BIOTECHNOLOGY

ABSTRACT

Biotechnology is an evolving and dynamic industry. In this era of rapid scientific advances in genomics, proteomics and biology, the biotech industry is playing an increasingly vital role in our economy, health and environment. It is essential to understand how to effectively apply the innovation of this industry to advance our economic competitiveness and national security needs. The United States is in a strong position with the world's most vibrant biotechnology sector. The applications of biotechnology, such as medicine, agribusiness, forensics, informatics and the defense sector, offer many benefits, but also bring some risk, requiring public policy decisions in such controversial areas as cloning and information privacy. A comprehensive national strategy that derives maximum advantage from biotechnology is required to ensure the greatest benefit to American prosperity.

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INTRODUCTION

In recent months, the world has witnessed several dramatic developments in the evolving and dynamic biotechnology industry, as mankind enters an era of rapid technological advances in genomics, proteomics and many other applications of molecular biology. The biotechnology industry, and its associated technologies, will unquestionably play an increasingly vital role in the world's economy, health care, and the environment.

Yet, for the very reasons of its novelty and potential pervasiveness, biotechnology has many controversial aspects, particularly the ethical implications of "engineering the engineer" and the impacts on the economies of developing nations, the world food supply, and the environment. [1] We also believe it is essential to explore the various ways in which the productivity and innovation of this industry can be applied to U.S. national security, specifically enhancing security among nations, promoting economic prosperity, democracy and human rights, as well as addressing its limitations and drawbacks, whether real or perceived.

This paper discusses the biotechnology industry, with emphasis on embracing technology for societal advantages through scientific discoveries, while minimizing risks of potential dangers – both unintended and unprecedented. Although biotechnology has great potential to address societal needs, public acceptance of biotechnology-derived products in the market place will ultimately determine whether the industry can achieve that potential.

Accordingly, biotechnology success is dependent upon continued industry innovation and government policies based on a solid scientific foundation coupled to comprehensive regulatory oversight and a predictable business environment. Strong cooperation between industry, government and academia, as well as public education are critical ingredients to building public confidence and encouraging investment in the industry, thus allowing the fruits of biotechnology to blossom.

INDUSTRY DEFINED

Biotechnology traces its roots back thousands of years to when the Sumerians began brewing beer four millennia ago. However, the "new" biotechnology industry started less than 30 years ago when the first genetic modification experiments began.[2] U.S. government publications have defined biotechnology as "techniques that use organisms or their cellular, subcellular, or molecular components to make products or modify plant, animals, and micro-organisms to carry desired traits."[3] The core of modern biotechnology is the use of genetic engineering and recombinant technology to insert genes from one organism into a different organism with the aim of producing a cellular product to induce a different trait for commercial or other purposes. The tools of biotechnology are revolutionizing drug, vaccine, diagnostic and agriculture product development, thus increasing the speed and accuracy of development, while lowering basic development costs. A brief discussion of the more prominent terms and technologies comprising modern biotechnology follows:

Molecular Biology – Understanding biology, at the molecular level, is at the heart of biotechnology. In the 1930s and '40s, microbiologist made great advances in understanding the physical basis of heredity. Advances in the world of molecular biology

since that time have enabled scientists to not only decode the Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA) in genes within the cells, but to understand their vital function in directing what each living thing is to become. Scientists today routinely perform all types of DNA extraction, synthesis, manipulation, insertion and transvection.

Genomics - Genomics is the study of the genome, which is the genetic basis of life. Complete sequences and maps are now published for several microbes, insects, parasites, plants and animals. The crowning achievement occurred in February 2001 with the simultaneous publication of the public and private results of a draft genomic map of the entire human genome. This landmark scientific accomplishment was made possible through effective application of high throughput automated biochemical sequencing and high performance computing – or bioinformatics. The human genome project has identified over 30,000 genes that make up a human being, surprisingly far fewer than predicted. Most of the identified genes, however, are based on computer analysis; only about 17,000 have experiential evidence as to their existence and function. The accuracy of the information of the original draft genomic map will have a huge impact on how effectively the scientific community can use the information to discover new biopharmaceuticals. The next step in genomics is functional genomics and proteomics – the task of determining the function of individual genes, their interrelation with other genes and regulatory proteins, and function of the genes encoded protein.

Proteomics - Genes encode for proteins. Proteins are responsible for normal biological functions, cellular integrity, and disease mechanisms. Proteomics is the complex study of the physical structure and function of proteins in health and disease; it is the next frontier to follow genomics. Advances in proteomics are elucidating three-dimensional structure/function relations, and are enabling new opportunities to rationally design biopharmaceutical drugs and other biotechnology related products for medical, agricultural and environmental applications.

CURRENT CONDITION

Healthcare remains the principal market; however, biotech products are expected to find widening applications in agriculture, food processing, environmental control and forensics. Standard and Poor's estimates that human therapeutics accounted for about 70% of industry sales in 1999, human diagnostics for 20%, agricultural products for 5%, and other products for 5%.[4] Therapeutics and diagnostics include drugs, vaccines, biologics and diagnostics to treat diseases such as cardiovascular disease, cancer, AIDS, and diabetes. Agricultural products have been developed to make plants and crops pest resistant, improve seed quality, modulate growth and maturity, enhance nutrient contents of foods and provide simple and inexpensive diagnostics for field testing contaminants and toxic materials. Industrial uses of biotechnology involve many different sectors that include enzymes to enhance bioremediation, diagnostics, and toxicity determinations.[5]

Large biotech firms are the exception rather than the rule in the biotech business. The five largest players – Amgen Inc., Biogen Inc., Chiron Corp., Genentech Inc., and Genzyme Corp. – accounted for over one-third of industry revenues in 1999.[6] Small entrepreneurial companies are the real heart of the biotechnology industry. In 1999, biotechnology employed 162,000 people across more than 1300 biotechnology companies.[7] Figure 1 presents the overall industry statistics for 1993 through 1999.

