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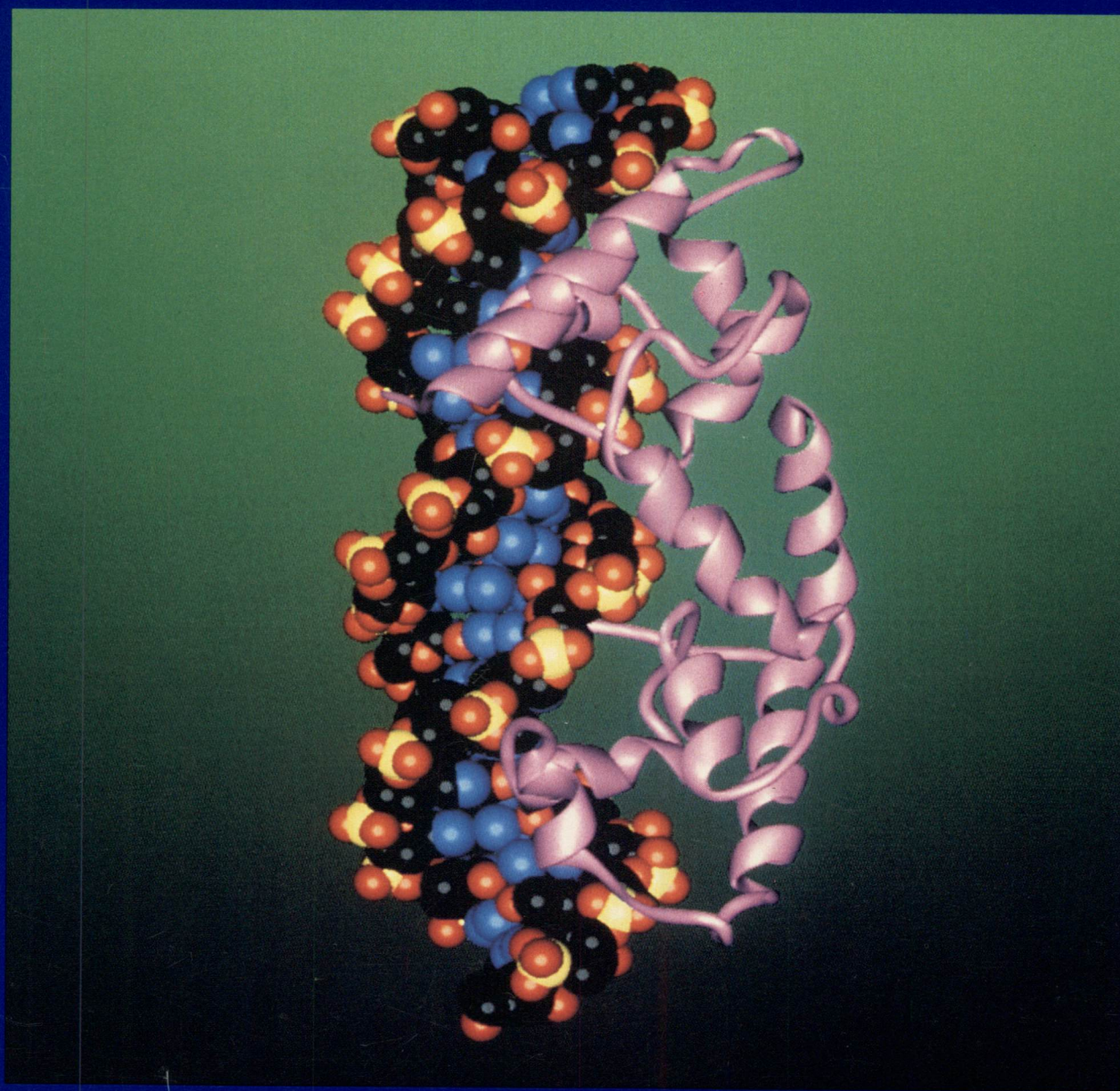
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THE PRESIDENT'S COUNCIL
ON COMPETITIVENESS

**REPORT ON NATIONAL
BIOTECHNOLOGY
POLICY**



FEBRUARY 1991

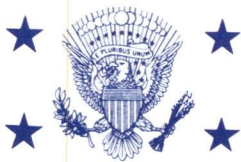
Cover photo: Operator site of viral DNA (Lambda) bound to a repressor. The atoms are colored by the Corey/Pauling scheme in which carbon is black, oxygen is red, phosphorus is yellow and nitrogen is blue. The repressor protein is depicted as a ribbon through the carbon-backbone of the protein. This image was created by Julie Newdoll using software written by Conrad Huang, Eric Pettersen, and Greg Crouch at the Computer Graphics Laboratory, University of California, San Francisco.

THE PRESIDENT'S COUNCIL
ON COMPETITIVENESS

**REPORT ON NATIONAL
BIOTECHNOLOGY
POLICY**

VICE PRESIDENT DAN QUAYLE
CHAIRMAN

FEBRUARY 1991



THE VICE PRESIDENT
WASHINGTON

MEMORANDUM FOR THE PRESIDENT

FROM: THE VICE PRESIDENT *Dan Quayle*
SUBJECT: PRESIDENT'S COUNCIL ON COMPETITIVENESS
REPORT ON NATIONAL BIOTECHNOLOGY POLICY

On behalf of the President's Council on Competitiveness, I am pleased to transmit our Report on National Biotechnology Policy.

The United States is the world leader in biotechnology. This \$2 billion domestic industry is expected to increase to \$50 billion by the year 2000. Some of the most promising advances will be in new drugs and gene therapies to treat previously incurable diseases. In the next decade biotechnology also will produce healthier foods, safer pesticides, additional energy resources, and innovative environmental clean-up techniques.

The United States will need to work hard to maintain and improve our competitiveness in this area. Our study lays out policies to support scientific research, reduce unnecessary regulation while protecting health and the environment, and create a climate in which the private sector can bring new discoveries to the market place to be available for all Americans and the rest of the world.

Our Report on National Biotechnology Policy recommends several immediate steps to implement these goals. These will follow up on the Principles of Regulatory Review that you approved in August 1990. The Report also identifies several areas for further study that will be pursued by the Council for future refinement of biotechnology policy.

I would like to thank the members of the Council and the Biotechnology Working Group for their excellent work.

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THE PRESIDENT'S COUNCIL
ON COMPETITIVENESS
**REPORT ON NATIONAL
BIOTECHNOLOGY
POLICY**

Summary of Recommendations

1. Science and Technology — Building for the 21st Century

Council on Competitiveness Actions

1-1 To foster competitiveness and the commercialization by the marketplace of discoveries, including new biotechnology research, each agency should vigorously implement the provisions of the Technology Transfer Act, as amended. Agencies should inform university administrators that seeking commercialization of research in cooperation with U.S. industry is an important element in Federally-supported university research.

1-2 To ensure the highest ethical standards by participants in the government regulatory process while facilitating the interaction between scientists and industry, guidelines should be developed to require full financial disclosure of relationships between Federally-supported or employed scientists and commercial entities when the scientist is involved in a clinical trial of an associated product.

1-3 The Federal government should facilitate the training of a sufficient number of scientists and engineers at the graduate, doctoral and post-doctoral levels in science and engineering fields, including those related to biotechnology. Programs should foster multi-disciplinary training, such as through biotechnology centers, and the training of women and minorities.

1-4 Federal immigration policies should consider the value of retaining our competitive edge in areas such as biotechnology by putting greater emphasis on a prospective immigrant's skills. The provisions of the Immigration Act of 1990 should be fully implemented to allow those who can make a major contribution in important fields to enter the country, and to encourage those who are here to stay.

Initiatives for Further Study by the Biotechnology Working Group

1-5 Federal funding allocations for biotechnology research within the fields of agricultural, biomedical, energy, and environmental research should be examined and areas of opportunity identified for support.

1-6 While Federal research programs should continue to have increased support for basic sciences as the top priority, further attention should be given to the need for funding to support the development of enabling and scale-up technologies. The Biotechnology Working Group should identify means within existing programs to encourage the development of these generic, pre-competitive technologies that benefit all firms.

2. Risk-Based Regulations — Protecting Safety Without Unnecessary Burdens

Council on Competitiveness Actions

2-1 The Administration should use the Four Principles of Regulatory Review to guide agencies in determining the level and type of necessary oversight or regulatory review. The goal of these principles is to ensure that regulations and guidelines affecting biotechnology are based solely on the potential risks and are carefully constructed and monitored to avoid excessive restrictions that curtail the benefits of biotechnology to society.

2-2 The Administration should publish in final form the "Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits."

2-3 The Administration should oppose any efforts to create new or modify existing regulatory structures for biotechnology through legislation. Any necessary adjustments can be accomplished through policies and regulation based on the Four Principles of Regulatory Review.

2-4 Agencies that oversee biotechnology products and research should adopt guidelines and regulations that are consistent with the Four Principles of Regulatory Review and the "Principles for Federal Oversight of Biotechnology."

2-5 The Biotechnology Working Group should prepare an oversight policy. Under the auspices of the Council on Competitiveness, a policy statement describing the Administration's oversight of new biotechnology research and products not in the 1986 Coordinated Framework should be prepared and published for public comment no later than spring 1991.

Initiatives for Further Study by the Biotechnology Working Group

2-6 The Biotechnology Working Group should consider proposals to remove regulatory burdens by improving interagency coordination, streamlining the regulatory agencies' evaluation processes, periodically reevaluating regulations, addressing problems with state and local laws, and exploring whether non-tariff trade policies are being applied in such a way as to create technical barriers to trade.

3. A Flourishing Free Market for Biotechnology — Providing Capital and Financial Resources and Protecting Intellectual Property Rights

Council on Competitiveness Actions

3-1 The Administration should continue to oppose fundamental legislative changes to the Orphan Drug Program that undermine the economic incentives to produce new drugs for rare diseases. The FDA should develop administrative proposals to address concerns about the definition of "disease" used in the program to avoid overextension of the program to treatments that are not "orphan."

3-2 The Administration should support passage of legislation to provide necessary process patent protection for products, such as those in the biotechnology area, which can be protected only through process patents.

Initiatives for Further Study by the Biotechnology Working Group

3-3 The Biotechnology Working Group should continue to examine tax issues that affect biotechnology and recommend ways of reconciling the need to remove barriers to growth and innovation generally with the other objectives of tax policy.

Introduction

This report describes the competitive status of American biotechnology and outlines the goals of Administration policy to support free market development of biotechnology products. It examines three critical policy areas — Support for Science and Technology, Risk-Based Regulation of Health and Safety, and Access to Capital and Financial Resources and Protection of Intellectual Property Rights.

