MEETING THE CHALLENGE:
U.S. INDUSTRY FACES THE 21ST CENTURY

THE U.S. BIOTECHNOLOGY INDUSTRY

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FOREWORD

For more than a decade there has been widespread and increasing concern that the ability of the United States to achieve sustained economic growth and long-term prosperity is adversely affected by declining industrial competitiveness. The Congress, in a bipartisan response, has introduced a wide range of programs and policies directed toward improving U.S. competitiveness.

Such policies—whether focused on building a 21st century infrastructure; stimulating technological innovation and commercialization; improving the business climate for investment and growth, education, and training; or promoting trade—start with assumptions, *often implicit*, about the competitive position of U.S. industry.

"Meeting the Challenge: U.S. Industry Faces the 21st Century" is a series produced by the Department of Commerce's Office of Technology Policy that assesses the competitive position of a number of major U.S. industries and the factors influencing their growth. Drawing principally from the experience and insight of the private sector, some 150 experts from over 30 organizations in industry, aca-demia, and government have contributed to the drafting and review of the series. Overall, the studies provide a framework for public policy that is better informed and more accurately reflective of the shifting, and often improving, competitive position of U.S. industry.

This report on the U.S. biotechnology industry discusses the structure of the industry and the current and emerging markets for biotechnology products. It discusses in detail the factors likely to be critical in determining the future competitiveness of the industry:

- Technology Infrastructure and Federal Research Initiatives
- Capital Formation
- The U.S. Health Care System
- Tax Policies
- The Regulatory Environment
- Foreign Competitors
- Trade Issues

The biotechnology industry is still young, especially compared with the automotive, chemical, and steel industries previously studied as a part of the "Meeting the Challenge" series. Despite its comparative youth, it is becoming an important influence on many other industry segments, as well as developing an impressive domestic presence of its own. Its technology base continues to grow dynamically and is melding medical science with information technology in new and exciting ways. While its relationship with capital markets has sometimes been stormy, that relationship now appears to be settling into maturity as its medically oriented companies bring growing numbers of new products to market.

The growth of the biotechnology industry is a unique story and yet it rests on foundations common to other segments of American industry. Years of research, both government funded and privately funded, continue to provide a knowledge base unequaled in the world. The domestic capital market provides the ability to transform this knowledge into unique products and processes for markets around the world. While there is inevitable tension between the industry's desire to bring new products to market and the concerns of the industry's regulators, both sides have found new and innovative ways to work together.

The future holds many competitive challenges for biotechnology, ranging from the dramatic evolution in the American health care system to the increasing strength of competitors in Europe and Asia. The report notes all of these factors, including those areas in which government policy will play an important role, such as product regulation, tax, trade, and intellectual property. It is our hope that this report will contribute to effective policymaking in these areas.

As in all of these reports, the views expressed are those of the authors and reviewers and not necessarily those of the Department of Commerce.

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EXECUTIVE SUMMARY

WHAT IS BIOTECHNOLOGY?

Perhaps unique among industries, biotechnology is not defined by its products, but by the technologies used to make those products. Biotechnology refers to a set of enabling technologies used by a broad array of companies in their research and development and manufacturing activities. These technologies have been used primarily by the pharmaceutical industry but are being used increasingly by other industries (agriculture, mining, and waste treatment).

U.S. government publications have defined biotechnology as "techniques that use organisms or their cellular, subcellular, or molecular components to make products or modify plants, animals, and micro-organisms to carry desired traits." This broad definition includes methods of treating disease developed from recent research in molecular biology and other fields, as well as the centuries-old practices of animal and plant breeding and the use of microorganisms to make leavened bread and fermented beverages.

In the roughly 25 years since the development of recombinant DNA technologies in research laboratories, over 2,000 firms have been founded in the United States alone to explore and take advantage of this new field. Approximately 30 new products have reached the medical market, and several hundred more are in human clinical trials. The market for such products is expected to grow dramatically—from $7.6 billion in 1996 to $24 billion by 2006. Similarly, the market for agricultural biotech products is expected to increase from $295 million in 1996 to $1.74 billion by 2006—with applications ranging from food crops with enhanced pest resistance to improved methods of food preservation.

INDUSTRY STRUCTURE

Creating a comprehensive profile of the biotechnology industry is difficult. The U.S. government gathers data concerning industries based on the product or service provided, not according to the method of manufacture. Consequently, there are no separate government data on biotech-related companies, sales, employment, trade, R&D, etc., and information of this type comes from organizations that study the industry.

Size of the Industry

Ernst & Young states that there are 1,308 companies in the United States that have been founded primarily to commercialize biotechnology. This figure includes suppliers, but not companies from other industries involved in biotechnology.

The Institute for Biotechnology Information (IBI) reports that 30 percent of the biotech companies it has identified are publicly traded, 54 percent are privately owned, and 16 percent are divisions/subsidiaries/joint ventures. Employment in biotechnology firms is estimated at 108,000 people by Ernst & Young and at 111,600 by IBI.

While IBI sets the mean number of employees per company at over 104, the median number is only 30 people. Information provided by the Biotechnology Industry Organization also indicates the relatively small size of the average firm, showing that more than one third of biotechnology companies employ fewer than 50 people and that more than two-thirds of the companies employ fewer than 135 employees.

Research Intensity and Wage Levels

The biotechnology industry is the most research-intensive industry in civilian manufacturing. According to a 1995 survey by *Business Week*, five of the top ten firms in research expenditures per employee were biotechnology companies. Estimates on total R&D spending by the biotechnology industry range from $7.9 billion (Ernst & Young) to $10 billion a year (IBI). According to Ernst & Young, R&D alone accounts for 36 percent of all costs incurred by public biotech companies. The average biotech company spent $69,000 per employee on research in 1995, about eight times the U.S. corporate average of $7,651.

MARKETS FOR BIOTECHNOLOGY PRODUCTS

The biotechnology industry serves both medical and nonmedical markets. The medical market includes human therapeutics and human diagnostics as well as applications in veterinary medicine. Nonmedical markets encompass both agriculture and industrial applications. Agricultural applications include making plants and crops pest resistant, providing improved seed quality, modulating growth and ripening times, enhancing nutrient content of foods, and providing simple and inexpensive diagnostics for use in field testing for contaminants and toxic materials. Industrial uses of biotechnology involve many different sectors and include industrial enzymes, waste management,

bioremediation, energy biomass, cosmetic formulations, and diagnostics for toxicity determinations.

The Medical Market

The majority of U.S. biotechnology firms are pursuing markets in human health care. An IBI study estimates that the primary interest of 29 percent of biotechnology companies lies in therapeutics, while the primary focus of 17 percent of companies is in diagnostics. Biotechnology companies in the human health care field focus on discovering and developing methods to prevent, diagnose, treat, and cure the dozens of life-threatening and serious diseases and conditions for which satisfactory medical therapies or preventive agents currently do not exist.

Consulting Resources Corporation estimates that the market for human therapeutic biotechnology products will grow from $7.6 billion in revenues in 1996 to more than $24 billion in 2006, an average annual growth rate of 13 percent. The human diagnostics biotechnology product sector is expected to grow at an average annual rate of 9 percent from $1.8 billion in 1996 to approximately $4 billion in 2006. At present, the bulk of the biotechnology market is derived from the sales of larger biotechnology companies, including Amgen, Genentech, and Genzyme, and such products as erythropoeitin (EPO), interferon, and insulin. According to a report by Frost and Sullivan, EPO, Amgen's first blockbuster product, accounted for approximately 25 percent of all biotech revenues. Colony stimulating factors, insulin, human growth hormone, beta and gamma interferon, and vaccines accounted for much of the remaining market.

A 1996 survey of biotech drugs under development by companies belonging to the Pharmaceutical Research and Manufacturers of America (PhRMA) found that there were 284 biotechnology drugs in human trials. This figure represents a 21 percent jump over the number (234) in development reported by PhRMA in the previous year. The survey found 18 drug applications pending approval at the FDA and 49 in the third and final stage of clinical testing. Of the 284 drugs in development reported by PhRMA, the largest group is monoclonal antibodies, with 78 drugs. About 40 percent are for the treatment of cancer. There are also 62 vaccines and 28 gene therapy drugs in development. The leading disease targets are cancer, AIDS, Alzheimer's, Parkinson's, arthritis, and stroke.

Nonmedical Markets

Biotechnology also offers significant applications in agriculture and industry. Industrial applications include specialty and fine chemicals and bioremediation. Biotechnology materials, specialized software

packages, and equipment used in drug development and production are also important adjuncts to the core biotechnology markets.

In nonmedical areas, there are a number of potentially important developments under way. Genetic modification of food crops, increasing protein content or salt resistance, may help to reduce world hunger. In addition, biotechnology has the potential to shift the world's fish supply from an uncertain and threatened wild food source to an agricultural analog cultivated through mariculture and fresh water aquaculture. The exploration, study, and harvesting of marine genetic resources through biotechnology are expected to produce important commercial applications, including improved diagnostics and pharmaceuticals, increased production of ocean foods, novel energy sources, and the engineering of micro-organisms to control and eliminate environmental contaminants.

MAJOR FACTORS IMPACTING COMPETITIVENESS

While the effects of biotechnology on various industry sectors are complex and difficult to measure, the available information suggests that United States industry leads the world in applying these new technologies to commercial uses. The foundation for this competitive advantage, particularly in the health care and life science areas, was laid by the substantial U.S. public and private sector investment in research and development. American researchers are responsible for much of the science of the new biotechnology, and many of the industry's top scientists were trained at NIH and other federally funded institutions.

A second key to the industry's growth and competitive success has been its ability to secure needed capital. The industry is regarded by many observers as one of the most capital intensive and research intensive industries in the history of civilian manufacturing. Because of the time required to bring new products to market, the vast majority of companies cannot rely on product revenues to meet these needs. Instead, the industry has used a wide variety of mechanisms, ranging from venture capital investments and public securities offerings to partnerships with other companies, to supply the money needed to fuel the industry's growth.

As the industry matures, it must come to grips with other factors that have the potential to affect its competitiveness. Domestic regulatory regimes intended to achieve public health, safety, and environmental goals impose both costs and other constraints on the operations of the companies. Federal tax laws are also of critical importance, especially

those provisions intended to encourage productive investment in capital assets. Finally, as cost concerns continue to dominate the health care industry, new biotechnology products will need to demonstrate clear therapeutic efficiency if they are to be commercially successful.

In addition, competing successfully in international markets is essential for the industry, and increasing competition from foreign-based companies seems inevitable. Biotechnology has been identified as a key growth technology by other industrialized countries. Although the United States industry leads in the discovery phase of biotechnology, Japan and the European Union are coordinating government, industrial, and academic resources in biotechnology and bioprocess engineering development to establish a strong, government-supported technology infrastructure. In this global context, the domestic industry has an interest both in harmonization of national regulatory regimes and in strong and effective international protection for intellectual property.

Technology Infrastructure and Federal Research Initiatives

The United States has been able to achieve and maintain its internationally competitive position in the biomedical sciences with the aid of research support from the federal government. A great deal of our present knowledge about the nature and function of cells, and the development of recombinant DNA technology, was a direct result of research supported by the U.S. government. In addition, this knowledge has led to the development of many new products through the operation of federal legislation enabling NIH, other federal agencies, and those performing federally funded research to transfer the results of that research to the private sector for commercial development and to conduct collaborative research with private sector partners.

Capital Formation

Capital formation remains a critical strength of and a continuing challenge to the biotech industry. Because of the extensive research efforts and testing necessary to bring new medical products to market, biotech companies have substantial and continuing needs for capital that cannot yet be met through product revenues. In the early 1990s, the industry was able to secure large amounts of funding through offerings on public markets. For example, in 1991 the industry acquired a record $3.27 billion from such public offerings. However, these sources of financing became far less productive in 1993 and 1994, and many in the industry predicted serious consequences for the industry, especially for smaller companies. In the past two years, however, the industry has shown great

creativity, both in managing its "burn rate" (the rate at which it consumes capital) and in finding new ways to secure capital. Many observers believe the industry has matured in its ability to raise and manage its capital, a view supported by the increasing number of planned product introductions and FDA product approvals.

Biotechnology companies have increasingly sought to spread the risks of their operations through partnerships with other companies. These partners brought both funding and expertise to the table, leveraging the resources of the participating companies. Under this new model, a public offering is only part of the process of securing capital. Strategic alliances, particularly those that coordinate the research interests of corporate partners, help companies maintain financial stability over the long term. Increasingly, venture capitalists are encouraging startups to enter into agreements with larger companies. At the same time, larger companies are turning to biotechnology to help them develop innovative drugs and increase the efficiency of their product development. Also, larger drug companies are investing more in smaller concerns that focus on the early stages of the research process and on the use of genomic information to target new diseases and to identify compounds potentially useful for those purposes.

One important trend evident in the strategic alliances presented here is the increasing investment by European and Japanese concerns in U.S. biotech companies. While U.S. companies far outpace their competitors in research discoveries and biotechnology innovations, foreign investors appear poised to reap significant benefits from the commercialization of products developed from U.S.-based R&D efforts. In 1994, no less than 47 percent of the research conducted by the U.S. pharmaceutical industry was funded by U.S. affiliates of foreign companies. Examples of foreign companies that have made significant investments in U.S. companies include the following: The Roche Group (Switzerland), Ciba Geigy (Switzerland), Glaxo Wellcome (U.K.), SmithKline Beecham (U.K.), Rhone-Poulenc (France), Eisai Pharmaceutical (Japan), Yamanouchi Pharmaceutical (Japan), and Pharmacia (Sweden).

The U.S. Health Care System: Controlling Costs While Expanding Access to New Therapies

The American health care system has been transformed within the past few years by the concept of managed care, in which the delivery and financing of health care services are more closely integrated than in more traditional health care delivery systems. While this integrated approach has been criticized recently for sometimes placing cost control ahead of

quality care, it continues to be the predominant response within the system to the problem of rapidly increasing costs. The effect that managed care will have on the introduction of new products and services like those offered by the biotechnology industry remains unclear, but many are concerned that it may become more difficult to secure industry support for their use.

Tax Policies

While the federal tax code contains provisions designed to encourage investments in new enterprises and corporate investments in research, the biotechnology industry has found it difficult to claim the benefit of these provisions. Current provisions for capital gains treatment for investments in start-up companies are so hedged with restrictions that they have not been effective. In addition, the companies themselves have had difficulty in claiming tax credits for research and new product development because few companies in the industry have had substantial revenues, let alone taxable net income.

The Regulatory Environment

Regulation has been and will continue to be a major factor influencing the development of the biotechnology industry and its international competitiveness, especially for products made from recombinant DNA technology. Health, safety, and environmental regulations are of critical importance, affecting the cost and time needed to get biotech products to market and the profits thereafter. At the same time, other federal regulations, such as those relating to the cleanup of waste sites and to air and water quality generally, can play an important role in the development of the markets served by the bioremediation portion of the biotech industry.

The Food and Drug Administration

The Food and Drug Administration (FDA) has broad powers to regulate new drugs, vaccines, diagnostics, cosmetics, foods and food additives, new animal drugs, and animal feed additives under the Federal Food, Drug and Cosmetic Act.

A particular industry concern with the FDA's process relates to the sequence of testing and reviews leading to approval of new drugs for domestic marketing. This concern relates both to the time required for and the cost of these processes. A final concern relates to the relative speed of U.S. regulatory processes compared to that of other developed countries with developing biotech industries. In the past four years, the FDA has taken a number of steps to address the concerns of the biotech and pharmaceutical industries. As a part of the Clinton administration's

Reinventing Government Initiative, the FDA has proposed six different reinvention reforms aimed at protecting public health through innovative, common-sense oversight of industry activities.