More than two-thirds of these firms employ fewer than 135 people, and approximately one-third employ fewer than 50 employees.[8] The typical biotech company has not yet delivered a product to market, and many never will. To date, most have never made a profit.[9] In 1999, the industry posted a net loss of $5.6 billion.

BIOTECHNOLOGY INDUSTRY STATISTICS

* US$ billions

Year:	1999	1998	1997	1996	1995	1994	1993
Sales*	13.4	13	10.8	9.3	7.7	7	5.9
Revenues*	18.6	17.4	14.6	12.7	11.2	10	8.1
R&D Expense*	9.9	9	7.9	7.7	7	5.7	4.9
Net Loss*	5.1	4.1	4.5	4.6	4.1	3.6	3.4
Market Capitalization*	97	93	83	52	41	45	n/a
Number of Public Companies	327	317	294	260	265	235	225
Number of Companies	1283	1274	1287	1308	1311	1272	1231
Employees	153,000	141,000	118,000	108,000	103,000	97,000	79,000

Source: Ernst & Young LLP, *Annual Biotechnology Industry Reports, 1993-1999*

Figure 1: Biotechnology Industry Statistics

Most biotech companies survive on their innovation, flexibility and speed; yet, they also rely on key relationships with the government, academia, venture capitalists, and big business, particularly large pharmaceutical companies, commonly referred to as "pharmas." The foundation of the biotechnology industry's success is the U.S. government investment in basic research and infrastructure; the regulatory agencies (Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and U.S. Department of Agriculture (USDA)) that oversee the industry; and intellectual property protection, tax incentives for R&D investments and trade policies. Biotechnology is one of the most research-intensive industries in the world. The top five biotech companies spent an average of $121,400 per employee on R&D compared to an average of $30,600 per employee for the top pharmaceutical companies.[10] Approximately 80 percent of the federal government's biotechnology investment supports medical-related projects and basic research that is broadly applicable to health care. Much of this support comes from the National Institutes of Health (NIH) within the Department of Health and Human Services.

The strong U.S. regulatory structure has helped ensure public confidence in biotechnology products. The Food and Drug Administration is the platinum standard for

the world. The reputation of the USDA gives consumers confidence in the safety and quality of their food. Finally, intellectual property laws and regulations give private industry the confidence their investments in biotechnology are protected.

Many biotech companies spin off from research conducted at universities and private sector non-profit research institutes. Although the founders of these "start-up" companies may be gifted scientists, few possess the financial acumen necessary to nurture a successful business venture. Financial failures are common to biotechnology, either because promising scientific paths often lead to dead ends or due to the lack of business experience and leadership. However, the chief executive officers for many of these failed companies are not necessarily stigmatized within the American financial or scientific communities, but are respected for their innovative spirit. This unique American "disposition" has fostered a climate favorable to the development of biotechnology.

The biotechnology industry carries an inordinate amount of business risk due to the high failure rate of experimental drugs, the high cost of development, and the length of time for the regulatory approval of commercial products.[11] The relationship between big pharma and the biotech industry is an important dimension; because the focus of the largest biotech markets is human therapeutics and diagnostics. It takes an average of $500 million and 10-15 years to bring a new drug to market. For every one million compounds screened, only one goes to market. Therefore, there is a growing trend for big pharma to rely on biotechnology innovation as a key driver of product development.[12] As the biotech industry matures and capitalization increases, the nature of the alliances between big pharma and biotech are changing. The industry is becoming more dependent on exclusive technology sharing agreements with big pharma. There is also an expectation for an increase in biotech-to-biotech deals over the next few years.[13]

Biotechnology companies often turn to the capital markets, especially venture capitalists, as a source of funds. Biotech stocks first boomed in the 1980's, with Genetech leading the way as the industries first IPO.[14] Then biotech stocks declined significantly in value in the mid 1990s. During that time, most capital markets largely abandoned biotech in favor of the dot-coms. One problem was the capital markets did not really understand the biotech business and lost patience. Nor did they appreciate the amount of money and time needed to bring a product to market through the FDA process. That attitude changed in 2000 with genomics leading the way. "The progress made by Celera Corporation and The Human Genome Project on a draft map of the human genome triggered an influx of biotechnology into the media and our vocabulary. With it came increasing public interest in the power of biotechnology to improve our lives."[15]

The recent convergence of biology and information technology (IT), which was not possible in the 80's, has helped make biotech much stronger today. Worldwide demographic trends bode well for the biotech industry's growth. Aging baby boomers with an increased life expectancy will drive the market for biotech products. An industry-friendly FDA is reviewing new biotech products more expeditiously, while the stream of such products is projected to rise, fueled by aggressive R&D spending.[16]

Biotech companies tend to cluster in regions throughout the country. New England, especially the Cambridge area, has recently edged out San Francisco as the leading biotech region in the U.S. On a statewide basis, California remains the strongest state, with San Francisco, San Diego, and the Los Angeles/Orange counties dominating

the biotech landscape. The Maryland-Washington D.C. area is a leading hub of biotech activity due to its proximity to the National Institutes of Health (NIH), other government agencies, surrounding universities and the strong presence of the IT software industry.

Internationally, four countries have sizeable biotechnology sectors, though none enjoy the strength of the U.S. biotechnology industry. The United Kingdom, bolstered by the scientific excellence of Oxford, Cambridge, and other regional centers, continues to be one of the world's leaders in biotechnology. Germany, though only actively promoting biotechnology centers in the last decade, has been successful in creating areas of excellence – especially in Bavaria. France's biotechnology centers are located in Paris and Lyon. Israel, though internally lacking developmental funding, rounds out the top four due to its highly developed scientific community. Japan, Taiwan, China, Australia and New Zealand also show promising developments in the industry. The former Soviet Union dedicated many resources to its offensive biological weapons program, employing over 25,000 scientists, engineers, and technicians during the height of the Cold War. With the end of the Cold War, the United States has quietly aided former offensive biological warfare research laboratories in the Russian BioPreparat network in an attempt to transform Russian biological scientific expertise into constructive peaceful research addressing public health needs.

