and ethical challenges to be the most significant.

Economic Challenges

Clinical Trials

One of the most pressing economic challenges in the industry is the need to improve clinical trial processes. The costs of bringing a new drug to market, which can be as much as $800 million, could be cut dramatically.[27] Scientists believe they can predict the effects of drugs before they are tested on humans by using genomics and in silico tools, allowing biotech companies to save money and time by withdrawing failures at an earlier stage.[28] By screening patients early in the clinical trials, and selectively defining the pool of patients for clinical testing, biotech companies will be better able to conduct testing of patients before entering clinical trials.

FDA Approval Process

The industry's economic growth hinges on its ability to navigate the maze of the FDA approval process. The FDA approval process is extremely costly and involves great risk for biotech companies. FDA approval requires proof of a drug's safety and efficacy and certification of the manufacturing processes used. The resources dedicated to the FDA approval process (human capital, financial capital, and time) by biotech companies have increased in recent years, to the detriment of the industry. The longer it takes for a new drug to hit the market, the greater the cost to the firm. Additionally, increased approval time reduces the patent protection period in which a company can recoup its investment.

The FDA admits that it needs to improve communications with biotech companies during the clinical trials design process and that it needs more staff to meet the needs to review the more than 350 drugs currently in process. The use of independent scientific and medical consultants can help improve speed and increase confidence in the FDA approval process, as can increase staff through use of PDUFA revenues. The future of the biotech industry will depend on the ability of the FDA to continue the enforcement of high safety standards while seeking to find ways to speed the drug approval process.

PDUFA requires biotech and pharmaceutical companies to pay the fees to help speed the review of new drug applications and biologics licensing applications. The companies also pay annual fees to the FDA for ongoing safety certification for the drug manufacturing process.[29] Some are concerned that requiring biotech companies to pay fees for speedy FDA approval may create a conflict of interest. Any compromise (real or perceived), in the FDA's independence or integrity in the drug safety approval process could undermine public confidence in the biotech industry. They hold that the perception of PDUFA compromises the integrity and independence of the FDA drug review process. Others, however, cite that application review periods shrank without any degradation in the approval process or the credibility of the process.[30] The President's budget request for the FDA for fiscal year 2003 totals $1.7 billion which includes $272 million in anticipated user fees collected under PDUFA.[31] In May 2002, the Senate passed the continuation of PDUFA, thereby making the future of drug approval environment more predictable for biotech companies.

Genetically Modified Organisms (GMO) Issues

FDA processes extend into the approval process for Genetically Modified Organisms (which the U.S. tends to call "genetically enhanced organisms."). The FDA's Center For Food Safety and Applied Nutrition (CFSAN) regulates foods and livestock feed derived from new plant varieties, including GMOs, under the authority of the 1938 Federal Food, Drug, and Cosmetic Act as amended by the FDA Modernization Act of 1997.[32] There are two categories of drugs the FDA regulates, traditional "synthetic pharmaceuticals," and "biologic pharmaceuticals." The FDA's Center for Drug Evaluation and Research (CDER) regulates synthetic pharmaceuticals under the Federal Food, Drug, and Cosmetic Act. The Center for Biologics Evaluation and Research (CBER) regulates biotechnology products under the 1944 Public Health Services Act.[33]

The major FDA mission for food is to protect its safety and wholesomeness by testing GMOs to see if any substances, such as pesticide residues, are present in unacceptable amounts. If contaminants are identified then FDA requires the producer to take corrective action. FDA also sets labeling standards to help consumers know what is in the foods they buy and regulating the development of new drugs.[34] The FDA provides current Good Manufacturing Practice requirements and Quality System Regulation Information, on the FDA Internet site, for all research it regulates.[35] It also provides ISO 9000 training programs for researchers seeking approval from international medicinal health agencies within the pharmaceutical, biotech, and medical device industries.[36] Meeting these standards streamlines the approval process, yet ensures highest compliance with standards.

GMO plays an important role in U.S. international trade. The globalization of agriculture means that agreement on the approach to use in evaluating agricultural biotechnology cannot be done entirely on a bilateral basis. The issues involved are eminently negotiable, given political will and willingness. The new round of World Trade Organization negotiations is the logical forum to address international acceptance for genetically modified crops.