One of the FDA's top priorities has been to reduce product review time while maintaining high standards of safety and effectiveness. A recent FDA study indicates that, in 1995, 82 new drugs had been approved in a median time of 16.5 months, compared with 62 new drugs approved in 19 months in 1994. Of the 1995 approvals, 28 were new molecular entities (NMEs) and were approved in a median time of 15.9 months, compared with 22 NMEs approved in 17.5 months in 1994. Industry sources also indicate that the time for product approval has decreased—from an average of 2.3 years in the early 1990s to 1.6 years in 1995. The FDA also pointed to other evidence that its processes were, at a minimum, keeping pace with those of foreign regulatory agencies.

The Environmental Protection Agency

The Environmental Protection Agency's (EPA's) effect on the domestic industry is complex. On one hand, it has regulatory authorities that it intends to use to regulate aspects of the industry's activities and that industry fears may result in new regulatory burdens. On the other hand, EPA's responsibilities for overseeing the cleanup of polluted sites give it the power to create important new markets for the industry.

EPA's broad responsibilities for the cleanup of hazardous waste sites under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA) give rise to important market opportunities for companies offering bioremediation technologies and services, but industry has pointed to several aspects of these activities that may discourage use of bioremediation technologies. EPA has initiated proceedings to reexamine its approaches to its cleanup responsibilities, and many within the biotechnology industry hope this will create more opportunities for bioremediation technologies in both the RCRA and Superfund programs.

Domestic Intellectual Property Rights Protection

The ability of companies to control their discoveries through the establishment of intellectual property rights is fundamental to the competitiveness of the biotechnology industry. As companies bring more products to market and revenues increase, these rights, and the prompt resolution of disputes concerning them, will become increasingly important. As a result, the Patent and Trademark Office (PTO) of the Department of Commerce plays a pivotal role through its decisions concerning

the patentability of biotechnology products and processes under U.S. law. The unique characteristics of biotechnology research and product development have raised some special issues under the patent laws, and the recent resolution of several of these, through the actions of the PTO and related legislation, seems likely to prove helpful to the patentability of genetic information.

Foreign Competitors

The rapid growth in industry alliances and the industry's maturing relationship with capital markets are the hallmarks of America's global leadership in biotechnology. Approximately one-half of all biotech companies worldwide are based in the United States, and these companies far outpace their competitors in innovation in this field. In 1995, U.S. companies received 81 percent of the 150 genetic engineering health care patents issued in the United States. United States companies received 122 genetic engineering patents, while companies from the EC countries received the second largest number, only 11, followed by Japanese companies with 6 patents.

In this new environment, the European industry is beginning to increase in both size and financial strength. A recent Ernst & Young report on European biotechnology reveals that the number of biotechnology firms in Europe increased from 486 in 1994 to 584 in 1995, while the number of industry employees increased 7 percent from 16,100 to 17,200. The report indicates that corporate revenues have improved by 20 percent (to $1.522 billion), spending on R&D has increased by 21 percent (to $795 million), and the industry's total net loss has decreased by 49 percent from the previous year (to $189 million).

To date there have not been any significant product approvals from Japan. The Japanese biopharmaceuticals industry has been observed to be years behind that of the United States, with currently fewer than 10 independent biotech companies in Japan. However, demand for biotechnology-derived products in Japan is substantial. Japan is the second largest pharmaceutical market in the world, accounting for 19 percent of the world market for ethical drugs with sales in excess of $37 billion. In addition, increased competition in its home market and a variety of other factors are causing the Japanese industry to increase its investment in research substantially and to expand its participation in foreign markets. These new directions seem likely to increase the role of the Japanese industry in the further evolution of the international biotechnology industry.

Trade Issues

Access to global markets is essential to obtaining returns on investment and maintaining the competitiveness of the American biotechnology industry. Trade in biotechnology is in its infancy, and the performance of biotech-derived products, outside of health care, is largely untested. The main barriers to trade in products of biotechnology are nontariff measures, including insufficient protection and enforcement of intellectual property rights and health, safety, and environmental regulations.

Tariffs and import quotas on biotech-derived products are generally not significant barriers in the U.S. industry's major export markets and will decline in importance as tariff cuts, negotiated under the Uruguay Round of the GATT and North America Free Trade Agreement, are phased in over a 5- to 15-year period. The United States, EU, Japan, Canada, and Korea agreed under the Chemical Tariff Harmonization Agreement to reduce pharmaceutical tariffs to zero, and put other chemical tariffs at levels ranging from zero to 6.5 percent. Other import barriers that often sprout to replace falling tariffs, such as import quotas, will be replaced by tariffs and subject to reduction commitments.

The TRIPS Agreement

One aspect of the domestic implementation of the TRIPS agreement that concerns industry is the possible impact of the new domestic laws in shortening the period of protection provided by domestic patents. Prior to the TRIPS agreement, a U.S. patent was granted for 17 years following the patent date of issuance, with extensions of the patent term possible under the Drug Price Competition and Patent Restoration Act of 1984 to compensate for delays in the premarket regulatory approval process. As a result of domestic implementation of TRIPS, the U.S. patent law has been modified to change the patent term to 20 years from the date of filing. However, because the processing of biotech patents is usually slower than that of the average patent, the 20-year period from the filing date has the potential to actually shorten the effective life of a patent.

Remedies for this concern, in addition to those provided by the Drug Price Competition and Patent Restoration Act, are possible on several fronts. The U.S. PTO, recognizing the importance of the issue, has been working closely with industry to continue to speed regulatory review of biotechnology patents. In addition, Congress is considering amendments to the GATT implementation law that could add up to an additional five years to the term of a patent where there were undue delays in the patent's issuance.

The Biodiversity Treaty

The biotechnology industry has two concerns under the United Nations Convention on Biological Diversity ("Biodiversity Treaty")—the treatment of genetic resources and questions concerning the safety of biomaterials. The first issue involves the compensation to be paid by developed country firms for the use of genetic resources of developing countries that serve as the basis for products later patented and sold in global markets. The United States maintains that the most effective way to achieve these objectives is through contracts between the developing countries and the firms using the genetic resources. Some countries have already entered into agreements with U.S. government agencies and pharmaceutical and biotechnology firms to provide access to their genetic resources under a mutually agreed benefit sharing arrangement. Adequate protection for intellectual property rights in these agreements is regarded as essential if the genetic resources are to be developed commercially, and the Biodiversity Treaty requires that all parties ensure that access to, or transfer of, technology is consistent with the protection of intellectual property rights.

With respect to the questions of safety, the Treaty requires the parties to consider the need for a protocol or international standards on the safe transfer, handling, and use of living modified organisms resulting from biotechnology. Among the issues raised by this protocol are the questions of whether any such obligation would extend to commodity products shipped in international commerce and what, if any, relationship this notification requirement would bear to the regulatory systems already in place in major import/export countries concerning notification. Those countries with more experience in the handling of biomaterials prefer to continue the development of biosafety standards at the national level while many developing countries wish to rely on multilateral fora, such as the Biodiversity Treaty proceedings, to sort out these issues.

What Is Biotechnology?

Perhaps unique among industries, biotechnology is not defined by its products but by the technologies used to make those products. Biotechnology refers to a set of enabling technologies used by a broad array of companies in their research, development, and manufacturing activities. To date, these technologies have been used primarily by the pharmaceutical industry, but they are being used increasingly by a variety of other industries, such as agriculture, mining, and waste treatment. Various U.S. government publications have defined biotechnology as a set of "techniques that use organisms or their cellular, subcellular, or molecular components, to make products or modify plants, animals, and micro-organisms to carry desired traits." This broad definition includes methods of treating disease developed from recent research in molecular biology and other fields, as well as the centuries-old practices of animal and plant breeding and the use of micro-organisms to make leavened bread and fermented beverages.

Advances in molecular biology over the past 25 years have led to the development of genetic engineering, monoclonal antibody technologies, DNA amplification, protein engineering, tissue engineering, and other methodologies with applications in the medical arena. These new techniques have enabled researchers to modify the genetic and biochemical makeup of organisms with far greater precision and speed. This report describes the impact of recent developments in modern biotechnology on both medical and industrial activity in several different areas.

In the roughly 25 years since the development of recombinant DNA technologies in research laboratories, more than 2,000 firms have been founded in the United States alone to explore and to take advantage of these new technologies.[1] Approximately 30 new products have reached the medical market, and several hundred more are in human clinical trials. The market for such products is expected to grow dramatically—from $7.6 billion in 1996 to $24 billion in 2006. Similarly, the market for agricultural biotech products is expected to increase from $295 million to $1.74 billion in the same period. Applications of the products will lead to enhanced pest resistance in food crops, improved methods of food preservation, and other advances.

[1] Kenneth B. Lee and Steven G. Burrill, *Biotech 96: Pursuing Sustainability: The Ernst & Young Tenth Annual Report on the Biotechnology Industry* (Palo Alto, Calif.: 1995); *U.S. Companies Database* (Durham, N.C.: Institute for Biotechnology Information, 1996).

Discoveries concerning the molecular bases of cellular processes will have a wide range of applications.

Core Technologies

The core technique of biotechnology is elegant in its simplicity. The cell is a miniature factory, containing genetic material—DNA—that acts as a blueprint for its structure and function. Biotechnology allows researchers to isolate, copy, and rearrange this genetic blueprint at the molecular level to manipulate the quantity, structure, and function of the biomolecules that control cellular processes. As a result, researchers are expanding their abilities to identify, isolate, and modify those molecular agents.

Discoveries concerning the molecular bases of cellular processes will have a wide range of applications. For example, in the area of health, these mechanisms may lead to therapies that fight disease by regulating specific cellular processes. With the help of molecular biology, biochemistry, and biophysics, the search for molecular information is yielding an increasingly detailed guide to cell behavior and its disruption. This knowledge allows biotechnologists to develop new products, processes, and therapies of commercial interest.

Biotechnology Materials

The raw materials of biotechnology are cells and their constituent biomolecules. These materials may be used for a variety of purposes, including drug synthesis, food production, and the bioremediation of hazardous waste. Examples of biotechnology materials include

- *Cytokines.* Hormone-like proteins that stimulate the growth or regulate the function of various cell types. They include such agents as erythropoeitin, which stimulates the production of red blood cells and can be used to treat severe anemia associated with renal disease; granulocyte colony-stimulating factor, which stimulates the production of white blood cells and is used to counter the loss of such cells in patients who have received anticancer therapy; and interferons, which help regulate and target the body's immune response and can be used to treat certain cancers and selected viral infections.

- *Antibodies.* Large protein molecules produced by the immune system that can bind specifically to discrete antigens, foreign substances recognized and then attacked by the immune system.

- *Enzymes.* Protein catalysts that facilitate specific chemical or metabolic reactions necessary for cell growth and function. Enzymes can be used in such activities as food processing, the bioremediation of hazardous waste, and the synthesis of certain drugs, vitamins, and fine chemicals.

- *Restriction enzymes.* Enzymes that break DNA in specific locations, creating gaps into which new genes can be inserted. These enzymes play a vital role in genetic engineering.

- *Viral vectors.* Modified, nonpathogenic viruses that deliver useful genetic information to host cells in gene therapy and genetic engineering. In gene therapy applications, such viruses are encoded with a specific gene, which, when incorporated into a host cell, confers a clinical benefit to the patient.

- *Antisense oligonucleotides.* Strands of DNA that bind to targeted messenger RNA molecules (which tell cells what proteins to make) and block the synthesis of specific proteins. In therapeutic applications, the synthesis of disease-related proteins is inhibited. These compounds are used in drug development and in agricultural biotechnology.

Drug Development

The acceleration of the drug discovery process resulting from biotechnology research is contributing to U.S. competitiveness in biotechnology. Many companies emerged in the past decade to become involved in this new approach to drug commercialization. Important areas of drug-related research include the following:

The acceleration of the drug discovery process resulting from biotechnology research is contributing to U.S. competitiveness in biotechnology.

- *Rational drug design.* Scientists are using a combination of chemistry, biology, biophysics, and computer modeling to determine the structure of target proteins in molecular detail and to then design specific small-molecule drugs for those target proteins. Companies involved in rational drug design include Agouron, Arris, BioCryst, Chiron, Procept, and Vertex.

- *Natural product screening.* New methods of screening materials extracted from animals and plants offer a rich source of potentially therapeutic compounds. NPS Pharmaceuticals, Magainin, Shaman, and Xenova are among the biotech firms that literally search the air, land, and sea for new drugs.

- *Combinatorial chemistry.* This technology allows chemists to synthesize large, diverse collections of molecules quickly and efficiently and to then identify the most active compound for a given application. Because combinatorial chemistry can identify promising compounds in a fraction of the time required by traditional methods of drug discovery, it can significantly reduce the cost of commercializing new drugs. Companies using such technology include Gilead Sciences, Isis, and Pharmacopeia.

Gene Sequencing and Bioinformatics

Rapid advances in the speed and accuracy of sequencing will revolutionize the discovery of innovative drugs and diagnostics.

Mutations are alterations in DNA sequence that may be associated with disease-causing genes. Such modified genes, and the proteins for which they encode, represent targets for drug therapy. Genes are sequenced by cutting pieces of DNA into small segments and cloning and copying those segments millions of times over. The order of the nucleotides (subunits of DNA) contained in those segments is then determined. A computer program is used to analyze and correlate the nucleotide sequences of the individual segments in order to create a map of the entire gene. The genes identified by this computer analysis are then scrutinized as possible drug targets. Rapid advances in the speed and accuracy of sequencing will revolutionize the discovery of innovative drugs and diagnostics. Companies in the business of gene sequencing include Darwin Molecular, Human Genome Sciences, Mercator Genetics, and Sequana.

Application of Biotechnology Information to Medicine

Biotechnology produces information that is used to alter and improve cell behavior. Many biotech companies specialize in finding ways to deliver and apply biotechnology information to cells to aid in identifying, preventing, and treating disease. Representative applications include

- *Diagnostics.* Tests that use biotechnology materials to detect the presence or risk of disease or pollution of a cell or material.

- *Vaccines.* Preparations of whole or significant structural portions of viruses, microbes, plants or other entities that are intended for active immunological prophylaxis. Companies working in this area may specialize in the route of administration as well as in the disease that the vaccine targets.

- *Gene therapy.* The process of replacing defective genes with healthy genes, either in vivo or ex vivo, in order to regulate cell replication or the production of proteins. Alternatively, gene function may be modulated by designing and delivering molecules to cells to inhibit or promote gene action.

Industry Structure

Creating a comprehensive profile of the biotechnology industry is difficult. The U.S. government gathers data about industries on the basis of the product or service provided, not the method of manufacture used. A facility operated by a biotechnology firm may be defined as pharmaceutical if it produces a genetically engineered drug or vaccine, or as a commercial research establishment if its principal activity is research. Consequently, while information about the industrial activity of biotechnology firms is collected in government statistics, the data are presented within traditional industry categories. There are no separate government data on biotech-related companies, sales, employment, trade, research and development, or the like. Table 1 illustrates how biotech-derived products and services are classified under the Standard Industrial Classification (SIC) system, the U.S. government's system for classifying industries.

