Chapter 1

Summary

"As we move through the next millennium, biotechnology will be as important as the computer. "

John Naisbitt & Patricia Aburdene
Megatrends 2000

"Biotechnology-the very word was invented on Wall Street-is a set of techniques, or tools, not a pure science like much of academic biology."

Robert Teitelman
Gene ***Dreams***

CONTENTS

Boxes

Figure

Tables

Chapter 1
Summary

INTRODUCTION

Biotechnology-both as a scientific art and commercial entity—is less than 20 years old (see table l-l). In that short period of time, however, it has revolutionized the way scientists view living matter and has resulted in research and development (R&D) that may lead to commercialization of products that can dramatically improve human and animal health, the food supply, and the quality of the environment (see box l-A). Developed Primarily in U.S. laboratories, many applications of biotechnology are now viewed by companies and governments throughout the world as essential for economic growth in several different, seemingly disparate industries.

To what degree is biotechnology being used as a tool in basic research, product development, and manufacturing? In what industries is biotechnology being used, and how are various national governments promoting and regulating its uses? Will the United States retain its preeminence in biotechnology, or will the products and services created by biotechnology be more successfully commercialized in other nations? What is the role played by multinational corporations, and how is international biotechnology R&D funded? Because of its importance to U.S. competitiveness in an increasingly global economy, biotechnology is viewed as one of the keys to U.S. competitiveness during the years ahead. This report describes the increasing international use of commercial biotechnology in industrialized and newly industrializing countries (NICs) (see box l-B) and the ways governments promote and regulate the uses of biotechnology.

COMMERCIAL ACTIVITY

Biotechnology is not an industry. It is, instead, a set of biological techniques, developed through decades of basic research, that are now being applied to research and product development in several existing industrial sectors. Biotechnology provides the potential to produce new, improved, safer, and less expensive products and processes. Pharmaceuticals and diagnostics for humans and animals, seeds, entire plants, animals, fertilizers, food additives, industrial enzymes, and oil-eating and other pollution degrading microbes are just a few of the things that can be created or enhanced through the use of biotechnology.

Many early claims about biotechnology, seen in retrospect, were premature. Products have not been developed and marketed as quickly as previously thought possible, and many scientific and public policy issues remain to be settled. However, biotechnology has arrived as an important tool for both scientific research and economic development. Its effect on the world's economy will certainly grow in the years ahead, as research leads to new products, processes, and services.

Financing of Biotechnology

The competitiveness of U.S.-developed biotechnology products ***and processes*** may ultimately depend on broad issues, e.g., fair trade practices, protection of intellectual property, regulatory climate, and tax policies. The competitiveness of U.S. ***innovation,*** however, could very well rely on the ability of biotechnology companies to stay in business. Because biotechnology is capital-intensive, staying in business means raising substantial sums of cash. Start-up companies' fundamental need for cash, coupled with the desire of venture capitalists in the United States to profit from the creation of high-value-added products (based' on cutting-edge technology) have led to the financial community's substantial involvement in the formation of biotechnology-based firms.

Venture Capital and the Dedicated Biotechnology Company

The United States has led the world in the commercial development of biotechnology because of its strong research base-most notably in biomedical sciences--and the ability of entrepreneurs to finance their ideas. During the early 1980s, a combination of large-scale Federal funding for basic biomedical research, hype surrounding commercial potential, and readily available venture capital funding led to the creation of hundreds of dedicated biotechnology companies (DBCs).

Dedicated biotechnology companies are almost exclusively a U.S. phenomenon; no other country has a remotely comparable number. Biotechnology companies are created specifically to exploit the

Table I-l—Major Events in the Commercialization of Biotechnology

1973	First cloning of a gene.
1974	Recombinant DNA (rDNA) experiments first discussed in a public forum (Gordon Conference).
1975	U.S. guidelines for rDNA research outlined (Asilomar Conference). First hybridoma created.
1976	First firm to exploit rDNA technology founded in the United States (Genentech). Genetic Manipulation Advisory Group started in the United Kingdom.
1980	Diamond v. Chakrabarty--U.S. Supreme Court rules that micro-organisms can be patented. Cohen/Boyer patent issued on the technique for the construction of rDNA. United Kingdom targets biotechnology for research and development (Spinks' report). Federal Republic of Germany targets biotechnology for R&D (Leistungsplan). initial public offering by Genentech sets Wall Street record for fastest price per share increase ($35 to $89 in 20 minutes).
1981	First monoclonal antibody diagnostic kits approved for use in the United States. First automated gene synthesizer marketed. Japan targets biotechnology (Ministry of international Trade and Technology declares 1981, "The Year of Biotechnology"). initial public offering by Cetus sets WallStreet record for the largest amount of money raked in an initial public offering ($1 15 million). Over 80 new biotechnology firms formed by the end of the year.
1982	First rDNA animal vaccine (for colibacillosis) approved for use in Europe. First rDNA pharmaceutical product (human insulin) approved for use in the United States and the United Kingdom.
1983	First expression of a plant gene in a plant of a different species. New biotechnology firms raise $500 million in U.S. public markets.
1984	California Assembly passes resolution establishing the creation of a task force on biotechnology. Two years later, a guide clarifying the regulatory procedures for biotechnology is published.
1985	Advanced Genetic Sciences, inc. receives first experimental use permit issued by EPA for small-scale environmental release of a genetically altered organism (strains *P.* syringae and P. fluorescens from which the gene for ice-nucleation protein had been deleted.
1986	Coordinated Framework for the Regulation of Biotechnology published by Office of Science and Technology Policy. Technology Transfer Act of 1986 provides expanded rights for companies to commercialize government-sponsored research.
1987	U.S. Patent and Trademark Office announces that nonhuman animals are patentable subject matter. October 19th-Dow Jones Industrial Average plunged a record 508 points. initial public offerings in biotechnology-based companies virtually cease for 2 years.
1988	NIH establishes program to map the human genome. First U.S. patent on an animal--transgenic mouse engineered to contain cancer genes.
1989	Bioremediation gains attention, as microbe-enhanced fertilizers are used to battle Exxon Valdezoil spill. Court in Federal Republic of Germany stops construction of a test plant for producing genetically engineered human insulin. Gen-Probe is first U.S. biotechnology company to be purchased by a Japanese company (Chugai Pharmaceuticals).
1990	FDA approves recombinant renin, an enzyme used to produce cheese; first bioengineered food additive to be approved in the United States. Federal Republic of Germany enacts Gene Law to govern use of biotechnology. Hoffman-LaRoche (Basel, Switzerland) announces intent to purchase a majority interest in Genentech. Mycogen becomes first company to begin large-scale testing of genetically engineered biopesticide, following EPA approval. First approval of human gene therapy clinical trial.
1991	Biotechnology companies sell $17.7 billion in new stock, the highest 5-month total in history. Chiron Corp. acquires Cetus Corp. for $660 million in the largest merger yet between two biotechnology companies. EPA approves the first genetically engineered biopesticide for sale in the United States.

SOURCE: Office of Technology Assessment, 1991.

Box 1-A—Defining Biotechnology

The first challenge in describing the effect of biotechnology on a global economy is to define what biotechnology is. The term "biotechnology" means different things to different people. Some view biotechnology as all forms of biological research, be it cheesemaking and brewing or recombinant DNA (rDNA) technology. Others, only view biotechnology as including modern biological techniques (e.g., rDNA, hybridoma technology, and monoclonal antibodies). Some people have analogized biotechnology to a set of new tools in the biologist's toolbox by referring to "biotechnologies.' To Wall Street financiers and venture capitalists who invested in the creation of companies in this area, biotechnology represents a hot new source of financial risk and opportunity. Congress, increasingly invoked in public policy questions raised by biotechnology, in one statute referred to products "primarily manufactured using recombinant DNA recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques" (35 U.S.C. 156(2)(B)).

In 1984, OTA arrived at two definitions of biotechnology. The first definition--broad in scope--described biotechnology as any technique that uses living organisms (or Parts of organisms) to make or mod@ products, to improve plants or animals, or to develop micro-organisms for specific uses. This definition encompassed both new biological tools as well as ancient uses of selecting organisms fur improving agriculture, animal husbandry, or brewing. A second, more narrow definition refers only to "new" biotechnology: the industrial use of rDNA, cell fusion, and novel bioprocessing techniques. It is the development and uses of the new biotechnology that has captured the imagination of scientists, financiers, policymakers, journalists, and the public. As in earlier OTA reports, the term biotechnology, unless otherwise specified, is wed in reference to new biotechnology.

SOURCE: *Office* of Technology Assessment, 1991.

Box 1-B--Sixteen Countries

In compiling this report, OTA focused on biotechnology-related developments in the following countries:

Australia
Brazil
Canada
Denmark
Federal Republic of Germany
France
Ireland
Japan
The Netherlands
Singapore
South Korea
Sweden
Switzerland
Taiwan (Republic of China)
United Kingdom
united states

In addition, the biotechnology-related activities of the European Community (EC) as a whole are considered. The countries chosen are representative of a range of commercial and governmental activity. This roster is not exhaustive; biotechnology plays an important role in many other nations. As this report was compiled, major political changes occurred including the merging of the Federal Republic of Germany and the German Democratic Republic. The merger of both countries raises many questions regarding industrial competitiveness that are beyond the scope of this report.

SOURCE: Office of Technology Assessment, 1991.

commercial potential of biotechnology. These companies generally start as research organizations with science and technology but without products. They do not undertake R&Don nearly so broad a scale as established companies. Instead, they focus on specific technologies, particular products, and niche markets. The companies must fund the initial costs of infrastructure development—including buildings, plants, equipment, and people-without the benefit of internally generated revenues. They depend on venture capital, stock offerings, and relationships with established companies for their financing needs.

The boom era for founding DBCs occurred between 1980 and 1984, when approximately 60 percent of existing companies were founded. In 1988, the Office of Technology Assessment (OTA) verified **that** there were 403 DBCs in existence and over 70 major corporations with significant investments in biotechnology. The majority of these companies have a strong focus on human health care products, largely because capital availability has been greater for pharmaceuticals than for food or agricultural products, due to the prospect of greater and faster market reward.