Ethical Concerns in the Biotech Industry

The capability to manipulate living matter poses new demands on society as well as on the biotechnology industry, as scientists develop the ability to manipulate cells for better or ill. Though scientists may provide justification for proceeding on research paths, the ultimate responsibility for determining what is acceptable rests with society and its government. The direct and unforeseen consequences of many biotech issues do not lend themselves to simple answers. Many research strategies, such as use of embryonic stem cells for medical research, promise the benefit of potential cures for diseases, but must be tempered by our realization that these cells are living matter and may constitute human life itself.

Perhaps the most important and intense current policy debate about the use of stem cells concerns centers on whether embryos constitute human life at this early stage of development. Few dispute that they are living matter, and that they contain all the genetic information available to constitute life for the 'potential' being, but is the embryo at this stage a human being? The resolution of this issue, like many pending questions in biotechnology, should not merely to be left to the judgment of the scientific community. The United States, the United Kingdom and the European Union, have established commissions composed of scientists, theologians, and academics to advise governments on bioethics policy directions. We possibly have the power to do great good. The means we use are critical – governments must decide.

Other Ethical Concerns

Advances in biotechnology raises other ethical and legal questions as scientists improve mapping of the human genome, it will become possible to gain significant genetic information on individuals. Such data will be extraordinarily useful for diagnostics, treatments, and counseling, but could also lead to an erosion of privacy. Similarly, tissue research will probably have a huge payoff in new treatments and diagnoses, but could erode privacy. Virtually all tissue samples are coded to identify donors, with information on their medical history. Employers, insurance companies, and law enforcement agencies have already obtained genetic information without consent, violating perceived privacy rights and resulting in lost jobs or insurance coverage.[37]

President Clinton's National Bioethics Advisory Commission said in 1999 that current federal regulations on human research "are inadequate to ensure the ethical use of human biological materials in research." Even the new Administration's regulations apply only to federally financed research. They do not cover privately financed research at universities or biotech or pharmaceutical companies. [38]

The demand for tissue is so great that its use in research has grown enormously, even though the ethical and privacy issues remain unresolved. The commission estimated the nation's tissue collections held 282 million samples and that the total was growing by 20 million per year. No one knows exactly how big the market is, but many tissue banks report they are making tens of thousands of samples available to research every year, so the total number of samples used is likely to be in the millions.[39] Therefore, we have need for

regulation of individual information, protecting people in a changing environment. We propose that Congress act with counsel from the bioethics commission to put safeguards in effect to resolve the potential for abuse.

Education –The Engine of Industry Growth

There are two major concerns over current university-industry partnerships and the support education provides the industry. First, the Bayh-Dole Act provides incentives for universities to conduct research on projects with commercial implications; second, the U.S. is not providing enough American citizens to fill doctorate/post-doctorate jobs in the industry, though few institutions see recruiting staff internationally as a problem or disadvantage. Government funding of basic research must be an integral part of our National Security Strategy, and funding university research leverages collaborative relationships with industry.

The Hart-Rudman commission's *Road Map for National Security* articulates the concern over our need to better educate American students in science and technology. U.S. education maintains pace with other nations through the fourth grade, then drops off notably at the 8th through 12th grade levels, particularly in math and science. While the U.S. university system is seen as best in the world, 37% of the doctorates in natural sciences, 50% of the doctorates in mathematics and computer science, and 53% of the doctorates in engineering at U.S. universities are awarded to non-U.S. citizens.[40] We are not attracting students into these disciplines because not enough are intellectually prepared when they enter college, and because they do not see the right incentives to draw them to the industry when they graduate.

Incentives for those to participate in science and technology disciplines need to be a collaborative effort that includes public-private partnerships and community partnerships, as well as strong support from parents. Since many of the incentives for science and technology have moved from the public sector to the private sector, industry needs to play a larger role in supporting education.[41] Furthermore, effective public policy can help influence and provide incentives through scholarships and programs supported by the National Science Foundation. Combined incentives and increased focus on the effectiveness of education is critical to the future of biotechnology.

Defending Against Biological Terrorism

"Disease has long been the deadliest enemy of mankind. Infectious diseases make no distinctions among people and recognize no borders. We have fought the causes and consequences of disease throughout history and must continue to do so with every available means. All civilized nations reject as intolerable the use of disease and biological weapons as instruments of war and terror." [42]

President George W. Bush
November 1, 2001

An effective bioterror defense system requires a long-term strategy and significant new investment in the U.S. healthcare system. The President is taking steps now that will significantly improve the nation's ability to protect its citizens against the threat of bioterrorism. President Bush submitted an FY 02 supplemental request for $1.2 billion, and the President's budget for 2003 proposes $5.9 billion for defense against biological terrorism,

an increase of $4.5 billion – 319 percent – from the 2002 level.[43] This new funding will focus on:

1. Infrastructure. Strengthen the state and local health systems by enhancing medical communications and disease surveillance capabilities. This will reduce our vulnerabilities to respond to bioterrorism as well as other emergencies

2. Response. Improve specialized Federal capabilities to coordinate response with state and local governments, and private capabilities in the event of a bioterrorist incident and build up the National Pharmaceutical Stockpile.