Size of the Industry

Several private sector studies of the biotech industry have produced comparable results concerning the size of the industry. They have, however, differed somewhat in their specific definition of the industry. Ernst & Young's 1996 report on the biotechnology industry identifies 1,308 companies in the United States that were founded primarily to commercialize biotechnology.[2] This figure includes suppliers but not companies from other industries involved in biotechnology. The Institute for Biotechnology Information (IBI) reported that there were 1,072 biotechnology companies in the United States in 1996.[3] IBI defines "biotechnology" companies as those formed around modern biotechnologies; it excludes suppliers, equipment manufacturers, and other companies ancillary to the industry from its count.[4] However, its 1996 database identifies 236 other companies that created biotechnology programs to diversify their product lines, resulting in a total of 1,308 firms in the United States that use modern biotechnology.

A total of 1,308 companies in the United States were founded primarily to commercialize biotechnology.

[2] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

[3] *U.S. Companies Database.*

[4] IBI defines "biotechnology" as including genetic engineering, transgenics, hybridomas (used in production of monoclonal antibodies), protein engineering, large-scale cell culture, new fermentation processes, liposomes, and combinatorial chemistry.

Table 1. Standard Industrial Classification (SIC) of Biotechnology Products and Services on the Market

SIC	Group Name	Examples
01	AGRICULTURE	
0161	Vegetables and melons	Recombinant DNA-derived (rDNA) tomatoes
0279	Animal specialties (not elsewhere classified)	Transgenic laboratory animals used in medical research
28	CHEMICALS	
2869	Industrial organic chemicals (not elsewhere classified)	rDNA-derived enzymes, except diagnostic substances
2879	Pesticides and agricultural chemicals	Insecticides, cattle dips
2899	Chemicals and chemical preparations	Food contamination test kits
283	PHARMACEUTICALS	
2834	Pharmaceutical preparations	rDNA drugs, hormones
2835	In vitro and in vivo diagnostic substances	Monoclonal antibody and rDNA-derived test kits, DNA probes
2836	Biological products, except diagnostic substances	rDNA-derived vaccines, blood derivatives, micro-organisms
38	LABORATORY APPARATUSES AND ANALYTICAL INSTRUMENTS	
3826	Laboratory analytical instruments	DNA sequencers, polymerase chain reaction equipment
49	ELECTRIC, GAS, AND SANITARY SERVICES	
4953	Refuse systems	Bioremediation
4959	Sanitary services (not elsewhere classified)	Oil-spill cleanup
80	HEALTH SERVICES	
8011	Medical services	Gene therapy
8071	Clinical medical laboratories	Diagnostic testing
87	ENGINEERING, ACCOUNTING, RESEARCH, MANAGEMENT, AND RELATED SERVICES	
8731	Commercial physical and biological research	Contract R&D services
8734	Testing laboratories	Forensic DNA testing

Source: Executive Office of the President, Office of Management and Budget, *Standard Industrial Classification Manual*, 1987.

IBI reports that 30 percent of the biotech companies it has identified are publicly traded; 54 percent are privately owned, while 16 percent are divisions, subsidiaries, or joint ventures. The subsidiaries and divisions may be either public or private. Employment in biotechnology firms is estimated at 108,000 people by Ernst & Young and at 111,600 by IBI. IBI sets the mean number of employees per company at more than 104 but the median number at only 30. The Biotechnology Industry Organization (BIO) also reports that the average firm is relatively small. BIO data show that more than one-third of biotechnology companies employ fewer than 50 people and that more than two-thirds of the companies employ fewer than 135.[5]

The peak years for new company formation occurred between 1981 and 1987. The average biotechnology company is now 10 years old. By far the largest concentration of biotechnology companies is in California, followed by Massachusetts and New Jersey (see table 2).[6]

Table 2. Leading Biotechnology States

Rank	State	Number of Companies
1	California	267
2	Massachusetts	130
3	New Jersey	80
4	North Carolina	71
5	Maryland	70
6	Pennsylvania	58
7	Wisconsin	56
8	New York	55
9	Texas	50
10	Washington	40

Source: *Biotechnology Guide U.S.A.*, Institute for Biotechnology Information, Research Triangle Park, N.C., 1995.

[5] Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology (1996–1997)* (Washington, D.C., 1996).

[6] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

Research Intensity and Wage Levels

The biotechnology industry is the most research-intensive industry in civilian manufacturing. According to a 1995 survey by *Business Week*, 5 of the top 10 firms in terms of research expenditures per employee were biotechnology companies.[7] Estimates on total research and development (R&D) spending by the biotechnology industry range from $7.9 billion (Ernst & Young) to $10 billion a year (IBI). Both estimates exclude spending by pharmaceutical companies and other industries. According to Ernst & Young, R&D alone accounts for 36 percent of all costs incurred by public biotech companies. The average biotech company spent $69,000 per employee on research in 1995, about eight times the United States corporate average of $7,651.[8]

Wage levels in biotechnology firms are higher than in manufacturing industries because biotechnology companies employ people who have high levels of skill and education, such as scientists, engineers, lawyers, and financial and regulatory experts. Biotechnology firms have traditionally offered incentives for the risks and extra hours associated with working for new companies. A survey by Radford Associates and BIO reports that many biotechnology companies offer stock and bonuses and extend these benefits to fairly low levels of their organizations.

[7] *Business Week*, 3 July 1995.

[8] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

Markets for Biotechnology Products

The biotechnology industry serves medical and nonmedical markets. The medical market includes human therapeutics and human diagnostics as well as applications in veterinary medicine. Nonmedical markets encompass both agriculture and industrial applications. Agricultural applications include making plants and crops pest resistant, improving seed quality, modulating growth and ripening times, enhancing nutrient contents of foods, and providing simple and inexpensive diagnostics for use in field testing for contaminants and toxic materials. Industrial uses of biotechnology involve many different sectors and include industrial enzymes, waste management, bioremediation, energy biomass, cosmetic formulations, and diagnostics for toxicity determinations.

Table 3 lists the primary areas of focus of United States biotechnology firms. Many companies are pursuing more than one area. When all of the areas pursued by each company are taken into account, the number of companies in each area rises considerably. For example, the number of firms pursuing human health-care targets exceeds 70 percent when thus measured (see table 4).

The Medical Market

The next decade will see further dramatic progress in biotechnology beyond the improvements that recombinant technologies have brought to the medical understanding of disease. Molecular biology is allowing researchers to interpret with increasing sophistication the lives and language of cells. Such processes as cell transformation, programmed cell death, and cell signal transduction help to determine the course of many diseases. Our increasing ability to identify genes that govern specific cell behaviors will allow us to better understand and possibly control these fundamental cellular processes. Such advances will be central to the creation of new markets and will help to shape perspectives on the character and financing of health care.

The next decade will see further dramatic progress in biotechnology beyond the improvements that recombinant technologies have brought to the medical understanding of disease.

The majority of United States biotechnology firms are pursuing markets in human health care. An IBI study estimates that 29 percent of biotechnology companies are primarily interested in therapeutics, while 17 percent focus primarily on diagnostics.[9] Biotechnology companies in the human health-care field focus on discovering and developing methods to

[9] *U.S. Companies Database.*

Table 3. Biotechnology Market Areas: Participation of Biotechnology Companies by Primary Focus

Market Area	Number of Companies	Percentage of All Companies
Therapeutics	315	29.4
Diagnostics	187	17.4
Reagents	84	7.8
Plant Agriculture	68	6.3
Specialty Chemicals	54	5.0
Immunological Products	36	3.4
Environmental Testing/Treatment	35	3.3
Testing/Analytical Services	32	3.0
Animal Agriculture	29	2.7
Biotechnology Equipment	26	2.4
Veterinary	26	2.4
Drug Delivery Systems	24	2.2
Vaccines	24	2.2

Source: *U.S. Companies Database,* Institute for Biotechnology Information, Research Triangle Park, N.C., 1996.

Table 4. Biotechnology Market Areas: Participation of Biotechnology Companies in All Areas

Market Area	Number of Companies	Percentage of All Companies
Therapeutics	448	41.8
Diagnostics	346	32.3
Reagents	224	20.9
Specialty Chemicals	159	14.8
Immunological Products	146	13.6
Cell Culture Products	133	12.4
Fermentation/Production	116	10.8
Plant Agriculture	106	9.9
Vaccines	105	9.8
Drug Delivery Systems	94	8.8
Environmental Treatment/Testing	93	8.7

Source: *U.S. Companies Database,* Institute for Biotechnology Information, Research Triangle Park, N.C., 1996.

prevent, diagnose, treat, and cure the dozens of life-threatening and serious diseases and conditions for which no satisfactory medical therapies or preventive agents exist. R&D activity is targeted at detecting, controlling, and curing some of the most debilitating and life-threatening diseases of our time. Almost 70 percent of biotechnology companies surveyed by the Gordon Public Policy Center at Brandeis University are developing treatments for cancer. Fifty percent are working on drugs for acquired immunodeficiency syndrome (AIDS), and another 50 percent are developing drugs for infectious diseases.[10]

While differing in some details, several recent assessments of drugs moving through the regulatory process indicate that a significant number of new products should be reaching the market in the near future. A 1996 survey of biotech drugs under development by companies belonging to the Pharmaceutical Research and Manufacturers of America (PhRMA) found that there were 284 biotechnology drugs in human trials,[11] a 21 percent jump over the number (234) reported by PhRMA in 1995. The survey found 18 drug applications pending approval at the Food and Drug Administration (FDA) and 49 in the third and final stage of clinical testing. Of those 284 drugs, most (78) are monoclonal antibodies. About 40 percent are for the treatment of cancer. There are also 62 vaccines and 28 gene therapy drugs in development. The leading disease targets are cancer, AIDS, Alzheimer's, Parkinson's, arthritis, and stroke.

Several recent assessment of drugs moving through the regulatory process indicate that a significant number of new products should be reaching the market in the near future.

Parexel's Pharmaceutical R&D Statistical Sourcebook 1996 reported that in June 1995, 723 biotechnology products were working their way through the FDA approval process, which includes clinical trial phases I through III and projects under FDA review.[12] Approximately 700 drugs are in early development stages (the research and preclinical phase). More than 200 products are in the final approval phases (phase III or under FDA review). Parexel notes that its count may include some double counts of certain products under development for different indications or by

[10] Robert Goldberg, *Price Controls and the Future of Biotechnology: The Results of a Survey* (Waltham, Mass.: Gordon Public Policy Center, Brandeis University, 1994).

[11] Pharmaceutical Research and Manufacturers of America, *Biotechnology Medicines in Development* (Washington, D.C., 1996).

[12] M. P. Mathieu, *Parexel's Pharmaceutical R&D Statistical Sourcebook 1996* (Waltham, Mass.: Parexel International Corp., 1996).

different companies. In addition, phase III numbers include products in pilot clinical trials for drugs and devices.[13]

Market Trends and Potential

According to Consulting Resources Corporation (Lexington, Massachusetts), global sales from U.S. biotechnology products in 1996 are expected to reach $10 billion (see table 5).[14] Therapeutic and diagnostic products will account for $7.55 billion and $1.76 billion in sales, respectively, or more than 92 percent of the total market. About 28 different drugs were approved by the FDA through 1995. Table 6 lists many of the medical and other products on the U.S. market developed through modern biotechnology.

Table 5. U.S. Biotechnology Product Sales Forecast for 2001 and 2006 (in millions of 1996 dollars)

Sector	Base Year 1996	Forecast Annual 2001	Forecast Annual 2006	Average Growth Rate 1996–2006 (Percentage)
Medical				
Human Therapeutics	7,555	13,935	24,545	13
Human Diagnostics	1,760	2,705	4,050	9
Subtotal	9,315	16,640	28,595	
Nonmedical				
Agriculture	285	740	1,740	20
Specialty Chemicals	275	690	1,600	19
Nonmedical Diagnostics	225	330	465	8
Subtotal	785	1,760	3,805	
Total	10,100	18,400	32,400	12

Source: "Biotechnology on the Rebound," *Consulting Resources Corporation Newsletter* (spring 1996).

[13] A positive assessment of the pipeline for biotech products is also offered by the most recent Ernst & Young assessment of the industry, which reports that a survey of 167 public companies by the firm of Robertson, Stephens, and Co. identified almost 700 products in clinical trials in the United States. Kenneth B. Lee and Steven G. Burrill, *Biotech 97, Alignment: The Ernst & Young Eleventh Industry Annual Report* (Palo Alto, Calif., 1996).

[14] "Biotechnology on the Rebound," *Consulting Resources Corporation Newsletter* (spring 1996).

Consulting Resources Corporation estimates that the market for human therapeutic biotechnology products will grow from $7.6 billion in revenues in 1996 to more than $24 billion in 2006, an average annual growth rate of 13 percent. The human diagnostics biotechnology product sector is expected to grow at an average annual rate of 9 percent—from $1.8 billion in 1996 to approximately $4 billion in 2006.[15]

At present, the bulk of the biotechnology market is derived from the sales of larger biotechnology companies, including Amgen and Genentech, and such products as erythropoeitin (EPO), interferon, and insulin (see table 7). According to a report by Frost and Sullivan, EPO, Amgen's first blockbuster product, accounted for approximately 25 percent of all biotech revenues. Colony-stimulating factors, insulin, human growth hormone, beta and gamma interferon, and vaccines accounted for much of the remaining market.

Diagnostics and New Medical Demands

The advent of rapid gene sequencing is likely to lead to the development of diagnostic tools that will permit individuals to know more about their inherited risks of disease. For example, the discovery of the hMLH1 gene, which is associated with 30 percent of inherited colon cancers; the p53 gene, which is implicated in nearly half of all tumors; and BRAC1 and BRAC2, the genes for breast cancer set the stage for developing diagnostics for such diseases. Genetic tests for Alzheimer's, high cholesterol, and schizophrenia are also being developed.

Improvements in diagnostics are showing that cancer and heart disease are polygenic in nature. In practice that means the single drug–single disease model will become increasingly obsolete. Individuals, armed with genetic profiles of their illness, will be able to seek treatments tailored to their genetic disease risk. At the same time, awareness of genetic risk may cause people to alter their lifestyles as part of a complete response to disease. The ability to individualize treatments based on genetic risk will broaden markets for medical products and services.

Improvements in diagnostics are showing that cancer and heart disease are polygenic in nature.

The current pace of genetic test development is relatively slow. Costs, regulatory delays, and ethical concerns cause entrepreneurs to proceed cautiously. To succeed, they must demonstrate that the benefits of early and rapid detection of disease risk are more important than competing concerns. If this can be done, new diagnostic tests may be the first fruits of the effort to commercialize genomic information. Entry of these tests

[15] Ibid.