In the early 1980s, companies had little trouble raising cash, often obtained by licensing away key first-generation products and vital market segments. As time passed, the term "biotechnology" lost its ability to turn promises of future products into instant cash. Several factors have been cited for tightened availability of venture capital financing:

- Basic gene-splicing technology became readily available to an increasing number of companies, both in the United States and abroad.
- Product development was slower than expected (e.g., unforeseen technical problems, slow regulatory approval and patent issuance, and difficulties in scale-up and in obtaining meaningful clinical results).
- The 1987 stock market crash slammed shut opportunities for initial public offerings, and for 18 months biotechnology companies had to get by with little new public financing.
- Expected returns on investments have not materialized as expected.

To date, most U.S. biotechnology companies have no sales and have been losing money since their inceptions. Capital and market value are concentrated in only a few of the hundreds of firms involved in biotechnology. Only one-fifth of biotechnology companies surveyed in 1990 were profitable. Most companies are still several years away from profitability and positive cash flow, but the top 20 firms could last more than 3 years on current cash levels without needing to raise additional money.

Despite the slower-than-expected commercialization of biotechnology, start-up firms have been able to raise cash in the initial stages of operation. Second and third rounds of needed financing, that are necessary to bridge the gap between basic research and a marketable product, are more difficult to come by. While the venture capital community has become more conservative in where they choose to invest, viable opportunities appear to remain for entrepreneurs with good ideas. However, a bottleneck is developing as start-up companies attempt to move forward toward development, testing, and marketing—the expensive part of the process. As much as $5 to $10 billion may be needed just to develop the 100 biotechnology products currently in human clinical trials.

Companies fortunate enough to have gone public before 1987 are generally able to obtain needed cash through limited partnerships, secondary public offerings, and strategic alliances. The stock market crash in October 1987 virtually stopped all initial public offerings in biotechnology-based companies. By 1991, however, stock offerings were again in vogue, both for new and established firms (see box l-C). The top DBCs will most likely remain stable, surrounded by an ever-changing backdrop of start-up companies. Those DBCs that do survive will rely on corporate relationships of every form and combination of forms imaginable (see box l-D).

Consolidation

Start-up companies will continue to appear, but these new DBCs will likely face the reality of merger or acquisition. Only a dramatic surge in the public markets or the creation of breakthrough products or processes will save some of these companies from this fate. Consolidation of DBCs is inevitable, most likely necessary, and desirable for some companies. What concerns some observers is the role that foreign acquisition and investment will play in the fate of many of these vulnerable fins. Although it is true that joint activity between firms has been on the rise (involving both U.S. companies with foreign firms and between U.S.-based firms themselves), much of this activity is necessary to conduct business in a global market, i.e., licensing, marketing, and co-marketing agreements. Currently, there is insufficient evidence to state that U.S. commercial interests in biotechnology are threatened by foreign acquisition. To date, most corporations have avoided this mechanism. As U.S. DBCs move closer to product reality, however, foreign corporations with large pools of cash may be more willing to pursue acquisition in order to ensure manufacturing rights. Executives of DBCs tend to feel that manufacturing rights will be crucial for the viability of their companies.

The recent merger of the United States' largest biotechnology company, Genentech, with Swiss-owned Hoffmann-LaRoche, has increased public interest and concern in foreign acquisition of U.S. biotechnology concerns. While some foreign firms (usually large, multinational corporations) are actively investing in U.S. DBCs, approximately three-quarters of all mergers and acquisitions involving biotechnology companies are between U.S.-based firms (e.g., the 1991 merger between Chiron and Cetus). However, U.S. corporations are disadvantaged when it comes to acquisition because

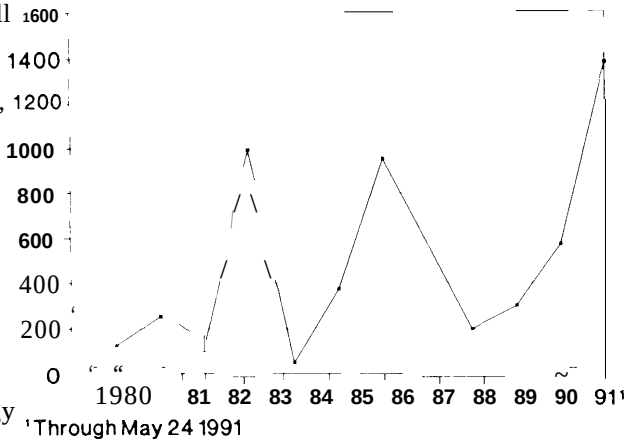
Box 1-C—Biotech's 1991 Stock Boom

On October 19, 1987, the Dow Jones Industrial Average plunged a record 508 points. Following the stock market crash, there was little interest on Wall Street in stock offerings for biotechnology-related companies. By early 1991, however, the U.S. market for new stock offerings had heated up to a record pace, despite the fact that the U.S. economy was in a recession and stock sales in general were sluggish.

Between January and May 1991, companies sold almost $18 billion in new stock the highest 5-month total in history. Various reasons were cited by analysts for the hot market: the approval by FDA of new products, the durability of health-related stocks during economic hard times, and pent-up demand following slow stock activity over a 3-year period.

Unlike earlier bull markets for biotechnology stocks, however, analysts generally view the 1991 boom as short term in nature. By the end of May, there were signs that the stock demand was cooling. For example, Regeneron Pharmaceuticals (Tarrytown, NY), a start-up company that had set a record for biotechnology companies by raising $99 million in its initial public offering in April (4.5 million shares sold at $22 per share), saw its stock value drop to $12 per share by the end of May after reporting first-quarter losses of $1.1 million.

Biotech's Surprising Stock Market Boom



SOURCE: IDD Information Services, Inc., New York.

SOURCE: Office of Technology Assessment, 1991, adapted from IDD Information Services; R. Rhein, "Biotech Stocks: Let the Good Times Roll," *Journal of NIH Research,* July 1991, pp. 54-55; *Biotechnology, "Regeneron* Gets Rich, Offerings Abound," vol. 9, May 1991, p. 404.

American accounting practices prevent them from deducting the full expense of acquisition in the year that it occurs. Some analysts believe that this difference in accounting practices allows foreign corporations to move more rapidly toward acquisition. In addition, the cost of capital in the United States makes it harder for U.S. corporations to save the sums needed for acquisition and more difficult for DBCs to raise the cash needed to take biotechnology products to market.

The Pharmaceutical Industry

Although the arrival of products has been slower than expected, the development of biotechnology-based pharmaceutical products is flourishing. To date, 15 biotechnology-based drugs and vaccines are on the market (see table 1-2). Both DBCs and established multinational pharmaceutical companies are utilizing the tools and techniques of biotechnology in their drug development efforts. Revenues in the United States from biotechnology-derived products were estimated to be approximately $1.5 billion in 1989, and $2 billion in 1990. Many new products are in the pipeline, and several are in the final stages of testing. Of the more than 100 biotechnology drugs and vaccines undergoing human testing for a variety of conditions, 18 have essentially completed clinical trials and are awaiting Food and Drug Administration (FDA) approval. Biotechnology is particularly important for research involving drug discovery as it allows for a molecular and cellular level approach to understanding disease, drug-disease interaction, and drug design. Biotechnology is likely to be the principal scientific driving force for the discovery of new drugs and therapeutic chemical entities as the industry enters the 21st century.

The modern pharmaceutical industry is a global, competitive, high-risk, high-return industry that develops and sells innovative high-value-added products in a tightly regulated process (see table 1-3). Because of the strong barriers to entry which characterize the global pharmaceutical industry, many DBCs are focusing on niche markets and developing biotechnology-based pharmaceutical products. Established pharmaceutical companies have been increasingly developing in-house capabilities to complement their conventional research with

Box *1-D--Arrangements Between Companies*

Acquisition. One company taking over controlling interest in another company. Investors are always looking for companies that are likely to be acquired, because those who want to acquire such companies are often willing to pay more than the market price for the shares they need to complete the acquisition.

Merger. Combination of two or more companies, either through a pooling of interests, where the accounts are combined; a purchase, where the amount paid over and above the acquired company's book value is carried on the books of the purchaser as goodwill; or a consolidation, where a new company is formed to acquire the net assets of the combining companies.

Strategic alliances. Associations between separate business entities that fall short of a formal merger but that unite certain agreed on resources of each entity for a limited purpose. Examples are equity purchase, licensing and marketing agreements, research contracts, and joint ventures.

SOURCE: Office of Technology Assessment, 1991.

biotechnological techniques for use as research tools. Strategic alliances and mergers between major multinational pharmaceutical companies and DBCs allow both to compete in the industry and combine their strengths: the innovative technologies and products of those DBCs with financial and marketing power blended with the development and regulatory experience of the major companies.

The original intent of many of the early DBCs was to become fully integrated, competitive pharmaceutical companies, but the economic realities of the pharmaceutical business will likely deny this opportunity to most DBCs. Biotechnology, while not likely to fundamentally change the structure of the pharmaceutical industry, has provided a much needed source of innovation for both research and product development. Currently, much of the success or failure with the commercialization of biotechnology in the pharmaceutical industry rests on economic, market, scientific, and technical considerations. Government policies that affect these conditions contribute to, but are not likely to independently determine, success or failure.

Agriculture

Biotechnology has the potential to be the latest in a series of technologies that have led to astonishing increases in the productivity of world agriculture in recent decades. Biotechnology can increase food production by contributing to further gains in yield, by lowering the cost of agricultural inputs; and by contributing to the development of new high-value-added products to meet the needs of consumers and food processors. These potential products include agricultural input (e.g., seeds and pesticides), veterinary diagnostics and therapeutics, food additives and food processing enzymes, more nutritious foods, and crops with improved food processing qualities. Thus far, R&D has focused on crops and traits that are easiest to manipulate, particularly single-gene traits in certain vegetable crops. As technical roadblocks are lifted, research is likely to increase and spread to other crops and other traits.