Modern Biotechnology — The New Frontier

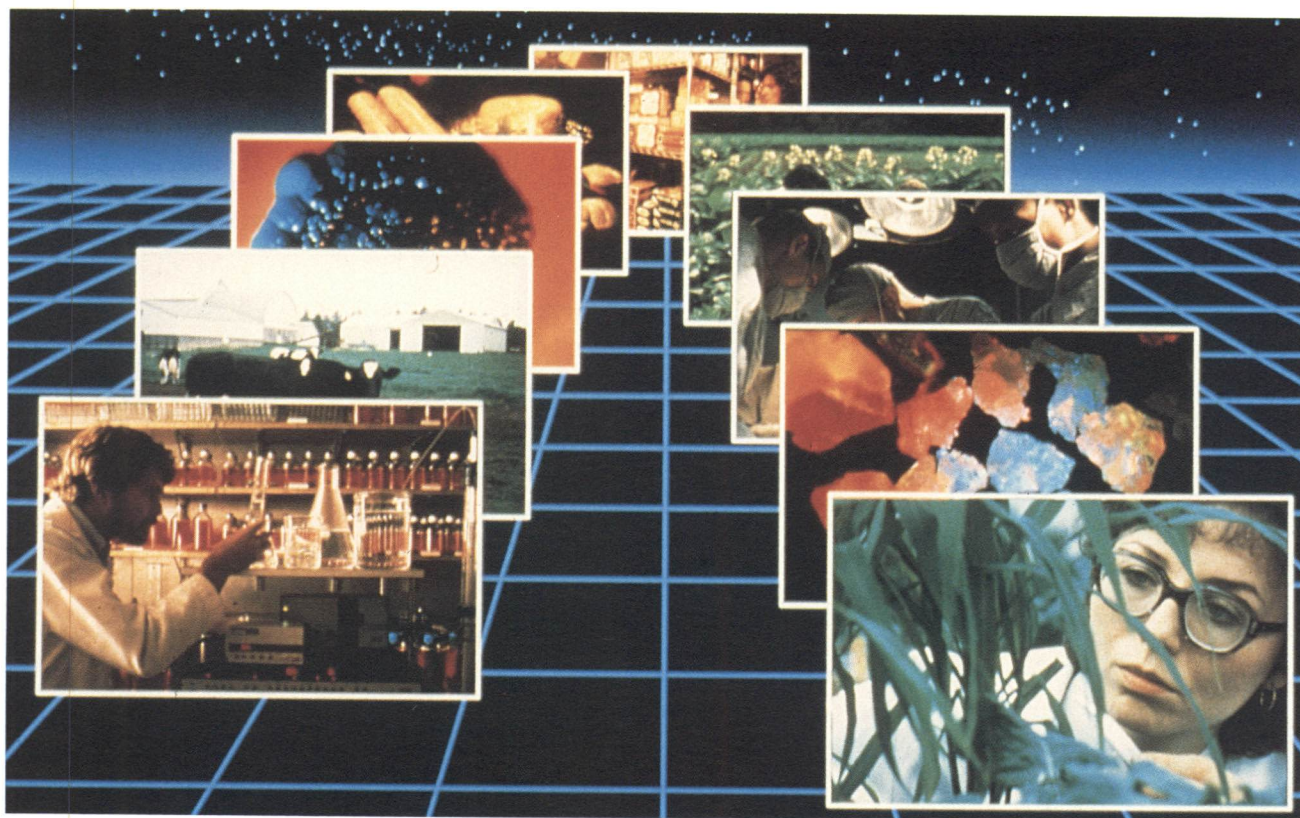
Biotechnology is the use of various biological processes¹ to make products and perform services from living organisms or their components. Biotechnology dates back thousands of years — to the time when human beings first began using microorganisms to produce foods such as bread and beer, or to modify

¹Rather than a single scientific discipline, biotechnology draws upon a number of relevant fields such as molecular biology, structural biology, molecular genetics, immunology, cell biology, biochemical engineering, protein engineering, and classic breeding techniques.

plants and animals through progressive selection for desired traits. The new biotechnology revolution began in the 1970s and 1980s when scientists learned to alter precisely the genetic constitution of living organisms. This breakthrough allows the production of large quantities of rare proteins. Additionally, it is now possible to modify plants and animals to carry specific desired genetic traits through much more precise techniques than traditional breeding.

The Full Potential of Biotechnology

Biotechnology holds the promise of new and additional breakthroughs in the fields of medicine, foods, agricultural products, energy, and environmental clean-up. Using the new biotechnology techniques, scientists predict that we will see a revolution in these industries. Biotechnology will give us the potential to treat previously incurable genetic diseases. It also can give us better and healthier food products, including meats, dairy products, fruits and vegetables, greatly reduce reliance on toxic pesticides, and im-



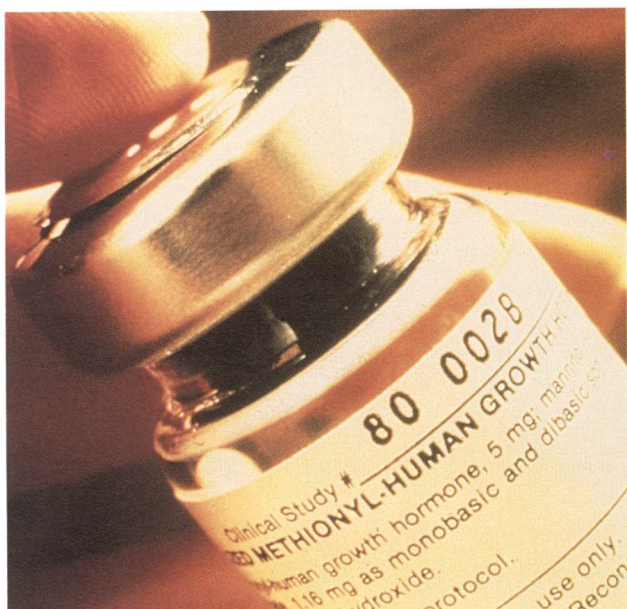
These applications of biotechnology comprise just a small sample of the hundreds of products under development at universities and biotechnology companies throughout the world. Photo courtesy of the Industrial Biotechnology Association.

prove pesticides, herbicides, and irrigation. Environmentalists look to biotechnology as a possible means of cleaning up oil spills and other environmental hazards more efficiently and with less disruption of the ecosystem.

Human Health

Remarkable new medical treatments based on biotechnology are appearing daily. The most recent advances have come in developing new gene therapies to insert genetic material into human cells. In one experiment, children who suffer from a rare and devastating immune disorder (Severe Combined Immune Deficiency Syndrome, SCIDS) are having corrective genetic material inserted into their white blood cells, which will seek to restore the cells' ability to fight infections. Similar experiments also are under way to test gene-insertion therapies to help cancer patients with advanced melanoma. If successful, similar treatments could be developed for other forms of cancer, hemophilia, sickle cell anemia, AIDS and other diseases. Another example is the recent discovery of the possible genetic basis for cystic fibrosis; this research suggests a potential means of treating this disease.

Biotechnology provides new drugs and better techniques for delivering medicines to diseased parts



This bottle of recombinant growth hormone will help a child with dwarfism grow to normal height. Photo courtesy of the Industrial Biotechnology Association.

of the body. So far, the Food and Drug Administration has approved preventative agents or treatments for:

- Hepatitis B (vaccine; therapeutic)
- Anemia
- Diabetes mellitus
- Acute myocardial infarction (heart attack)
- Human growth hormone deficiency
- AIDS-related Kaposi's sarcoma
- Hairy cell leukemia
- Venereal warts
- Kidney transplant rejection.

More than 1,000 clinical trials of new drugs and biologics are under way. A majority of these are for cancer or cancer-related conditions and more than 15 percent are for AIDS or HIV-related conditions.



The effect of a plant growth hormone is shown here with the differences between a normal petunia plant (left) and a genetically engineered petunia plant (right). Scientists have inserted a gene into the modified plant that allows them to selectively turn on and off a plant growth hormone using higher and lower temperatures. Photo courtesy of Dr. June Medford, Pennsylvania State University.

Biotechnology also allows companies to make purer, more effective, and more readily available drugs and medical treatments. The most dramatic example is human insulin. Prior to 1982, diabetics were treated with insulin derived from pork and beef pancreases. In the late 1970s and early 1980s, concern was raised about a possible shortage of world-wide supplies of these products. At the same time a new biotechnology technique was developed to insert genetic material into microorganisms causing them to secrete clinically purer human insulin, which can now be mass-produced to treat diabetes.

Biotechnology has made it easier to detect and diagnose diseases. With remarkable simplicity and precision, these methods can now detect a variety of genetically caused and other conditions. They vary from easily usable and inexpensive home diagnostic kits for pregnancy, to physician performed tests that simplify formerly complex laboratory procedures. More than 400 clinical diagnostic devices using biotechnology products are used in clinical practice today. Of these, the most important have been the screening tests for blood products that have safeguarded the blood supply from contamination by the AIDS and the hepatitis B and C viruses.

Agriculture, Foods, and Animal Husbandry

New biotechnology can produce the same benefits as traditional techniques only more quickly and with greater precision. The modern tools of biotechnology can improve the nutrition, taste, and appearance of plant, animal and other food products. Enhancements of certain characteristics of tomatoes, for example, are expected to provide increased resistance to pests, thus reducing the need for chemical pesticides. They also should produce fruits that will have less spoilage between the farm and the consumer and will improve the texture. Companies are field-testing a variety of crops with enhanced resistance to specific viruses, insect pests and safer herbicides. Under development are improved staple crops such as soybean or corn with higher levels of specific nutrients, and oil-yielding plants with lower levels of saturated fatty acids.

Many manufactured foods such as cheese and yogurt require the use of bacteria or enzymes in their production. Scientists are modifying existing food-use enzymes, isolating new varieties of food-use enzymes, and cloning other enzymes into microorganisms for easier isolation and purification. For

example, chymosin, the enzyme used in the manufacture of cheese, traditionally available from the cow can now be made from specially developed microorganisms. This product has been affirmed by the Food and Drug Administration as generally recognized as safe.

Scientists are genetically improving microorganisms used for fermentation to produce many food stuffs and beverages. Microorganisms can produce food utilizing traditional food byproducts such as the whey remaining from cheese production. New food colorings and flavorings are under development. Researchers are making new probes for rapid detection and accurate identification of specific microbial pathogens in food.

In the area of animal husbandry, biotechnology has enabled development of hormones that increase the protein to fat ratio in pigs and the milk yield from cows. Additionally, veterinary diagnostics and therapeutics similar to those for humans are under development with several having reached the marketplace. One vaccine under testing holds great promise for effectively and inexpensively controlling rabies in wild and domestic animal populations.

Energy

New biotechnology will find many energy-related applications. For producing renewable energy, scientists are studying the use of microorganisms, modified plants, plant material, municipal and animal wastes, and other renewable sources to yield different types of fuels such as gasoline and natural gas. Examples include the use of wood to produce gasoline substitutes, and wood waste products (bark and sawdust) to yield ethanol. Other fossil energy-related research is aimed at the use of biological systems for enhanced oil recovery, for coal desulfurization (clean coal), and conversion of coal to gaseous and liquid fuels. For example, quantities of oil that otherwise would be lost may be recovered through the application of certain microorganisms to oil wells. Research is under way investigating biotechnology applications for reducing wastes from energy-generating processes and for clean-up of energy-related waste.

Environment

New biotechnology promises products that will clean up the environment, provide alternatives to chemicals, and perform other tasks such as mineral recovery.

"Bioremediation" is a process that involves the use of microorganisms for clean-up. For example, certain microorganisms "eat" (degrade) oil and produce environmentally safe, fatty substances as byproducts. Recent experiments in Prince William Sound, Alaska and the Gulf of Mexico have demonstrated the value of microorganisms for clean-up of oil spills in the sea, on the shore and in wetlands². Bioremediation is also used for cleansing soil contaminated by gasoline. While these experiments have used non-modified microorganisms, microorganisms developed through biotechnology will have enhanced clean-up capabilities.

Biotechnology can produce more effective and environmentally safe microorganisms for industry, agriculture, and mining. "Biorational" pesticides that employ microorganisms to attack pests are well known. A common example is BT (*Bacillus thuringiensis*) used to control gypsy moths. Biorational pesticides

quickly break down into harmless components, thus avoiding residue problems associated with chemical pesticides. Seeds can be made to be more pest resistant with the insertion of genetic material from a known biological pesticide such as BT. Similarly, seeds can be enhanced to yield plants with greater resistance to drought. Microbial degradation of sewage forms the basis of a substantial portion of the waste treatment industry. Microorganisms are used for mineral recovery. For example, certain microorganisms can refine copper ore.