A Technology Explosion

Advances in our understanding of the nature of living matter have led to a technology explosion, with many of today's most innovative discoveries being the result of advances in molecular modeling, genomics, proteomics, physiomics, nanotechnology, bioinformatics and bioremediation, to name only a few. By integrating knowledge from a variety of scientific disciplines with these new technologies, companies have begun to simulate living cells, the human body's metabolic pathways, and whole organs by using computational and mathematical models.[17] The following describe just two emerging innovations related to biotechnology. The first, bioinformatics, has emerged as a critical tool for biotechnology as biology and computational mathematics have joined forces; and second, nanotechnology, is benefiting from the application of biotechnology.

Bioinformatics: Applying the Information Technology Revolution to Evolution

Bioinformatics arose from the information technology (IT) revolution colliding with scientific discovery in biology. Bioinformatics is the means by which vast amounts of data is organized, processed, and shared at speeds beyond human capability. The application of high-speed information technology computing capabilities to scientific experimentation enhances discovery and is changing the very nature of the life sciences. Developing a bioinformatics capability was crucial as the race began to decode the human genome. The human genome database is approximately three terabytes of data, or the equivalent of 150 million pages of information. The volume of life sciences data is doubling every six months.[18] Today, a $300 million industry has emerged around turning raw genome data into knowledge for making new drugs.[19] Predictions are that life science companies will spend $6.5 billion on IT services by 2004, with the bioinformatics industry growing to $9 billion by 2003.[20]

Like the Internet, bioinformatics began as a government project that quickly transferred to the commercial sector for useful global applications. It has come full circle with government and defense applications arising from commercial discovery. Today, government agencies collaborate with academia and the private sector to hasten the discovery process in the medical, agricultural, and environmental arenas. What once took years, through careful experimentation, is accomplished in record time today through creative interpretation and analysis of biological databases. This process shortens the discovery process and the amount of funds necessary to target and develop new drugs that will benefit our society.

Nanotechnology: Assembly of Materials and Devices at the Molecular Level

Nanotechnology is knowledge of matter at the atomic and molecular level, 1-100 nanometer range. For a perspective of this size, recognize that a human hair is about 10,000 nanometers thick. Manipulation of matter at this level creates possibilities for the development of materials and devices with previously unimaginable properties: materials possessing ten times the strength of steel with a fraction of its weight; chips the size of sugar cubes which can contain all the information housed in the Library of Congress; and devices which can detect and deliver treatment to cancerous tumors only a few cells in size! Scientists predict the ability to move and combine individual atoms and molecules will revolutionize the production of virtually every human-made object and usher in a new technology revolution at least as significant as the silicon revolution of the 20th century.

Researchers at the University of California at Berkeley reported in March 2001 they had built a minute, complex electronic device that could open and close the membranes of human cells—a development which may enable the pinpoint delivery of medications to disease sites.[21] Scientists are now experimenting with nano-machines that guide themselves through the blood stream delivering medicine targeted to specified areas. In cancer treatment, targeting only the specific cancer cell reduces many side effects cancer patients now suffer.

CHALLENGES

The promise of biotechnology across a broad spectrum of issues is tremendous. In the span of a few short decades, the powerful tools of biotechnology have revolutionized medicine, agriculture and environmental protection. Biotechnology will affect each of us on a daily basis, if it has not already. The biggest challenge will be to embrace the opportunities of biotechnology while mitigating the risks associated with the many advances in the science.

Vaccine Development

There are tremendous opportunities for biotechnology in vaccine research and development. The goals within the public health community are to develop safe and effective vaccines that will eradicate infectious diseases and provide therapeutic treatments for non-infectious diseases. Using biotechnology, the sequencing of disease

pathogens allows for a better understanding of diseases that can then lead to development of more effective vaccines. Advances are being made in recombinant techniques for the production of protein-based vaccines. The recombinant DNA-derived vaccine was proven safe and effective for a yeast-derived hepatitis-B vaccine (HBV). A new generation of diphtheria and tetanus (DPT) and acellular pertussis vaccines using recombinant technology are expected to follow within a few years.[22] A great deal of current vaccine research is focused on treatments and cures for cancer, AIDS and malaria. New and better delivery systems for vaccines are being developed which include more oral and nasal methods.[23] Other major opportunities for biotechnology in vaccine research involve more combination vaccines for infants and the use of transgenic plants for vaccines. Advances in these two areas might lead to greater acceptance and use of certain vaccines.

There are major risks associated with vaccine research and development. Beyond the obvious risks of safety and effectiveness, which are addressed through lengthy clinical trials, there are risks associated with the lack of research and development on needed vaccines. In some cases, as with malaria, research funding has increased worldwide, but will vaccines be developed? The risk in not moving from the research phase to the development phase can be tremendous. Many of the research institutions do not do the development work. The development of the vaccine candidates established by the Institute of Medicine (IOM) costs between $120 million and $400 million and could take up to fifteen years to reach licensure.[24] Vaccine development competes with other opportunities facing the major pharmaceutical firms who are more likely to bring a product to the market. The firm evaluates its financial risks, looking at its return on investment, the market for the product, the likelihood of receiving licensure, and the cost of development and production. The high costs and low potential returns are likely to be the case for many needed vaccines. The lack of development of needed vaccines could pose major public health risks that could become transnational health issues. There is an essential need for greater public-private partnerships to ensure continuous research and provide mechanisms that lead to the development of appropriate vaccines.