In the United States, DBCs are applying biotechnology to agriculture, and well-established firms are adapting biotechnology to their existing research programs. The ability to profit from new products depends on a variety of factors, such as the potential size of the market for these products, the existence of substitutes, the rate at which new products and technologies are adopted, the potential for repeat sales using patent or technical protection, the existence of regulatory hurdles, and the prospect for consumer acceptance of these new foods. Because these factors vary considerably from country-to-

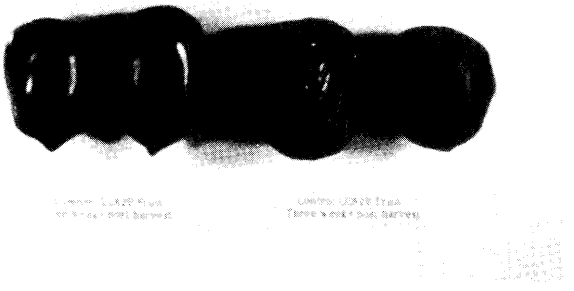


Photo credit: Calgene

Tomatoes, 25 days postharvest. The transgenic tomatoes, left, have not deteriorated, contrasted to the nonengineered tomatoes, right.

Table 1-2—Approved Biotechnology Drugs/Vaccines

Product name	Company	Indication	U.S. approval	Revenues* 1989	Revenues* 1990
Epogen (tin)** Epoetin Alfa	Amgen Thousand Oaks, CA	Dialysis anemia	June 1989	95	300
Neupogen** Granulocyte colony stimulating factor G-CSF	Amgen Thousand Oaks, CA	Chemotherapy effects	February 1891	NA	NA
Humatrope (R)** Somatotropin rDNA origin for injection	Eli Lilly Indianapolis, IN	Human growth hormone deficiency in children	March 1987	40	50
HumuIln(R) Human insulin rDNA origin	Eli Lilly Indianapolis, IN	Diabetes	October 1982	200	250
Actimmune** Interferon gamma 1-b	Genentech San Francisco, CA	Infection/chronic granulomatous disease	December 1990	NA	NA
Activase (R) Alteplase, rDNA origin	Genentech San Francisco, CA	Acute myocardial infarction	November 1987	175	200
Protropln (R)** Somatrem for injection	Genentech San Francisco, CA	Human growth hormone deficiency in children	October 1985	100	120
Roferon (R)-A** Interferon alfa-2a (recombinant/Roche)	Hoffmann-La Roche Nutley, NJ	Hairy cell leukemia AIDS-related Kaposi's sarcoma	June 1986 November 1988	40	60
Leukine** Granulocyte microphage colony stimulating factor GM-CSF	Immunex Seattle, WA	Infection related to bone marrow transplant	March 1991	NA	NA
Recombivax HB (R) Hepatitis B vaccine (recombinant MSD)	Merck Rahway, NJ	Hepatitis B prevention	July 1986	100	110
Orthoclone OKT(R)3 Muromonab CD3	Ortho Biotech Raritan, NJ	Kidney transplant rejection	June 1986	30	35
Procrit** Erythropoietin	Ortho Biotech Raritan, NJ	AIDS-related anemia Pre-dialysis anemia	December 1990	NA	NA
HibTiter (tin) Haemophilus B conjugate vaccine	Praxis Biologics Rochester, NY	Haemophilus influenza type B	December 1988	10	30
Intron (R) A** Interferon-alpha2b	Schering-Plough Madison, NJ	Hairy cell leukemia	June 1986	60	80
		Genital warts AIDS-related Kaposi's sarcoma	June 1988 November 1988		
		Hepatitis C	February 1991	NA	NA
Energix-B Hepatitis B vaccine (recombinant)	SmithKline Beecham Philadelphia PA	Hepatitis B	September 1989	20	30

● Estimated U.S. revenues in millions of dollars
● *Orphan Drug
NA = not applicable

SOURCE: Office of Technology Assessment, 1991; adapted from Pharmaceutical Manufacturers Association-Biotechnology Medicines in Development, 1990 Annual Survey.

Table 1-3-Characteristics, Pharmaceutical Industry

- Top firms are huge, multinational firms primarily based in the United States and Europe.
- Significant entry barriers; very expensive to develop, test, and market new products.
- Not particularly concentrated.
- Tightly regulated.
- Development of high-value-added products.
- Consolidation of companies occurring.
- Size of global market in 1989: $150 billion.
- United States the largest market; combined EC is second; Japan is second largest single country.
- Major companies are financially strong and vertically integrated firms, controlling all aspects of business (R&D, manufacturing, and marketing).
- Main competitors for the world pharmaceutical market: huge, multinational companies based in the United States, Switzerland, the United Kingdom, Germany, and increasingly, Japan.
- Japanese market historically difficult to enter; U.S. and European companies, to ensure market presence, have collaborated with those Japanese companies that dominate their domestic market. Japanese companies are now beginning to globalize their operations.

SOURCE: Office of Technology Assessment, 1991.

country, the climate for application of biotechnology to agriculture also varies. These applications are being explored throughout the world, mainly in developed countries that are major food exporters (e.g., Australia, Canada, France, and the United States).

Because most biotechnology products for agricultural use are still being developed, comparison of numbers of products actually manufactured in different countries is not yet meaningful. However, since field tests of many potential plant products are regulated by national agricultural or environmental authorities, comparison of some test numbers is possible. As of 1990, over 60 percent of all field tests worldwide (most involving transgenic plants) have occurred in the United States (see table 1-4).

Although there is much active European agricultural biotechnology research in northern Europe, particularly Germany and Denmark, public concern about possible environmental risks and ethical issues associated with biotechnology has translated into regulations that discourage field testing of genetically engineered organisms. The lack of patent protection for transgenic organisms also tends to inhibit investment in transgenic plants in Europe. In Japan and other Asian countries, public perception of biotechnology appears to be mixed. Biotechnological methods used to produce pharmaceuticals and industrial and food processing enzymes are accepted, however, agricultural applications are less so. Consequently, relatively little attention has been paid to transgenic plants and animals in Asia. One exception is work on plants, especially rice, derived from plant cell cultures. The application of biotechnology to food processing has received a great deal of interest in Japan, where the country's expertise in fermentation is likely to be applied to food production.

The Chemical Industry

The chemical industry is one of the largest manufacturing industries in the United States and Europe. Currently, over 50,000 chemicals and formulations are produced in the United States. The consumption of chemical products by industry gives these products a degree of anonymity as they usually reach consumers in altered forms or as parts of other goods.

Biotechnology has a limited, though varied, role in chemical production. The production of some chemicals now produced by fermentation, such as amino acids and industrial enzymes, may be improved using biotechnology. Similarly, biotechnology can be used to produce enzymes with altered characteristics (e.g., greater" stability in harsh solvents or greater heat resistance). In many instances, biotechnology products will probably be developed and introduced by major firms without the fanfare that has accompanied other biotechnology developments and, like much of chemical production, will remain unknown to those outside the industry. The

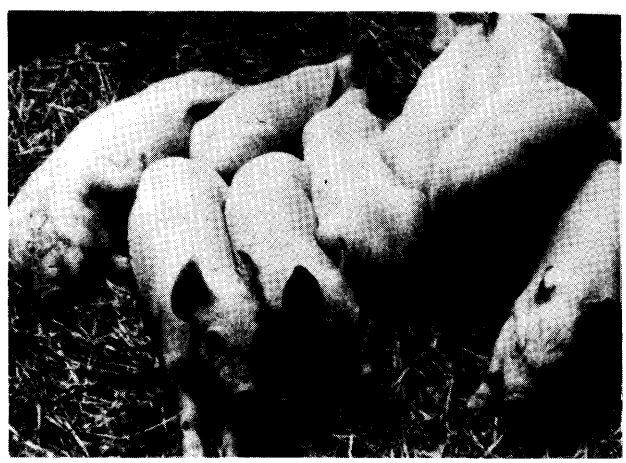


Photo credit: Kevin O'Connor

Transgenic pigs born with a bovine growth hormone gene inserted in the embryo.

Table 1-4-Proposed Pending or Performed Field Tests

	1986	1987	1988	1989	1990	Undated	Total
Australia	—	1	—	—	—	4	5
Belgium	1	2	6	5	—	—	14
Canada	—	—	4	14	—	3	21
Denmark	—	—	—	—	2	—	2
Finland	—	—	—	—	—	1	1
France	1	2	4	3	—	—	10
Ireland	—	—	—	—	—	1	1
tidy.	—	—	1	—	—	1	2
The Netherlands	—	—	1	1	—	2	4
New Zealand	—	—	1	1	—	4	6
Spain	—	—	2	1	—	—	3
Sweden		—	—	1	—	—	1
United Kingdom	1	4	1	4	—	—	10
United States	4	15	34	56	—	23	132
Total	7	24	54	86	2	39	212

SOURCE: Organization for Economic Co-operation and Development, 1990.