Table 6. Products and Services Developed Through Biotechnology on the U.S. Market

Industry Sector	Year First Approved	Indication/Use
HUMAN HEALTH CARE		
Therapeutics		
Insulin	1982	Diabetes
Human growth hormone	1985	Dwarfism; short stature associated with chronic renal insufficiencies (1993); growth hormone deficiency (1994)
Alpha interferon	1986	Hairy-cell leukemia; Kaposi's sarcoma (1988); venereal warts (1988); hepatitis-C (1991); hepatitis-B (1992)
OKT3	1986	Monoclonal antibody (MAB) used to treat kidney transplant rejection
Vaccines	1986	Hepatitis-B
Factor VIII (MAB purified)	1987	Hemophilia
Tissue plasminogen activator (TPA)	1987	Acute myocardial infarction; acute pulmonary embolism (1990)
Erythropoietin (EPO)	1989	Anemia associated with kidney disease; AIDS-related anemia (1991)
Gamma interferon	1990	Chronic granulomatous disease
Glucocerebrosidase (Ceredase/Cerezyme)	1991	Gaucher's disease; recombinant DNA (rDNA) version (1994)
Granulocyte colony-stimulating factor (G-CSF)	1991	Adjuvant to chemotherapy; neutropenia (1994); bone marrow transplants (1994)
Granulocyte macrophage colony-stimulating factor (GM-CSF)	1991	Adjuvant to certain bone marrow transplants
Factor VIII (rDNA)	1992	Hemophilia
Interleukin-2	1992	Kidney cancer
Beta interferon	1993	Multiple sclerosis
Dornase alfa inhalation solution (Pulmozyme)	1993	Cystic fibrosis
ReoPro	1994	MAB used to reduce clots in angioplasty procedures
Avonex	1995	Recombinant beta interferon 1a relapsing multiple sclerosis
BioTropin	1995	Human growth hormone for human growth deficiency in children
Genotropin (rDNA origin somatotropin, for injection)	1995	Short stature in children due to growth hormone deficiency

Table 6. ***Continued***

Industry Sector	Year First Approved	Indication/Use
Nutropin AQ (liquid somatotropin)	1995	Growth failure in children due to chronic renal insufficiency; growth hormone inadequacy in children
Norditropin (rDNA origin somatotropin, for injection)	1995	Growth failure in children due to inadequate growth hormone secretion
Diagnostics		
In vivo MAB diagnostic tests	1992	Detect colorectal cancer, ovarian cancer
In vitro MAB/DNA probe diagnostic tests	*	Diagnose infections, pregnancy and infertility, cancers, genetic diseases; forensic and paternity testing; DNA profiling
AGRICULTURE/VETERINARY		
Vaccines	1984	Colibacillosis or scours; pseudorabies (1987); feline leukemia (1990); Newcastle disease and fowlpox (1994)
Therapeutics	1991	MAB used in treatment of canine lymphoma
Bovine somatotropin (BST)	1993	Hormone used to enhance dairy milk production
Diagnostic tests	*	Diagnose infections, pregnancy, presence of antibiotic residues
AGRICULTURE/PLANTS		
Micro-organisms	1991	Pesticide using killed bacteria, used against certain caterpillars and beetles
Tomatoes	1994	Enhance freshness and shelf life
Diagnostic tests	*	Detect turfgrass fungi
FOOD PROCESSING/ SPECIALTY CHEMICALS		
Chymosin, or rennet	1990	Enzyme used in cheese making
Alpha amylase	1990	Enzyme used in corn syrup and textile manufacturing
Lipase	1991	Enzyme used in detergents
Xylanase	1992	Enzyme used in pulp and paper industry
Food safety diagnostic tests	*	Detect salmonella, listeria, aflatoxin, camplylobacter, yersinia entercolitica
OTHER		
Transgenic mice	*	Medical research
Luciferase	*	Luminescent agent used in diagnostic tests
Environmental diagnostic tests	*	Detect legionella bacteria in water samples

*Data not available

Table 7. Leading Biotechnology Products

Therapeutic/Vaccine	Brand Name	Developer	Marketing Partner	1993 Net Sales (in millions of dollars)
Erythropoeitin (EPO)	Epogen	Amgen	Amgen	721.0
	Procrit	Amgen	Ortho Biotech	600.0
Alpha interferon	Intron A	Biogen	Schering-Plough	426.0
	Roferon-A	Genentech	Hoffmann-La Roche	172.0
Hepatitis-B vaccine	Recombivax HB	Chiron	Merck	210.0
	Engerix-B	Genentech	SmithKline Beecham	624.1
Granulocyte colony-stimulating factor (G-CSF)	Neupogen	Amgen	Amgen	829.0
Insulin	Humulin	Genentech	Eli Lilly	665.0
Human growth hormone	Protropin	Genentech	Genentech	219.4
	Humatrope	Eli Lilly	Eli Lilly	269.1
	Genotropin	Genentech	Pharmacia & Upjohn	388.0
Tissue plasminogen activator (TPA)	Activase	Genentech	Genentech	301.0
TOTAL				5,424.6

Source: *Med Ad News*, July 1996.

into the marketplace could help to reshape the structure of medicine. According to a report by Volpe, Welty and Company, "gene probes will expand from about 0.5 percent of current testing to 8 percent of all diagnostic procedures within a decade, with the market for gene probes reaching $600 million by 2000 and $2 billion by 2004."

Biotechnology and the Most Costly Forms of Illness

At present, medicine is effective only in compensating for the debilitating consequences of the most costly forms of illness. Advances in the treatment of such illnesses, particularly advances that reduce treatment costs and help restore people to health, will be in great demand. Growth in this area has been spurred largely by the introduction of cytokines, such as Amgen's Epogen and Neupogen, as well as Genentech's tissue plasminogen activator (TPA), Activase. Over the next decade, biotechnology is expected to produce medical innovations aimed at most of the major

diseases of our time. Innovations in this industry are expected to occur on all fronts. Examples of R&D impact in several important areas follow.

Cancer

Cancer is one of the leading causes of untimely death in America and around the world. According to the American Cancer Society, more than 547,000 people died from some form of cancer in the United States in 1995, while more than 1.2 million cases were diagnosed.[16] The cost of caring for U.S. cancer patients exceeds $104 billion per year. Early detection, surgery, radiation, and chemotherapy are still the mainstays of fighting cancer. Because cancer is a complex disease involving multiple mechanisms, many different approaches are represented in the research projects under way. Several examples of biotechnology products that may reach the market in the next 10 years follow.

Over the next decade, biotechnology is expected to produce medical innovations aimed at most of the major diseases of our time. Innovations in this industry are expected to occur on all fronts.

- Many types of cancer cells carry an IL-2 receptor. Injection of a receptor-targeted fusion toxin in patients with advanced cutaneous T-cell lymphoma (CTCL) has reduced tumors by 50 to 100 percent in 42 percent of patients who had not responded to any other therapy. There is currently no effective treatment for CTCL.

- New strains of mice can now make specific human antibodies in response to challenges by antigens that affect humans. Such antibodies may be able to fight some forms of cancer. Testing has shown that some genetically engineered antibodies reduce tumor growth better and with fewer side effects than chemotherapy.

- A gene therapy system using the gene that directs the synthesis of gamma interferon is in clinical trials with advanced melanoma patients. Tumor growth has subsided in response to the gene therapy, which has produced only mild side effects compared with chemotherapy.

- Phase I studies are under way to test a cancer vaccine for use in treating advanced melanoma patients. The treatment involves removing cancerous cells from the patient and genetically engineering them with the gene for granulocyte macrophage colony-stimulating factor. After irradiation to prevent further division, the cells are used to vaccinate the patient.

- Taxol is a natural product with potent activity against a range of cancers, including ovarian and breast cancer. Several key

[16] American Cancer Society, *Cancer Facts & Figures 1996.*

biotransformations are being developed to bring about a totally synthetic route to making this compound (whose generic name is paclitaxel), which otherwise cannot be synthesized in large quantities.

Neurodegenerative Illnesses

Alzheimer's and Parkinson's diseases, cerebral stroke, and brain and spinal injuries are medical conditions that currently receive mainly palliative treatment. Caring for people with these conditions is an enormous economic and emotional burden on society precisely because so little can be done to significantly delay or reverse the progression of the diseases. In the next few years, however, biotechnology may yield important advances in treating such neurodegenerative conditions:

- Neuron loss in Parkinson's disease and amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is being countered through a search for growth factors that promote the proliferation and regeneration of neuron cells. Cephalon's insulin-like growth factor 1 (rhIGF-1) is a neurotrophic factor (a naturally occurring protein that keeps neurons alive and helps them recover from injury) that has been shown in phase III clinical trials to slow the progression of ALS, help patients with ALS retain functional ability, and prolong survival. These trials are the first successful demonstration that a neurotrophic factor can alter the course of a neurodegenerative disease. Cephalon is also evaluating small organic compounds that stimulate production of neurotrophic factors throughout the central nervous system and that may thereby influence diseases such as ALS and Alzheimer's disease.

- Companies are conducting preclinical research on a glial cell-line derived neurotrophic factor (GDNF). In an example of the kinds of collaborative research communities emerging in biotechnology, GDNF was discovered by researchers at Synergen and Genentech in cooperation with four academic research teams. Discovered less than two years ago, GDNF is now the subject of animal experiments by both companies. These tests show that GDNF keeps alive brain cells that would have died from the attack of Parkinson's disease and ALS.

- Each year, about 500,000 to 600,000 Americans have a stroke. Nearly 150,000 die from strokes. At present, medicine has a limited ability to prevent strokes or minimize their effects. However, several recent advances offer hope for limiting or even

preventing the irreversible brain damage strokes can cause. Cambridge NeuroScience's drug Cerestat® has demonstrated statistically significant improvement in neurological function in stroke patients, and the company has initiated a phase III trial in patients. Cerestat® is also the subject of a phase III trial in patients with traumatic brain injury. Genentech's blood clot-dissolving drug Activase, a genetically engineered version of the naturally occurring TPA, has been approved for the treatment of acute ischemic stroke. Clinical trials showed that individuals treated with Activase within three hours of symptom onset were at least 33 percent more likely to exhibit minimal or no disability compared with individuals treated with placebo. Finally, Cephalon and SmithKline Beecham are collaborating to develop inhibitors of the enzyme calpain, which causes damage to nerve cells when a stroke occurs.

- Athena Neurosciences and Eli Lilly have developed a strain of transgenic mice that exhibit the key symptoms of Alzheimer's disease. Company researchers placed a mutated human gene into mouse embryos. After a year, the mice developed an Alzheimer's-like condition. The availability of an animal model for Alzheimer's disease is a breakthrough that will allow companies to develop drugs more quickly to treat this illness.

Autoimmune Diseases

This market encompasses products targeted to a broad range of inflammatory illnesses, including asthma, rheumatoid arthritis, multiple sclerosis, and lupus. The social costs of these diseases are substantial. The Arthritis Foundation reports that more than 40 million people have rheumatic diseases accompanied by some disability. Among that group, 25 million suffer from diseases that are autoimmune in nature, such as rheumatoid arthritis, lupus, and scleroderma. The cost of medical care and lost wages for people with rheumatic diseases is estimated at $64.8 billion; it is about $40 billion for those with the autoimmune rheumatoid diseases. A recent study estimates that 300,000 to 350,000 patients in the United States have multiple sclerosis, a neurological autoimmune disease. The social costs of the disease are not easily estimated, in part because patients are often categorized according to secondary disabilities. However, a recent study estimated that the total loss to society in 1991 dollars is $110 billion per 100,000 patients over the course of the patients' lives.[17] For diabetes, the direct costs associated with treatment in

[17] Sarah L. Minden, et al., *Multiple Sclerosis: A Statistical Portrait* (Cambridge, Mass.: Abt Associates Inc., 1996).

1994 were $45.2 billion, which represented 5.8 percent of the total personal health-care expenditures in the United States. Another $46.6 billion were attributed to indirect costs associated with the disease.[18]

Several pharmaceutical companies are developing treatments for autoimmune disorders:

- In the area of asthma research, Cytomed and ICOS are independently developing therapeutics that target the pathways controlling the body's inflammatory process. Immulogic Pharmaceutical Corporation is developing an immunotherapeutic vaccine; Sequana is searching for the genetic causes of asthma in population groups susceptible to the disease; and Genentech has an immunoglobulin E humanized monoclonal antibody (MAB) in phase II clinical trials.

- Centocor is developing a treatment for rheumatoid arthritis that uses antibodies directed against tumor necrosis factor-a (TNF-a). After a single dose of anti-TNF-a antibody, almost 80 percent of patients found that their arthritis partially reversed itself.

- Chiron developed a method for producing beta-interferon, and the resulting product was the first approved by FDA for treating multiple sclerosis. More recently, FDA approved Biogen's product, Avonex™, "for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations."[19] ICOS and Athena Neurosciences are developing antibody products against adhesion molecules for multiple sclerosis.

- La Jolla Pharmaceuticals Company is about to begin phase II and III testing of its LJP 394 in lupus patients. The drug is a double-stranded piece of DNA with epitopes that bind to antibodies on the surface of B cells (lymphocytes).[20]

- Transkaryotic Therapies is developing a gene therapy for diabetes. A dime-sized piece of skin is removed from a patient. An

[18] Edith Schwartz, "Tissue Engineering: A White Paper" (NIST, Advanced Technology Program, 1995).

[19] C. Craig, "Biogen Gets FDA Approval for MS Drug," *Bioworld Today*, 20 May 1996.

[20] *Technical Insight*, Dec. 1996.

insulin gene is added to the skin cells, tested for safety and function, and then sent to a physician. The genetically engineered insulin-producing cells are injected into the patient, where they may produce a lifetime supply of insulin. Two other companies, VivoRx and BioHybrid Pharmaceuticals, are taking a different approach, using a tissue-engineering procedure to create an artificial pancreas that would be equivalent to a normally functioning organ. The device consists of encapsulated beta-islet cells, which, when injected into the body, permit ready bidirectional flow of insulin and glucose but inhibit the inward flow of immune molecules that could destroy the insulin-secreting cells.[21]

Cardiovascular Diseases

While the death rate for cardiovascular disease has declined over the past 20 years, it is still the leading cause of death in the United States. Nearly 1 million people die of heart disease each year, and its medical and social costs are estimated at $117 billion. The market for biotech products in treating heart disease is broad and diverse and will be an important source of growth in the industry over the next five years. In particular, new thrombolytic therapies will be used for the 30 percent of heart attack patients whose arteries become clogged again after being opened, for patients with pulmonary embolisms, and for those suffering from acute ischemic stroke. A few of the initiatives in this area are described below:

The market for biotech products in treating heart disease is broad and diverse and will be an important source of growth in the industry over the next five years.

- The approval of Centocor's ReoPro, a monoclonal antibody that treats unstable angina and restonosis, marks the success of a new class of cardiovascular drugs.

- Researchers at the University of Michigan Medical Center have used gene therapy to stop reblockage of arteries that have been opened by angioplasty or replaced in bypass operations.

- Millenium Pharmaceuticals has entered into three collaborations aimed at understanding the genetic and molecular basis of arteriosclerosis with the Cleveland Clinic, Rockefeller University, and Harvard Medical School.

Potential Commercial Applications of Gene Therapy

Gene therapy has been described as a technology with exceptional long-term potential. It is still in the exploratory stages, and little clinical benefit has been demonstrated to date, but gene therapy seems likely to be an important source of future medical advances.

[21] Edith Schwartz, "Tissue Engineering."

The creation of the federal Human Genome Project and the establishment of a commercial gene sequencing industry are setting the stage for further progress.

The infrastructure of gene-based biotechnology is strong and substantial. The creation of the federal Human Genome Project, corporate investment in gene therapies, and the establishment of a commercial gene sequencing industry are setting the stage for further progress. Because of private sector commitment to commercializing genomics, the U.S. biomedical research enterprise is more advanced than that of other countries that also have access to genetic information. As of June 1995, 106 clinical protocols involving gene transfer on 597 subjects were under way in the United States.[22]

Research is under way in applying gene therapy to cure cancer, hepatitis, AIDS, Alzheimer's disease, Parkinson's disease, and genetic diseases such as cystic fibrosis, sickle cell anemia, hemophilia, rheumatoid arthritis, asthma, and hypercholesterolemia. Technology Catalysts International estimates that by 2000, global revenues from gene therapy could reach $7 billion. There are more than 30 gene therapy companies in America, making the United States the world leader in gene therapy.[23]

It is difficult to predict the pace of progress in gene therapy. Using gene sequencing to identify which genes cause disease and how they do so is a relatively recent development, yet the pace of gene sequencing and its consequences for medical treatment are increasing geometrically. Collaborative research communities, fueled by private funding and commercial opportunities, have made substantial progress. One example is the commercialization of gene therapy technology developed by Dr. James Wilson at the Institute for Human Gene Therapy at the University of Pennsylvania. The Genovo company, which was founded in 1995 to apply this technology, has secured an investment of over $35 million from Biogen, one of the biotechnology industry's top-tier companies.