United States as World Leader in Biotechnology

American researchers developed much of the basic science of the new biotechnology, and the United States continues to lead the world in the commercialization of most emerging biotechnology products. The new techniques have spawned a variety of industries that now comprise more than 400 start-up firms, more than 200 established firms that have diversified into biotechnology, and more than 200 supply firms in the United States alone. Just a decade-and-a-half after its beginnings, the new biotechnology industry in

²U.S. Environmental Protection Agency. Alaskan Oil Spill Bioremediation Project-Update. July 1990



From the air, a bioremediated test plot resembled a clean rectangle etched upon the surface of the beach. The cobblestone plot, which was located in Snug Harbor, was treated with oleophilic fertilizer during the summer of 1989 after the Alaskan oil spill. Photo courtesy Environmental Protection Agency.

the U.S. produced pharmaceuticals, diagnostic tests, and agricultural products worth close to \$2 billion. In the long run, because of the pervasive role of biologically produced substances in everyday life, biotechnology has the potential to surpass the computer industry in size and importance.

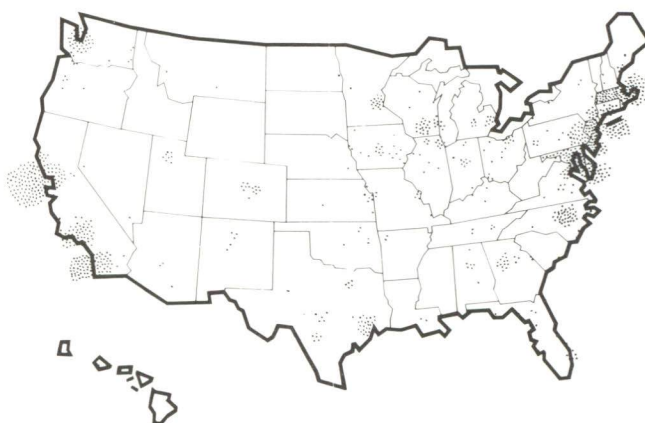
Foreign governments have targeted biotechnology as of vital economic importance and are beginning to seriously challenge the American lead in particular areas. For example, Japan is also a major player in the new biotechnology and is targeting pharmaceutical applications in the same way that it earlier targeted the semiconductor and consumer electronic industries. Significantly, the Japanese government is focusing its support on pre-competitive and applied research and product development, building on Japanese industry's traditional strengths in fermentation technology. In addition, the European investment in the new biotechnology is close to that of the United States, and Europe actually leads in the production of monoclonal antibodies.

The Role of the Federal Government

The proper role for the U.S. government is to (1) provide needed support to activities that are undersupported by the market when they generate social benefits that greatly exceed their private profitability, and (2) reduce artificial barriers to proper market functioning. Policies include actions to: ensure safety and public confidence; support science education and training; maintain and enhance basic research; support applied research with generic applicability, including especially methods for production scale-up; transfer the fruits of government-sponsored research to the private sector; remove undue regulatory burdens while creating and protecting property rights in new innovations; and allow industry to operate in a strong financial market.

These U.S. government actions allow our research institutions and private sector industries to maintain and enhance their roles as world leaders in the development of biotechnology derived organisms, experiment with new and safe processes, and develop and produce innovative biotechnology products that benefit society.

These goals are implemented by various agencies that provide: support for research; regulation of the development, sale and use of a wide range of products; and financial policies that affect biotechnology



Biotech 91: The Landscape of an Industry
Courtesy of G. Steven Burrill, Ernst & Young

industries. Oversight of biotechnology safety is guided by the principles of the 1986 "Coordinated Framework for Regulation of Biotechnology" (Coordinated Framework)³.

Ethics also have been a concern of the Federal government from the perspective of the safety and appropriateness of using the new techniques of genetic manipulation. Almost two decades of new biotechnology research and biotechnology product development and use have provided assurance that safety can be properly maintained. This experience combined with careful deliberation by scientists, policy makers and the public, has led to a view that ethical approaches suitable to traditional methods apply equally well to the new biotechnology. Modifications of plants, animals and microorganisms may be made to improve important beneficial characteristics, and should not be used to create or enhance dangerous, harmful characteristics. Special research such as human gene therapy, has been approached cautiously and with careful consideration to ensure that the applications are limited to treating conditions of known debilitating or fatal genetic defects and other disease states such as cancer or AIDS.

³51 FR 23302, June 26, 1986

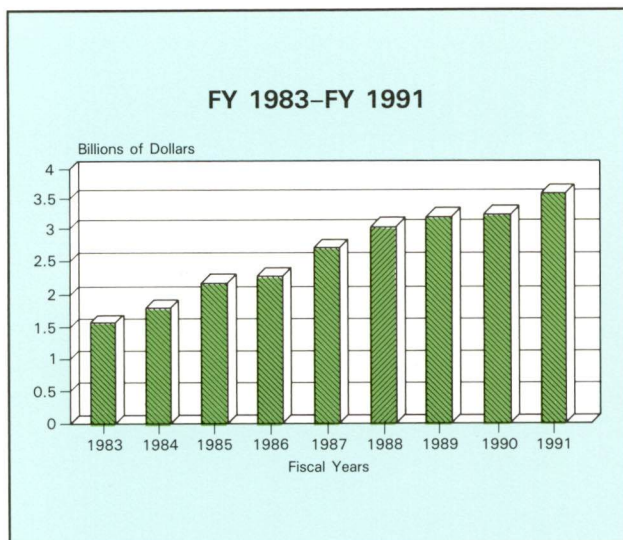
1. Science and Technology — Building for the 21st Century

Current Administration Policies

The key to maintaining our competitive position in the world biotechnology marketplace continues to be strong support for basic research and research training. In Fiscal Year 1990 (FY '90), the total Federal investment in biological research related to biotechnology was approximately \$3.5 billion. Of this sum, more than 80 percent was awarded through the National Institutes of Health. Of particular impact is the human genome project — designed to map the location of all the genes in the human body — supported by the Department of Health and Human Services and the Department of Energy. This research should provide major technological spinoffs for pharmaceuticals, medical devices, diagnostic methodologies, and informatics.

Eleven other Federal agencies in addition to NIH support programs related to biotechnology in fields that are poised for substantial growth, such as agricultural, energy and environmental research. The Administration currently supports biotechnology research and training through grants for multi-disciplinary centers as well as investigator-initiated research grants.

The industrial sector also provides about \$2 billion for biotechnology research and development (R&D), most of which is committed to specific product development.



Federal funding of biotechnology research
Source, Office of Science and Technology Policy.

Council on Competitiveness Policy Actions

Technology Transfer

The U.S. biotechnology and other industries were greatly assisted by the technology transfer policies begun in 1980 and accelerated in the Reagan-Bush Administration. These policies fostered joint R&D projects between industry and Federally-supported universities. More recently, this process was extended to Federally-owned and operated laboratories by protecting private sector commercial rights to subsequent discoveries. Such joint R&D allows industry to gain access to unique state-of-the-art scientific knowledge.

The pursuit of scientific knowledge is an end worthy of national attention. The translation of new ideas into the market place is an equally laudable national goal. While the commercialization of technology is not the dominant objective of Federally supported scientific research, society can often benefit from the commercial application of scientific knowledge through these efforts. For example, President Bush awarded the National Medal of Technology to a Stanford University Professor in recognition of his breakthrough, basic biological research resulting in the first process patent in biotechnology.

Joint efforts among the public, university and private sectors to promote the transfer of scientific knowledge to the market place should be encouraged wherever possible. The number of cooperative R&D agreements (CRADAs) under the Technology Transfer Act has increased fourfold during the Bush-Quayle Administration (from approximately 110 in 1988 to more than 400 today). Japan is now seeking to copy our model for linking its industry, universities, and national laboratories.

Recommendation:

1-1 To foster competitiveness and the commercialization by the marketplace of discoveries, including new biotechnology research, each agency should vigorously implement the provisions of the Technology Transfer Act, as amended. Agencies should inform university administrators that seeking commercialization of research in cooperation with U.S. industry is an important element in Federally-supported university research.

Conflict of Interest Guidelines for Federal Research Grantees

The marked increase in the frequency of joint government/industry research projects has highlighted the need to avoid conflicts of interest. A possible conflict of interest arises when an individual involved in conducting evaluative tests of new products (e.g. clinical trials) also holds an interest in a company that stands to gain from the results of the study. In response, the National Institutes of Health proposed guidelines in 1989 that would have applied conflict of interest standards not only to clinical trials, but also to many facets of government-sponsored research.

This proposal raised substantial concerns both from academia and industry. The guidelines were considered to be overly broad and would have had a chilling effect on the cooperative agreements between industry and Federally-supported universities or Federal research laboratories.

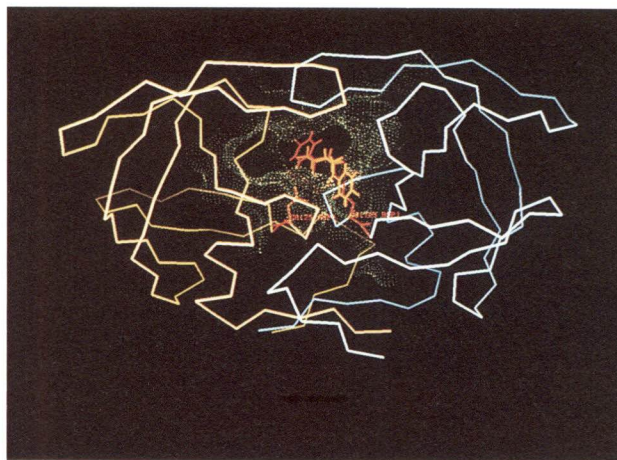
Health and Human Services Secretary Sullivan rejected the proposed guidelines on December 29, 1989. In response to comments received urging that the conflict of interest standards should focus on clinical trials, a new proposal is under review within the Department of Health and Human Services.

Recommendation:

1-2 To ensure the highest ethical standards by participants in the government regulatory process while facilitating the interaction between scientists and industry, guidelines should be developed to require full financial disclosure of relationships between Federally-supported or employed scientists and commercial entities when the scientist is involved in a clinical trial of an associated product.

Improving U.S. Intellectual Resources

The present and future health of science, in general, and the biotechnology industry, in particular, in both the academic and private sectors, depends, in part, upon the availability of a cadre of broadly trained researchers, bioprocess engineers, and technologists. The need for increased funding for the training of our future biologists and other scientific disciplines was recognized in the President's FY '91 budget. Adequate training at the elementary and secondary levels is also needed. President Bush and the Nation's Governors jointly have established national goals in education, one of which is to make American high

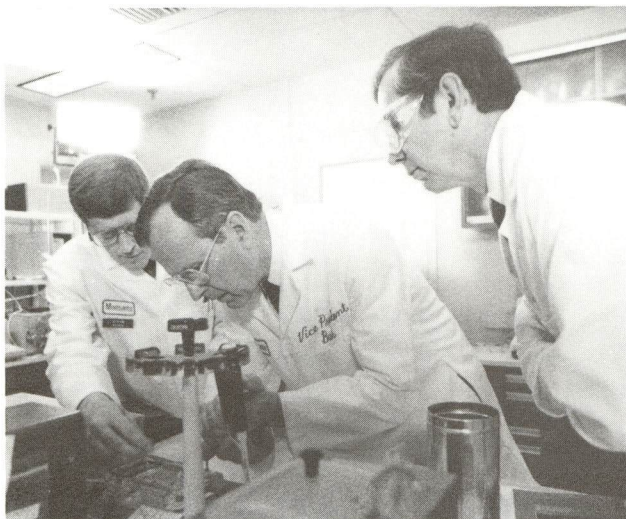


An example of rational drug design using computer modeling techniques to predict how a drug will bind to the active site of a target molecule. The orange structure in this picture is the drug Haloperidol, which is bound to the HIV-1 protease, an enzyme necessary for viral replication. The protease is not able to release the drug and is, therefore, unable to function. This work was done by Renee Desjarlais, Irwin Kuntz, et al., at the University of California, San Francisco. The image was created by Julie Newdell at the UCSF Computer Graphics Laboratory.

school graduates rank first in mathematics and science by the end of the century.