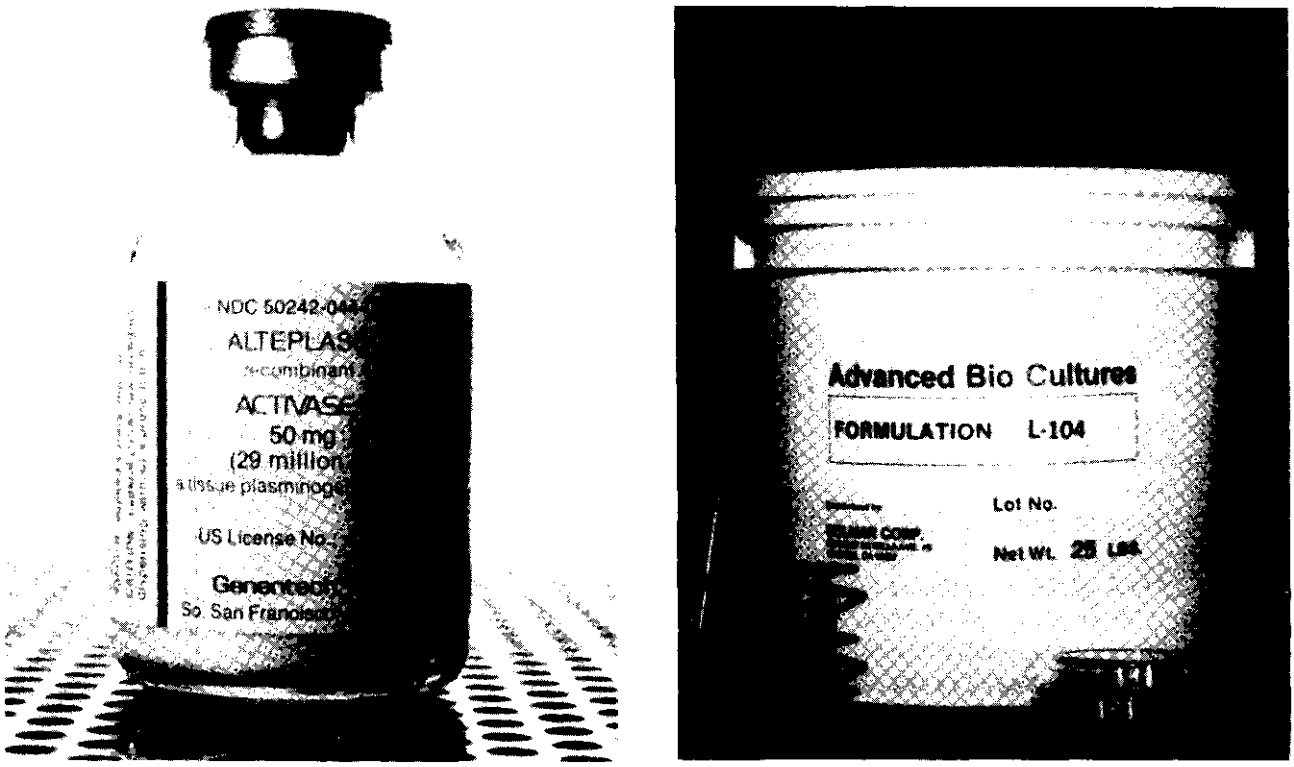


Photo credit: Genentech, Solmar Corp.

The abilityto produce high-value-added products is one reason the pharmaceutical industry is attractiveto venture capitalists. Genentech's tissue plasminogen activator (left) costs $2,200 per dose. In contrast, Solmar Corp's. Bio Cultures, used in waste cleanup (right) sells for approximately $400 per 25-pound container.

chemical industry's greatest use of biotechnology may be the result of the industry's expanding investment in pharmaceuticals and agriculture. This reflects the industry's shift away from the production of bulk chemicals and toward investment in research-intensive, high-value-added products; the worldwide industry response to oil shocks, recessions, and increasing competition.

The use of biochemistry or fermentation to produce chemicals has historically received a great deal of attention in Japan, and the Ministry of

International Trade and Industry (MITI) targeted improvements in these processes through biotechnology in 1980. Another application that has received particular attention in Japan is the biosensor (a device that uses immobilized biomolecules to interact with specific environmental chemicals and then detects and quantifies either the interaction itself or the product of the interaction, e.g., a change in color, fluorescence, temperature, current, or voltage).

In the very long run, biotechnology may have a major impact in shifting the production of fuel and bulk chemicals away from reliance on nonrenewable resources (e.g., oil) and toward renewable resources (e.g., biomass). However, current work in this field appears to be limited, in part, because the international price of oil has remained too low to encourage investment in alternatives, and, in part, because the chemical industry throughout the world has restructured during the last 10 years, moving away from bulk chemical production and toward the production of specialty chemicals, pharmaceuticals, and agricultural products.

Photo credit: Exxon Corp.

Worker applying fertilizer to the cobble beaches of Prince William Sound.

Environmental Applications

Although biotechnology has several potential environmental applications-including pollution control, crop enhancement, pest control, mining, and microbial enhanced oil recovery (MEOR)—commercial activity to date is minuscule compared to other industrial sectors. Bioremediation, efforts to use biotechnology for waste cleanup, has received public attention recently because of the use of naturally occurring micro-organisms in oil-spill cleanups. The U.S. bioremediation industry includes more than 130 firms, but it is the focus of few DBCs. Nevertheless, though small, the size of the commercial bioremediation sector in the United States far exceeds activity in other nations.

Although bioremediation offers several advantages over more conventional waste treatment technologies, several factors hinder its widespread use. Relatively little is known about the effects of micro-organisms in various ecosystems. Research data are not disseminated as well as research in other industrial sectors because of limited Federal funding of basic research and the proprietary nature of business relationships under which bioremediation is most often used. Regulations provide a market for bioremediation by dictating what must be cleaned up, how clean it must be, and which cleanup methods may be used; but regulations also hinder commercial development, due to their sheer volume and lack of standards governing biological waste treatment.

Bioremediation, unlike the pharmaceutical industry, does not result in the production of high-value-added products. Thus, venture capital has been slow to invest in the technology, and little incentive exists for product development. The majority of the bioremediation firms are small and lack sufficient capital to finance sophisticated research and product development programs. Bioremediation primarily depends on trade secrets, not patents, for intellectual property protection.

Although some research is being conducted on genetically engineered organisms for use in bioremediation, today's bioremediation sector relies on naturally occurring micro-organisms. Scientific, economic, regulatory, and public perception limitations that were viewed as barriers to the development of bioremediation a decade ago still exist. Thus, the commercial use of bioengineered micro-organisms for environmental cleanup is not likely for the near future.

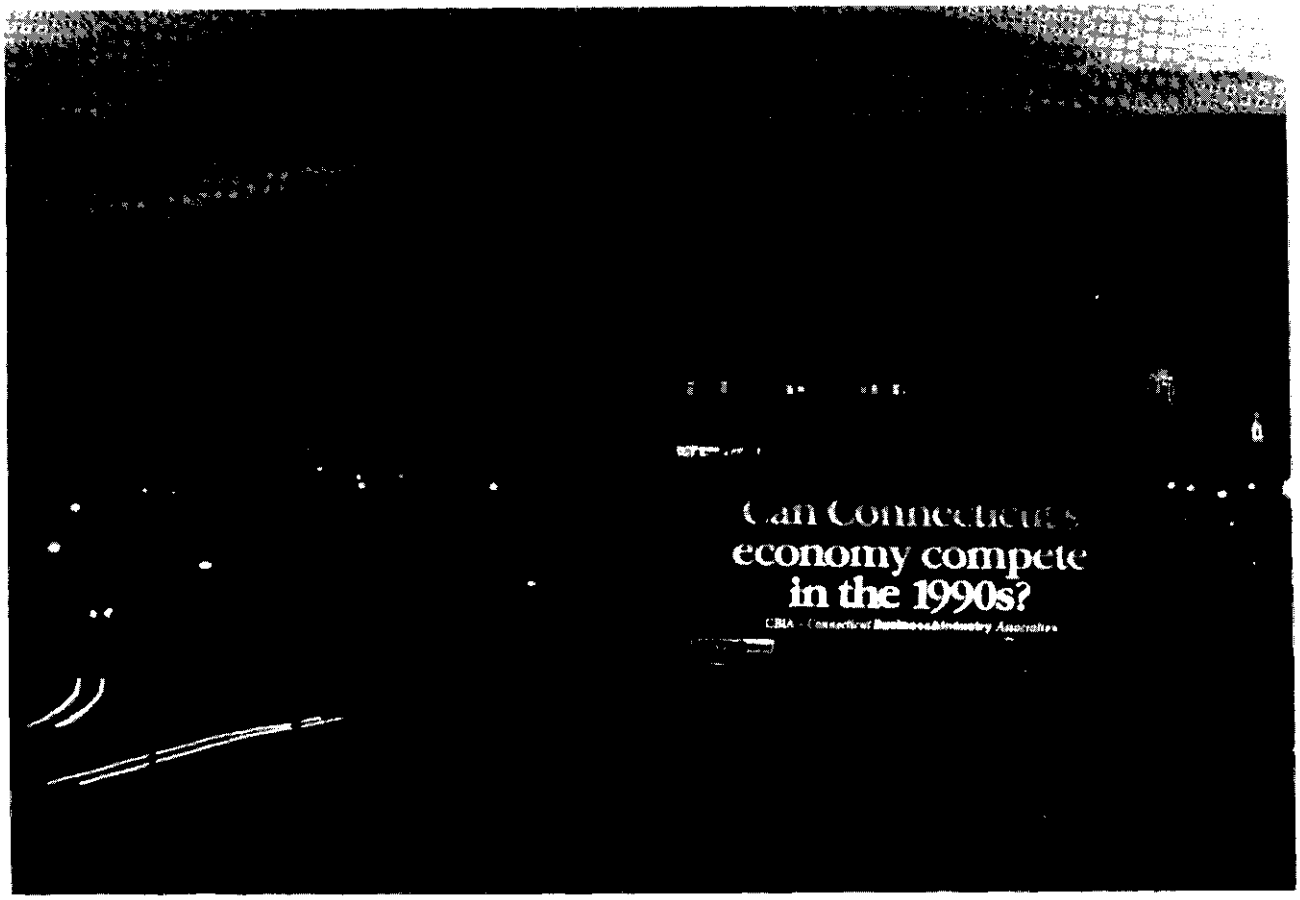


Photo credit: CBIA

Billboard, Hartford, CT.

INDUSTRIAL POLICY

Industrial policy is the deliberate attempt by a government to influence the level and composition of a nation's industrial output. Industrial policies can be implemented through measures such as allocation of R&D funds, subsidies, tax incentives, industry regulation, protection of intellectual property, and trade actions.

Industrial policies in the United States are complex, fragmented, continually evolving, and rarely targeted comprehensively at a specific industry. There is no industrial policy pertaining to biotechnology per se, but rather, a series of policies formulated by various agencies to encourage growth, innovation, and capital formation in various high-technology industries. And, just as there is no biotechnology policy in the United States, biotechnology companies tend to behave not as an industry but rather, as agrichemical firms, diagnostic firms, or human therapeutic firms. Biotechnology companies have been built on a unique system of financing, but they largely confront the same regulatory, intellectual property, and trade policies faced by other U.S. high-technology firms. There may be a need for the Federal bureaucracy to fine-tune its policies as biotechnology moves through the system, but, to date, Federal agencies have not seen the need to revolutionize their practices for biotechnology.

Science and Technology Policy

National policies promoting biotechnology R&D can be categorized as targeted or diffuse. In general, countries that have targeted biotechnology (e.g., Japan, Korea, Singapore, and Taiwan) share an

emphasis on export-driven growth, and they view comprehensive government policies strongly promoting biotechnology and other critical technologies as key to future development. In the United States and much of Europe, in contrast, growth promotion is less prominent and is one of many competing social concerns. In these countries, fundamental goals are more diffuse.