Biopharmaceuticals, Tissues and Diagnostics

Biotechnology has revolutionized the drug discovery process. Traditional drug discovery has evolved from the blind screening of millions of small chemical molecules, to a process of rational discovery and design using computational modeling and molecular engineering of natural human molecules – genes, proteins, antibodies, and cells. One of the earliest biotechnology-derived drug that came to the market in the 1980s was human insulin produced from the common bacterium, *E. coli,* instead of the previous method of extracting it from animals. Today, there are hundreds of biotechnology-derived drug candidates in clinical and pre-clinical trials for all major disease categories, including cancer, cardiovascular, respiratory, neurological, hemapeotic, infectious diseases, wound healing, transplantation, and others.

The next wave of biotechnology promises to unlock the power of biology even more through the application of genomics, proteomics, transgenics, cloning, and reprogramming cellular activity. This will facilitate the development of entirely new medical options. Biotechnology-derived biopharmaceuticals have already delivered more effective and safer drugs that are reducing hospital and rehabilitation costs.[25] Future

biopharmaceuticals will enable very specific cellular/tissue targeting of drugs and tissue replacements incapable of invoking an immune rejection response.

Biotechnology is also being successfully applied to improve the sensitivity and specificity of medical diagnostics and to help understand the genetic basis of disease. Monoclonal antibody-based tests, genetic probes using DNA amplification, and micro-array gene chips are being developed to diagnose diseases, study gene regulation in health and disease, and to identify pathogenic organisms. These new diagnostic technologies are also being applied to veterinary medicine, as well as law enforcement, as an aid to forensic identification.

DNA Profiling and Forensic Pathology

DNA profiling, the process of characterizing small portions of DNA, is one of the most widely known applications of biotechnology. This profiling offers tremendous opportunities for detecting infectious diseases, determining predisposition to genetic diseases, revolutionizing criminal forensics and making it more feasible to identify the remains of unknown soldiers. Despite the undisputed reliability and accuracy of DNA analysis among the scientific community, state and federal laws are still evolving to address the risks that unlimited access to genetic typing information could violate an individual's civil liberties or deny access to health care and employment.[26]

Since the late 1980's, it has been practical to use DNA markers as fingerprints for identifying criminals, exonerating suspects, or overturning previous convictions. Conventional typing techniques, using the two copies of DNA found in the nucleus of cells, can take several weeks to perform and require large amounts of sample material. A few years ago, scientists began using a so-called polymerase chain reaction process to amplify these small traces of DNA. Most recently, scientists started profiling mitochondrial DNA that is maternally inherited, contains thousands of copies in each cell and can be sequenced in a matter of hours after the sample has been extracted.[27] This approach is ideal when dealing with only traces of degraded tissue or bone fragment, such as matching a DNA sample from the saliva on an envelope licked by a soldier fifty years ago or when the parent of a missing soldier is no longer alive to make a match.

Although the Federal Bureau of Investigation (FBI) performs the majority of the forensic DNA analysis for state and local law enforcement agencies, private biotechnology companies are quickly emerging to support states passing laws requiring DNA fingerprinting for convicted offenders of capital offenses. The Armed Forces Institute of Pathology's DNA Identification Laboratory, established shortly after the Gulf War to maintain a registry and blood specimen repository for DoD personnel, is the world leader in DNA analysis of degraded specimens. The unit has played a significant role in identifying soldiers missing in action in past military conflicts, including Vietnam, Korea, WWII, and as far back as the Civil War.

Education

Incredible advances in computer technology have proven essential for the enormous task of mapping the more than 3 billion base pairs of DNA in the human genome. Consequently, biotechnology now frequently requires a biological scientist to

acquire an adjunct degree in mathematics, computer science, or at minimum, to form close collaborations with mathematicians and computer engineers.

The biotechnology workforce increased from 79,000 in 1993 to 153,000 in 1999 and is forecasted to continue growing. By itself, our educational system has not been able to produce nearly enough people with the requisite education to support such growth. Although entering college freshmen report having taken four years of high school mathematics and two to three years of science courses, 22 percent of first-year college students who intended to become science and/or engineering majors reported that they needed remedial work in mathematics. Nearly 10 percent reported that they needed remedial work in the sciences. Repeated studies during the past three decades indicate that U.S. students do not perform as well in mathematics or sciences as do their peers in many other nations. In the Third International Mathematics and Science Study conducted in 1999, U.S. students placed relatively low out of 23 countries which took the tests. For now, immigration of technically skilled personnel is filling the gap between what the industry demands and what our education system can provide. However, this situation could potentially compromise our long-term competitive advantage in personnel skills.

Thus, in education as elsewhere, we find ourselves at a crossroads, caught between the beguiling allure of new bio-based possibilities with the tremendous investment of educating our workforce and the research required to take maximum advantage of these opportunities. The good news is that we still lead the world in entrepreneurial spirit and the relatively free flow of venture capital toward new ideas.

Privacy and Information Assurance

Our ability to harness information and direct its application to most segments of society provides exponential benefits that transcend all elements of power. The field of bioinformatics captures and combines the essence of the biotechnology and information fields. However, there are critical privacy and information assurance issues (i.e., security, protection, availability, reliability and nonrepudiation) that are fundamental to both the biotechnology and information domains that must be resolved.

Information and biotechnology are inextricably linked, just as the security and privacy of our information are linked. As we move forward to more fully map the human genome and build databases that catalogue information, we must be mindful of the value of this information. We must consider the privacy issues of databases that catalogue DNA and the potential identification and predisposition of a specific person to a potential disease based on this DNA mapping. For example, who will have access to one's personal and private information? Should an insurance company have access to this information before offering coverage? Should individuals share their genetic information with their mate before marriage? We must address the ethical dilemmas before they consume us in controversy.

Ethical Considerations

Concerns about privacy and intellectual property rights are not the only ethical issues to consider. Recent discoveries in the medical and agricultural fields have spawned much controversy in spite of the benefits associated with these advancements.