For biotechnology, different combinations of expertise will be called upon. Examples include: pharmacology, toxicology, immunology, molecular biology, industrial microbiology, chemistry, theoretical mathematics, biochemical engineering, and computer and information sciences. Individuals possessing cross-cutting skills in these fields are necessary to continue to produce the scientific advances that undergird commercial product development, and to support the growing number of companies utilizing biotechnology. Furthermore, it is important to provide training opportunities to women and minorities in these fields.

The traditional approach to cross-cutting training has been through interdisciplinary programs within the traditional university structure. While the number of interdisciplinary programs for biotechnology is increasing, such programs are sometimes treated as "step-children" within the traditional university structure.



Then-Vice President Bush at Chesterfield Laboratory, Monsanto Company, on May 15, 1987 shown splicing a plant gene to increase resistance to disease. Photo courtesy of Monsanto Company.

Biotechnology centers are a new approach for promoting interdisciplinary training and soliciting input from industry as to research needs and specific project support. The National Science Foundation now funds engineering centers dedicated to biotechnology at the Massachusetts Institute of Technology and Montana State University. There are a number of other centers, many established through state initiatives.

In addition to American students, the United States traditionally has been an attractive place for foreign scientists to study and work. Our universities continue to be a major "export earner" by attracting students from all over the world. Many graduates stay in the United States and contribute to U.S. universities and industry. The Immigration Act of 1990 changes U.S. policy to allow increased immigration of those who can make a major contribution to technologies such as biotechnology.

The Administration supports a significant increase in the number of skill-based immigrant visas permitted under the Immigration Act of 1990. This Act will admit skill-based immigrants on the basis of employer needs or upon meeting certain objective criteria related to the immigrant's potential contribution to the United States.

In FY'88, employer-selected immigrants (i.e. labor market bound immigrants with their families) accounted for about 54,000 (9 percent) of the total number. The Immigration Act of 1990 will increase the annual number of visas for skill-based immigrants to 140,000. The Immigration Act of 1990, passed in the closing days of the 101st Congress was signed by President Bush on November 29, 1990.

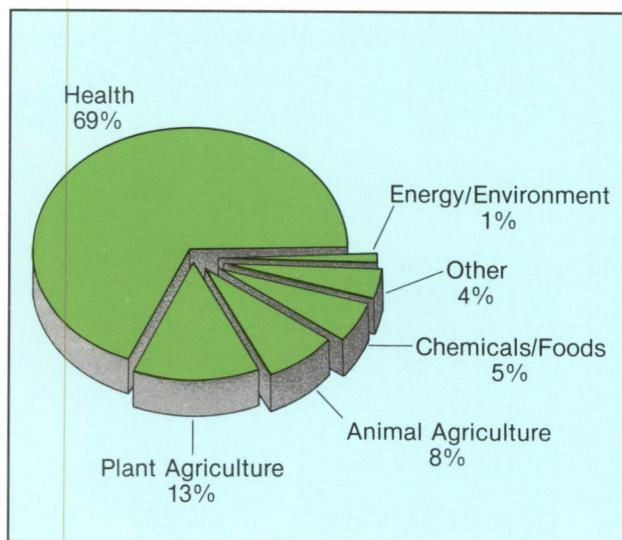
Recommendations:

1-3 The Federal government should facilitate the training of a sufficient number of scientists and engineers at the graduate, doctoral and post-doctoral levels in science and engineering fields, including those related to biotechnology. Programs should foster multi-disciplinary training, such as through biotechnology centers, and the training of women and minorities.

1-4 Federal immigration policies should consider the value of retaining our competitive edge in areas such as biotechnology by putting greater emphasis on a prospective immigrant's skills. The provisions of the Immigration Act of 1990 should be fully implemented to allow those who can make a major contribution in important fields to enter the country, and to encourage those who are here to stay.

Initiatives for Further Study by the Biotechnology Working Group

Federal funding of basic R&D over the last two decades has been a critical element in the scientific advances underlying biotechnology. In the United States, public funding for biotechnology goes almost entirely to support basic research in universities and research institutes. Many believe that continuing our strong support for this basic research represents the key to retaining our competitive position in the biotechnology marketplace. Other governments, however, direct their expenditures toward somewhat different goals. In Japan, for example, governmental funding is directed much more toward applied research, including product development and production scale-up. Differences in governmental funding patterns raise some fundamental questions about the current allocation of R&D funds in the U.S.



Industrial Biotechnology R&D by Application
Source, Office of Science and Technology Policy.

Adequacy of Funding for Agricultural and Environmental Research

Led by the pioneering research supported by the National Institutes of Health, the biotechnology industry has flourished particularly well in the fields of pharmaceuticals and medical devices. In comparison, research in other biotechnology areas such as agricultural, energy, and environmental applications has received less support. The use of biotechnology techniques to develop agricultural products presents an enormous opportunity to improve the productivity of U.S. agriculture. Assuring a rich science base that can nourish technological developments similar to the gains over the last two decades in the biomedical field will be critical to bringing U.S. agriculture into the next century. Other promising areas for research include development of renewable and enhanced energy sources, bioremediation, the use of microorganisms to break down toxic wastes, the development of biopesticides as a substitute for chemical pesticides, and veterinary applications.

The broadening of biotechnology research was addressed in the recent report of the National Research Council (NRC), *Investing in Research: A Proposal to Strengthen the Agricultural, Food, and Environmental System*. The President's budget request for FY '91 includes \$100 million for projects in the areas identified as high priority by the NRC.

Recommendation:

1-5 Federal funding allocations for biotechnology research within the fields of agricultural, biomedical, energy, and environmental research should be examined and areas of opportunity identified for support.

Support for Scale-Up From Basic Discovery to Production

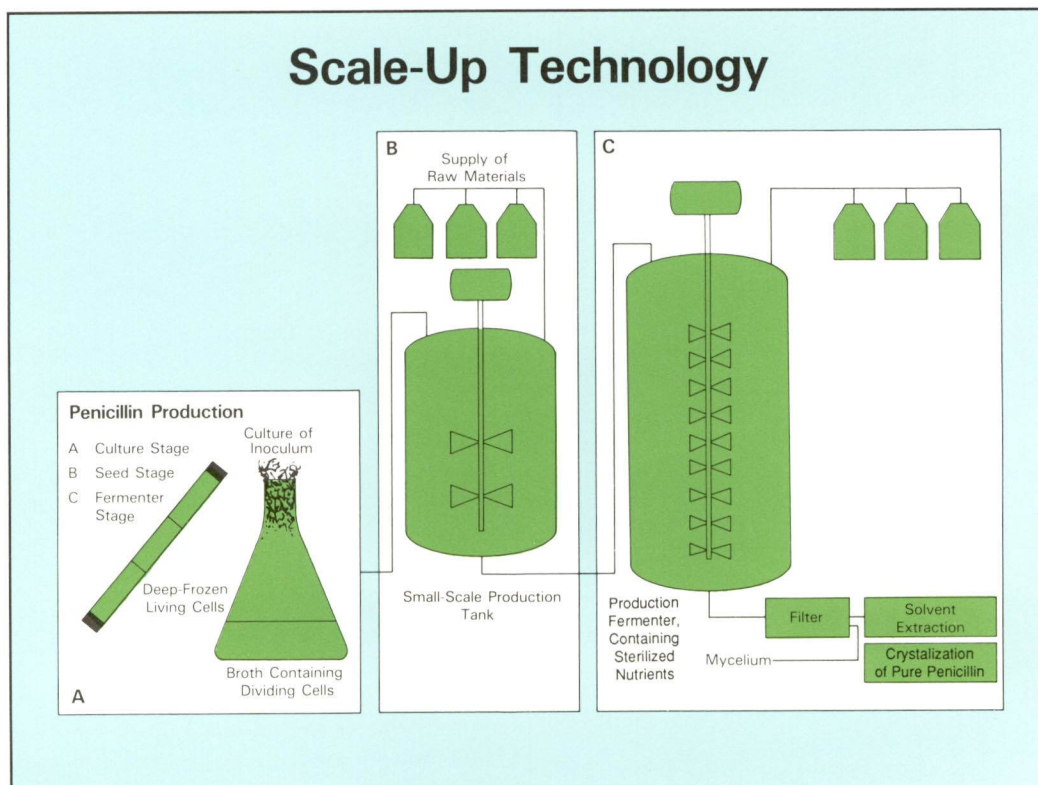
The United States is at a critical juncture. Although we retain our lead in the basic sciences, we face vital hurdles in translating fundamental scientific information into commercially viable products.

Each of the progressive steps of biotechnology scale-up from test tube to flask, to small fermentation vessel, to pilot plant, to large-scale production facilities involves new scientific questions. At each step in scale-up, the development of a viable product requires dealing with living cells vulnerable to shear forces, temperature and oxygen regulation, growth conditions and nutritional requirements, inhibiting effects of metabolic byproducts, and other factors. Furthermore, greater understanding of gene expression — how genes work to cause the organism to make products in model systems — is very important. Attention should also be directed toward fundamental research on factors that affect the technical aspects of scale-up, e.g. cellular growth and gene expression in both liquid phase and solid/liquid phases of growth. Finally, basic research in structural biology, including protein structure-function relationships and the impact of metabolism on gene expression will lead to future product development stages.

Multi-disciplinary research is required for these developmental steps of products. Research focused on generic principles and procedures common to scale-up processes could generate large spillover benefits that could not be captured by any one firm and hence would be an appropriate area for Federal support. But this research generally falls outside the normal area of interest for peer review committees that evaluate research projects for Federal funding.

To help address this problem, the Administration supports the Advanced Technologies Program (ATP) of the Department of Commerce. ATP emphasizes enabling technologies that underlie a wide range of potential applications that offer significant benefits to the nation's economy. While the program does not

Scale-Up Technology



Source, Office of Science and Technology Policy.

target specific fields, proposals in the field of biotechnology are eligible for funding under this program.

Recommendation:

1-6 While Federal research programs should continue to have increased support for basic sciences as the top priority, further attention should be given to the need for funding to support the development of enabling and scale-up technologies. The Biotechnology Working Group should identify means within existing programs to encourage the development of these generic, pre-competitive technologies providing broad benefits.