A challenge to the adoption of a national biotechnology policy is the increasing internationalization of research, development, and product commercialization. The advent of EC 1992 has led to the creation of unique regional biotechnology research programs that offer yet another approach to strategic planning. These programs are currently modest in size, and their eventual success will likely hinge on political and economic integration of the European Community (EC).

Government targeting of biotechnology for special support is one of the least significant factors affecting competitiveness in the technology. Many components of targeting strategies such as the emphasis on technology transfer, the development of incubator facilities and venture capital for start-up fins, and the establishment of interdisciplinary centers for research are certainly helpful for focusing attention. However, in a sense, they operate at the margins.

There are two prerequisites for a nation to fully compete in biotechnology: 1) a strong research base and 2) the industrial capacity to convert the basic research into products. A strong research base is the first priority, allowing small companies and venture capitalists the opportunity to take risks. Without this, industry-oriented programs will not be very successful. Targeted national biotechnology strategies have been generally unsuccessful, in large part because of the way biotechnology arose out of basic biomedical research only to become fully integrated into the various fields of life sciences. The term 'biotechnology' retains coherence only to the extent that regulation, public perception, and intellectual property law deal with specific biotechnology techniques as something unique.

A major challenge for national governments is to sort out national from private interests, a task that will become more difficult as competitiveness is used as a justification for particular expenditures. Economic nationalism may be particularly difficult to define and pursue, given the pluralistic, incremental, and increasingly global nature of the world's R&D system. In the emerging global research and commercial environment, aggressive companies, whether large multinationals or savvy newcomers, seek the best ideas regardless of nationality. Likewise, they produce goods and services to effectively compete in international markets regardless of nationality. It is no longer always clear what constitutes an American firm in a global economy.

Regulations

Governments impose regulations to avert the costs associated with mitigating adverse effects expected to result from the use of the technology. But, developing regulations is difficult when a technology is new and the risks associated with it are uncertain or poorly understood. Because there have been no examples of adverse effects caused by biotechnology, projecting potential hazards rests on extrapolations from problems that have arisen using naturally occurring organisms. The consensus among scientists is that risks associated with genetically engineered organisms are similar to those associated with nonengineered organisms or organisms genetically modified by traditional methods, and that they may be assessed in the same way. Where similar technologies have been used extensively, past experience can be an important guide for risk assessment.

Many countries, in addition to the United States, have adapted existing laws and institutions to accommodate advances in biotechnology. However, it is no simple matter to base scientifically sound biotechnology regulation on legislation written for other purposes. The differences in approach from nation to nation, particularly through their effects on investment and innovation, will influence the ability of the United States to remain competitive in biotechnology on the international scene.

Worldwide, there have been three basic approaches to the regulation of biotechnology:

- No regulations. A number of countries with active investment in biotechnology have no regulations specific to biotechnology. In most of the growth-oriented countries of the Pacific Rim, such as Taiwan, South Korea, and Singapore, biotechnology has been targeted as a strategic industry. Some industrialized European nations, including Italy and Spain, which have no regulations specifically dealing with

Photo credit: Advanced Genetic Sciences

Two applications of "ice-minus" bacteria at Advanced Genetic Sciences in 1987 reflect varying requirements of regulation. At left, worker in protective clothing applies bacteria on strawberry test plot in April 1987; at right, worker in minimal protective gear applies bacteria on strawberry test plot in December 1987.

biotechnology, expect to develop them to harmonize with EC directives on biotechnology.

- Stringent biotechnology-specific regulations. Some northern European countries have responded to public pressure to impose stringent regulations specific to biotechnology by enacting new legislation. Under a 1986 law, Denmark prohibits the deliberate release of genetically engineered organisms without the express permission of the Minister of the Environment. Germany enacted new legislation imposing tight restrictions, in 1990. The **EC's 1990 directives** on contained use and deliberate release of modified organisms, while not as restrictive as the Danish or German laws, follow a similar approach in regulating products based on the means by which they were produced, rather than based on their intended use.
- Limited restrictions. Australia, Brazil, France, Japan, The Netherlands, the United Kingdom, and the United States allow the use of biotechnology with some restrictions and oversight. In these countries, regulations based on existing or amended legislation governing drugs, worker health and safety, agriculture, and environmental protection are being applied to the use of biotechnology. Stringency varies, as do the enforcement mechanisms.

In 1986, the Office of Science and Technology Policy (OSTP) of the White House described the regulatory policy of the Federal agencies in the Coordinated Framework for Regulation of Biotechnology. Recognizing that biotechnology is basically a set of techniques for producing new biochemical and altered organisms, and that chemicals and organisms are usually regulated according to their intended use and not their method of production; Federal policy fit the products of biotechnology into the existing web of Federal legislation and regulation. The framework also outlined the approach to interagency coordination, identifying the lead agency in several areas of overlapping jurisdiction.

Under the existing Framework for Regulation of Biotechnology, FDA has approved hundreds of diagnostic kits, 15 drugs and biologics, and 1 food additive; the Department of Agriculture (USDA) and the Environmental Protection Agency (EPA)

have established procedures for reviewing field tests of modified plants and micro-organisms, and have approved 236 field tests as of May 1991 (see figure l-l). Although farm activists are concerned about the potential economic effects of bovine somatotropin (bST), public concern about the contained uses of modified organisms and their testing in the field has dissipated in the United States. However, some problems remain:

- Mechanisms established to provide Federal coordination of activities related to biotechnology have instead become the center of interagency ideological disputes over the scope of proposed regulations.
- The time required for clinical trials necessary for FDA approval of new drugs and biologics hurts young firms attempting to commercialize their first products.
- EPA has yet to publish proposed rules for the regulation of micro-organisms under the Toxic Substances Control Act of 1976 (TSCA) and Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).
- EPA considers micro-organisms to be chemical substances subject to TSCA, an interpretation that could be legally challenged.
- There is little funding for research that would support risk assessment of planned introductions.
- FDA has given little indication of its intentions for the development of regulations and procedures for evaluating the food safety of genetically modified plants and animals.
- Field-testing requirements have been criticized as too burdensome, especially for the academic community, and disproportionate to the small risk associated with these organisms, particularly transgenic crops with no nearby wild, weedy relatives.

The problems associated with developing regulations add to the costs borne by firms, and is especially burdensome for small biotechnology-based firms. Despite these difficulties, however, there is anecdotal evidence that some European firms have decided to open research and production facilities in Japan and the United States, in part because of the more favorable regulatory climate.

Intellectual Property Protection

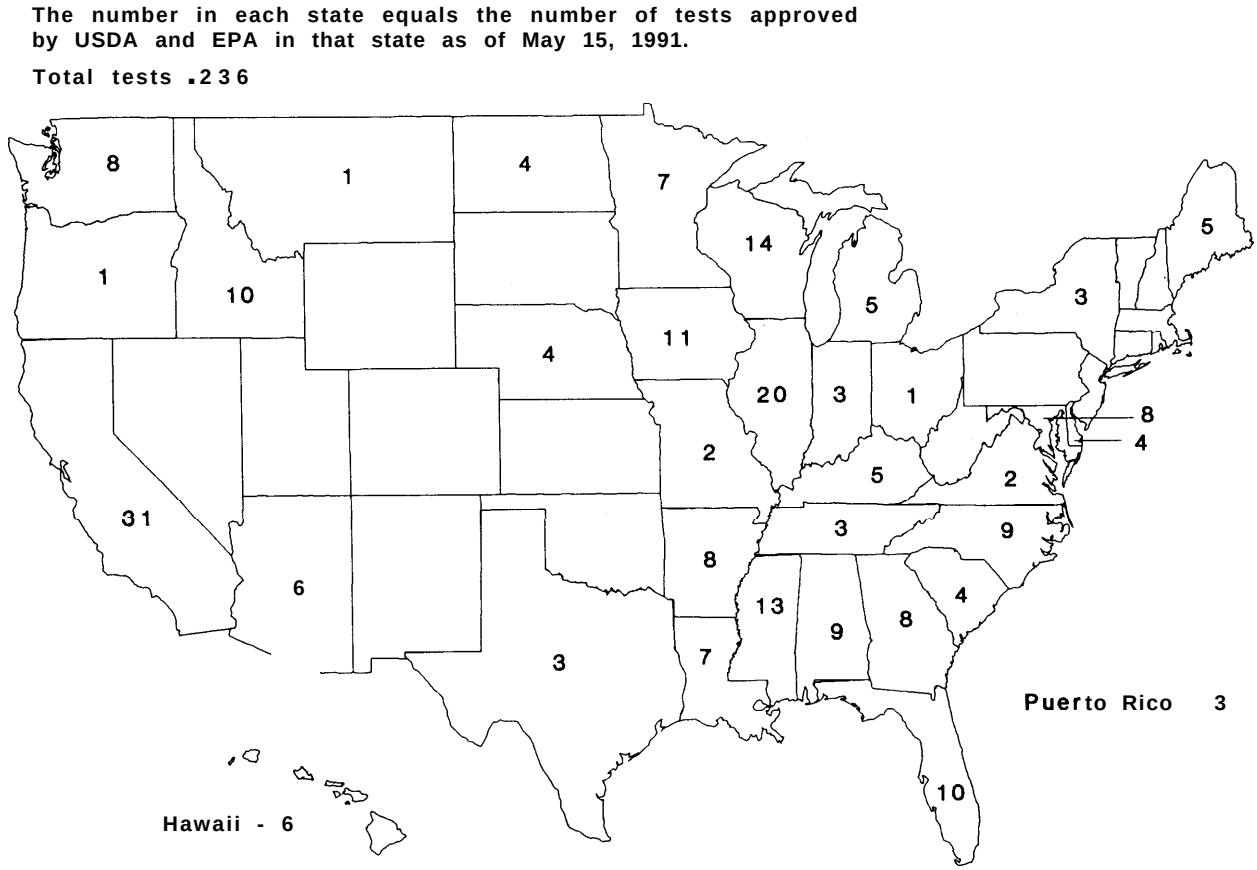
Intellectual-property law, which provides a personal property interest in the work of the mind, is of increasing importance to people using biotechnology to create new inventions. Intellectual property involves several areas of the law: patent, copyright, trademark, trade secret, and plant variety protection. All affect emerging high-technology industries because they provide incentives for individuals and organizations to invest in and carry out R&D. Many see protection of intellectual property as a paramount consideration when discussing a nation's competitiveness in industries fostered by the new biology.