Historically, biotechnology has been a beneficial enabler in the fields of medicine and agriculture. In the early part of the 20th century, Fleming discovered penicillin, while other research led to discoveries that helped cure disease and prolong life. On the agricultural side, gene splicing occurred around the middle of the 20th century. Genetic recombination soon followed and science proved that genetic and biological material could be combined to form totally new structures. As our knowledge increased, so did the risks.

During the latter part of the 20th century, as genetic research progressed, society faced many ethical issues. The scientific world successfully cloned plants and animals, discovered and created new pharmaceuticals and mapped the human genome. However, where does man draw the line? When do we decide what should and should not be pursued? As Leon Kass states, "Science—however much it contributes to health, wealth and safety—is neither in spirit nor in manner friendly to the concerns of governance or the moral and civic education of human beings and citizens. Science fosters and encourages novelty; political society, governed by the rule of law, cannot do without stability. Science rejects all authority save the truth, and prefers skepticism to trust and submission when truth is unavailing."[28]

…In the Medical Arena

Among the many ethical concerns currently being debated are the FDA's requirements for testing new pharmaceuticals before being approved for use. Generally, the American people have faith in this process. Internationally, items that are approved by the FDA enjoy credibility due to the rigorous testing required. Yet, many terminally ill patients are prevented from being treated with drugs that have not received FDA approval. Many question how ethical or humanitarian it is to deny a dying patient an unapproved experimental drug when it is their only hope? For example, Rheumatoid arthritis patients lived in constant pain as they watched their joints cripple before Enbrel was finally approved in 1998. Many patients have to wait months or years before testing is completed on a new medication. On the other hand, if pharmaceuticals were not regulated before use, the incidence of adverse effects would increase. It is difficult to know what is right. An additional dilemma concerns government policy dealing with companies who test their product in Third World countries. They can experiment on human beings, thereby speeding up the test time, resulting in quicker approval by the FDA. This not only puts it in doctors' hands quicker, but the company also acquires revenue sooner. "The rules are often more lenient and less rigorously enforced than in the United States and Western Europe—a gap that some drug companies shamelessly exploit. Reportedly, some companies use lower standards of treatment in the Third World as an excuse not to provide potentially life-saving treatment to some subjects. The poor people who test new drugs for Americans often never see those drugs marketed in their countries—and only rarely do they see tests of drugs that would attack the diseases that most plague Africa and Asia, such as malaria."[29]

Many ethical questions come to mind regarding testing in Third World countries. Do patients really know what is happening? Who takes care of them when things go wrong? Are these patients being taken advantage of without their knowledge? On the other hand, some hope may be better than none at all. It may be their only chance of

relief. Humanitarian issues such as medical care for patients and the age-old adage of "sacrificing a few for the good of many" might be reasons, but are they the correct reasons? Once again, we need international policies and guidelines for such testing to prevent potential abuses. The World Medical Association recently updated its Declaration of Helinski, a statement of principles guiding ethical decisions for clinical trials, making it unethical to use dummy medicines on some patient trials of diseases for which there are proven treatments. The FDA, government and industry must ensure all clinical studies, whether conducted in the U.S. or offshore, meet FDA regulatory and ethical standards.

There are also ethical issues in the medical fields that pose practical problems, such as the use and cloning of human embryonic stem cell. Stem cell research requires the use of embryonic stem cells. These cells mature into specialized cell types, such as heart, nerve or skin cells as the fetus develops".[30] To advance human embryonic stem cell cloning, research is performed on human embryos. Embryonic stem cell cloning offers the prospect of creating tailor-made cells and organs for transplant. It is also possible this will lead to cures for degenerative diseases and the ability to grow entire limbs in laboratories.[31] While this type of cloning has potential, it is not clear that it will provide the cures or the necessary organs. This technology could *potentially* be a vital answer to many forms of illness, but the question remains whether we should be cloning human embryos in the first place.

Many questions surround the issue of human cloning. For example, does man have the right to create life? How do we treat a clone? After all, it is not a new human being…or is it? How will cloning affect our society and our family structure? How will the role of a parent of a clone be affected? These questions must be dealt with, solved, and accepted before such a step is taken. Furthermore, in trying to clone sheep and cows, researchers failed many times during their attempts. Scientists know there is significant potential for complications in the process of cloning humans. These complications include the risk of hormonal manipulation in the egg donor, multiple miscarriages in the birth mother, and the possibility of severe developmental abnormalities in the cloned child.[32] The key question is…are we willing to chance failing on a human being?

…In the Agricultural Arena

There are many agricultural ethical issues as the industry attempts to balance the economic benefits of biotechnology with health concerns and food demands of the developing world. Biotechnology can contribute to feeding growing populations, which some estimate will grow to 9 billion people in the next 30 years. Modern biotechnology can increase the nutritional value of current crops, increase the yield, reduce crop stress, reduce water/herbicide usage, create longer shelf life and increase economic returns for farmers and consumers.[33]

Genetically modified organisms (GMOs) are touted as the answer to feeding the world's hungry. However, supplying GMOs is not the sole answer. Curing malnutrition, sickness and plain starvation will require more than providing a new and abundant food source. The majority of these disadvantaged countries have no social system, a broken government and little, if any, economic structure. Therein lies the problem or "ill" which must be cured in order for these countries to benefit from GMOs. The discussion should

not be whether the developing world needs biotechnology, but how can it be promoted, supported, and applied in ways that enable biotechnology to make a positive and sustainable contribution to public welfare in the Third World.

…In the Environment

Experimental research over the past several decades has shown that bioremediation can be a fairly effective means of remediating soil or water contaminated with toxic organic chemicals, including gasoline, oil, polyaromatic hydrocarbons, chlorinated hydrocarbons and halogenated solvents. Bioremediation is a process of cleaning contaminated sites, either by enhancing the natural populations of microorganisms or by adding high amounts of specially developed microbial cultures grown through fermentation.