3. Science. Meet the medical needs of our bioterrorism response plans by developing specific new vaccines, medicines, and diagnostic tests through an aggressive research and development program.

Before September 11, the National Institutes of Health (NIH) had a budget of only $50 million a year on anti-bioterrorism planning and research. After the attacks, the FY 03 budget sent to Congress increased NIH funding to more than $1.7 billion a year.[44] The following graph depicts the increase in funding for Homeland Security. Even with this tremendous increase in government investment, Congress is also considering a series of additional incentives to help mobilize federal, state and local health care professionals on the most pressing areas of bioterrorism defense. What appears to be lacking at this point is a coherent national strategy. Officials in several affected agencies suggested to us this year that they may not have the capability to absorb such large and sudden budget increases. Many also note a lack of priorities – although the greatest identified need for the public health is improved communications, half of CDC's budget increase goes for pharmaceutical stockpiles. The President will submit a comprehensive counter terrorism plan to the Congress. This will be a major step toward a coherent plan, incorporating military, public and private sector, and individual citizen participation.

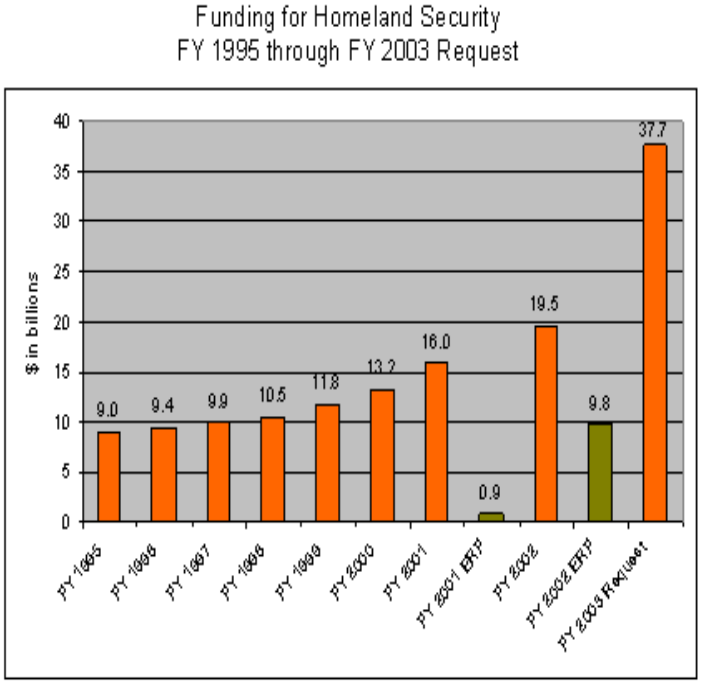


Figure 5: Funding for U.S.Homeland Security

Bioterror Priorities and Concerns

Advances in biotechnology have raised new concerns over the potential use of genetic knowledge in the development of a new generation of biological weapons. Scientists are beginning to develop the capability to detect bioterror attacks. Detectors may simply provide

early warning that a biological attack is being launched, or they may be able to identify the actual agent used. The ultimate detector would provide identification and early warning over a wide range of biological and chemical agents. We are only beginning to understand how biological weapons could affect military operations. Our understanding of the use of biological agents in a bioterrorism attack is even more limited. A biological detector the size and cost of a smoke alarm could provide tremendous benefit in protecting public places. Before the anthrax letter attacks, biological detectors had a limited market outside the military. The market may now be increasing, making it possible to focus more resources on developing practical detectors. This offers potential cooperation between DoD and private sector developers.

Second, even after September 11 and the anthrax outbreak, only 20 percent of local public health agencies had a comprehensive bio-terrorism response plan. Any future bioterror event would overwhelm public health care capacity. There is a need to review and improve our public health infrastructure and emergency response capabilities.