Broad patent protection exists for all types of biotechnology-related inventions in the United States. The Supreme Court decision in ***Diamond v. Chakrabarty,*** that a living organism was patentable, along with action by Congress and the executive branch changing Federal policy to increase opportunities for patenting products and processes resulting from federally funded research have spurred biotechnology-related patent activity. Internationally, several agreements (e.g., the Paris Union Convention, the Patent Cooperation Treaty, the Budapest Treaty, the Union for the Protection of New Varieties of Plants, and the European Patent Convention) provide substantive and procedural protection for inventions created through the use of biotechnology.

Despite a generally favorable international climate, a number of elements affect U.S. competitiveness in protecting intellectual property. The patent application backlog at the Patent and Trademark Office (PTO), domestic and international uncertainties regarding what constitutes patentable subject matter, procedural distinctions in U.S. law (e.g., first-to-invent versus frost-to-file, priority dates, grace periods, secrecy of patent applications, and deposit considerations), uncertainties in interpreting process patent protection, and the spate of patent infringement litigation, all constitute unsettled areas that could affect incentives for developing new inventions.

The backlog of patent applications at PTO is frequently cited as the primary impediment to commercialization of biotechnology-related processes and products. Recent studies reveal that the pendency period for biotechnology patent applications is longer than that of any other technology.

Figure 1-1--States Where Releases of Genetically Engineered Organisms Have Been Approved



SOURCE: National Wildlife Federation, 1991, adapted from data provided by U.S. Department of Agriculture and U.S. Environmental Protection Agency.

IWO, in an effort to reduce the backlog, created a special biotechnology examining group and instituted an action plan to reduce the average pendancy. The PTO plan, while showing some promise, stands little chance of significantly reducing the backlog for two reasons: the number of filed biotechnology patent applications grows at a significantly higher average rate than that for all other types of patent applications, and PTO is unable to train and keep qualified patent examiners. The backlog creates uncertainty for business planning and a disincentive for proceeding with some R&D projects; however, there is no evidence to suggest that it significantly affects international competitiveness in biotechnology. Accelerated examination, a procedural option open to those needing expedited examination of a patent application, is rarely used for biotechnology applications. When compared to other countries, biotechnology patents are granted faster in the United States than in any major examining office in the world. And, for products that have a long regulatory approval time, the delay in obtaining a patent can result in an extended length of protection, since the 17-year term does not begin until the patent is actually issued.

Subject matter protection—what can and cannot be patented—is an issue that has received much attention because of the types of inventions created through biotechnology. U.S. law is the broadest and most inventor-generous statute in the world; in addition to processes, patents have now issued for microbes, plants, and, in one instance, a transgenic animal. The subject of patenting plant and animal varieties (permitted in the United States but not in most other countries) and products (pharma-

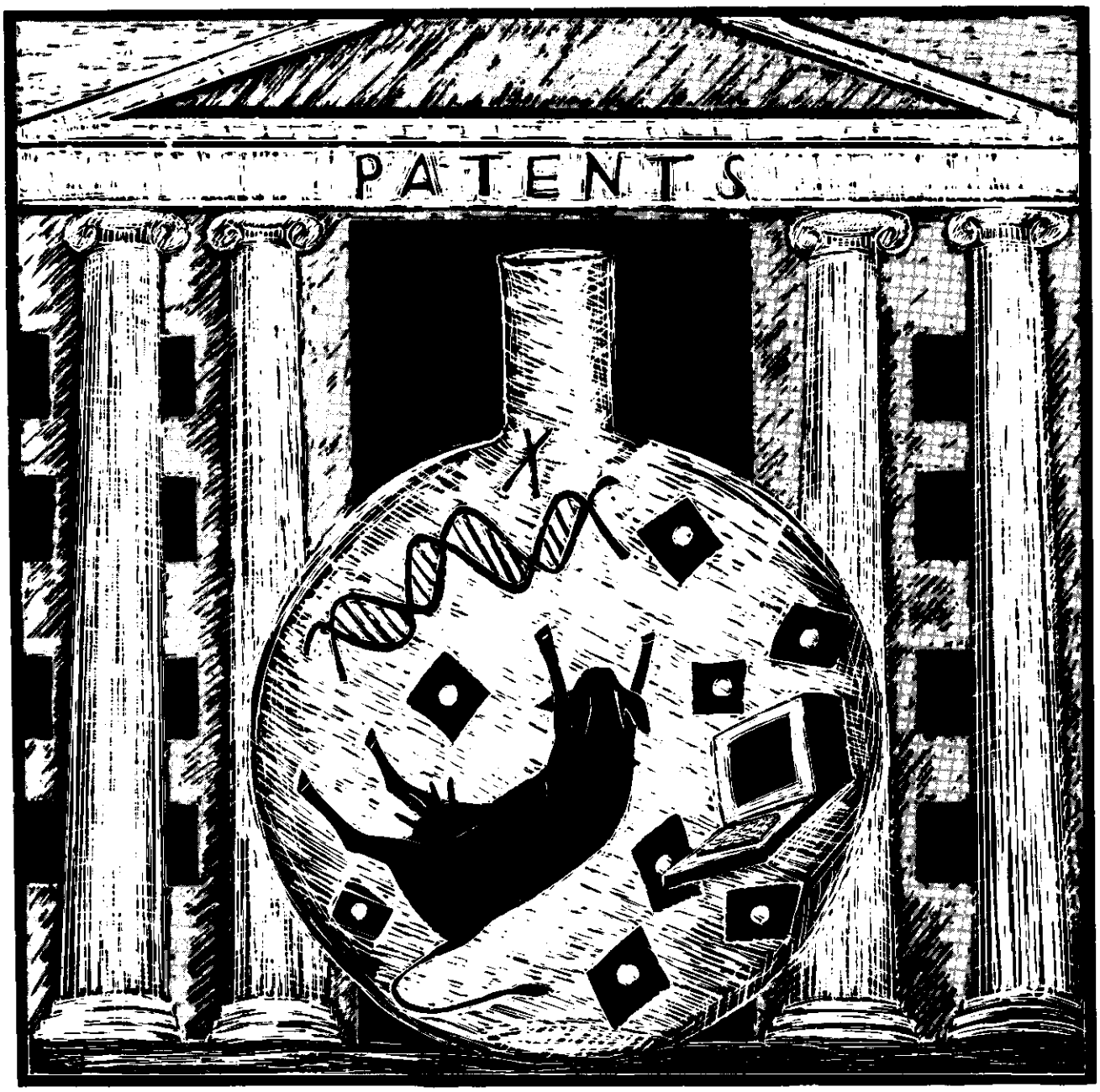


Photo credit: Claudia Tantillo Waters

ceuticals, for example, are patentable in some countries but not in others) is of concern to those who seek consistent worldwide protection for their inventions.

Procedural distinctions between the laws of various nations are receiving increased attention in forums convened to harmonize international patent law. The ability of inventors to understand and easily meet the procedural requirements of various patent offices may, in the long term, be the issue of most importance to inventors of biotechnology products and processes. Procedural issues currently under debate in international forums include: determining how a priority date is set, establishing a consistent grace period, determining

requirements for publication of patent applications, and standardizing translation requirements of applications.

A major concern of U.S. biotechnology companies is the adequacy of U.S. laws to protect against patent piracy. Process patents constitute the majority of patents issued in the biotechnology area. Such patents can be vital, especially if they cover a new process for making a known product. Congress enacted legislation in 1988 to address concerns regarding process patent protection. Debate, however, continues as to whether additional protection is needed. The large number of patents in the emerging biotechnology field has resulted in a surge of litigation as companies seek to enforce their rights against infringement and defend the patent grant in opposition or revocation proceedings. Such litigation is not surprising given the web of partially overlapping patent claims, the high-value products, the problem of prior publication, and the fact that many companies are interested in the same products. Litigation, while important to those staking their property claims, is extremely expensive and a major drain on finances that could otherwise be directed toward R&D.

INTERNATIONAL COMPETITIVENESS

Industrial competitiveness is viewed by some as the ability of companies in one country to develop, produce, and market equivalent goods or services at lower costs than firms in other countries. The increasingly global economy, however, makes it more difficult to view industrial competitiveness this way. Many companies actively investing in biotechnology are multinational, conducting research, manufacturing, and marketing throughout the world. These companies contribute to the economies of nations other than the one in which they are headquartered. Despite these complications, it is still possible to broadly discuss strengths and weaknesses in various countries with respect to biotechnology.

A number of nations have targeted biotechnology as being critical for future economic growth. Nationally based R&D programs have arisen in several countries, and biotechnology has been singled out in many public policy debates as having economic, social, ethical, and legal consequences. Using a number of measures (see box l-E), in 1984 OTA found that the United States was at the forefront in the commercialization of biotechnology, that Japan was likely to be the leading competitor of the United States, and that European countries were not moving as rapidly toward commercialization of biotechnology as either the United States or Japan.

United States

In retrospect, the diffusion of biotechnology into several industrial sectors in many nations makes it difficult to define what constitutes a strong national program in biotechnology and to rank the countries in competitive order. By many measures, the United States remains preeminent in biotechnology, based on strong research programs and well-established foundations in pharmaceuticals and agriculture. Broad-based, federally funded basic research-especially in biomedicine-is a hallmark of U.S. capability in biotechnology. In fiscal year 1990 alone, the Federal Government spent more than $3.4 billion to support R&D in biotechnology-related areas (see table 1-5).

Dedicated biotechnology companies, a uniquely American phenomenon, aided by the vast resources of venture capital and public markets have provided innovation to a number of preexisting industries. U.S. patent law provides generous protection for all kinds of biotechnology-derived inventions, and laws and regulations are largely in place to protect the public health and the environment. Public concern regarding the uses of biotechnology is minimal when compared to many other nations.