This technology, in addition to being relatively cost-effective, is practical and flexible because of its portability to hard to reach locations and adaptability to specific sites. In addition, bioremediation is recognized as an environmentally-friendly technology because its products are natural and indigenous. In addition, some of these enzymes act to break down or biodegrade pollutants. This natural process can be exploited for the treatment of industrial, agricultural, or municipal wastes.

A variety of societal concerns are raised with bioremediation field testing and deliberate release of microorganisms for environmental cleanup, whether those organisms are native to a site, imported from another site, or genetically modified. Other concerns are the technology's ethical ramifications, impacts on the environment, potential health risks, affect on agriculture, and extent to which the technology and its management by government and industry are trusted by concerned consumers.

Society's interpretation of what is morally good or ethical is not always substantiated by scientific means. Some sort of authoritative governance must be established as a guideline to preserve order in our current way of life. In short, we must ponder the full range of questions raised by the relation between knowledge and human life, or between science and the broader community.[34] It is in this vein that it becomes obvious there need to be global policies concerning biotechnology.

How we respond to these challenges, politically, economically and militarily, will be a major factor in determining how far into the 21st century the American Age will endure.

OUTLOOK

The biotechnology industry is an emerging and dynamic industry that has wide-ranging possibilities and potential. As discussed, biotechnology will revolutionize health care, agriculture and environmental cleanup. The technology is already revolutionizing the drug discovery process leading to the development of completely new biopharmaceuticals and medical diagnostics.

Various commercial applications are coming to fruition at an expanded pace, as start-up and established companies exploit biotechnology's potential. The biotechnology industry is young and dynamic, but experiencing substantial growth. Extraordinary scientific innovation and the entrepreneurial spirit, fueled by the convergence of industry,

academia, and government, and coupled to a favorable business/government climate are responsible for biotechnology's rapid growth.

Biotechnology is a high-risk, expensive business enterprise requiring long-term capital investment in facilities and equipment, in addition to highly specialized scientific/technical personnel. Venture capitalists and Wall Street now understand. More importantly, Wall Street recognizes the tremendous potential of biotechnology and is beginning to accept the long-term investment commitment. Today, there are several hundred very promising biotechnology-derived medical products in clinical and/or pre-clinical trials, in addition to products in other sectors, which will improve the industry's balance sheet in the not so distant future.

Although there are profitable biotechnology companies, the industry is still largely dependent on venture capital, government grants, private philanthropy and corporate mergers and buy-outs. Overall, the industry continues to produce at a net loss – largely because the industry is very research intensive. Despite this challenge, the future is very bright for biotechnology.

GOVERNMENT: GOALS AND ROLE

The U.S. is the international leader, but industry and government must strive to maintain that leadership role and ensure the industry not only survives, but also thrives so that biotechnology's tremendous potential can be achieved. A national strategy for biotechnology should include continued government investment in biotechnology-related basic research, coupled with sensible government policies. Government policies must promote continued technology transfer, protection of intellectual property and enactment of permanent tax incentives that encourage industry/private investment in research and development. Creation of a business/government climate that promotes industry, academic and government collaboration, as well as investment in modernizing critical laboratory infrastructures and workforce and secondary science and technology education are also critical components. The strategic importance of biotech to our national strategy falls into four broad categories: economic, diplomatic, military and informational.

Strategic Importance of the Economics of Biotechnology

The strategic importance of the economics of biotechnology can be considered from two perspectives; first, the current economic and fiscal contributions of the biotech industry to the US economy and second, the tremendous opportunities that biotechnology presents.

The biotech industry already makes significant contributions to the U.S. economy despite its lack of overall profits. Even biotechnology companies that have yet to bring a product to market contribute to national income by engaging in research and development and purchasing inputs from companies such as contract research organizations and equipment manufacturers. Biotechnology firms employ workers, who purchase goods and services in the general economy. The industry also generates significant tax revenues for federal, state and local governments from property taxes, sales and use taxes, income taxes and other taxes.[35]

In 1999, the biotechnology industry generated 437,400 U.S. jobs. Biotechnology companies directly generated 150,800 jobs. For comparison, that puts biotech considerably above the toys and sporting goods industry, and slightly less than the cable television industry. Companies providing goods and services to biotechnology employees also generated the remaining jobs.[36]

The biotechnology industry, as a whole, produced $47 billion in revenues. Although the industry remains unprofitable, biotech companies produced revenues of $20 billion, while companies selling goods and services to biotech employees generated revenues of $27 billion. Biotechnology companies spent $11 billion on research and development and generated $10 billion in tax revenues, including federal state and local taxes.[37]

The strategic contribution of the biotech industry also relates to the tremendous opportunities it presents, from therapeutics, diagnostics, and agriculture to industrial and environmental products and services. First and foremost is the ability to practice a new type of medicine directed at the very heart of disease; addressing things such as cardiovascular disease, cancer, AIDS and diabetes head on; offering cost savings through avoidance of disease and tailored treatment, and issuing new strategic challenges such as the impact of increased longevity.

The biotechnology industry is poised to usher in a new wave of technological innovation that has great potential to revolutionize health care, agriculture, and the environment, providing the next major stimulus to the U.S. economy. To take full advantage of biotechnology's potential, U.S. regulatory and fiscal policy must continue to promote an environment conducive to scientific innovation and entrepreneurship, as well as to encourage the continuing flow of investment venture capital into the industry. Continued growth and success will depend on sound government policies that promote patent protection, facilitate profitability, seek international regulatory harmonization, and implement the Food and Drug Modernization Act without compromising public confidence in governmental regulatory oversight responsibilities. This would include creating a more predictable patent environment, providing permanent research and development tax incentives, avoiding the politically expedient, but naïve imposition of price controls on prescription drugs and establishing Securities and Exchange Commission standards for biotechnology corporate valuation[81].