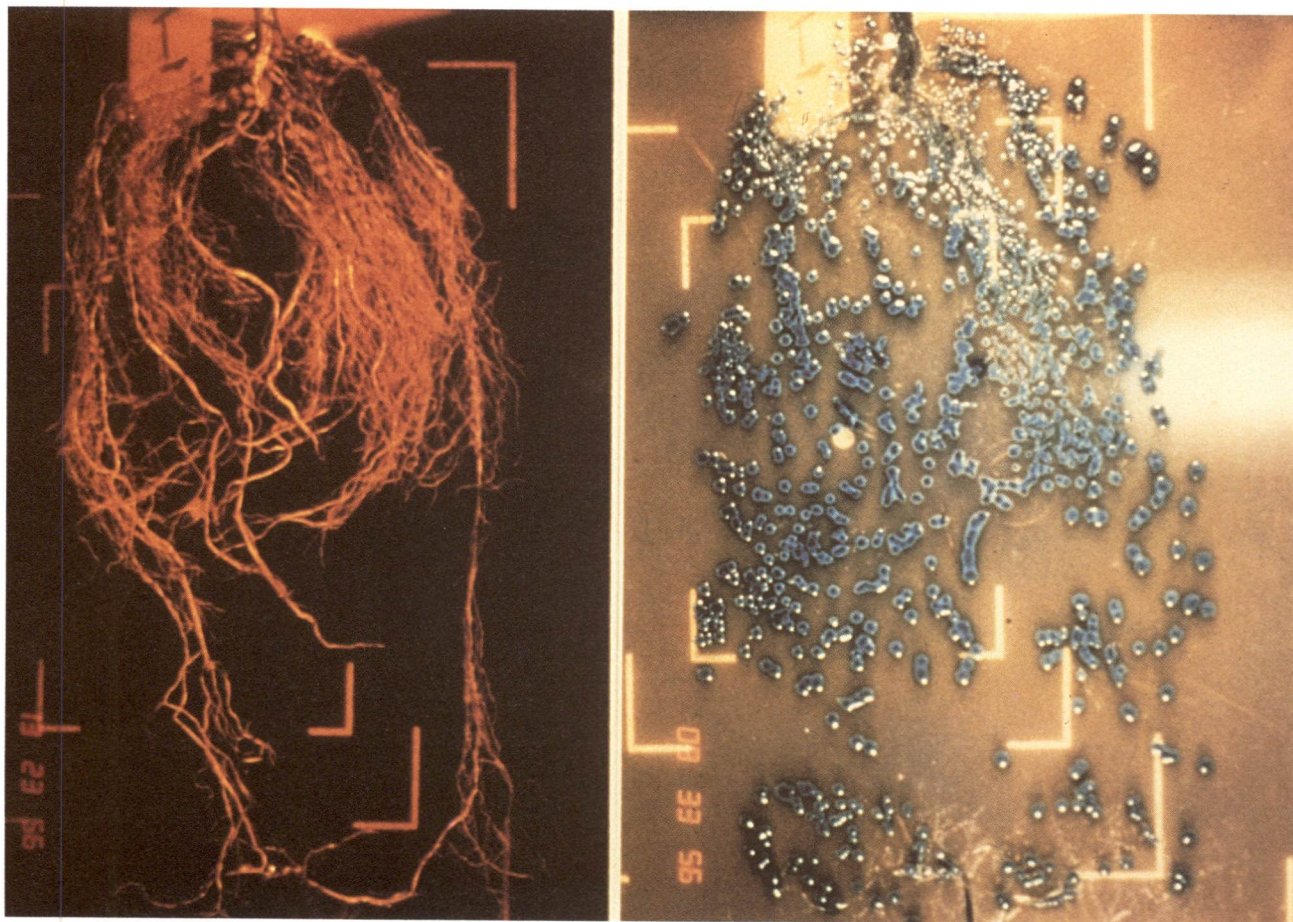
2. Risk-Based Regulation — Protecting Safety Without Unnecessary Burdens

Current Administration Policies

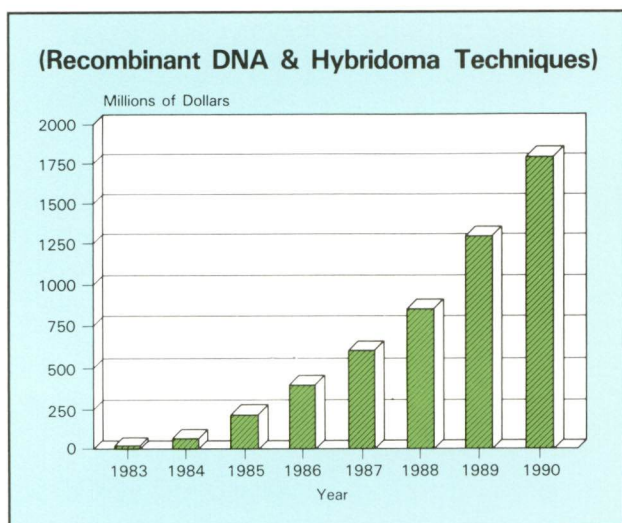
In biotechnology, as in many other high technology industries, Federal regulation is a critical determinant of the time and the cost to bring a product to market. In serving as "gatekeepers" for the development and use of new products, regulatory agencies may create substantial barriers to product development. These barriers result from the costs of testing to meet regulatory requirements, the potential for delay in regulatory approval, and the uncertainty associated with the possible imposition of extensive restrictions or outright disapproval of new biotechnology research or products. In addition, uncertainty related to the extent or effectiveness of Federal regulation may lead to the enactment of a patchwork of conflicting and burdensome state regulations. Delay, cost, and regulatory uncertainty discourage new research in regulated

areas and curtail the development of new products, as well as undermine public confidence.

In general, to avoid unnecessary burdens on biotechnology, the Administration has sought to eliminate unneeded regulatory burdens for all phases of developing new biotechnology products — laboratory and field experiments, product development, and eventual sale and use. Existing regulatory structures for plants, animals, pharmaceuticals, chemicals and toxic substances provide an adequate framework for regulation of biotechnology in those instances where private markets fail to provide adequate incentives to avoid unreasonable risks to health and the environment. In these instances, regulation also can help shield industry from avoidable incidents that could tarnish its image and impair its development.



*The seed producing the soybean root (left) was treated with genetically marked bacteria (*Pseudomonas fluorescens* 701L5) prior to planting. Monitoring technology makes it possible to visualize the bacteria (right). Photo courtesy of Monsanto Company.*



Sales of Biotechnology Products, 1983-90
Source, Office of Science and Technology Policy.

The 1986 Coordinated Framework established a roadmap for Federal regulation of biotechnology, and incorporated the principle that regulation should focus on the characteristics and risks of an organism, not the process used to produce it. Based on the principles outlined in the Coordinated Framework, the Food and Drug Administration (FDA) announced that it did not need to establish new procedures or requirements for the review of new biotechnology derived products. FDA's review of products is based on case-by-case review of risks and use, and this review would address any risks involved in new biotechnology products. However, the other two major regulatory agencies — the Environmental Protection Agency (EPA) and the Department of Agriculture (USDA) — announced policies for developing additional rules and guidelines⁴. In implementing these policies, the

⁴EPA proposed to develop new regulations that give "... particular attention, under both FIFRA and TSCA, to microorganisms that [1] are used in the environment, [2] are pathogenic or contain genetic material from pathogens, or [3] contain new combinations of traits. EPA believes these categories have sufficiently high potential for widespread exposure, adverse effects, or uncertainty concerning potential effects to deserve particular regulatory scrutiny. This approach takes a significant step towards separating products on the basis of potential risk," 51 FR 23315. USDA also proposed new rules for genetically engineered organisms and products that could pose potential risks as plant pests, 51 FR 23342. These rules were published in final form on June 16, 1987, 52 FR 22892. USDA also considered possible guidelines for certain Federally-funded agricultural research.

agencies confronted unresolved issues regarding the scope of oversight and the underlying regulatory principles necessary to guide them.

Council on Competitiveness Policy Actions

The delayed development of promised rules and guidelines has resulted in some inconsistencies in the stringency of oversight and in the extent to which regulation is "risk-based" rather than "process-based" or "turf-based" across agency boundaries. This has created an uncertain regulatory environment in some areas. The Council, therefore, recommends that the following guide regulatory policy.

Four Principles of Regulatory Review

1. Federal government regulatory oversight should focus on the characteristics and risks of the biotechnology product — not the process by which it is created.

Products developed through biotechnology processes do not, *per se* pose risks to human health and the environment; risk depends instead on the characteristics and use of individual products. Biotechnology products that pose little or no risk should not be subject to unnecessary regulatory review during testing and commercialization. This allows agencies to concentrate resources in areas that may pose substantial risks and leaves relatively unfettered the development of biotechnology products posing little or no risk.

2. For biotechnology products that require review, regulatory review should be designed to minimize regulatory burden while assuring protection of public health and welfare.

Expedited review procedures should be adopted for products likely to pose lesser risk. The jurisdiction of the several regulatory agencies should be clarified to avoid unnecessary confusion and delay and agencies should use the same standards and apply them consistently. This is especially important where a product could be regulated by several agencies. For example, pest-resistant plants may be subject to regulation by both the Environmental Protection Agency (for its pesticidal properties) and by the Food and Drug Administration (for food safety).

3. Regulatory programs should be designed to accommodate the rapid advances in biotechnology. Performance-based standards are, therefore, generally preferred over design standards.

A performance standard sets the ends or goals to be achieved, rather than specifying the means to achieve it (e.g., through a design standard). This provides firms and researchers with flexibility in choosing the best means of compliance. A performance-based standard for containment, for example, would permit alternative biological approaches for assuring containment in place of a design-based standard requiring specific physical barriers.

The adoption of performance criteria in developing regulations reduces the need to rely on a lengthy and contentious regulatory process to revise regulations. Such unwieldy regulatory procedures inevitably inhibit the changes in regulatory structure needed to accommodate advances in science knowledge. Procedures should be adopted to provide agency decision-makers with up-to-date scientific opinion and knowledge — for example, through the use of science advisory panels.

4. In order to create opportunities for the application of innovative new biotechnology products, all regulation in environmental and health areas — whether or not they address biotechnology — should use performance standards rather than specifying rigid controls or specific designs for compliance.

“Design-based” requirements may preclude use of biotechnology products even when such approaches may be both less costly and more effective. For example, a requirement to employ specific pollution control equipment would prevent use of innovative biotechnology pollution remediation or control techniques.

In accord with the following recommendation, Vice President Quayle on August 14, 1990, announced approval by President Bush of the Four Principles of Regulatory Review.

Recommendation:

2-1 The Administration should use the Four Principles of Regulatory Review to guide agencies in determining the level and type of necessary oversight or regulatory review. The goal of these principles is to ensure that regulations and guidelines affecting bio-

technology are based solely on the potential risks and are carefully constructed and monitored to avoid excessive restrictions that curtail the benefits of biotechnology to society.

Publication of the “Scope” Paper—“Principles for Federal Scope of Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits.”

The Council's Biotechnology Working Group addressed one oversight issue of particular concern to the public and biotechnology industries. Implementation of the Coordinated Framework did not resolve completely which planned introduction of organisms into the environment should and should not be subject to regulatory oversight. For example, which field tests — a phase of taking a new discovery and developing it as a product — do not require prior scrutiny by a regulatory agency.

As long as this issue of the “scope” of biotechnology oversight remained unresolved, firms and researchers have typically submitted all environmental introduction experiments — whether safe or potentially risky — to agencies for review. This process has subjected the industry and the research community to greater oversight burdens than were appropriate in light of risk considerations. All sectors of the biotechnology community have requested that the Administration move expeditiously to resolve this issue and publish EPA regulations and USDA policies for planned introduction experiments based on the new policy.