Collaborations between companies such as Isis and Human Genome Sciences are producing information on the relationship between genes and the regulatory mechanisms of a cell. A team of researchers from the National Institutes of Health (NIH), Johns Hopkins University, and Glaxo have found that the p53 tumor suppressor gene not only stops DNA replication but also stimulates the repair of damaged DNA by activating another gene that generates a protein that aids in the resynthe-

[22] L. Clark, ed., "Gene Therapy—Extraordinary Potential but Oversold," Biotechnology Business News, *Financial Times*, 17 Jan. 1996, 7–8.

[23] Estimates made by Technology Catalysts International and taken from Susan L. Danheiser, "Safe and Efficient Synthetic Gene Transfer Techniques Needed to Carry Therapeutics," *Genetic Engineering News*, 15 Nov. 1995, 26–27.

sis of DNA. Alliances such as these will shed more light on how genes behave in each target cell, allowing researchers to establish which form of genetic intervention will yield the best medical outcome.

Discussions with biotechnology executives suggest that gene therapy will be brought to market some time in the next five years. The likely targets for gene therapy include cystic fibrosis, Gaucher's disease, and certain forms of cancer. Therapies for these conditions will face regulatory approvals and questions concerning insurance reimbursement—setting the stage for the commercialization of this new category of therapies.

Nonmedical Markets

In addition to human therapeutic and diagnostic applications, biotechnology has important applications in industry and agriculture. Industrial applications include the development of specialty and fine chemicals and bioremediation techniques. It has been predicted that the need for chiral pharmaceuticals will lead to revolutionary new processes for synthesizing drug intermediates. Many of these processes will require that chemical reactions be carried out with the aid of enzymes or with whole-cell biocatalysts that contain the proper enzyme systems. Similar revolutionary synthetic routes are expected for the next generation of chiral pesticides and herbicides. Many of these new compounds will possess superior environmental compatibility. The production of biotechnology materials, specialized software packages, and equipment for use in drug development and production are important adjuncts to the core biotechnology markets.

In addition to human therapeutic and diagnostic applications, biotechnology has important applications in industry and agriculture.

A number of potentially important developments are under way in other nonmedical areas. Genetic modification of food crops to increase protein content or salt resistance may help to reduce world hunger. In addition, biotechnology has the potential to shift the world's fish supply from an uncertain and threatened wild food source to an agricultural analogue cultivated through mariculture and freshwater aquaculture. The exploration, study, and harvesting of marine genetic resources through biotechnology is expected to produce important commercial applications, including improved diagnostics and pharmaceuticals, increased production of ocean foods, novel energy sources, and the engineering of micro-organisms to control or eliminate environmental contaminants.

Agricultural Biotechnology

A stable food supply is of long-term strategic importance to the United States. The United States is the leading exporter of agricultural products; it exported $57 billion worth in 1994, creating approximately 1 million jobs. Biotechnology has the potential to play a key role in maintaining U.S. leadership in food production. It is also likely to increase the efficiency of domestic and foreign food production. U.S. superiority in the molecular techniques used to develop new plant varieties, enzymes, and animal products will be of central importance to this continued leadership.

In 1995, it was estimated that over the next 10 years, sales of U.S. ag-biotech products would grow at an average annual rate of 20 percent, from $285 million in 1996 to almost $1.74 billion in 2006, the highest projected growth rate among the biotechnology sectors.[24] More recent assessments have noted that despite their potential for future growth, ag-biotech companies have generated lower returns on investment than other biotech sectors. Recently, control of many of the companies working in this area has passed to larger agricultural companies with broader product lines.[25]

Currently, U.S. ag-biotech companies spend an average of $38,000 per employee on R&D and have sales of $112,000 per employee.[26] The Department of Agriculture spends an additional $234 million. Global R&D for ag-biotech was recently estimated at approximately $1 billion annually.[27] Patent protection is expected to play an important role in the development of this sector, particularly in emerging markets.

Ag-biotech uses genetic engineering to achieve what farmers and scientists throughout the ages have sought: better tasting food, higher yields, and protection against disease and pestilence. In addition to genetic engineering, ag-biotech encompasses a wide range of biological products and processes, including micropropagation, fermentation and biocultures, plant and animal health diagnostics, vaccines, and biopesticides. The concepts of genetically engineered tomatoes and growth hormones that increase milk production have sparked debates over ethics, biosafety, food safety, and food labeling. In fact, biotechnol-

[24] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

[25] Kenneth B. Lee and Steven G. Burrill, *Biotech 97.*

[26] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

[27] *Biotech '95 Video Conference: Agricultural Biotechnology for the Twenty-First Century, Exploring Exciting Opportunities in North America,* 1995.

ogy processes are faster, more precise versions of breeding and agricultural techniques that are centuries old.

Traditional breeding to develop better tasting crops or hardier, more productive livestock takes at least 10 to 12 years. Rather than combining hundreds of genes to improve a crop or using arduous selective breeding to improve livestock, farmers can now use biotechnology to select a specific genetic trait from one plant and move it into another plant or stimulate natural body functions to enhance animal well-being. "Agricultural biotechnology is the latest stage in a continuum of agricultural evolution. It complements, but does not replace, traditional methods of improving agricultural productivity."[28]

U.S. ag-biotech companies have already commercialized innovative products, and many others are under development (see tables 8 and 9). Some of the products, such as transgenic crops and biopesticides are related to animal and plant health. While progress in ag-biotech has been slower than in the human health arena, the introduction of two high-profile products—bovine somatotropin (BST) and the Flavr-Savr™ tomato—has brought the sector much publicity and demonstrated the particularly strong role played by consumer attitudes in markets for agricultural products.

Advantages of Agricultural Biotechnology

Biotechnology will allow the world to develop an even more abundant, safe food supply while reducing reliance on chemical-based herbicides and pesticides. At present, farmers, particularly in underdeveloped countries, must rely on animal and chemical fertilizers to sustain crop production. Biotechnology will expand the list of crops that can withstand drought, frost, insects, and disease.

Biotechnology will allow the world to develop an even more abundant, safe food supply while reducing reliance on chemical-based herbicides and pesticides.

Ag-biotech reduces the taxing impact of traditional agriculture practices on the environment and conserves soil and other resources. For example, chemical insecticides can be replaced by bioinsecticides, which are more environmentally benign and readily biodegradable. Biotechnology can also enhance plants' use of soil nutrients, reducing reliance on synthetic fertilizers. In addition, biotechnology can aid conversion of agricultural wastes to feed, fuel, and other products, and it can lead to broader use of biodegradable agricultural products—such as vegetable oils for lubricants, fuels, and detergents. Ag-biotech also improves food safety by controlling micro-organisms that cause disease. Technology is being

[28] Ibid.

Table 8A. Agricultural Biotech Products on the Market or Planned for 1996

Company	Product	Comments
Asgrow	Freedom II™ squash	Squash with a natural resistance to plant viruses.
Calgene, Inc	BXN™ cotton	Cotton plants that require fewer chemical herbicides. Commercial introduction planned for 1995.
	Flavr Savr™ tomato	A high-quality, fresh-market tomato that has been modified using antisense technology to ripen on the vine.[1] It reached supermarket shelves in 1994.
	High laurate canola oil	A less expensive source of high-quality raw materials for soaps, detergents, and cocoa butter replacement fats. Rapeseed plants with more than 40 percent laureate in oil have been produced and are in field trials. The first oil sales were planned for the summer of 1995.
Ciba Seeds	CIBA Maximizer™ hybrid corn	Corn modified to have natural protection against the European corn borer, one of the most devastating insect pests in modern U.S. agriculture.
DNA Plant Technology	Fresh World Farms™ tomato	A premium, fresh-market tomato developed through somaclonal variation to have superior color, taste, and texture and a 10- to 14-day shelf life.[2] It is currently sold in approximately 1,200 stores in the mid-Atlantic, Northeast, and Midwest since being introduced in April 1993.

[1] Antisense technology involves taking the gene in the tomato that is responsible for softening, creating a duplicate of that genetic sequence in reverse, and inserting it in the tomato. The new genetic information effectively "turns off" the ripening process, which allows the tomato to ripen longer on the plant.

[2] Somaclonal variation is a biotechnology process that involves breaking a plant sample down to its individual cells, putting the cells in a growth medium, and regenerating new plant "clones" from the cells. The new plants will have a broad diversity of characteristics. Those with the desired characteristics are used to create new plant lines through traditional breeding techniques.

Table 8A. ***Continued***

Company	Product	Comments
DNA Plant Technology *(continued)*	Fresh World Farms Endless Summer™ tomato	A genetically engineered version of the Fresh World Farms™ tomato that shares its superior color, taste, and texture. Its shelf life of over 30 to 40 days after harvest is, however, much longer. Company scientists used Transwitch technology to suppress production of ethylene, the hormone that causes tomatoes and other fruits to ripen. The tomato, the company's first whole-food product developed through recombinant DNA technology, entered the test market in March 1995.
	Fresh World Farms™ carrot bites	Crisp, juicy, baby whole carrots that are sold ready to eat in one-pound bags.
	VegiSnax® carrot sticks	Packaged, ready-to-eat carrot sticks, perfect for lunch boxes and healthy snacking.
	Fresh World Farms™ Sweet minipeppers	A red pepper with a novel sweet taste and deep red color that is nearly seedless. It was developed through anther culture, an advanced breeding technique that captures and stabilizes preferred characteristics such as taste, texture, and low seed count.
	Fresh World Farms™ cherry tomato	A cherry tomato that is specially bred for superior taste, color, and texture. It is now being sold through distributors and supermarket chains in the mid-Atlantic, Northwest, and Midwest.
Genencor International, Inc.	Chymogen®	The biotechnology-produced version of an enzyme (chymosin) found in calves that makes milk curdle to produce cheese. Because it is produced through biotechnology, it is purer and more plentiful and eliminates variability in the quality and availability of calf's stomachs. It is used in approximately 60 percent of all hard cheese products made today.
Monsanto	Bollgard™	Introduced in 1995, cotton with Monsanto's Bollgard gene is protected against cotton bollworms, pink bollworms, and tobacco budworms.

Table 8A. ***Continued***

Company	Product	Comments
Monsanto *(continued)*	New Leaf® insect-protected potato	Introduced in 1995, the NewLeaf® potato is the first commercial crop to be protected against insect pests through biotechnology. Thanks to a gene from a variety of the B.t. bacteria, the potato is resistant to the Colorado potato beetle.
	Posilac® bovine somatotropin (BST)	BST is a naturally occurring protein hormone in cows that induces them to produce milk. Recombinant BST improves milk production by as much as 10 to 15 percent and is now used by farmers whose herds represent 30 percent of the nation's cows. It was approved by FDA in 1993.
	Roundup Ready™ cotton	Approved in 1996, Roundup Ready™ cotton tolerates both topical and postdirected applications of Roundup herbicide.
	Roundup Ready™ soybeans	Introduced in 1996, Roundup Ready™ soybeans allow growers to apply Roundup herbicide over the top during growing season. The result is dependable, superior weed control with no effect on crop performance or yield.
Mycogen	NaturGard™ corn	These corn plants express a protein toxic to various caterpillar pests, which will allow for less use of insecticides.
Pfizer FSG	Chy Max®	Chy Max® is another version of chymosin, an enzyme that causes milk to coagulate. It is an advanced fermentation ingredient that is of higher purity, quality, and activity than natural rennet.
Vinifera, Inc.	VitroGraft® grapevine	VitroGraft® grafted grapevine plants represent the highest quality planting material available to the U.S. grapevine industry. Rootstock and scion materials were disease tested and grafted in-house using proprietary green-grafting techniques.
Zeneca Plant Sciences	Increased-pectin tomatoes	Tomatoes that have been genetically modified to remain firm longer and retain pectin during processing into tomato paste.

Source: Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology (1996–1997),* Washington, D.C., 1996.

Table 8B. Agricultural Biotech Products Expected on the Market Within Six Years

Company	Product	Comments
A/F Protein	BioGrow® salmon	The BioGrow® salmon can grow from egg to market size (8 to 10 lbs.) in one to one and one-half years. Conventional fish breeding techniques require three years. A/F Protein expects to introduce the BioGrow® salmon within four to six years to a public for whom salmon is an increasingly popular food.
Agracetus	Genetically engineered cotton fiber	This biotech product will have enhanced fiber performance, and it will reduce dye-shop pollution and improve textile manufacturing efficiency.
Agritope	Fruits and vegetables	These products use ethylene-control technology to create delayed-ripening, longer lasting tomatoes, raspberries, and strawberries.
Calgene	B.t. cotton	These cotton plants will require less chemical insecticide to achieve greater crop yield. Initial varieties are in field trials. Market introduction is planned for 1997.
	Ethylene-controlled tomato	This new tomato will be a controlled-ripening, high-quality, fresh-market variety. Tomato plants with delayed fruit ripening ability are in field trials.
	High-stearate oil	High-stearate oil is an ingredient in margarine and shortening that would require no hydrogenation. It will also be a less expensive source of supply for cocoa butter replacement fats. Rapeseed plants with more than 30 percent stearate in the oil have been produced and are in field trials.
	High-myristate oil	This oil will be a less expensive and more abundant source of raw materials for soaps and personal care products. Rapeseed plants containing 14 percent myristate in the oil have been produced in the greenhouse.

Table 8B. ***Continued***

Company	Product	Comments
Calgene *(continued)*	Medium-chain fatty acids/ triglycerides	This product will be a less expensive source of raw materials for high-performance lubricants, nutritional formulas, and high-energy foods. Rapeseed plants with up to 38 percent medium-chain fatty acids have been produced in the greenhouse.
	Low-saturate oil	Low-saturate oil is a healthier liquid salad and cooking oil. Rapeseed plants with 45 percent lower saturates in the oil have been produced in the greenhouse.
DNA Plant Technology	Elongated sweet pepper	This sweet pepper is specially bred for flavor and ease of preparation.
	Precut salads	Branded, precut salads using Fresh World products with enhanced shelf life and convenience.
	Ripening-controlled cherry tomatoes	Using the same technology as in its Endless Summer fresh market tomato, the company has developed cherry tomatoes with longer market life, improved flavor, and better harvest traits.
	Seedless minimelon	This minimelon is specially bred for its convenient single-serve size and flavor.
	Sweeter peas	Sugar snap peas have been modified for sweeter flavor and higher yield by controlling the conversion of sugar to starch using Transwitch technology. Pea plants are currently in field evaluations.
	Firmer peppers	This sweet pepper has been modified using Transwitch technology to remain firmer after harvest. Pepper plants are currently in field evaluations.
	Sweeter peppers	This pepper has been modified to be sweeter and tastier by overexpressing a gene for sweetness. Pepper plants are in early stages of seed increase and field evaluation.