Third, the cost of developing bioterrorism defense – both the antidotes and the facilities for handling them – is a significant deterrent. Handling toxic materials is dangerous and expensive, requiring dedicated biocontainment facilities, decontamination systems, and security procedures. The clinical testing required for a new bioterror vaccine is very expensive and risky, both because of the lethality of the toxins involved and because of the rigor of FDA standards. Liability concerns further discourage biotech companies from pursuing new vaccines. BIOPORT's production of anthrax vaccine for DoD demonstrated the risks: after four years of testing and numerous public embarrassments working on a vaccine that has been manufactured for half a century, did BIOPORT finally received FDA approval in January 2002.[45] Finally, the stigma of past U.S. offensive biological warfare research discourages biotech companies from working with biological warfare agents, even if only for defensive applications.

During our industry visits, several firms expressed the desire to work with DoD but frustration at their inability to find a point of entry into the bureaucracy. Industry representatives stressed this point at a Senate Commerce subcommittee hearing on bioterrorism preparedness on February 5, 2002. They identified standardizing the process across all government agencies and streamlining the acquisition process as keys. The establishment of a single authority for bioterrorism research could solve any disconnects between government leaders and biotech business executives.[46]

Future Trends in the Biotech Industry

The biotech industry is still in its infancy. The Rand Corporation and the Hart-Rudman Commission have developed analytical economic models that use key variables as predictors of potential industry growth.[47] Each model considers a range of occurrences to help determine whether an industry is truly revolutionary or evolutionary in nature. The variety of emerging technologies in the biotech industry makes it unusually difficult to assess

the industry's future, but both models see it positively. The Rand model characterizes the biotechnology industry as having the potential for revolutionary or exponential growth, and the Hart-Rudman model identifies the enablers in biotechnology will encourage a high growth potential for the industry.

Despite the great diversity of subjects that compose the industry, an overall assessment can still be made. The industry is on a high growth vector and the U.S. economy will enjoy greater prosperity from the biotechnology discoveries yet to be made in the coming decades.

First, there is significant investment in the industry. Though there may be concern at recently declining investment in research, there is still surplus capital available. Over time, the industry will attract enough capital to fund new drugs, products, and discoveries. Capital flows will enable segments within the industry to come to the fore and develop into full-fledged industries in their own right. As Americans live longer and the population ages, there will be greater demand for health care.

A second important enabler that will keep the industry on a high growth vector is the enforcement of intellectual property right protections which provide tremendous incentives to companies for product development. Without this protection, the industry would have no incentive to invest or develop. International protections are equally important to ensure viable markets globally.

Third, the rate of progress, explosion of new ideas, discoveries, and development of new products in biotech is outpacing other industries, including information technology. Biotech is still on the early growth curve, spawning other new opportunities.

Fourth, the continuing growth of the IT industry will provide the computing power for biotech's bioinformatic models, visualizations, and data storage. IT capability and information management are currently lagging behind and are limiting factors for the biotech industry.

Fifth, the biotech industry, although in competition with other high growth industries, continues to attract some of the "best and the brightest" from U.S. and foreign higher education institutions, though there is some concern that it does not attract sufficient U.S. students. Biotech companies are tending to congregate in several well-defined areas, creating "brain centers" with the potential for greater collaboration, synergies of effort, and sharing of ideas.

Finally, the U.S. healthcare industry is generally receptive to breakthrough technologies that reduce overall costs for patient care, the arena in which most biomedical efforts are currently directed. Many of the strides in genomics and proteomics are geared towards both preventative and curative applications and, although expensive initially, offer long-term savings. We also can expect European and Japanese competition to help lower prices.

There are some barriers that could slow down biotech growth. These barriers include foreign competition, potential "brain drain" to other industries, ethical and social limitations on the industry (e.g. stem cell research and cloning), as well as high research costs. Since September 11, concerns over bioterrorism have become a higher priority, diverting some resources. The enablers, however, far outweigh the barriers to industry growth. Biotech is clearly on an evolutionary path, on a high growth trajectory.

U.S. Grand Strategy and Biotechnology

Biotechnology is emerging as a significant factor in America's growth, prosperity, and defense, building on the information technology wave that began to crest ten years ago. Biotechnology has crept into our national strategy by design and default. The most affluent generation in US history has been demanding a better quality of life and improved health care. Science has been aided by improvements in information technology that facilitated collaboration, experimentation, and modeling. Biotechnology has been a critical enabler in increased productivity in our agricultural sector. Since September 11, we have seen clearly that the security of our nation requires that we invest in preparedness and response to biological warfare and bioterrorism. Government and private investment will remain necessary for the biotechnology industry to grow and compete internationally. As a sign of its commitment to the industry, three of the four policy initiatives in the Administration's FY 2003 budget center directly or indirectly on biotechnology: support to first responders, defending against bioterrorism, and using 21st century technology for homeland security.