Last year, the interagency Biotechnology Science Coordinating Committee (BSCC) conducted a review of the appropriate scope for Federal oversight but did not reach a consensus. The White House Office of Science and Technology Policy requested that this review be referred to the Council on Competitiveness Working Group on Biotechnology to resolve underlying policy issues. The Working Group review resulted in the proposed paper “Principles for Scope of Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits.” This “scope” proposal reflects the Four Principles of Regulatory Review outlined above.

Specifically, the proposal requires oversight only when the information available about the new product indicates that it poses an increased risk to health,

safety, or the environment, unless otherwise required by law. The paper focuses on "organisms with deliberately modified hereditary traits." This term narrows the scope of oversight to organisms with modified hereditary traits, whether modified by traditional breeding or newer techniques, such as recombinant DNA. One reason for using this new term is to avoid the incorrect implication that the use of a particular genetic modification process *per se* makes a modified organism of greater risk than its unmodified parent. The paper sets forth general criteria to assist agencies in developing categories for exclusion from oversight, including whether existing practices or regulations adequately address possible risks.

Based on the "scope" principles, USDA and EPA are developing proposed policies governing field experiments. These will significantly reduce the regulatory burden on biotechnology firms seeking to conduct field experiments using new products, while ensuring an appropriate safety focus on potential risks.

In accord with the following recommendation, a proposed "scope" paper was published in the Federal Register by the Office of Science and Technology Policy for public review and comment on July 31, 1990.⁵

Recommendation:

2-2 The Administration should publish in final form the "Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits."

Oversight Policy

Since publication of the Coordinated Framework for Regulation of Biotechnology, rapid scientific and technological advances have led to more than two hundred environmental field trials of new biotechnology products alone. Some new plants, foods, microorganisms, and other products will be soon ready for commercial marketing. Although there have been periodic efforts to legislate new regulatory regimes for these biotechnology products and research, the Council strongly reaffirms the conclusion of the Coordinated Framework that such legislation is unnecessary. The Council, however, recognizes an urgent need for the Administration to articulate an oversight policy supplementing the Coordinated Framework

that describes proposed policies, procedures and requirements for research and products not in the 1986 Coordinated Framework.

Recommendations:

2-3 The Administration should oppose any efforts to create new or modify existing regulatory structures for biotechnology through legislation. Any necessary adjustments can be accomplished through policies and regulation based on the Four Principles of Regulatory Review.

2-4 Agencies that oversee biotechnology products and research should adopt guidelines and regulations that are consistent with the Four Principles of Regulatory Review and the "Principles for Federal Oversight of Biotechnology."

2-5 The Biotechnology Working Group should prepare an oversight policy. Under the auspices of the Council on Competitiveness, a policy statement describing the Administration's oversight of new biotechnology research and products not in the 1986 Coordinated Framework should be prepared and published for public comment no later than spring 1991.

Initiatives for Further Study by the Biotechnology Working Group

In several areas, current regulation should be reviewed to identify possible means to remove unnecessary burdens on the development of biotechnology products. The Biotechnology Working Group proposes to pursue these areas and, where appropriate, propose additional initiatives for Administration policy.

- **Improve Interagency Coordination.** In a few areas additional interagency coordination of regulation would reduce regulatory delays and jurisdictional uncertainties. For example, would the insertion of a gene encoding pest resistance into a tomato require review of the product by USDA, EPA, or FDA prior to use? Clarifying jurisdiction may be especially important in facing new challenges now on the horizon, such as the commercialization of transgenic crop species and other food products.
- **Streamline the Product Evaluation Process.** Regulatory review processes should build upon the successful reforms for expediting drugs for the desperately ill, and these reforms should be applied

⁵55 FR 31118

to other biotechnology products as well. The goal would be to reduce the total average time required for commercial development of a biologic or drug from the current eight years (including 27 months of evaluation within FDA). A wide spectrum of proposals has been presented in the public literature to improve this system — including improving the design of small-scale clinical trials (Phase II) and eliminating or greatly reducing the requirements for large-scale clinical trials (Phase III), where possible. The Council on Competitiveness has established a Working Group on the Drug Approval Process to consider these types of proposals.

- **Ongoing Reevaluation of Regulations.** Since the biotechnology industry experiences rapid breakthroughs in the discovery of new techniques and products, it is important to ensure that regulatory systems do not lag behind these developments. Provisions to review and where appropriate to sunset existing or new regulations or other mechanisms are necessary to provide the regulatory flexibility for responding to rapid advances in the science base.
- **Address Inconsistencies Among Federal, State and Local Laws.** Some state and local governments have adopted regulatory requirements (and even prohibited activities) that are specifically directed to new biotechnology research and development. These are typically process-based regulations. For example, the "NIMBY" (not in my backyard) syndrome may result in strong opposition to field tests of new biotechnology products. Federal oversight resulting from implementation of regulatory initiatives under the Coordinated Framework, the Four Principles of Regulatory Review, and the "scope" principles, should obviate the need for states to act on their own.
- **Exploring the Application of Non-Tariff Trade Barriers to Biotechnology Products.** Foreign nations may seek to ban certain biotechnology products developed in the U.S. without sound scientific basis. They may also attempt to create informal barriers such as labeling and inspection requirements or lack of adequate and effective property protection which limit access to American biotechnology products. An example discussed in Europe is the possible "fourth hurdle," that subjects product approval to "social and economic" needs tests in addition to appropriate standards for safety,

efficiency and purity. The "social and economic" tests, for example, would include consideration of potential impacts on farmers and the food supply industry in a particular country or region. The Council believes that free market forces, and not government policies will best determine whether a product meets social and economic needs. Our trade representatives should be aware of this strategy and take action to protect free trade and access to foreign markets for U.S. products, and to seek favorable harmonization of relevant laws among our trading partners.

Recommendation:

2-6 The Biotechnology Working Group should consider proposals to remove regulatory burdens by improving interagency coordination, streamlining the regulatory agencies' evaluation processes, periodically re-evaluating regulations, addressing problems with state and local laws, and exploring whether non-tariff trade policies are being applied in such a way as to create technical barriers to trade.

3. A Flourishing Free Market for Biotechnology — Providing Capital and Financial Resources and Protecting Intellectual Property Rights

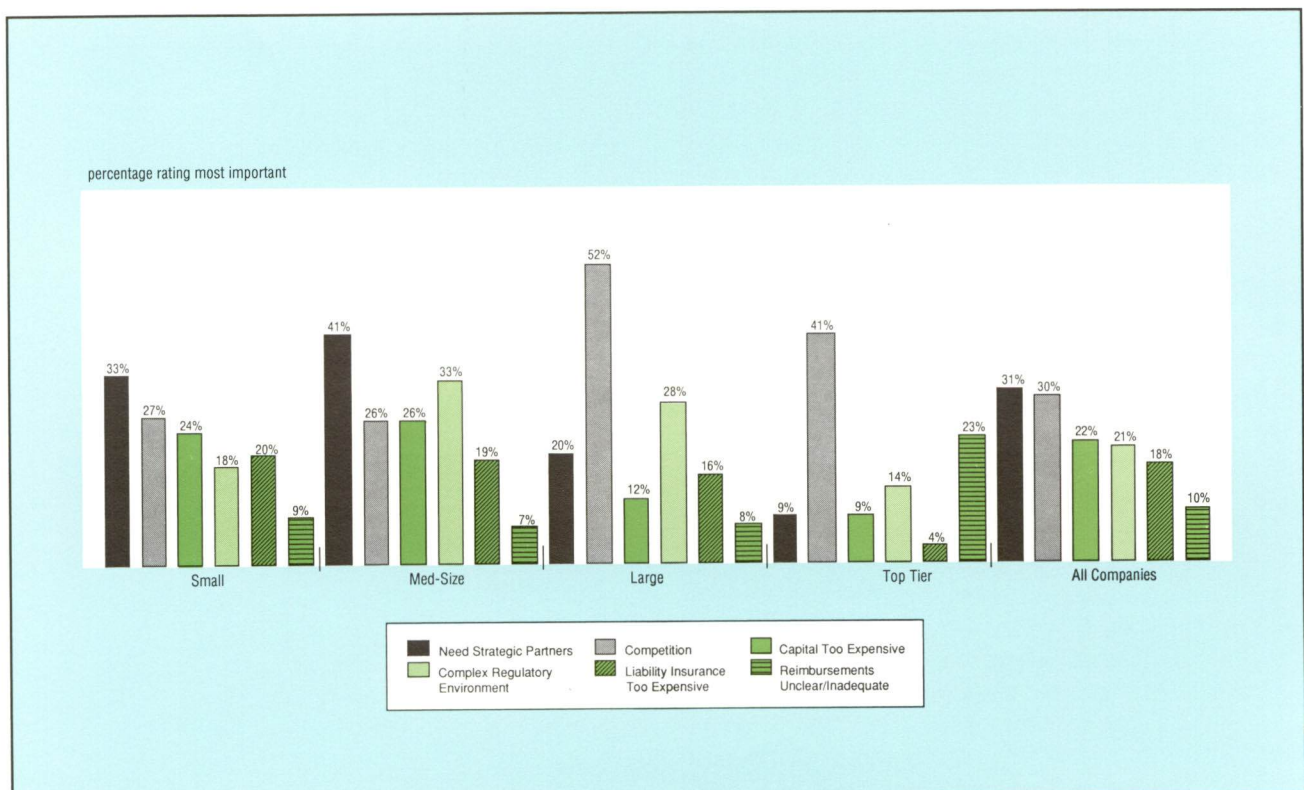
Large integrated firms may have inherent advantages for bringing new products to market. These may include access to capital and expertise in meeting regulatory requirements, in manufacturing and in marketing. On the other hand, small biotechnology firms have inherent advantages for developing new products and new ideas. Their advantages may include an increased effort by employees who feel part of a small team and who benefit greatly from their success as well as a less bureaucratic and more entrepreneurial company ethos. This leads to a number of observations.

1. Government policies should permit the market structure of the industry to include both small and large firms. Small firms frequently have proven to be the industry's inventors and innovators but sometimes experience difficulty bringing these inventions and innovations to market.
2. Corporate buyouts in the industry should be expected. When a small firm has developed a product, it is natural for the firm to be acquired by a larger firm with expertise and resources in manu-

facturing and marketing. The opportunity for such acquisitions and attendant financial inflow may be an incentive encouraging entrepreneurial activity in small firms. A free market for corporate control is therefore beneficial to the competitiveness of the industry.

3. Public policy should not tilt in favor of either small firms or large firms. On the one hand, overly aggressive and myopic anti-trust enforcement is inappropriate. It will be natural for firms to obtain a temporary comparative advantage in narrowly defined market niches as the industry grows. Joint production and research ventures should be encouraged as a way of minimizing capital costs and risks. The current tax law bias against small firms may cause an over concentration in the industry and an excessive reliance on large, diversified manufacturers. These larger firms may not place sufficient emphasis on their biotechnology divisions.

Intellectual property rights are one of the foundations for the successful operation of any innovative



Key Problems Currently Facing Companies by Company Size. Courtesy of G. Steven Burrill, Ernst and Young.

market. In the area of biotechnology, the appropriate definition of intellectual property rights is a crucial area requiring careful thought. The challenge is to provide the legal framework within which intellectual property rights can be defined and protected so that the full commercial value of research can be achieved and the rewards of the market earned by those who maximize benefits to society (i.e. markets should provide internalization of social benefits).