Table 8B. ***Continued***

Company	Product	Comments
DNA Plant Technology *(continued)*	Ripening-controlled bananas/ pineapple	Using the same ripening-control technology as in its Endless Summer tomato, the company is developing banana and pineapple varieties with extended market life.
	Strawberry	Frozen strawberries' texture is improved by adding genes to control freeze-thaw tolerance.
Monsanto	Enhanced flavor tomato	Monsanto scientists have identified a gene in a naturally occurring soil bacterium that reduces the production of ethylene. When this gene is inserted into a tomato plant, it slows the ripening process. This allows the tomatoes to reach maturity on the plant, providing consumers with vine-ripened tomatoes year-round.
	High-solids potato	Monsanto has developed a higher solids (or starch content) potato by introducing a starch-producing gene from a soil bacteria into a potato plant. With the reduction in the percentage of water in the genetically improved potato, less oil is absorbed during processing, resulting in a reduction of cooking time and costs, better tasting french fries, and an economic benefit to the processor.
	High-solids tomato	Using the same technology used for high-solids potatoes, Monsanto is working on increasing the solids of a tomato and reducing the water content.
	YieldGard™ insect-protected corn	YieldGard™ corn is protected against the European corn borer and related insects in the family of Lepidoptera.

Table 8B. ***Continued***

Company	Product	Comments
Zeneca Plant Science	Black banana	Zeneca is developing an inherent resistance in bananas to Sigatoka and modifying ripening characteristics in them. This will reduce the need for chemical fungicides and improve the agronomics of production and the quality of the product.
	Fresh-market tomatoes	Zeneca is modifying the tomatoes for enhanced flavor and color and increased antioxidant vitamin content.
Zeneca with Shell Forestry and Nippon Paper	Modified lignin in paper pulp trees	By making lignin easier to remove from cellulose—the primary ingredient in paper—paper makers can make high-quality paper with less energy and bleaching, which results in benefits to both the paper processor and the environment.

Source: Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology (1996–1997),* Washington, D.C., 1996.

Table 9A. Biopesticide Products on the Market Today

Company	Product	Comments
Crop Genetics International	Disease-free Kleentek™	Increases sugar yield.
	Spod-X™	Controls beet armyworm via a natural insect virus. Safer to use and better for the environment than chemical insecticides.
Ecogen	Aspire™	A biofungicide used to protect fresh produce from postharvest rot. It is used on citrus, pome fruits, berries, and grapes. The active ingredient is a naturally occurring yeast that is harmless to all nontargeted organisms.
	Foil®	A bioinsecticide that is effective against the Colorado potato beetle, the European corn borer, armyworms, and loopers.
	Condor®	A bioinsecticide that is effective against the tobacco budworm, cotton bollworm, soybean looper, gypsy moth, green clover worm, velvetbean caterpillar, and spruce budworm.
	Cutlass®	Broad-spectrum bioinsecticide, effective against the beet armyworm, diamond-back moth, cabbage looper, cabbage webworm, and imported cabbage webworm.
	AQ-10®	A biofungicide that protects crops from powdery mildew. It is used on strawberries, grapes, tomatoes, cucumbers, and ornamentals. It reduces the use of conventional fungicides.
	Otinem® Insecticide, Bee-scent,® and No-Mate	
Mycogen	MVP®	Used on corn, tree fruits, vines, cotton, and vegetables to control leaf-eating caterpillar pests.
	M-Trak®	Used on potatoes, tomatoes, and eggplants to control the Colorado potato beetle.
	M-Peril™	Used on corn to combat the European corn borer.
	M-Pede™	Used on fruits, vegetables, grapes, and ornamentals to resist soft-body insects and powdery mildew.
	DeMoss™	Used on roofs, buildings, sidewalks, and greenhouses to resist moss, algae, and lichens.

Source: Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology (1996–1997),* Washington, D.C., 1996.

Table 9B. Biopesticide Products Coming to the Market

Company	Product	Comments
AgrEvo USA	Liberty™-resistant	Corn, soybeans, and canola crops resistant to Liberty herbicide.
American Cyanamid	IMI-corn	Imidazolinone herbicide tolerant.
	RAPTOR™ insecticide	Soil microbe combats budworm and bollworm on cotton.
Dominion Biosciences	Ecologix™ cockroach bait	Regulates insect growth.
	Leone™ biofungicide	Controls plant diseases by relying on anti-microbial "predator" bacteria.
Ecogen	Crymax™ bioinsecticide	Developed for vegetables, trees, nuts, and vines.
	EG7826™	Will control fall armyworm.
Mycogen	Scythe™	Used for horticulture and landscape management to combat a broad spectrum of weeds.
	MYX-4801™	To thin blossoms on apples, pears, and stone fruits.
	B.t. plants	Corn, cotton, alfalfa, canola, and sunflower plants toxic to pests.
Ciba Geigy Ag Group	Agree® B.t.-based bioinsecticide	For tobacco, corn, and soybeans.
	Design® B.t.-based bioinsecticide	For cotton and soybeans.
	Exhibit® B.t.-based bioinsecticide	Parasitic nematode for ornamental plants and turf.
Monsanto	Yield Guard™ insect-protected corn	Modified to control the European corn borer.
	Herbicide-tolerant crops	Canola/oilseed rape, corn, and sugarbeets tolerant of Roundup® herbicide.

Source: Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology (1996–1997)*, Washington, D.C., 1996.

developed to distinguish pathogenic organisms from harmless ones and to detect and measure the presence of pathogens.

Gene-Based Research and Advances in Agricultural Biotechnology

New research that isolates genes that control resistance to funguses, viruses, and bacteria will make it easier to apply genetic engineering to a variety of plants. Until now, the only practical way to cultivate crops with resistance to these pathogens has been to crossbreed a resistant variety with a commonly grown stock. This approach takes nearly 10 years to carry out. Research is generating faster alternatives based on the mapping and identification of specific genes involved in resistance to pathogens. Sequencing the genes that confer disease resistance is the key to such progress.[29]

Products resulting from research in ag-biotech are being introduced to the market at an increasing rate. Among them are plants that have acquired desirable traits, such as pest resistance, through gene transfer. The genes that deter or harm pests may be encoded in an agent applied exogenously to plants or soil, or they may be incorporated in the plant's own genome. Biopesticides already on the market include Ecogen's Aspire™, a biofungicide for citrus fruits, berries, and grapes; Ecogen's Condor™, a bioinsecticide used against tobacco budworm, cotton bollworm, soybean looper, and other pests; and Mycogen's Scythe™, an antiweed product. Products that target pests on corn, potatoes, and a variety of trees and vines are in development.[30]

Food Preservation Applications

Preservatives provide a low-cost way of protecting food from spoilage. The food preservative market is now dominated by large multinational companies. The total market for food preservatives, estimated at $1.5 billion, is distributed among acidulants, preservatives, and antioxidants. While this market is expected to grow slowly (3.2 percent per year over the next decade), there will be increasing demand for foods that rely on preservatives other than nitrates, nitrites, and sulfur. *Genetic Engineering News* reports that new biotechnologies for producing food preservatives are emerging just as "market forces and the drive for cost efficiency are making innovative natural substitutes more attractive than ever."[31]

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[29] Anne Simon Moffet, "Mapping the Sequence of Disease Resistance," *Science*, 23 Sept. 1994, 1804–5.

[30] *Genetic Engineering News*, July 1995.

[31] William H. Stroh, "New Biotechnologies Set to Impact Industrial Food Preservative Market," *Genetic Engineering News*, 15 Oct. 1993, 10.

Biotechnology-based preservatives will compete with advanced packaging and other natural preservation additives. U.S. companies are leading in the technology and production processes from which new products will emerge.

Bioengineered food-related products already available include Genecor's Chymogen™, a bioproduced enzyme that facilitates milk curdling in cheese production; Calgene's Flavr Savr™ tomato that ripens on the vine; and DNA Plant Technology's Fresh World Farms™ sweet minipeppers with stabilized color, taste, and seed counts.

Public Acceptance of Agricultural Biotechnology

As noted earlier, biotechnology offers a precise way of accomplishing what nature and farmers have done in less precise ways for centuries. Yet the processing of food, whether by canning or genetic manipulation, has always created uncertainty in the public mind. Fear and misinformation about the use and effect of biotechnology in food products have forced companies to find ways of reassuring the public that such foods are safe. The continuing controversy about milk from cows treated with BST demonstrates the challenge companies face in marketing such new products.

It is anticipated that public acceptance will grow as more genetically enhanced products reach the market and are consumed without incident. Consumers must be confident that such foods are as risk free as those that they now purchase. While FDA may confirm the safety of biotechnology-based agricultural products, only time and experience will convince some consumers. To this day, hundreds of thousands of people refuse to eat canned foods for reasons having little to do with science or nutrition. By the same token, despite the risk of food pathogens in poultry and beef, consumption of these products has not declined.

Industrial Biotechnology

Industrial biotechnology provides the ability to create new products or replace existing ones at lower cost with higher purity and improved user benefits. Industrial biotechnology can be used to develop innovative enzyme applications, to produce consumer and industrial products, and to develop alternative methods of synthesizing specialty and fine chemicals. Industrial biotechnology will contribute to reductions in energy consumption and reduce waste by using renewable raw materials.

Some of the most important applications are aimed at achieving environmental goals. These applications relate mainly to waste remediation, but the industry is also expanding into testing and monitoring, "end-of-pipe" treatment, and value-added processes that convert waste into useful products. About a thousand U.S. firms now use environmental biotechnology commercially. The industry includes a significant number of companies that specialize in supplying naturally occurring microbes for use in remediation processes. The vast majority of environmental biotech companies are small businesses, some with only one or two employees. The Organization for Economic Cooperation and Development (OECD) reports in its recent study, *Biotechnology for a Clean Environment – Prevention, Direction, Remediation*, that the rapid growth in the industry has come about because of increasing pollution "across all sectors and countries" and because of the "improving relative cost-efficiency of biological clean-up methods as compared to the more traditional physical and chemical ones." According to the study, the market for environmental biotechnologies will increase from $40 billion in the early 1990s to some $75 billion by the turn of the century.

About a thousand U.S. firms now use environmental biotechnology commercially.

Industrial Enzymes, Biocatalysts, and Chemicals

One of the most successful applications of biotechnology has been the use of enzymes and whole-cell biocatalysts in commercial food preparation and industrial manufacturing. Industrial enzymes offer applications in cleaning products, textile processing, starch processing, animal feeds, pulp and paper production, leather processing, food processing, and other areas. For example, industrial enzymes are used in laundry detergents to break down stains and improve detergent performance in the warm-water cycle. These enzymes are biodegradable and save energy by requiring lower water temperatures for washing.

Enzyme use is being studied as an alternative to traditional chemical processes for manufacturing dyes and pharmaceuticals. Most of the 50 or so enzymes now in use help break large molecules down into smaller ones, like the laundry detergent proteases. Enzyme applications are being pursued for creating complex molecules from simpler ones and for transforming existing chemical structures into more active compounds (e.g., taxol synthesis). Production of sweeter corn syrup by the enzyme glucose isomerase is a noteworthy example of how a biotransformation can be carried out on an industrial scale. In whole-cell biocatalysis, a process using a genetically engineered micro-organism to produce indigo has received FDA approval and is being commercialized.[32]

[32] Biotechnology Industry Organization, *U.S. Biotechnology Fact Sheet* (Washington, D.C., 1995).

Specialty chemicals are promoted and sold on the basis of their functionality, while fine chemicals are promoted and sold on the basis of the molecules they contain and the specific characteristics of those molecules. Opportunities for using biochemicals exist in the following specialty and fine chemical sectors: pharmaceuticals, food additives, dyes, agrichemicals, and detergents. New biosynthetic methods of producing chemicals can help producers lower manufacturing costs, giving them a competitive advantage. Sales of industrial biotechnology products for chemical production are expected to grow at a rate averaging 19 percent a year, from $275 million in 1996 to $690 million in 2001 to $1.6 billion in 2006.[33]

Bioremediation

Bioremediation is the use of micro-organisms to degrade or destroy hazardous organic wastes. In its most commonly applied form, bioremediation is an aerobic bacterial process that uses microbes to oxidize organic compounds. The four main segments of the industry are producers of microbes or microbe-enhancing products, environmental engineering and consulting companies that plan and conduct cleanups, specialty laboratories that perform chemical and biological analyses, and firms that produce instrumentation and diagnostics in the bioremediation process.

Estimates of the value of the bioremediation market vary, in large part because the industry is so new and has not been analyzed carefully. However, it was estimated that in 1993 the bioremediation market earned $150 million to $175 million for consulting and remediation services, $7 million for microbe production, and approximately $4 million from equipment sales. The fact that less than 15 percent of today's bioremediation companies were in business before 1985 attests to the newness of the field. Most firms are small: 39 of the 102 consulting and remediation firms employ fewer than 50 people, as do 90 percent of the microbe producers and 60 percent of the equipment manufacturers.[34]

One estimate suggests bioremediation sales of more than $500 million by 2000.[35] A more pessimistic assessment emerged at a conference sponsored by the Biotechnology Industry Organization in Philadelphia in June 1996.

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[33] "Biotechnology on the Rebound," *Consulting Resources Corporation Newsletter.*

[34] Devo Enterprise, Jennings Group, Inc., *U.S. Bioremediation Market, 1994–2000,* (Columbia, N.J., 1994).

[35] Biotechnology Research Subcommittee, Committee on Fundamental Science, National Science and Technology Council, *Biotechnology for the 21st Century: New Horizons* (Washington, D.C., 1995).

The conference participants predicted that growth of the environmental biotechnology industry will peak around 2000. After that time, improvements in manufacturing practices and declining numbers of sites requiring reclamation will lead to the decline of the industry. Some bioremediation techniques will be subsumed into manufacturing practices. Already, some soil microbial transformations useful for eliminating environmental contaminants are finding uses as biocatalysts and are replacing some of the messier steps in traditional organic synthesis routes.

The recent growth in bioremediation is due in part to the expensive cleanup requirements of both government and industry. The cost of cleaning up federal lands has been estimated at near $450 million, and the combined estimate for both federal and nonfederal lands could run as high as $1.7 trillion if conventional techniques are used.[36] Cost-effectiveness is one of the principal advantages of using bioremediation at environmental cleanup sites. For example, "bioventing" has reduced the cost of bioremediation for many fuel sites by a factor of 5 to 10. According to a recent OECD report, "Experience in the United States shows that 65 to 86 percent savings occur when biological methods are used instead of physical/chemical procedures. Whereas incineration usually costs $250 to $500 per ton of soil, biological methods can cost as little as $40 to $70 per ton."

The cost of cleaning up federal lands has been estimated at near $450 million.

A study prepared last year by M&M Environmental Safety Services reported that the three-year cost of using bioremediation to treat 1,500 cubic yards of soil contaminated with heat-transfer fluid was one-sixth the cost of incinerating the soil and less than one-half the cost of relying on a landfill.

The environmental remediation industry has been slow to take advantage of biotechnology, despite its advantages. Investment in environmental biotech has been minimal relative to investment in medicine and agriculture. As an article in *Genetic Engineering News* points out, "Indeed, much funding of environmental research has been reactive in character, as for example, in supporting ways to clean Superfund waste sites."[37]

[36] Ibid.

[37] Anne Simon Moffat, "Recent Advances in Environmental Biotech Impact Agriculture and Mining," *Genetic Engineering News*, 15 Oct. 1993, 10.

Biotechnology is coming into its own as a cost-effective alternative to other forms of environmental remediation.