We believe biotechnology can be the next engine for economic growth. The life sciences sector as a whole provides fertile ground for continued research and development that will expand our technological base, create jobs, and develop several economic sectors. The biggest economic benefit will come to the regional centers where the industry already is centered. Several states such as California, Massachusetts, and Maryland have developed biotechnology strategies of their own to encourage university research and commercial opportunities as well as partnerships among government, business, and higher education. The biotechnology industry itself actively pursues collegial efforts to promote the emerging technology. The Biotechnology Industry Organization (BIO) seeks to encourage economic opportunities and supportive government policies for the industry.

Current and future applications of biotechnology will provide better health care and food production, lessening the effects of poverty and improving the quality of life. Our higher educational situation has profited as it attracts the most gifted students, both from the U.S. and abroad. We still need to do more to bring U.S. students into the sciences at the undergraduate and graduate levels, but the influx of different perspectives and personal drive of immigrants adds to our national strength.

Each version of the National Security Strategy for the past ten years has called for security through technological innovation in one form or another. The tragic events of September 11 prompted our leaders to call on Americans to bring out their best to secure our way of life. Even before last fall, information campaigns in support of technology were prevalent in both the private and public sector. Biotechnology figures prominently in

improving our ability to prevent and respond to bioterrorism. More importantly, as the various disciplines of biotechnology mature, they will foster a unity of effort that strengthens our country.

Our diplomats continue to address the challenges from abroad concerning biotechnology. In many regards, this means combating anti-globalization and anti-Americanism, as in some parts of the world, fear of biotechnology is synonymous with antagonism to American power. Our foreign policy is committed to gaining world acceptance of human and agricultural biotechnology products as a means of promoting development and feeding the world. We have the most technologically advanced economy in the world. Biotechnology contributes heavily to our trade through agriculture, medicine, and education, and indirectly may reduce the chances of crises that could lead to the need for military solutions.

Biotechnology has the potential to strengthen our defense and security through innovations and practical applications. Above all, it will contribute to force protection through advanced vaccines, drugs, and wound-healing technologies. The confluence of biotechnology with IT and nanotechnology also holds promises for greater awareness of combat and hazardous environments through improvements in biological sensors. Novel materials such as biopolymers may provide potential improvements for future combat clothing and gear. Biotechnology also has possibilities for creating new kinds of computers that do not use silicon-based chips. Biological computation is conceivable using unique properties of DNA, genes, and proteins. In the long term, biotechnology may help increase the strength and endurance of our combat personnel as well lead to unique applications of the emerging science in venues such as mimicking of biological functions and patterns. We may only be a decade or so away from seeing a measurable impact of biotechnology on our defense and security in the way that electricity or petroleum did in the early 20th century. Although the potential of biotechnology may not be apparent to the general public yet, it has the potential to change the way we order our security.

Conclusion

Biotechnology is an evolving industry that has yet to be fully exploited. It represents fertile ground with significant opportunities for economic growth, advances in health and welfare, and enhanced military capabilities. Biotechnology not only is an industry in itself, but also provides tools and techniques that benefit other industries such as health services, pharmaceuticals, agriculture, and environmental services.

The initial development of the biotechnology industry saw significant investment from the hope of revolutionary discoveries from technologies such as genomics. This year, reduced investor confidence in the near term capability for genomics to deliver breakthrough drugs has led to a decline in venture capital. The likely result over the next several years will be the merger of the stronger biotechnology companies and the bankruptcies of weaker ones as the industry evolves from one of research to one of product development.

Significant barriers remain that could impede the biotechnology industry growth or limit certain technologies. These barriers include: ethical challenges associated with acceptance of work in areas such as stem cell research and cloning; economic challenges associated with high costs for basic research and FDA approval; and trade issues associated with foreign acceptance of genetically enhanced crops. The ability to overcome these barriers will be critical to the continued success of the biotechnology industry and the ability to take full advantage of biotechnology advances.

The immaturity of the industry and the complexity of the challenges it faces make predicting the future of the biotechnology industry extraordinarily difficult. National security implications and the significant potential contributions of biotechnology to advance U.S. economic growth and prosperity make the survival of the biotechnology industry imperative. A national strategy, sound government policies, and adequate government and private funding are all critical to take full advantage of the U.S. biotechnology edge while adequately addressing the societal concerns of this emerging industry.