Strategic Importance of Information and Biotechnology

Information permeates everything in society, though some may question its formal place alongside economics, diplomatic, and the military at the table of national power. One thing cannot be disputed is the pervasiveness of information. Whether one views information as its own element of power or as an enhancer or enabler of power is not the issue. For this discussion, the issue is the role information as it relates to the biotechnology field and plays in our national security.

There are a number of national security concerns regarding biotech information. These concerns include unlawful access and use of knowledge, the storage and location of large amounts of information that make product abuse or misuse easier to accomplish, intellectual property rights and public trust and confidence erosion. From a defensive posture, two significant issues come to the forefront, security of our biotechnological

information and privacy concerns. In the past, we viewed these as two separate issues, but because of computers, large databases, the Internet, automation and the interlinking of information, we must now view these as inseparable.

The President's Critical Infrastructure proposals, as outlined in Presidential Decision Directive 63 (PDD-63) issued 22 May 1998, address both of these challenges. The PDD-63 directly states that "physical and cyber-based systems are essential to the minimum operations of the economy and government." Biotech information is clearly a subject of concern and the protection of the information systems carrying this information are specifically addressed in the Presidents directive. The consequence of not adequately protecting this information and maintaining the privacy the American public demands will be catastrophic.

Strategic Importance of Diplomacy and Biotechnology

The biotechnology industry presents a challenge for the United States from a diplomatic standpoint. The industry is well established in the U.S. Efforts to capitalize on this area of comparative advantage are viewed very differently by many parties. Ethical issues and how they are handled in the U.S. could have a significant impact on relations abroad.

In Europe, the sensitivities about genetically altered foods run high. If the U.S. presses too hard to minimize labeling requirements, without acknowledging and working to accommodate local concerns, the U.S. could damage relations with European Union (EU) countries. Yet, there is some hope that individuals in the European scientific community, particularly in Britain, share the views of the U.S. regarding GMO's. Science-based benefit-to-risk analysis could have a major positive impact on the world's food supply. It may just be a matter of the U.S. backing off enough to let the hysteria in Europe run its course. The leadership in the EU may then arrive at the same conclusions as the US, but without the sense of it being forced upon them.

The medical arena is even more controversial as there are laws against human cloning in most EU countries. If an overzealous scientific team were to proceed with human cloning activities in the U.S., EU-U.S. relations would likely be further strained. Yet to prohibit all research could hinder legitimate scientific inquiry on the use of stem cells for possible organ regeneration and tissue replacement. This would deny the medical and scientific professionals the opportunity to reduce suffering and improve quality of life for future generations. Clearly, human cloning is not yet a mature technology, and so we do not endorse its legalization, much less its support by federal or private research dollars. However, if we are honest about the implications of supporting the related research, the U.S. government will have to revisit this possibility eventually, when the downside risks have mostly been addressed.

If the U.S. takes a hard stand on intellectual property issues in the Third World, where access to biotech solutions seems to be solving problems of hunger and disease, there is the potential that the U.S. will be seen as caring only about big business and big profits and not about the world's underprivileged. Another key issue for the U.S. on the diplomatic front is how to handle the negative issues surrounding biotechnology, particularly biological warfare and biological terrorism. However, if these issues are

managed well on the international front, the U.S. could enhance its standing as a reasonable and compassionate partner in international affairs.

The proliferation of biological weapons is a real and growing concern. The Biological Weapons Convention Treaty (BWC) of 1972 prohibits the development, possession and use of biological weapons, but the treaty lacks a means of verifying compliance. There is international agreement on the need to develop verification and enforcement measures to put teeth into the treaty, but achieving international consensus amongst the 143 national signatures to the treaty has been elusive. Diplomatic negotiations have intensified during the senior Bush and Clinton Administrations, and have led to a draft verification and inspection protocol negotiated with U.S. input from the former Clinton Administration.

A recent re-review of the draft protocol by the new Bush Administration, however, revealed that the current version of the protocol is insufficient to hinder a determined biological warfare proliferator. Furthermore, the protocol increases vulnerability of U.S. biotechnology and pharmaceutical companies to loss of trade secrets, critical to their economic viability and profitability.

This leaves the U.S. in a precarious diplomatic situation. The U.S. cannot acquiesce to an inadequate verification protocol or a protocol that may harm our legitimate scientific enterprise. Therefore, tremendous diplomatic and political costs are associated with changing U.S. positions and/or halting negotiations on the verification protocol for the BWC treaty. U.S. critics, adversaries and even some allies will wrongly accuse the new administration of not supporting nonproliferation efforts in a propaganda campaign. This will only heighten the sensitivities as the Bush Administration begins diplomatic negotiations on missile defense.

Strategic Military Importance of Biotechnology

The revolutionary advances in life sciences and biotechnology offer great potential to achieve leap-ahead capabilities for several DoD research thrusts, particularly in military medicine/human performance, material sciences, sensors, logistics and computational sciences. Moreover, throughout much of the previous century, military requirements spawned technical innovations with broad applications across society, as in the instances of jet aircraft and nuclear power. The last few decades, however, have seen a gradual transition toward other sectors as the motivators for widely applicable advances in technology, from the spin-offs generated by NASA's lunar missions and the National Weather Service's use of supercomputers for weather forecasting, to the global expansion of digital telecommunications. The U.S. military should anticipate capitalizing on biotechnology as well. This will take the form of direct applications such as advancements in medicines and human performance enhancement; and embracing new paradigms for defense and processes for systems development and logistics support.[38]

Within military medicine and health, the opportunity exists to develop new vaccines as deterrents to biowarfare or simply to ensure a healthier military force. These vaccines would then become available to the civilian population for preventive inoculation or disease control. Further, the need for battlefield triage is spurring innovations in wound repair, which similarly will become available for civilians who suffer traumatic injury. Finally, such previously fantastic possibilities as human

performance enhancement (going sleepless for days on end or hibernating between missions) are becoming distinct possibilities.