However, biotechnology is coming into its own as a cost-effective alternative to other forms of environmental remediation. For example, Envirogen Inc., has isolated a common form of bacteria that rapidly breaks down hydrochlorofluorocarbons and hydrofluorocarbons. Another start-up company, Geobiotics, is developing an oxidizing bacteria called *Thiobacillus ferrooxidans* that allows mining operations to extract precious metals in a way that is neither costly nor destructive. According to industry experts, biotechnology is already being applied in 30 percent of copper mines and will be a major application for cleaning up and increasing mining efficiency in the years to come.[38]

Much more needs to be done to reap the full commercial value of this technology. Where there is demand for bioremediation, alliances with larger reclamation and environmental service companies may be required to support the development of environmentally relevant test systems that can be used to evaluate bioremediation.[39]

Bioreagents

Bioreagents are biotechnology-produced compounds used in a chemical reaction to detect, measure, examine, or produce other compounds. The sector of the biotechnology industry that supplies test kits for research and diagnostic purposes has grown substantially in recent years. Bioreagents in such kits may include growth factors, cytokines and lymphokines, immunochemicals, peptides and proteins, or RNA and DNA probes. For in vitro tissue culture experiments, other bioreagents, such as serum factors, hormones, antibiotics, and growth factors, are required. Other examples of bioreagents include restriction enzymes for recombinant DNA techniques, agarose and other solid-phase materials for electrophoresis, dyes for spectroscopic measurements, and monoclonal and polyclonal antibodies for various research and diagnostic applications.

The demand for better and more diverse bioreagents is expected to fuel the growth of the market (now valued at $3.3 billion a year) at an annual rate of 10 percent through the end of the century. According to Amvir Associates, a biotechnology consulting firm, new bioreagents are being introduced into the U.S. market at a rate of 2,500 to 4,000 per year. The

[38] Ibid., 13.

[39] Sue Markland Day, "AAM Concludes That Bioremediation Applications Will Grow in the Future," *Genetic Engineering News*, 1 May 1993, 16.

United States has established a commanding lead in developing and marketing bioreagents primarily because many compounds tested in the search for new drugs also work as reagents for other experiments and production processes.

Once again, the United States is the clear market leader in this sector, which is currently dominated by four companies that supply 45 to 55 percent of all bioreagents in the country. There are only a dozen foreign reagent suppliers compared with several hundred American firms.

The demand for better and more diverse bioreagents is expected to fuel the growth of the market.

Nonmedical Diagnostics

Heightened interest in the quality, composition, and safety of the global food supply, as well as increasing concerns about environmental contamination, drive the nonmedical diagnostics market. Included in this category are products used to detect chemicals, pathogens, and other contaminants in the food supply and the environment. According to Consulting Resources Corporation, sales in this segment are expected to grow from $225 million in 1996 to $465 million in 2006.[40]

Traditional testing methodologies are based on the classical techniques used in analytical chemistry, microbiology, and biochemistry to detect pesticides and other chemical contaminants in food, water, and soil. Biotechnology is providing new, more efficient diagnostic tools for food; the tools can be grouped into three categories: immunoassays, nucleic acid probes, and biosensors. It has been expected for some time that early detection of organic or microbial food contamination through the use of biotechnology will transform the food industry. Today, biosensors and other testing tools are becoming the critical detection and control devices in the food industry. Indeed, biosensors are likely to experience great growth as the technology becomes more advanced and easier to use.

[40] "Biotechnology on the Rebound," *Consulting Resources Corporation Newsletter.*

Determinants of Future Competitiveness

While the effects of biotechnology on various industry sectors are complex and difficult to measure, the available information suggests that U.S. industry leads the world in applying biotechnology to commercial uses. The foundation for this competitive advantage, particularly in the health-care and life-science areas, was laid by the substantial investment of the U.S. public and private sectors in research and development. American researchers are responsible for much of the science of the new biotechnology, and many of them were trained at NIH and other federally funded institutions.

A key to the industry's competitive success has been its ability to secure needed capital. Many observers regard biotechnology as one of the most capital-intensive and research-intensive industries in the history of civilian manufacturing. Because of the time required to bring new products to market, the vast majority of companies cannot rely on product revenues to meet their funding needs. Instead, the industry has used mechanisms ranging from venture-capital investments and public securities offerings to partnerships with other companies to fuel its growth.

As the industry matures, it must come to grips with other factors that may affect its competitiveness. Domestic regulatory regimes intended to achieve public health, safety, and environmental goals impose costs and other constraints on the companies' operations. Federal tax laws are also important, especially those provisions intended to encourage productive investment in capital assets. Finally, as cost concerns continue to dominate the health-care industry, new biotechnology products will need to demonstrate clear therapeutic efficiency if they are to be commercially successful.

New biotechnology products will need to demonstrate clear therapeutic efficiency if they are to be commercially successful.

Competing successfully in international markets is essential for the industry, and increasing competition from foreign-based companies seems inevitable. Biotechnology has been identified as a transformative growth technology not only in the United States, but also in other industrialized countries. Although the U.S. industry leads in the discovery phase of biotechnology, Japan and the European Union (EU) are coordinating government, industrial, and academic resources in biotechnology and bioprocess engineering development to establish strong, government-supported technology infrastructures. In this global context, the domestic industry has an interest both in harmonization of national regulatory regimes and in strong and effective international protection for intellectual property.

Technology Infrastructure and Federal Research Initiatives

The United States has attained its competitive position in the biomedical sciences thanks to research support from the federal government. A great deal of our knowledge about the nature and function of cells and recombinant DNA technology is a direct result of government-supported research. This knowledge has led to the development of many new products because federal legislation has enabled NIH, other federal agencies, and federally funded researchers to transfer their research results to the private sector for commercial development and to conduct collaborative research with private sector partners.

Twelve federal agencies are engaged in biotechnology research focusing on six major areas: agriculture, energy, environment, health, manufacturing and bioprocessing, and general foundations (scientific and technical research applicable to all areas). The government also supports infrastructural research related to training, facilities, and research resources; structural biology; marine biotechnology; genome projects; and technology development and commercialization (see table 10). In 1994, health-related research accounted for 41 percent of the federal biotech-related budget, while 39 percent supported broad-based general foundations research.

In connection with this mission research, the federal agencies are authorized by the Bayh-Dole Act, the Federal Technology Transfer Act, and other legislation to facilitate private sector commercialization of new ideas generated by government research programs. This assistance can include transferring or licensing rights to inventions generated by government research to the private sector and conducting collaborative research with private sector partners in areas of mutual interest. In addition, the Bayh-Dole Act and related executive orders enable third parties performing federally funded research to claim title to inventions resulting from that research and to license those inventions to the private sector.

Research funded by NIH, both internally and externally, has led to the formation of many companies important to the biotechnology field.

The activities of NIH demonstrate the utility of such legislation. Research funded by NIH, both internally and externally, has led to the formation of many companies important to the biotechnology field and to the development of new health care products, ranging from AIDS and cancer therapeutics to vaccines and diagnostics. In fact, virtually all the products described in table 7 resulted from research funded in part by NIH. In addition, as table 11 shows, an impressive number of these new products have resulted from research conducted within NIH itself.

Table 10. Federal Biotechnology Research Initiative—Fiscal 1994

Initiative	R&D Allocation ($millions)	Percentage of Total Federal R&D Allocation
Research		
Health	1,742.1	40.5
General Foundations	1,668.3	38.8
Agriculture	234.2	5.4
Manufacturing/Bioprocessing	160.8	3.7
Environment	90.2	2.1
Energy	58.1	1.4
Subtotal	3,953.7	91.9
Infrastructure		
Training	152.3	3.5
Instrumentation	66.2	1.5
Facilities	43.6	1.0
Repositories	37.9	0.9
Databases	36.4	0.8
Subtotal	336.4	7.7
Social Impact	9.2	0.2
Total	4,299.3	100

Source: Committee on Life Sciences and Health of the Federal Coordinating Council for Science, Engineering, and Technology, *Biotechnology for the 21st Century: Realizing the Promise* (1993).

An important yardstick of this success is provided by the technology transfer activities of the Department of Health and Human Services (HHS) reported by NIH's Office of Technology Transfer. As figure 1 shows, the number of patents issued annually to HHS more than tripled from Fiscal 1985 to Fiscal 1996, and most of them were issued to NIH. The annual number of patent licenses executed by HHS increased from 25 to 193 during the same period, with almost all involving NIH.

The royalties reported by NIH's Office of Technology Transfer for fiscal 1987–1996 are a particularly useful measure of the commercial success of the licensed inventions (see Figure 2). During that period, annual royalties received by HHS increased from $4.245 million to $27.277 million.

Table 11. NIH Inventions with Significant Current Commercial Product Sales

I. DIAGNOSTICS

Antibodies Against Human *Pneumocystis carinii*, Clinical Center. Monoclonal antibodies specific to human *Pneumocystis carinii* can be used to detect the presence of the organism, which causes pneumonia in immunocompromised individuals, particularly those with AIDS. These antibodies are a reliable, efficient, and simple diagnostic tool for detecting this organism, which cannot be cultured from humans. The invention is licensed co-exclusively to three companies.

Serological Detection of Antibodies to HIV-1, National Cancer Institute. The product from this invention is the AIDS Test Kit, which is used as a diagnostic to determine whether patients are HIV positive and to screen blood supplies. The invention is licensed nonexclusively to a number of companies and sold throughout the world.

Serological Detection of Antibodies to HTLV-I, National Cancer Institute. Infection from Human T-Cell Lymphotropic Virus Type I (HTLV-I) can be diagnosed through the use of test kits based on the cloned HTLV-I envelope genes of this invention. This invention has been licensed on a non-exclusive basis to several companies.

erb-2 Oncogene Receptor, National Cancer Institute. erb-2 is a retroviral oncogene expressed in human breast cancer. Proteins encoded by this gene and antibodies against those proteins are useful as diagnostic tools in detecting and treating cancers. This invention has been licensed on a nonexclusive basis to Berlex Laboratories and several other companies.

Breast Cancer Monoclonal Antibodies, National Cancer Institute. This invention describes monoclonal antibodies demonstrating a reactivity with human breast cancer. The invention has been licensed by many companies for research reagent use, diagnostic test-kit use, and therapeutic purposes involving breast cancer and related cancers.

Soluble Interleukin-2 Receptor, National Cancer Institute. A new diagnostic kit for detecting soluble interleukin (IL-2) receptors offers an improved method for detecting various infections or diseases. The release of soluble IL-2 receptors is associated with immune activation or malignant conditions. This technology has been nonexclusively licensed to several companies.

Recombinant Cytochrome P-450, National Cancer Institute. P-450 cytochromes are a family of blood proteins that metabolize biologically active compounds such as drugs, carcinogens, pollutants, and hormones. These recombinant cytochromes have proven useful in toxicity and carcinogenicity testing of materials and products. This invention has been nonexclusively licensed to Gentest and several other companies.

Table 11. *Continued*

II. VACCINES AND THERAPEUTICS

Cancer Chemotherapeutic Drug, 2-F-AraA, National Cancer Institute. This compound, a DNA polymerase inhibitor, has exhibited potent activity in the treatment of B-cell leukemia. Licensed exclusively to Berlex Laboratories, 2-F-AraA has been approved by FDA as a cancer therapeutic drug and is marketed under the trade name, Fludarabine.

Antisense Phosphorothioate Nucleotides, National Cancer Institute. Antisense drugs are a new class of therapeutic agents that function by preventing select RNA molecules from being translated into proteins. Several licensees are developing phosphorothioate antisense drugs for a variety of diseases, including AIDS and other viral diseases, cancer, cardiovascular diseases, and autoimmune disorders.

Hepatitis A Vaccine, National Institute of Allergy and Infectious Diseases. Hepatitis A is probably the most widespread of viral hepatitis diseases and is an endemic childhood disease in the underdeveloped countries. The vaccine for Hepatitis A is now being sold in the United States and abroad by SmithKline Beecham under the trade name Havrix.

Treatment of HIV Infection with ddI, National Cancer Institute. ddI, similar in action to AZT, selectively inhibits the replication of HIV by interfering with the production of a critical enzyme known as reverse transcriptase. Because ddI may be better tolerated or have different patterns of toxicity than AZT, it may be useful in individual or combination treatment therapy. Licensed exclusively to Bristol-Myers Squib, it completed clinical testing in 1991 and was approved for use by FDA.

Treatment of HIV Infection with ddC, National Cancer Institute. ddC, also similar in action to AZT, selectively inhibits the replication of HIV by interfering with the production of reverse transcriptase. Because it may be better tolerated or have different patterns of toxicity than either AZT or ddI, it may be useful in individual or combination treatment therapy. Licensed exclusively to Hoffmann LaRoche, it completed clinical testing in 1992 and was approved for use by FDA.

Trimetrexate as an Antiparasitic Agent, National Cancer Institute/Clinical Center. Infections caused by *Toxoplasma gondii* and *Pneumocystis carinii* are often seen in patients with AIDS and are extremely refractory to standard therapy. They can be treated effectively by administering trimetrexate. This invention is licensed exclusively to U.S. Bioscience.

Table 11. *Continued*

III. INSTRUMENTATION AND DEVICES

Flow-Through Blood Centrifuge, National Heart, Lung, and Blood Institute. The product from this invention is a high-tech blood-cell separator that separates and packages blood components.

IV. RESEARCH MATERIALS

Nondenaturing Zwitterionic Detergents, National Institute for Child Health and Human Development. The product from this invention is the detergent CHAPS, used extensively in buffers in laboratory research. The invention is licensed nonexclusively to a number of companies and sold throughout the world.

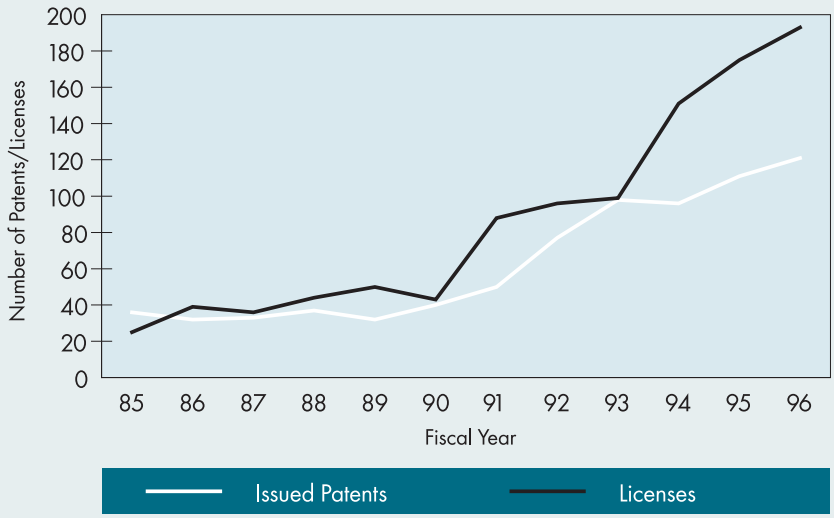
Reconstituted Basement Membrane Protein Complex, National Institute of Dental Research. This invention describes a reconstituted basement membrane protein complex. Basement membranes are thin but continuous sheets that surround nerves, muscle fibers, smooth muscle cells, and fat cells. The matrix is marketed as a research reagent and in culture is employed as a cell attachment factor for the propagation and differentiation of anchorage-dependent cells of ectodermal, neuroectodermal, and endodermal origin. It is sold under the trade name Matrigel by Becton Dickinson, a nonexclusive licensee.

Neurotransmitter Antibodies, National Institute on Deafness and Other Communication Disorders. This invention concerns polyclonal antibodies that are specific for neurotransmitters. The antibodies, peptide-serum conjugates for neurotransmitters, and chromatography media were licensed to Chemicon International, Inc., for research reagent sales.