Current Administration Policies

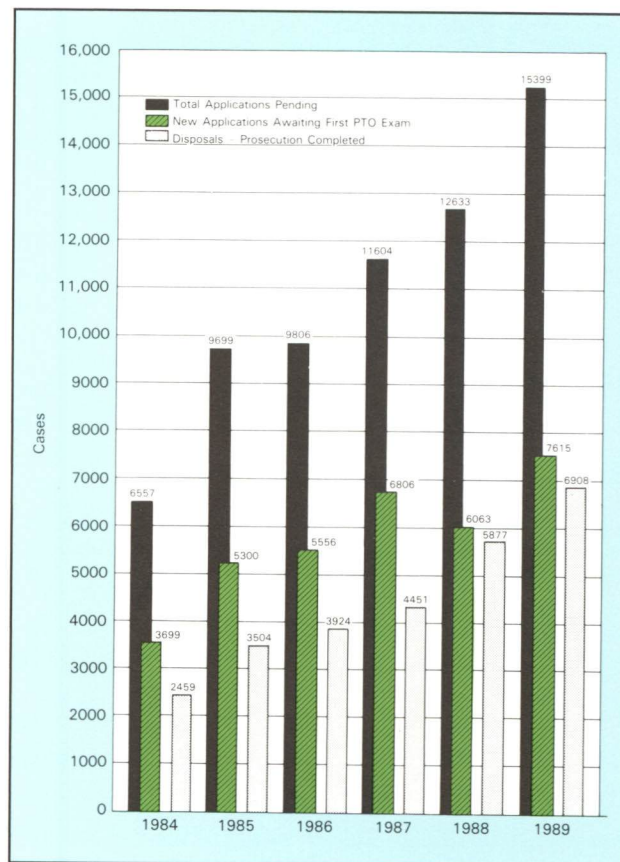
Capital Gains Rate Reduction

A principal aid to the biotechnology industry, and small firms in particular, would be the passage of a capital gains tax rate reduction. Investors in start-up biotechnology firms are high-risk investors who must tie up their funds for an extended period of time. Passage of the Administration's proposed capital gains tax rate reduction would significantly increase investment in new biotechnology enterprises. Although large firms are less reliant on informal investors and on equity generally, they also will benefit from a capital gains tax rate reduction.

Adequate Protection for Intellectual Property

Improvements continue to be made in the U.S. Patent and Trademark Office. In other countries, however, improvements in intellectual property laws, including procedures for granting protection and enforcing rights, are clearly needed. The Administration is committed to pursuing the protection of intellectual property as a top priority in the Uruguay Round of the GATT negotiations.

- Improvements at the U.S. Patent and Trademark Office should be continued. Backlogs in approval of patent applications can discourage both investment in biotechnology research and the development of new products. As a consequence, the Patent and Trademark Office plans on hiring 270 new patent examiners over the next five years in the biotechnology area along with improving training for examiners. In addition, the Patent and Trademark Office is setting up an information system that will establish a comprehensive data base of patent information, substantially facilitating the review of patent applications. Clearly, increased resources



Biotechnology Patent Applications Backlog
Source, Department of Commerce

will be needed in the biotechnology field as the industry continues to grow and serious attention must be paid to retaining experienced biotechnology patent examiners.

- International cooperation in patenting should be considered. It is difficult and expensive to obtain patents in every country. Accordingly, efforts should be continued to harmonize and improve patent laws throughout the world, as well as patent granting and enforcement procedures.

Council on Competitiveness Policy Actions

Amendments to the Orphan Drug Act

The Orphan Drug Act of 1983 grants certain benefits to companies that develop new drugs for dis-

eases affecting fewer than 200,000 people. Chief among these benefits is a 7 year exclusive marketing privilege. There is widespread agreement that the Act has been a tremendous success at developing new drugs to treat rare diseases and without such incentives, drugs for rare diseases would not receive sufficient development. As of the end of November 1990, 416 drug products have received designation under the Orphan Drug Act, and 47 have been approved for 53 indications.

In response to recent legislative proposals to amend the Act, the Council in the spring of 1990 unanimously agreed on four principles:

1. The Orphan Drug Act has been an effective mechanism in furthering research and development on drugs for rare diseases and conditions, and should not be altered in any fundamental manner.
2. The Council does not believe that current legislative proposals will prove successful at improving the Act's administration or effectiveness.
3. The Council is strongly opposed to any measure that would retroactively remove rights assigned under the Act.
4. The Council urges the Food and Drug Administration to continue to refine its efforts to implement the Act in a manner that limits its special provisions to development of treatments for patient populations of fewer than 200,000 persons.

Consistent with the Council's four principles, President Bush withheld approval of H.R. 4638, the "Orphan Drug Amendments of 1990" passed in the closing days of 101st Congress because of the detrimental effect two major changes would have had to the market exclusivity provisions of the Orphan Drug Act.

Recommendation:

3-1 The Administration should continue to oppose fundamental legislative changes to the Orphan Drug Program that undermine the economic incentives to produce new drugs for rare diseases. The FDA should develop administrative proposals to address concerns about the definition of "disease" used in the program to avoid overextension of the program to treatments that are not "orphan."

Securing Intellectual Property Rights in Biotechnology — Improved Patent Protection

The uncertainties in intellectual property rights for innovations in the biotechnology area continue to hamper the industry. Changes in U.S. law have been suggested as a way of improving patent protection. Legislation has been introduced to overturn a court case (*In re Durden*⁶) that suggests that use of a novel starting material in combination with a known chemical process is not eligible for a process patent. The application of *Durden* in the biotechnology area could deny protection to innovations that only can be protected through process patents. If *Durden* were overturned, patenting these processes would permit the patent holder to exclude the importation into this country of a product produced by using a patented biotechnological material.

Representative Boucher introduced legislation, H.R. 5664, in the 101st Congress that would have furthered these objectives. The Administration testified in support of this legislation.

Recommendation:

3-2 The Administration should support passage of legislation to provide necessary process patent protection for products, such as those in the biotechnology area, that can be protected only through process patents.

Initiatives for Further Study by the Biotechnology Working Group

Discriminatory Tax Rules — Specific Challenges Facing Small Biotechnology Companies

Two important provisions of the Tax Reform Act of 1986 "tilted the playing field" against small start-up ventures. These were the new passive loss rules and the increase in the capital gains tax rate to a record average level. New technology-intensive ventures in general and biotechnology firms in particular were especially adversely affected by these changes. While the Administration's proposal for a capital gains tax rate reduction would be of tremendous benefit to the biotechnology industry, and to technology-intensive industry in general, the further study of other growth-oriented changes in tax policy might be considered. Examples include the following:

⁶763 F. 2d 1406 (1985)

- **Asymmetric Treatment of Profits and Losses.**

Losses may be carried forward for up to 15 years or back for 3 years. But, the development time for research-based new products, particularly those based on biotechnology, is often quite long. Thus, technology-intensive start-up firms often do not show a profit for many years. Even when a successful firm becomes profitable, the present value of the tax loss is substantially reduced compared with the tax loss permitted an ongoing firm. Firms that never become profitable receive no tax benefit.

- **Limits on the Research and Experimentation Credit.**

The credit, like losses, may be carried forward for 15 years or back 3 years. A firm can use this credit only if it has tax liability. So the credit only becomes applicable when the firm is profitable and after it has exhausted any existing loss carry-forwards. Thus, rapidly growing firms in biotechnology and other research-intensive areas might lose the benefits of this tax provision. Others that may receive the credit receive it only at a sharply reduced present value.

- **Transfers of Assets.** These problems are exacerbated when a biotechnology firm is sold or even goes to market with a new equity offering. The Tax Reform Act of 1986 limited the transferability of tax loss carry forwards if more than 50 percent of the equity in a firm changes hands. Thus, rapidly growing biotechnology firms might lose this tax advantage. Study of possible alternatives to protect legitimate transfers may be in order. It is important to balance these considerations against possible abuse and potential revenue loss.

- **Good Will.** Most of the value of a biotechnology firm, like many other high technology firms, is intangible — the human capital of the employees. FASB⁷ rules require that this be depreciated, thus lowering the apparent earnings of the firm. Biotechnology firms are, thereby, penalized by the FASB treatment of good will in profit comparisons with other firms. Alternative accounting standards that provide a better picture of the true value of biotechnology firms may be worthy of consideration.

Recommendation:

3-3 The Biotechnology Working Group should continue to examine tax issues that affect biotechnology and recommend ways of reconciling the need to remove barriers to growth and innovation generally with the other objectives of tax policy.

⁷Financial Accounting Standards Board, American Institute of Certified Public Accountants

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Glossary*

Amino acid: Any of a group of 20 molecules that are linked together in various combinations to form proteins. Each different protein is made up of a specific sequence of these molecules with the unique sequence coded for by DNA.

Anaerobic: Growth or activity that does not require free oxygen.

Animal: A nonhuman living being with a capacity for spontaneous movement and a rapid motor response to stimulation. Animals can be divided into two groups, invertebrates (animals without backbones) and vertebrates (animals with backbones).

Antibody: A protein molecule, also called immunoglobulin, produced by the immune system in response to exposure to a foreign substance. An antibody is characterized by a structure complementary to the foreign substance, the antigen, that provoked its formation and is thus capable of binding specifically to the foreign substance to neutralize. (See **antigen** and **monoclonal antibodies**.)

Antigen: A molecule introduced into an organism and recognized as a foreign substance, resulting in the elicitation of an immune response (antibody production, lymphokine production, or both) directed specifically against the molecule. (See **antibody** and **monoclonal antibodies**.)

B lymphocyte: A specialized white blood cell involved in the immune response of vertebrates that originates in the bone marrow and produces antibody molecules after challenge by an antigen. In hybridoma technology, these cells contribute antibody-producing capability to a hybridoma. (See **T lymphocyte**.)

Bacterium (pl. bacteria): Any of a group of one-celled microorganisms having round, rodlike, spiral, or filamentous bodies that are enclosed by a cell wall or membrane and lack fully differentiated nuclei.

Biotechnology: Any technique that uses living organisms or substances from those organisms to make or modify a product and perform services, to improve plants or animals, or to develop microorganisms for specific uses. These techniques include the use of novel technologies such as recombinant DNA, cell fusion, and other new bioprocesses. (See genetic engineering and recombinant DNA.)

Cell: The smallest component of life capable of carrying on all essential life processes. A single unit is a complex collection of molecules with many different activities all integrated to form a functional self-assembling, self-regulating, self-reproducing biological unit.

Cell culture: The propagation of cells removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements; also used to refer to any particular individual sample. (See **cell** and **cell line**.)

Cell fusion: The joining of the membrane of two cells, thus creating a single hybrid cell that contains the nuclear matter from the parent cells.

Cell line: A sample of cells that has undergone the process of adaptation to artificial laboratory cultivation and is capable of sustaining continuous, long-term growth in culture. (See **cell** and **cell culture**.)

Chromosome: The physical, threadlike structures within the nucleus of a cell composed of a DNA-protein complex and containing the hereditary material, i.e., genes. In bacteria, it is the DNA molecule—a single, closed circle (no associated protein)—comprising the cell's total genetic information.

Cloning: The process of asexually producing many copies of a biological material, all identical to the original ancestor. In tissue and cell culture technology, the process by which a culture is grown and amplified starting from a single cell; in recombinant DNA technology, the process of using a variety of recombinant DNA procedures to produce multiple copies of a single gene or segment of DNA.

DNA sequencing: Determining the sequence of nucleotides in DNA.

Cultivar: An international term denoting certain cultivated plants that are clearly distinguishable from others by one or more characteristics and which when reproduced retain those characteristics. In the United States "variety" is considered to be synonymous with cultivar (derived from cultivated variety).