Notes:

[1] U.S. Congress, Senate Resolution 243 – Designating the week of April 21 through April 28, 2002, as "National Biotechnology Week," Online. http://Thomas.gov/. Internet, Accessed: March 12, 2002.

[2] U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy*, (Washington DC: U.S. Government Printing Office, October 1991). Online. http://www.ota.nap.edu/. Internet. Accessed: March 12, 2002.

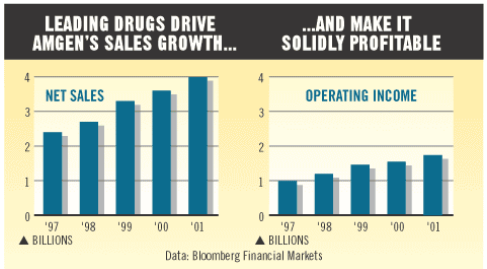
> *One widely accepted definition of biotechnology is "engineering problems associated with the production and processing of substances obtained through the application of principles and techniques of modern molecular biology."*
> UniGuide, "Academic Guide to the Internet Biotechnology Definition," Online. http://www.aldea.com/guides/ag/biotx.html Internet. Accessed: March 2, 2002.

[3] Biotechnology Industry Organization, *Guide to Biotechnology: The Technologies and their Applications*. March 13, 2002. Online. http://www.bio.org/er/applications.asp Internet. Accessed: April 7, 2002.

[4] Deoxyribonucleic acid (DNA) is the principal constituent of genes directing the genetic action of chromosomes. Ribonucleic acid (RNA) is a nucleic acid of high molecular weight found in the cytoplasm and nuclei of cells and associated with DNA in the synthesis of cell proteins.

[5] David Stipp, "Biotech's New Colossus – Move over, Big Pharma. AMGEN boasts better growth," *Fortune*, April 15, 2002. p.150.

> *The costs associated with producing a biotech drug are estimated to range from $300 to $800 million dollars. The hope for high profits on the sale of a successful biotech drug is what encourages companies to pursue this high risk/high return business model. The following chart demonstrates the success of Amgen:*



[6] United States Patent and Trademark Office, *Frequently Asked Questions About Patent.* Online. US Patent and Trademark Office Homepage. http://www.uspto.gov/. Internet. Accessed: March 12, 2002.

[7] According to US Code (35 U.S.C. §§101, 103), in order for something to be patentable, an invention must be novel, useful and not obvious. "Novelty" for this purpose means that the

patent application has to be filed within one year of invention. United States Patent and Trademark Office, *Patents*. http://patents.uspto.gov/. Internet. Accessed: March 12, 2002.

[8] United States Patent and Trademark Office, *Patents*, Online. http://patents.uspto.gov/. Internet. Accessed: March 12, 2002.

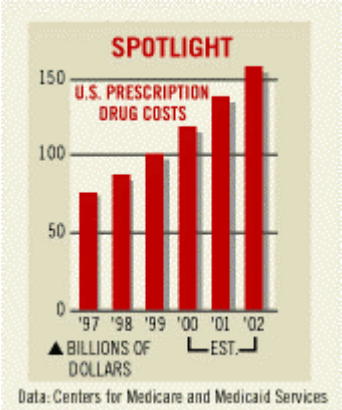
[9] Ibid.

[10] Animal and Plant Health Inspection Service, *United States, Regulatory Oversight in Biotechnology*, Online. http://www.aphis.usda.gov/. Internet. Accessed: March 15, 2002.

[11] M. Tetsuya, Organization for Economic Cooperation and Development, *Regulatory Developments in Biotechnology in the United States*, 1 August 2001. Online. Copernic Internet Search Engine, Internet. http://www1.oecd.org/. Internet. Accessed: March 12, 2002.

[12] Ernst & Young Economic Consulting, "Biotech Companies Focus on Fundamentals to Sustain Financial Strength," *Ernst & Young*, October 4, 2001. Online. http://www.ey.com/. Internet. Accessed: March 1, 2002.

> *"Biotech companies are in the best financial shape of their 25-year history, with strong capital reserves and a significant investment in research and development". The future for biotech drug companies looks very bright as demonstrated in the following forecast for U.S. prescription drug sales:*



[13] Catherine Arnst, "Biotech Outlook: The challenges facing this young industry don't end with drug discovery and FDA approval," *Business Week Online*, March 25, 2002. Online. http://www.businessweek.com/. Internet. April 19, 2002.