The ongoing Revolution in Military Affairs dictates that DoD pursue some revolutionary approaches to classic military challenges. Biotechnology should certainly be a player in those discussions. As precision and speed replace mass and endurance as measures of warfighting potential, rapid introduction of new technologies will transform American sea, air and land forces. Biotechnology will have an impact across the spectrum of DoD's system of systems, from weapons system subcomponents to new operational concepts. Meanwhile, the Defense Advanced Research Projects Agency (DARPA) is studying the application of biological processes as a metaphor for solving practical problems. These "bio metaphors" are considered, at the lowest level, for information gathering and processing, potentially using the paradigm of the five senses to outperform currently employed digital techniques. Additionally, bio metaphors are considered for applications such as sensor networking and platform enhancements, including self-repair capability. Finally, as an operational concept, the metaphor of swarming bees could greatly enhance ballistic missile defense by populating the engagement space with a swarm of maneuvering interceptors. Under this approach, each of the interceptors follows simple rules for moving and sensing, then react to others' reactions and converge rapidly.[39] During the 1980s, the Strategic Defense Initiative Office did extensive analysis on Brilliant Pebbles, a similar, physics-based approach.[40] This provides an opportunity to contrast a physics-based solution with a bio-based solution by comparing the acquisition and operational costs, expected performance, and overall program risk of the two approaches. The swarming metaphor also applies in the case of minehunting and is extendable to many other forms of reconnaissance. Even the acquisition process, whereby systems are bought and fielded, could be overhauled to look more like natural evolution, i.e., to examine more variations or mutations early, but carry fewer forward to maturity. As more of our leaders realize the potential of such bio metaphors, new thresholds of performance and efficiency may become possible. Regarding risk, however, there certainly exists the potential for a wily adversary to use these same concepts against the U.S., which is all the more reason why the U.S. needs to explore them, and possible responses to them, so as not to fall victim to the deadly sin of complacency versus an asymmetric threat.

The Strategic Importance of Biological Defense

The misuse of biotechnology in a biowarfare and bioterrorism context is a real and growing threat. Biological weapons are one of the major new threats to military forces and civilian populations. DoD should promote significant biological defense organizational reform to reduce military vulnerabilities and support interagency public health initiatives to improve bioterrorism preparedness. The revolution in biotechnology and the life sciences will no doubt yield many beneficial consequences for medicine, agriculture and the environment. More to the point, however, this Pandora's box is open, and the intentional or inadvertent misapplication of biotechnology may yield catastrophic consequences. In the face of U.S. conventional superiority, biological weapons are a growing risk to the success of U.S. and Allied military operations and civilian populations. Advances in biotechnology and the ubiquity of technical expertise and

materials ensure that the biological terrorism threat will evolve in unpredictable and ominous ways.

National Strategy in Perspective

Biotechnology clearly has national security implications and is important for continued economic prosperity and well-being. However, profligate government regulations and bureaucracies are not the answer to ensure future success of the industry. The biotechnology industry itself has an enormous responsibility to engage in responsible business and scientific practices that not only maintain, but also build stronger public understanding, trust and confidence in biotechnology. Government does have an important role…to enact sensible government policies based upon sound science that fosters a suitable business climate and not political agendas. A competitive business climate that allows profitability, while maintaining public confidence in U.S. medicines, foods, and other products derived from biotechnology processes, is critical for success and survival of the industry.

Execution of the Food and Drug Modernization Act and continued efforts to seek international regulatory harmonization should proceed promptly. More efficient and timely regulatory approval will speed life saving medicines and other biotech products to the market and reduce development costs. However, government policies must never allow the Food and Drug Administration, the United States Department of Agriculture and the Environmental Protection Agency to compromise their rigorous regulatory standards. To do so would risk loss of public confidence in our medicines and foods and thus the biotechnology industry.

Finally, government must work collaboratively with industry and academia to address the biotechnology-related ethical and societal controversies. We must establish appropriate forums to make sure appropriate ethical and legal frameworks are in place to support the rapid pace of scientific innovation.

CONCLUSION

Extraordinary advances in the biological and life sciences are greatly expanding our knowledge of how the body works at the most fundamental molecular levels. The exploitation of modern biotechnology and information technologies are fueling this explosion of knowledge in the life sciences. Genes, proteins and antibodies are already providing new drugs and vaccines, as well as hardier and more nutritious crops for the agriculture sector. The use of microbes and biotechnology processes for bioremediation also offers great potential for improving water and soil quality in the environment. The science of genomics, proteomics, bioinformatics, pharmacogenetics, and microbiology promises to transform medicine, agriculture and the environment in an unprecedented manner.

Biotechnology, however, is not without risks. Controversial ethical, societal, and trade questions – whether animal/human cloning, stem cell research, gene therapy, genetically modified foods or fear of accidental damage to man or the environment – could hinder public acceptance of biotechnology. Ultimately, public acceptance of biotechnology-derived products in the market place will play a key role in determining

the future of biotechnology. More worrisome, the technology could be deliberately misused to cause disease and suffering in humans, animals and plants, either as an act of war, or as an act of terrorism.

The industry has definite national security implications and will contribute evermore significantly to U.S. economic growth and societal well-being. The U.S. is the international leader, but industry and government must strive to maintain that leadership role to ensure that the industry not only survives, but also thrives so that biotechnology's tremendous potential is achieved. Improved health, quality of life, and economic prosperity are dependent upon it.

Many believe that we have entered a revolutionary era of biology and that the first 100 years of the new millennium will constitute "the biotechnology century". As with all revolutions, the outcome of the biotechnology revolution remains unclear. The outcome could exceed all expectations, or the outcome could bring unintended negative consequences depending on the course of actions pursued by society, industry and government. Sound and sensible government policies, responsible industry practices and appropriate long-term capital investment should ensure that the U.S. and the society at large reaps the full benefits of the biotechnology revolution.

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