Deoxyribonucleic acid (DNA): The molecule in chromosomes that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is ribonucleic acid—RNA). The information coded by DNA determines the structure and function of an organism.

*Adopted from the definitions included in: Office of Technology Assessment publications listed in the General References; and, Understanding our Genetic Inheritance; The U.S. Human Genome Project: The First Five Years FY 1991-1995, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, and the U.S. Department of Energy, Office of Energy Research, Office of Health and Environmental Research, Washington, D.C., April 1990.

Depositories: A facility that accepts, maintains, classifies, and distributes cultures of microorganisms, viruses, cells, and other genetic and biological material. Since 1983, a few depositories have begun to accept seeds and plant tissue cultures, but to date no depository has accepted any animal. Depositories can be public, private, for profit, or nonprofit. Three depositories in the United States are currently recognized as International Depositary Authorities (IDAs) for patent purposes.

Dominant: An allele or characteristic whose expression prevails over alternatives for a given trait. (Compare **recessive**.)

Endogenous: Developing or originating within the organism, or arising from causes within the organism.

Enzyme: Any of a group of catalytic proteins that are produced by living cells and that mediate and provide chemical processes without themselves being destroyed or altered.

Gamete: A mature reproductive cell (haploid set of chromosomes) capable of fusing with a similar cell of opposite sex to yield a zygote; also called a sex cell.

Gene: The fundamental physical and functional unit of heredity, the portion of a DNA molecule that is made up of an ordered sequence of nucleotide base pairs that produce a specific product or have an assigned function.

Gene family: A group of related genes exhibiting a high degree of homology in function and nucleotide base sequence.

Gene mapping: Determining the relative locations of different genes on chromosomes.

Gene pool: The sum total of genes in a breeding population.

Gene probe: A molecule of known structure and/or function used to locate and identify a specific region or nucleotide sequence of a genome; usually a piece of complementary DNA that has been labeled with a tracer substance, such as a dye or radioactive label.

Genetic code: The manner in which DNA or RNA represents, through chemical subunits, information that is translated into protein. The genetic code is read in groups of three nucleotides called codons, each of which specifies a single amino acid. (See also **nucleotide**.)

Genetic engineering: Technologies (including recombinant DNA methods) used by scientists to isolate genes from an organism, manipulate them in the laboratory, and insert them stably in another organism. (See **recombinant DNA** and **biotechnology**).

Genetic linkage map: A map of the relative positions of genetic loci on a chromosome, determined on the basis of how often the loci are inherited together.

Genetic variance: The fraction of the phenotypic variance due to differences in the genetic constitution of individuals in a population. (Compare **Phenotypic variance**.)

Genome: The genetic content encoded in a haploid organism's genes; in eukaryotes, a haploid set of chromosomes.

Genome projects: Research and technology development efforts aimed at mapping and sequencing some or all of the genome of human beings and other organisms.

Genotype: The sum total of genetic information contained in an organism; the genetic constitution of an organism with respect to one or a few loci under consideration. (Compare **phenotype**.)

Harvard mouse: A transgenically engineered mouse developed at Harvard and patented in April 1988, the first animal ever to be patented. The Harvard mouse was engineered to be unusually susceptible to cancer and was developed for use in the testing of carcinogens and cancer therapies.

Horizontal transfer: The passage of genetic material from one organism to another via nonsexual mechanisms.

Human Genome Initiative: An initiative whose goal is to map and sequence the human genome. The concept was first formally proposed in 1986.

Hybrid: An offspring of a cross between two genetically unlike and individual plants or animals.

Hybridization: In cell culture, the formation of new cells as a result of the fusion of whole cells or cell parts of different parental origin. In recombinant DNA, a procedure in which single-stranded nucleic acid segments are allowed to bind to identical or nearly identical sequences, forming hybrid double-stranded helices.

Hybridoma: A new cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody-producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific (i.e., monoclonal) antibody production.

Ice-minus (ice-): A bacterium lacking a functional gene coding for a protein that promotes the formation of ice crystals by providing a physical nucleus around which ice crystallizes. The gene has been deleted from strains of *Pseudomonas syringae*, *Pseudomonas fluorescens*, and *Erwinia herbicola*.

Immunization: The injection of an antigen into an organism resulting in an immune response that may include the production of antibodies.

Intellectual property: That area of the law involving patents, copyrights, trademarks, trade secrets, and plant variety protection.

Invention: An original device, contraption, or process developed after study and experiment. Genetically engineered animals, plants, and microorganisms have been recognized as patentable forms of biological invention in the United States, but this is not always the case in other countries, especially where animals are concerned.

In vitro: Literally, "in glass." Refers to a process, test, or procedure in which something is measured, observed, or produced outside a living organism after extraction from the organism.

Lymphocytes: See B lymphocyte and T lymphocyte.

Lymphokine: A group of proteins that modulate the immune response and that are necessary for proper function of the entire immune system. Interferon and interleukin-2 are lymphokines.

Microinjection: A technique used for the insertion of genes from one cell into another cell, in which highly purified copies of a specific gene of interest are injected into a cell. Copies of one specific gene of interest can be injected into a fertilized animal egg. The egg is then surgically implanted in a female animal's reproductive tract.

Monoclonal antibodies: Identical antibodies that recognize a single, specific antigen and are produced by a clone of specialized cells. Commercial quantities of these molecules are now produced by hybridomas. (See **antibody**, **antigen**, and **hybridoma**.)

Myeloma: A malignant tumor of an antibody-producing cell. In hybridoma technology, some of these tumor cells have been adapted to cell culture, and these cells contribute immortality to a hybridoma cell line.

Natural selection: The process of differential reproductive success by which genes in a population increase or decrease in frequency with the passage of generations, depending on their contribution to the survival of offspring in which they are carried; arguably the most important of the several mechanisms by which evolution takes place, discovered by Darwin and first described in 1858-59.

Novelty: One of the criteria used in the evaluation of patent applications. The invention or discovery being evaluated must be new and must not have previously existed through the work of others in order to be accepted on the grounds of novelty.

Nucleic acid: A macromolecule composed of sequences of nucleotide bases; DNA or RNA.

Nucleotide (base): The unit of nucleic acids. The molecules consist of one of four bases—adenine, guanine, cytosine, or thymine/uracil (DNA/RNA) attached to a phosphate-sugar group. The sugar group is deoxyribose in DNA; in RNA it is ribose.

Nucleus: The membrane-enclosed structure in a cell that contains the chromosomes.

Organelle: A structure in the cytoplasm of a cell that is specialized in its ultrastructure and biochemical composition to serve a particular function (e.g., mitochondria, endoplasmic reticulum, chloroplast).

Phenotype: The observable characteristics of an organism produced by the interaction of the genotype and the environment. (Compare **genotype**.)

Phenotypic variance: The variation among genetically identical individual organisms in external appearance caused by the interaction of environment with the genotype during development. (Compare **genetic variance**.)

Physical map: A map of the locations of identifiable landmarks of DNA (e.g., restriction enzyme cutting sites, genes, RFLP markers). A physical map may also be a set of overlapping clones, called a contig. Distance is measured in base pairs. For the human genome, the lowest-resolution physical map is the banding patterns of the 24 different chromosomes; the highest-resolution map would be the complete nucleotide sequence of the chromosomes.

Plasmid: An extrachromosomal, circular piece of DNA found in the cytoplasm and capable of replicating and segregating independently of the host chromosome. (See **vector**.)

Polymerase chain reaction (PCR): An enzymatic reaction that precisely and rapidly amplifies a small segment of DNA millions of times or more. The reaction can start with one molecule of DNA.

Protein: A molecule composed of a few to hundreds of amino acids linked in a specific sequence determined by the sequence of a gene in the DNA. These molecules are required for the structure and function of all living organisms.

Recessive: An allele or characteristic whose expression occurs only in the absence of a dominant trait. (Compare **dominant**.)

Recombinant DNA(rDNA): A broad range of techniques involving the controlled manipulation of the genetic material of organisms. These techniques and their products have enormous potential in the development of new and improved products and processes in a wide variety of industrial sectors. The

term is often used synonymously with genetic engineering. It is also used to describe a DNA molecule constructed by genetic engineering techniques composed of DNA from different individuals or species. (See **biotechnology** and **genetic engineering**.)

Restriction endonuclease: An enzyme isolated from bacteria that selectively recognizes and clips double-stranded DNA at specific sequences. More than 400 different restriction enzymes are known to recognize over 100 different DNA sequences.

Restriction enzyme: See **restriction endonuclease**.

Restriction fragment length polymorphism (RFLP): The presence of two or more variants in the size of DNA fragments from a specific region of DNA that has been exposed to a particular restriction enzyme. These fragments differ in length because of an inherited variation in a restriction enzyme recognition site. (See **Physical map**, **Restriction endonuclease**.)

Retrovirus: A family of viruses whose genetic material is RNA and is further characterized by the presence of reverse transcriptase in the virion; also called tumor virus.

Reverse transcriptase: An enzyme capable of directing the production of a single strand DNA copy from an RNA template.

Ribonucleic acid: See **RNA**.

RNA (ribonucleic acid): A molecule existing in three forms—messenger RNA, transfer RNA, and ribosomal RNA—responsible for translating the genetic information encoded by an organism (i.e., DNA) into a protein product; the hereditary material of some viruses.

Selective advantage: An organism's increased probability of reproduction and producing offspring, conferred by its genetic characteristics.

Sequence-tagged site (STS): A short DNA sequence that uniquely identifies a mapped gene or other marker. The order and spacing of these sequences comprise an STS map.

Species: Reproductive communities and populations that are distinguished by their collective manifestation of ranges of variation with respect to many different characteristics and qualities.

Species barrier: The idea that there is a natural barrier between species that preserves their integrity or identity. This idea has no known foundation in biology. The parameters that limit the ranges and variations of species are fluid and variable, and species exist as reproductive communities rather than as separate creatures.

Species integrity: The idea that a species has integrity as a biological unit. This would have to be based on the identity of the genetic material carried by the species. However, it is not clear how a species might be defined genetically, and this issue is the subject of debate among those seeking to understand the nature of species.

Strain: A pure culture of organisms within a species, characterized by one or more particular physical or genetic properties. (See **cultivar**.)

T lymphocyte: Specialized white blood cell involved in the immune response of vertebrates that originates in the bone marrow, matures in the thymus gland, and produces some lymphokines. Subclasses of T lymphocytes are important to antibody production and the enhancement or suppression of an immune response. (See **B lymphocyte** and **macrophage**.)

Tissue culture: See **cell culture**.

Tissue plasminogen activator (tPA): A protein drug that helps to dissolve blood clots in patients who have suffered heart attacks.

Transgenic animals: Animals whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm usually from another animal or a human, in a laboratory, using recombinant DNA techniques. At the moment, most of the research in this field is done on mice, but major research efforts in transgenic animal modification are also focusing on cattle, swine, sheep, poultry, rabbits, and fish.

Vector: A carrier or transmission agent. In the context of recombinant DNA technology, a vector is the DNA molecule used to introduce foreign DNA into host cells. Recombinant DNA vectors include plasmids, bacteriophages, and other forms of DNA.

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President George Bush established the Council on March 31, 1989 to continue United States economic progress by maintaining and improving our international competitiveness. Our ability to do that depends on: the full development of our human resource potential; the promotion of scientific and technological progress; removal of barriers to innovation; careful assessment of any governmentally-imposed burdens on the free enterprise system; and removal of domestic barriers to the flow of goods and services.

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*Names listed are as of September 30, 1990.

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