[14] David Stipp, "Biotech's New Colossus – Move over, Big Pharma. AMGEN boasts better growth," *Fortune*, April 15, 2002. page 150.

[15] National Science Foundation, *R&D Expenditures by Industry Category*, U.S. Corporate R&D, Vol 1, Top 500 Firms in R&D by Industry Category, 2000, Online. http:/www.NSF.gov/, Internet. Accessed: March 5, 2002.

[16] Richard R. Nelson, "Observations on the Post-Bayh-Dole Rise of Patenting at American Universities," *Journal of Technology Transfer*, Volume 26, pages 13-19, 2001.

[17] Biotechnology Industry Organization, *Biotechnology Industry Statistics*. 2002, Online http://BIO.org/, Internet. Accessed: March 5, 2002.

[18] National Science Foundation, *Characteristics of Doctoral Scientists and Engineers in the U.S.* 1999 Early Release Tables. http://NSF.gov/sbe/srs/. Internet. Accessed: March 5, 2002.

[19] Robert P. Morgan, and Donald E. Strickland, "*Academic Research, University research contributions to industry: findings and conjectures*, Science and Public Policy, April 2001, volume 2, pages 113-121.

[20] Commission of the European Commission, "Life Sciences and biotechnology – A Strategy for Europe," January 23, 2002.

[21] A Selected Look at the State of Biotechnology abroad:

Country	Strategic Approaches	Industry Strengths	Industry Weaknesses	Cooperative Arrangements
Australia	1998 Biotechnology Action Agenda; 1999 Australian Biotechnology Directory	Agricultural, pharmaceutical, medical, governmental advocacy		U.S., EU
Brazil	2000 Biotechnology and Genetic Resources Program	Conservation, Agriculture		China, France, South Korea
Canada	1983 National Biotechnology Strategy; updated 1998	Health & Social, governmental advocacy	Defense	U.S., Europe
China	1986 National High Technology Research and Development Program	Demographic resources, facilities	Restrictive regulatory policies	Brazil, India
EU	2001 Life Sciences and Biotechnology - Towards a Strategic Vision (document in development)	Research institutions, education	Cohesion of the decision making process and comprehensive European approach	US, Canada
India	1982 National Biotechnology Board; 1986 Biotechnology Department	R&D, international cooperation, IT integration	Global marketing	China, Burma, Germany, Russia, Syria, Vietnam
Iran	1994 Biotechnology Studies Center	Leader in SW Asia, R&D, suspect military capabilities	Infrastructure on most fronts	Russia
Israel	Israel Biotechnology Organization	Interplay between academia, government, and industry	Regulatory issues, small business flight	U.S.
Japan	2000 Millennium Project	Industrial sector R&D	Minimal patent holdings	U.S.
Russia	1998 Association for High Technology Medicine	Defense & Offense; R&D	Health	India, U.S.

[22] Biotechnology Industry Organization Web Page, "Statement on Ethical Use of Biotechnology to Promote Public Health and National Security and to Fight Against Bioterrorism," Internet. http://www.bio.org/. Internet. Accessed: March 13, 2002.

[23] Tara O'Toole, MD, "Reforming Public Health for Bioterrorism," *Blueprint Magazine*, January 16, 2002. Online. http://www.ndol.org/. Internet. April 11, 2002.

[24] Recent examples of the extent of delay in approving new biopharmaceuticals, illustrative of the complexity and cost of the process:

Company	Drug	Delay
Corixa:	Bexxar (cancer)	FDA has twice delayed review of this novel antibody for non-Hodgkin's lymphoma, most recently in January, because it needs more time to review the lengthy filing.
Amylin:	Smylin (diabetes)	FDA issued a likely-to-approve letter in October, contingent on additional safety trials, which will take about a year.
Genentech/Xoma:	Xanelim	FDA asked for more safety and efficacy tests in October, delaying approval filing by at least six months.
Genentech/Novartis:	Xolair (asthma)	In July, the FDA rejected the drug, asking for additional safety data. New clinical trials are under way, and the companies expect to resubmit the drug at the end of 2002.
Chiron:	Procleix (blood test)	The application for this highly sensitive HIV blood test was accepted by the FDA in March, 2001, but despite being granted fast-track status, approval wasn't granted until February 28, 2002.