Japan

In 1981, Japan's MITI announced that biotechnology, along with microelectronics and new materials, was a key technology for future industries. The announcement attracted interest and concern abroad, largely because of the key role MITI played in guiding Japan's economic growth in the postwar period. While government policies encouraged biotechnology investment by a large variety of companies, Japanese investment in biotechnology predates MITI's 1981 action. Regardless of earlier actions, MITI's naming of biotechnology as an area of interest probably gave it the legitimacy it previously lacked and eased financing for private investment—as it had done earlier for other industries and technologies. As in the United States and elsewhere, however, the broad range of potential biotechnology applications has led to a wide variety of frequently

Box 1-E—Measuring International Competitiveness

In investigating international competitiveness in biotechnology, in 1984 OTA used the following approach.

The first step in the analysis of international competitiveness in biotechnology was to consider the aggregate level of industrial activity and the number and kinds of firms commercializing biotechnology in the competitor countries. The industrial analysis was approached from three perspectives:

- the number and kinds of companies commercializing biotechnology,
- the markets targeted by industrial biotechnology R&D, and
- the interrelationships among companies applying biotechnology, and the overall organization of the commercial effort.

The second step in providing an overall picture of competitiveness in biotechnology involved the evaluation of 10 factors identified as potentially important in determining the future position of the United States and other countries in the commercialization of biotechnology: government funding of applied and basic research; personnel availability and training; financing and tax incentives for firms; health, safety, and environmental regulation; intellectual property law; university/industry relationships; targeting policies in biotechnology; international technology transfer, investment, and trade; antitrust law; and public perceptions.

Additional considerations taken into account in the analysis were historical patterns of industrial commercialization, the lack or abundance of particular natural resources, and the tendency toward risk taking in various countries.

SOURCE: Office of Technology Assessment, 1984.

Table 1-5--U.S. Federal Funding for Biotechnology, Fiscal Year 1990 (millions of dollars)

Agency	Amount
National Institutes of Health	$2,900.0
National Science Foundation	167.9
Department of Agriculture	116.0
Department of Defense	98.0
Department of Energy	82.2
Agency for International Development	28.7
Food and Drug Administration	19.4
Environmental Protection Agency	8.3
Veterans Administration	7.5
National Institute of Standards and Technology	4.8
National Aeronautics and Space Administration	4.5
National Oceanic and Atmospheric Administration	2.0
Total	$3,439.3

SOURCE: Office of Technology Assessment, 1991.

overlapping initiatives by various Japanese agencies.

Today, MITI is continuing to support R&D efforts in areas such as: marine biotechnology and biodegradable plastics, addressing relevant industrial policy (e.g., tax incentives, Japan Development Bank, and Small Business Finance Corp. loans, and promotion of industry standards), improving safety measures (new contained-use regulations and developing lists of industrially exploitable organisms), and internationalization (regulatory harmonization, international R&D cooperation, and funding developing country research). However, in contrast to the United States, Japan suffers from the lack of a strong research base, which has led firms to seek access to research and training abroad, especially in the United States.

Japan also suffers some weaknesses in the industrial sectors to which biotechnology is most applicable. Japan's pharmaceutical industry, for example, was sheltered from international competition until recently and is only now beginning to develop international skills in drug development, testing, and marketing. In agriculture, research is limited to specialized areas (e.g., rice), as Japan is not a food exporting country. Additionally, concern regarding field testing of genetically modified organisms is pervasive; governmental approval for the first environmental release of a genetically engineered organism-a transgenic tomato---did not occur until January 1991.

Japan is, however, effectively combining biotechnology with its traditional strength in fermentation, especially in the production of amino acids and industrial enzymes. There is also active research with biosensors, based on Japan's strength in micro-electronics. The efforts of MITI to promote biotechnology as a key technology, intergrate biotechnology into existing industrial sectors, while at the same time bearing some fruit, clearly has been less successful than many anticipated. As in the United States and Europe, commercialization has taken longer, been more technically difficult, and been more dependent on factors unique to each industrial sector than expected. Biotechnology has not yet achieved the spectacular success for Japanese

industry that other fields have in the past. For the foreseeable future, corporate strategies, rather than MITI initiatives, will likely determine Japan's investment in biotechnology.

Europe

A number of European countries have technology policies that resemble those of the United States National policies, however, are becoming less distinctive as Europe moves closer to economic integration.

Unlike Japan, Europe's strengths in pharmaceuticals and agriculture lend themselves to the adoption of biotechnology. Germany, Switzerland, and the United Kingdom are home to major multinational pharmaceutical companies. These companies are investing heavily in both in-house and collaborative research in biotechnology, with much of the latter conducted with U.S. DBCs. Promising research in agricultural biotechnology is under way in several countries, especially Belgium, France, Germany, and the United Kingdom. The picture is clouded, however, by several factors: the fragmentation of research efforts, adverse public opinion, and uncertain effects of recently enacted European Community directives on field testing of genetically modified organisms.

While many countries are targeting biotechnology, those that have not developed a research base and the industrial capacity to convert basic research into products are not likely to be serious commercial competitors in the near future.

OPTIONS FOR ACTION BY CONGRESS

There is no way to directly measure a nation's competitiveness in biotechnology. Modern biology is being used in many nations, by many multinational corporations, and in many industrial sectors. In addition, there is no consensus as to what constitutes the so-called "national interest" in promoting a technology. Some view competitiveness in terms of who ultimately owns a company (i.e., where do the profits eventually go), while others view competitiveness as where jobs and skills are located.

U.S. competitiveness in the global commercialization of biotechnology has come to the attention of Congress for three reasons. First, the U.S. Government indirectly supports industrial applications of biotechnology by funding basic research in a wide range of relevant disciplines. Second, Federal agencies have the authority to regulate the commercial development of biotechnology. Third, international economic competitiveness in various technologies, including biotechnology, has emerged as a key bipartisan concern.

In all three areas, Congress plays a direct role. Through its annual appropriations to Federal agencies, it increases or decreases the level of research and regulatory oversight. Through its authorization powers, Congress can create programs and set priorities for Federal agencies. Through oversight of agencies' conduct of research and regulatory programs, Congress can express its enthusiasm and concern.

Seven policy issues relevant to U.S. competitiveness in biotechnology were identified during the course of this study:

- Federal funding for biotechnology research,
- targeting biotechnology development,
- developing regulations,
- coordinating Federal agencies,
- protecting intellectual property,
- improving industry-university relationships, and
- structuring coherent tax policies.

Options for congressional action discussed here build on the discussion in chapters 3 through 12 of this report. Some options are oriented toward the actions of the executive branch but involve congressional oversight or direction. The order in which the options are presented does not imply their priority. Moreover, the options are not mutually exclusive.

Federal Funding for Biotechnology Research

An issue central to the competitive position of U.S. efforts in biotechnology is a sufficient and stable level of funding for areas of science crucial to the field. In relative and absolute terms, the United States supports more research relevant to biotechnology than any other country. Clearly, intensive and sustained Federal investment in applications of biotechnology to the life sciences has been transformed into commercial products in some industries faster than others. Commercial applications continue to be more advanced in areas such as human therapeutics and diagnostics, largely due to the high

levels of funding of basic biological research by the National Institutes of Health (NIH). Other areas, such as agriculture, chemicals, and waste degradation, have not come close to approaching the same levels of funding enjoyed by the biomedical sciences. In some cases, such as agriculture and waste degradation, slow progress in commercial activity could be due in part to insufficient funds for basic research; in other cases, such as chemicals, potential products are simply not being developed because industry does not consider the biotechnology products or processes sufficiently better (either functionally or economically) than those that already exist.

Congress could determine that Federal levels of investment in R&D over recent years have adequately supported the forward integration of biotechnology into many sectors and have contributed to the commercial successes of U.S. biotechnology companies. Proceeding with the current funding patterns would ensure a stable level of research relevant to biotechnology and its applications. Such an approach, however, would perpetuate current disparities in research emphases, with biomedicine continuing to fare better than agriculture and waste management.

Congress could conclude that because of social, economic, and strategic importance, biotechnology research relevant to agriculture, chemicals, and waste management deserves additional support. Or it could direct Federal agencies to dedicate more of their budgets to applied and multidisciplinary research in biotechnology critical to those industries at a competitive disadvantage. This option would not necessarily require new money but would direct agencies to identify areas of applied research in biotechnology where awards could be made. Applied areas deserving increased funding could be identified by committees of peers comprised of government, academic, and industrial scientists. In addition, areas of research that require multidisciplinary involvement could receive higher levels of support. However, any effort to increase emphases on applied research carries the risk of harming the support base for basic research. Each agency needs to consider the balance of support between basic and applied work within its mission.

Targeting Biotechnology Development

Because it encompasses several processes that have applications to many sectors of the U.S. economy, some argue that biotechnology should be targeted by the Federal Government for aggressive government support and promotion. Currently, U.S. industrial growth depends on private sector entrepreneurship, Federal funding of research, and regulatory oversight of various research applications and commercial development.

Congress could target biotechnology through legislation that broadly singles it out for favorable treatment, or through measures that address specific problems faced by researchers and companies seeking to commercialize products developed through biotechnology. Legislative attempts to target biotechnology have focused on the establishment of national biotechnology policy boards and advisory panels for specific areas of research interest (e.g., agriculture, human genome, and biomedical ethics) and development of a national center for biotechnology information. Those who argue against targeting biotechnology say that it is not the role of the Federal Government to pick winners and losers in the world of commerce, that such efforts have more often failed than succeeded, and that attempts to target biotechnology cannot succeed due to the number of industries involved, all of which face different scientific, regulatory, patent, and commercial problems. Targeting biotechnology alone cannot assure increased competitiveness; fostering a research base (funding, training, and personnel) and maintaining an industrial capacity to convert basic research into products also is required.