Source: Catherine Arnst, "New Drugs: Why So Many Delays?," *Business Week*, March 11, 2002. Online at http://www.businessweek.com/. Accessed April 20, 2002.

[25] Press Release, "Biotech Acreage Increases in 2001," Biotechnology Industry Organization, October 16, 2001. Online, available at http://www.bio.org/foodag/weekly/20011024.asp.

[26] There were also reports of successful implantation of cloned human embryos in several countries, but none of these were documented or subjected to peer review in reputable scientific journals, and the scientific community has tended to dismiss them.

[27] Geoff Dyer, "Survey-Biotechnology: The book of life has yet to transfer to the bottom line," *Financial Times*, November 27, 2001.

[28] Geoff Dyer, "Survey-Biotechnology: The book of life has yet to transfer to the bottom line," *Financial Times*, November 27, 2001.

[29] Carl Feldbaum, "Discussions Produce Set of Recommendations for PDUFA Renewal," *Biotechnology Industry Organization*, March 13, 2002. Online. http://www.bio.org/. Internet. March 17, 2002.

[30] Alan Goldhammer, Ph.D., "Response to FDA's Message to Stakeholders Presented to the Center for Biologics Evaluation and Research Public Meeting" BIO, 14 August 1998.

[31] "FDA FY 2003 Budget Proposal." *Food and Drug Administration*. Online. http://www.fda.gov/. Internet. April 24, 2002.

[32] US Food and Drug Administration, *Federal Food Drug and Cosmetic Act, Chapter IV – Food*, Online. FDA Homepage. Internet. http://www.fda.gov/, 28 January, 2002.

[33] Celia Henry, "FDA, Reform, and the Well-Characterized Biologic" *Analytical Chemistry,* 68 (November 1, 1996): 674A-677A.

[34] United States Food and Drug Administration, *Overview and History of FDA and the Center for Food Safety and Applied Nutrition,* May 23, 2001, Online. FDA Homepage, Internet. Accessed: March 14, 2002.

[35] Food and Drug Administration, *Good Manufacturing Practice (GMP) Requirements Quality System (QS) Regulation Information.* 21 July, 2001. Online FDA Homepage. Internet. Accessed: 22 March 2002.

[36] Ibid.

[37] Paul Raeburn, "Human Tissue: Handle with Care," *Business Week Online,* April 15, 2002. Online. http://www.businessweek.com/. Internet. Accessed: April 19, 2002.

[38] Ibid.

[39] Ibid.

[40] The United States Commission on National Security/21st Century, Road Map for National Security, 15 Mar 2001, Phase III of the Report, page 45.

[41] The United States Commission on National Security/21st Century, Road Map for National Security, 15 Mar 2001, Phase III of the Report, page 33.

[42] White House, "Defending Against Biological Terrorism," February 5, 2002. Online. http://www.whitehouse.gov/news/releases/2002/02. Internet. Accessed: March 6, 2002.

[43] White House, "Defending Against Biological Terrorism," February 5, 2002. Online. http://www.whitehouse.gov/news/releases/2002/02. Internet. Accessed: March 6, 2002.

[44] National Institute of Allergy and Infectious Diseases, "HHS Accelerates Bioterrorism Research: New Programs Expedite Ideas from Concerned Scientists," *U.S. Department of Health and Human Services*, December 6, 2001. Online. http://www.niaid.nih.gov/newsroom/releases/. Internet. Accessed: March 10, 2002.

[45] "BIOPORT Corporation gains FDA Approval," January 31, 2002. The BIOPORT anthrax vaccine started FDA review process in 1998 and after almost four years gains approval. Online. http://www.bioport.com/. Internet. Accessed: March 22, 2002.

[46] Carl B. Feldman, President, BIO, made the following insightful assessment of the state of the Biotech Industry:

> *"Changes in public policy may represent the only major threat to the [biotech] industry's positive trends. The sector's viability hinges on predictable intellectual property laws, a science-based regulatory system, and market-based incentives for rewarding the enormous investments of the time and money required to develop innovative products."*
> *Biotechnology Industry Organization*. Online. http://www.bio.org/. Internet. Accessed: March 6, 2002.

[47] Anton, Philip S., Silberglitt, Richard; Schneider, James. "*The Global Technology Revolution, Bio/Nano/ Materials Trends and Their Synergies with Information Technology by 2015*." Rand National Defense Research Institute, 2001. Hart-Rudman Model, "The Spectrum from Nightmare to Glorious Future," and the Rand Model, "Range of Possible Future Developments," pages 5-15.