Developing Regulations

Six years after the Coordinated Framework for Regulation of Biotechnology was first proposed and 4 years after it became final, regulations for genetically modified pesticides and for certain microorganisms have yet to be issued. This is due to disagreements among some Federal agencies about the need for and appropriate scope of regulations. The failure to promulgate final regulations has led to complaints by industry representatives that the regulatory approval process is unclear and inhibits investment. Manufacturers have also complained of a lack of guidance on food biotechnology and a lack of information on FDA's regulatory intentions. The Biotechnology Science Coordinating Committee (BSCC), in one of its last acts before disbanding, issued a policy statement giving guidance on the scope of organisms to be regulated. But still no proposed rules are in sight. Congress could decide to

use its oversight authority to encourage the agencies to give informal guidance to manufacturers and to encourage the rapid development of rules.

TSCA includes a regulatory scheme to screen new chemicals for their potential to cause unreasonable risk to human health and the environment. Manufacturers and importers must notify EPA 90 days before manufacturing or importing a new chemical or before a chemical is put to a' 'significant new use.' If EPA determines that the chemical poses an unreasonable risk of injury to health or the environment, EPA can prohibit or limit its manufacture, import, or use. As a matter of policy, EPA considers micro-organisms to be chemical substances subject to TSCA. EPA's interpretation has not been challenged in court, and it is not clear how the courts would rule if it were challenged. Congress could decide to amend TSCA to specifically include micro-organisms within its scope. This would assure EPA review of micro-organisms not fitting under the jurisdiction of other statutes prior to field testing.

Coordinating Federal Agencies

There will be a continuing need for interagency consideration of scientific advances, research needs, and regulatory jurisdiction. OSTP founded the Biotechnology Science Coordinating Committee (BSCC) to provide a formal mechanism for discussion of these issues. BSCC became embroiled in questions of agency policy, specifically in the content of EPA's proposed rules, which caused it to neglect its role as a forum for discussion of broad scientific issues and as a mechanism for interagency cooperation. BSCC was also criticized for conducting many of its activities away from public view. OSTP disbanded the BSCC and replaced it with the Biotechnology Research Subcommittee (BRS). BRS has been asked to focus on scientific issues, but the subcommittee will continue to be involved in regulatory matters as well. However, BRS has no statutory authority nor was its formation or purpose published in the ***Federal Register.*** It is not clear what measures are being taken to ensure that BRS avoids the difficulties that stymied its predecessor, nor is it clear that steps are being taken to open its activities to public scrutiny.

Congress could decides that interagency coordination is adequate or that problems of coordination are best resolved through Congress' oversight authority.

Protecting Intellectual Property

Many researchers and companies cite protection of intellectual property as being of utmost importance to preserving competitiveness in biotechnology. This is less a domestic issue than an international one as U.S. law provides broad protection for those who invent new and useful processes and products. However, as markets in biotechnology become increasingly global, issues arise regarding subject matter protection, harmonization of patent procedure, and the context of intellectual property in international trade.

U.S. law permits patents to issue for any new, useful and unobvious process, machine, manufacture, composition of matter, or new and useful improvement of these items. As a result, U.S. law has permitted the patenting of micro-organisms, plants, and nonhuman animals. The patenting of nonhuman animals has led to legislative debate regarding subject matter protection. Options for congressional action-which included discussion on issues such as deposit considerations and exemptions from infringement for certain classes of users—were presented in an earlier OTA report (New ***Developments in Biotechnology: Patenting Life)*** and are incorporated here by reference. In terms of patentable subject matter, U.S. patent law is the most inventor-friendly statute in the world; it is unique in that it makes no exceptions to patentability, which are often found in the statutes of other countries (e.g., animal and plant varieties, public order or morality, and products such as pharmaceuticals and foods). If Congress takes no action regarding patentable subject matter, broad protection for inventions created by biotechnology will continue. Laws created by Congress to regulate interstate commerce would be relied on to govern the development, approval, sale, and use of such inventions. Congress could, either through moratorium or prohibition, specifically bar patents from issuing for nonhuman animals or human beings. Such action would clarify congressional intent regarding the limits of subject matter protection, but it would also create the precedent of using patent law, rather than laws regulating commerce, to limit the creation of certain types of inventions.

Harmonization of U.S. patent law with the laws of other nations is likely to come to Congress' attention as a result of several ongoing efforts: the General Agreement on Tariffs and Trade, the World Intellec-

tual Property Organization, amendments to the Union for the Protection of New Varieties of Plants, and other bilateral and multilateral trade discussions. It is too early to predict specific options arising from each of these forums. In all cases, the goal of harmonization should be the creation of consistent laws addressing substantive and procedural issues in patent practice.

Process patent protection is also of increasing importance to industry. Legislation was introduced in the 101st and 102d Congresses to grant the International Trade Commission the right to bar entry into the United States products made using any component manufactured in violation of a U.S. patent and to allow process patent protection on biotechnology production processes as long as the starting material is novel. Issues related to the scope of process patents, obviousness, and import into the United States of products containing patented parts will continue to arise. Consensus among companies is unlikely in many of these policy disputes as many of these problems involve competing biotechnology companies that are staking out corporate competitive positions.

Improving Industry-University Relationships

Through a series of actions, both Congress and the executive branch have encouraged the transfer of research findings into commercial applications. Industrial sponsorship of university-based biotechnology research has become a widespread and generally accepted phenomenon over the past 10 years. The resulting links between academic-based biotechnology research and industry have several beneficial effects (e.g., additional resources for R&D and training, more focus on applied research, and the development and use of patented inventions). Questions have been recently raised about possible negative affects of some of these relationships, particularly the conflicts that could arise when a researcher is involved in trials or testing of new drugs developed by companies in which they have a personal financial or fiduciary interest. Some industrialists have expressed concern that guidelines or regulations requiring disclosure of potential conflicts of interest for federally funded scientists will have a negative impact on the ability of U.S. biotechnology firms to transfer the results of federally funded research into commercial application.

Currently, NIH and the Alcohol, Drug Abuse, and Mental Health Administration have no rules concerning conflicts of interest for grantees, although NIH must approve any outside financial arrangements for its employees that could pose potential conflicts of interest. To date, the Public Health Service (PHS) has only proposed that investigators who design, conduct, or report research disclose financial interests to institutions. Comments on the proposal were received at a November 1990 public meeting.

Congress could take no action if it concludes that the number of cases of alleged conflict of interest and misconduct have been too few to warrant legislative action, or that oversight of conflict of interest is best managed at the university level. If Congress decides that action is needed, it could direct the Department of Health and Human Services (DHHS) to promulgate PHS regulations that clearly spell out or restrict financial ties for researchers who conduct evaluations of a product or treatment in which they have a vested interest. In the absence of action by DHHS, Congress could also enact legislation to achieve the same goal.

Legislation that restricts the ability of publicly funded researchers to collaborate with industry could discourage the entrepreneurial initiative of scientists and possibly limit the value of government-sponsored research. However, a lack of action by either Congress or executive agencies to clarify the limits of such collaboration could result in cases of actual or perceived conflict of interest with resulting public concern about the safety of some biotechnology-derived products.

Structuring Coherent Tax Policies

The Tax Reform Act of 1986 (Public Law 99-514) contained numerous provisions, including extension and reduction from 25 to 20 percent of the R&D tax credit, repeal of the investment tax credit for equipment investment, and abolition of the preferential treatment for capital gains. Five options for congressional action were presented in an earlier OTA report (New ***Developments in Biotechnology: U.S. Investment in Biotechnology).*** One of the options—restoration of preferential treatment of capital gains—was addressed by the 101st Congress.

Other options discussed the R&D tax credit, which is designed to provide an incentive to companies to increase their commitment to indus-

trial R&D. Firms that annually increase R&D spending can apply for an R&D tax credit against Federal income taxes. The credit has been available since 1981 but is not a permanent part of the tax code, rather it has been extended several times through various legislation. Most recently it was extended through December 31, 1991, by the Omnibus Budget Reconciliation Act of 1990. Congress could grant the R&D tax credit permanent status when it expires at the end of 1991. A permanent credit would reduce the uncertainty that exists for industrial R&D planners concerning the credit's future existence.

The statutory rate of the credit is 20 percent, and the credit is calculated based on the excess of qualified research over abase amount linked to R&D spending in a specific historical period. The base amount is figured by multiplying a "fixed-base percentage" by a firm's average gross receipts over the preceding 4 years. As currently structured, companies that do not have positive gross receipts for the preceding 4 years are not eligible to receive the R&D credit in the same year as the research expenses are made. The credit is not refundable in the current year, so only firms with positive tax liabilities can use it immediately. Those companies without current tax liabilities, which include many DBCs, can carry forward tax credits to offset taxes up to 15 years in the future. For a DBC, this carried-forward credit is less valuable than a refundable credit, that would provide immediate returns. In addition, when considering the time-value of money, carried-forward tax benefits are less valuable than tax benefits rendered in the current year. Despite these facts, some successful biotechnology companies have expressed the opinion that the R&D tax credit is beneficial and that it does factor into their decisionmaking practices in terms of R&D expenditures. Congress may wish to consider changing the structure of the R&D credit to provide more **immediate** benefits to biotechnology and other small high-technology companies that are not yet profitable, by making the credit refundable in the year of research expenditures.

One particular accounting standard that has received recent attention is the inability of U.S. firms to amortize goodwill for tax purposes as quickly as foreign firms. Amortization refers to an accounting procedure that gradually reduces the cost-value of a limited-life or intangible asset through periodic charges to income. Goodwill is a term used in acquisition accounting to refer to the going-concern value (defined as the value of a company as an operating business to another company or individual) in excess of asset value and is considered an intangible asset. Goodwill represents things such as the value of a well-respected business name, good customer relations, and other intangible factors that lead to greater than normal earning power. Goodwill has no independent market or liquidation value and must be written off over time, or amortized. Accounting standards are set by the Financial Accounting Standards Board (FASB), an independent professional board over which Congress has no authority. Foreign companies are not held to FASB rules and are not required to amortize goodwill, rather they can write it off immediately as an expense and in some cases receive a tax deduction. This gives foreign companies an advantage over U.S. companies with respect to acquisitions because the former do not have to carry a balance sheet of goodwill over time. Since Congress has no legislative authority over the FASB, there is no specific legislative action that can be taken to change FASB's rules. Congress could, however, change the tax code to offer a tax deduction on goodwill that is amortized. Such action would recognize the disadvantage that U.S. companies are facing in acquiring U.S. assets, but it could also fuel further controversial corporate acquisitions in a number of industries.