G-Protein Antibodies, National Institute of Diabetes and Digestive and Kidney Diseases. This invention describes synthetic peptides and probes corresponding to specific epitope sites of various G-proteins and antibodies having binding affinities for these sites. The invention describes a kit for identifying various G-proteins. It was licensed to DuPont in the field of research reagents for sales of the antibodies and probes.

Human D2 Dopamine Receptor, National Institute of Neurological Disorders and Stroke. A DNA segment encoding a functional, long isoform of the human D2 dopamine receptor was sequenced, cloned, and expressed following transfection in eukaryotic cells. Both isolated receptors and receptors incorporated into cell membranes are sold as products to screen and develop drugs for treatment of Parkinson's disease and other neurodegenerative disorders. This technology is nonexclusively licensed to several companies.

Figure 1. Patent and Licensing Activity of the Department of Health and Human Services FY85–FY96

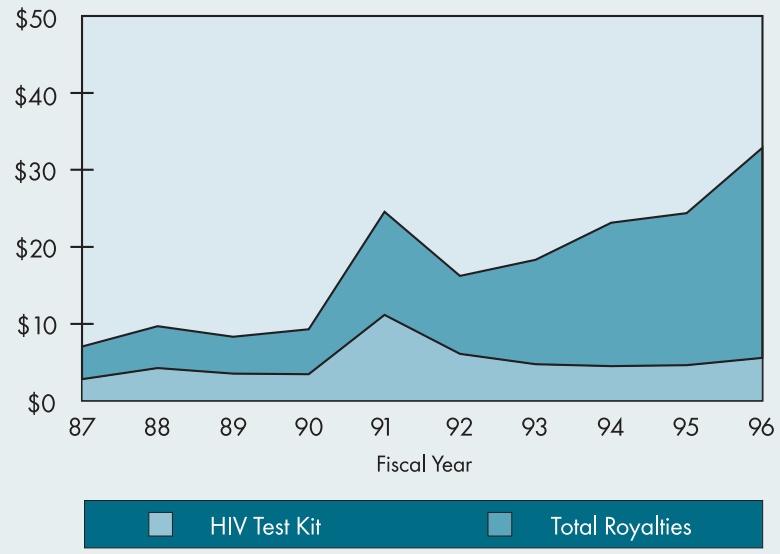


While a large portion of these royalties were initially attributable to a single technology, an HIV-antibody test kit ($2.8 million of the $4.245 million total in fiscal 1987), the royalty stream now reflects a variety of important technologies; the HIV-antibody test kit constituted only $5.5 million of $27.277 million in fiscal 1996 royalties.

The National Institute of Standards and Technology in the Department of Commerce has been supporting the development of high-risk enabling technologies through the Advanced Technology Program (ATP). ATP shares with private companies the cost of developing technologies that underlie a broad spectrum of new applications, commercial products, and services to spur economic growth. About 16 percent of the competitive awards made under ATP have gone to biotechnology projects. ATP has also supported strategic technology development programs in conjunction with industry. These programs focus on the developing of better biocatalysts for industrial applications and establishing automated, cost-effective methods for sequencing, interpreting, and storing DNA sequences for diagnostic applications.

The National Oceanic and Atmospheric Administration of the Department of Commerce has made important contributions to the

Figure 2. Royalties Received by the Department of Health and Human Services from Licensed Technology (in millions of dollars) (FY87–FY96)



development of marine biotechnology, supporting research in that area through the National Sea Grant College Program. Since 1993, $12 million ($8 million in federal funds and $4.5 million in matching funds) has been spent on using biotechnology to address marine and coastal issues and on using marine and coastal resources as biotechnological substrates. Sea Grant funding has supported the development of products and processes addressing challenges such as beach and dune restoration (sea oats: Horticultural Systems, Inc.), bioremediation (novel micro-organisms: Manville Corp.), agricultural biodegradable fertilizer enhancement (polyaspartic acid: Donlar Corp.), and the rapid detection and identification of pathogens in seafood (dipstick for *Vibrio chloerae:* New Horizons, Inc.).

Because of increasing budgetary pressures, recent federal spending on biotech-related research has barely kept pace with inflation. According to information collected by the agencies, the fiscal 1993 budget increased 5.2 percent over the fiscal 1992 budget of $4.058 billion, but the fiscal 1994 budget of $4.299 billion increased less than 1 percent over fiscal 1993

expenditures of $4.269 billion.[41] Specific information about biotech spending is not available for fiscal 1995 or fiscal 1996. While NIH R&D outlays increased 5 percent for fiscal 1995 and 4 percent for fiscal 1996, nonmedical research programs generally increased at a lower rate during this period.

The rate of increase in biotech research funding is consistent with the pattern of federal funding for research in the life sciences generally. After significant increases in the late 1980s and early 1990s, funding has grown more slowly in recent years. For example, according to the National Science Foundation (NSF), spending increased by 9 percent between fiscal 1990 ($8.829 billion) and fiscal 1991 ($9.621 billion) and by 8.7 percent between fiscal 1992 ($9.910 billion) and fiscal 1993 ($10.772 billion). During the past three years, however, spending has increased more modestly. Based on fiscal 1995 and fiscal 1996 estimates, spending increased by only 2.9 percent between fiscal 1994 ($11.078 billion) and fiscal 1995 and by 2.3 percent between fiscal 1995 and fiscal 1996 ($11.662 billion).

Political pressures to bring down the federal budget deficit make it extremely difficult to increase real spending without making cutbacks elsewhere. For example, for the past five years, the Department of Agriculture's National Research Initiative has been funded at 20 percent of the target level recommended by the National Research Council's Board on Agriculture. For fiscal 1997, the Clinton administration has proposed a 34 percent increase in funding to $130 million. The biotechnology industry has suggested that a portion of the savings realized through reductions in agricultural support programs be allocated to the National Research Initiative.

NIH is the leading recipient of federal biotechnology funds; it received $4.7 billion in fiscal 1996, a majority of total federal spending on biotechnology. Funding for genome research increases by more than 6 percent under the Clinton administration's budget for fiscal 1997, and funding for general biotech research should increase by a similar percentage. The

[41] The federal government spent $4.3 billion on biotechnology-related research in fiscal 1994. See *Biotechnology for the 21st Century: Realizing the Promise*, a 1993 report by the Committee on Life Sciences and Health of the Federal Coordinating Council for Science, Engineering, and Technology; also see previous committee reports. Reporting by this interagency group on federal biotechnology spending was discontinued after collection of the fiscal 1994 numbers. For that reason, similar estimates for fiscal 1995 and fiscal 1996 are not available.

Continued federal support for research is critical to maintaining and expanding the knowledge base that underlies advances in biotechnology.

next largest programs are funded by the Department of Energy, the Department of Agriculture, and the NSF; funding for these programs is also increased. Table 12 shows federal government support by agency.

Continued federal support for research is critical to maintaining and expanding the knowledge base that underlies advances in biotechnology. The challenge lies in finding ways to sustain real growth in federal research funding over the long term and ways to initiate research programs in promising new areas—in an era of cost cutting and downsizing.

A recent report by the National Science and Technology Council concluded,

> To date, the Federal investment in biotechnology has been focused primarily in the health field. The results of this research are having a profound impact on medicine and health care, providing improved approaches to the diagnosis, treatment, and prevention of disease. While health-related research must remain a national priority, researchers are poised to build on the common foundation in basic science to bring the power of biotechnology to bear in other fields. Modest investments now in several rapidly developing areas of biotechnology research will lead to major economic and societal benefits, including foods that are more abundant and nutritious, a cleaner environment, and non-toxic biomanufacturing.[42]

Capital Formation

Capital formation is a critical strength of the biotech industry—and a continuing challenge. Because of the extensive research efforts and testing necessary to bring new medical products to market, biotech companies have substantial continuing needs for capital that cannot yet be met through product revenues. In the early 1990s, the industry secured large amounts of funding through public offerings. For example, in

[42] Biotechnology Research Subcommittee, Committee on Fundamental Science, National Science and Technology Council, *Biotechnology for the 21st Century: New Horizons* (Washington, D.C., 1995). The National Science and Technology Council (NSTC), formed in November 1993, is chaired by the president of the United States and operated by the Office of Science and Technology Policy. The NSTC works to enhance the effectiveness of U.S. science and technology programs. The report identifies opportunities for federal investment in research in agricultural biotechnology, environmental biotechnology, manufacturing and bioprocessing, and marine biotechnology and aquaculture.

Table 12. Federal Biotechnology Research and Development Funding—Fiscal 1994

Agency	R&D Budget ($ millions)	Percentage of Total Federal Biotech R&D Budget
Health and Human Services		
National Institutes of Health	3,298.2	76.7
Food and Drug Administration	35.7	0.8
Centers for Disease Control	33.7	0.8
Subtotal	3,367.6	78.3
Department of Energy	244.7	5.7
National Science Foundation	215.6	5.0
Department of Agriculture	190.6	4.4
Department of Defense	94.0	2.2
Department of Veterans Affairs	72.0	1.7
National Aeronautics and Space Administration	40.3	0.9
Agency for International Development	30.9	0.7
Environmental Protection Agency	20.3	0.5
Department of Commerce	13.9	0.3
Department of the Interior	6.4	0.1
Department of Justice	1.9	—
TOTAL	4,298.2	100

Source: Committee on Life Sciences and Health of the Federal Coordinating Council for Science, Engineering, and Technology, *Biotechnology for the 21st Century: Realizing the Promise* (1993).

1991 the industry acquired a record $3.27 billion from public offerings. However, these sources became far less productive in 1993 and 1994, and many in the industry predicted serious consequences, especially for smaller companies. In the past two years, however, the industry has shown great creativity, both in managing its "burn rate" (the rate at which it consumes capital) and in finding new ways to secure capital. Many observers believe that the industry has matured in its ability to raise and manage capital, a view supported by the increasing number of planned product introductions and FDA product approvals.

Evolving Industry Approaches to Raising Capital

The first biotechnology companies to reach the public capital markets often sought to follow in the footsteps of the larger pharmaceutical companies. They sought money from public markets to develop and market their own integrated product lines. This model held the promise of significant returns on successful products but also carried a large number of risks.

First, the costs and time commitment required to bring a new pharmaceutical product through the regulatory process to market were substantial and were increasing during the early 1990s. It was not unusual for a firm to spend several hundred million dollars shepherding a product through phase III clinical trials. Equally important, the costs and effort forced most companies to focus on one or two products and to thus place themselves at risk in the event of delays or unfavorable developments. Finally, the burn rate for these companies increased dramatically, with one study suggesting a tripling of annual costs from $6 million in 1992 to $18.8 million in 1994.[43] During this period, public markets became increasingly cautious about investing in biotech companies because few products had reached the marketplace.

Biotechnology companies reacted by finding new ways to manage their risks and maintain financial support. Increasingly, they began to spread the risks of their operations through partnerships with other companies. These partners brought both funding and expertise to the table, leveraging the resources of the participating companies. Under this new model, a public offering was only part of the process of securing capital.

Strategic alliances, particularly those that coordinate the research interests of corporate partners, help companies maintain financial stability

[43] Lisa Piercey, "Flush with Cash, Industry Faces a More Stable Future," *Bioworld Today*, 14 Aug. 1996.

over the long term. Increasingly, venture capitalists are encouraging start-up firms to enter into agreements with larger companies. At the same time, larger companies are turning to biotechnology to help them develop innovative drugs and increase the efficiency of their product development. In addition, larger drug companies are investing in smaller concerns that focus on the early stages of the research process and on the use of genomic information to target new diseases and to identify compounds potentially useful in dealing with those diseases. Such investments allow larger firms to avoid being priced out of the market for products that result from the intensive research efforts of smaller companies. Larger firms no longer have the luxury of waiting until a product enters clinical trials before investing in it.

Strategic alliances, particularly those that coordinate the research interests of corporate partners, help companies maintain financial stability over the long term.

Earlier in the evolution of the industry, public markets offered high prices for companies whose products were in the early stages of development, allowing them to go public at high multiples. Today, other companies are willing to support early science, while investors and the public markets are focusing on companies with advanced products. The success of Millennium Pharmaceuticals, a company that is attempting to characterize the multigenic nature of certain diseases, reveals the benefits of strategic partnerships. It has established alliances with several larger companies, including Eli Lilly, Hoffman-LaRoche, and Astra AB, to commercialize potential therapies for hypertension, diabetes, schizophrenia, and other chronic diseases. Its most recent agreement, with the Wyeth-Ayerst division of American Home Products, was estimated to have a potential value of $90 million, and its four agreements are valued at $250 million over the next five to seven years.[44] Similarly, Tularik, Inc., has created a broad core technology in transcription factors, proteins that regulate gene expression and have potential as treatments for several diseases. Tularik has established development alliances with such large firms as Merck and Yamanouchi Pharmaceutical.

Larger biotechnology firms are also taking positions in smaller start-up companies. Amgen has taken a 4 percent stake in Regeneron, a biotech firm specializing in neurological growth factors. Genentech has taken a 20 percent stake in GenVec Inc., a gene therapy start-up that is developing a cure for cystic fibrosis. Chiron joined with venture capitalists to help fund Onyx Pharmaceuticals, which is developing small molecules to regulate cellular growth through signal transduction. And Onyx has alliances with such larger drug companies as Pfizer and Glaxo-Wellcome.

[44] Kenneth B. Lee and Steven G. Burrill, *Biotech 97.*

In yet another type of alliance, Sandoz Pharmaceuticals (now merged with Ciba Geigy to form Novartis) formed Avalon Medical Partners with the venture capital firm Avalon Ventures. The partnership gave Sandoz a toehold in breakthrough technologies that it could obtain through licensing deals. Start-up companies funded by Avalon Medical Partners include Onyx, Sequana Therapeutics (a gene sequencing company), and Idun Pharmaceuticals, a company researching the regulation of cell death. Sandoz and Avalon Venture investments included $40 million in seven start-ups. The $30 billion merger of Sandoz with Ciba Geigy that created Novartis will consolidate these interests into a large portfolio of investments in U.S. biotechnology firms and research relationships with prominent U.S. research institutions.[45]

SmithKline Beecham invested $125 million in Human Genome Sciences, a gene sequencing firm established with seed capital from Hillman Ventures. The genomic information assembled by Human Genome Sciences was of sufficient interest to cause four other companies to join the collaborative effort. Rhone-Poulenc Rorer has set up a gene therapy alliance by making venture capital investments in several biotech companies working on complementary technologies. Isis Pharmaceuticals recently signed a collaborative agreement with Human Genome Sciences to market their core technologies with Eisai Pharmaceutical and to codevelop a treatment for cytomegalovirus retinitis in AIDS patients.

Ag-biotech companies are also seeking the benefits of such strategic alliances. Small and medium-sized ag-biotech companies are focusing on niche markets, (i.e., "areas of core expertise") and partnering with larger diversified agricultural companies that provide access to capital, distribution chains, marketing expertise, and international contacts. Monsanto's purchase of a controlling interest in Calgene is one strong example of this trend. Mycogen, a company developing seeds for genetically engineered pest-resistant crop plants and biopesticides, was recently involved in two important alliances. Pioneer Hi-Bred International, the world's largest seed company, invested more than $50 million in Mycogen, while DowElanco, a joint venture of Dow Chemical and Eli Lilly, acquired a 46 percent interest in Mycogen for $222 million.[46]

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[45] Institute for Biotechnology Information, "Mergers and Acquisitions Continue to Impact Biotechnology Industry," *Strategic Developments in Biotechnology,* 6, no. 3 (April 1996).

[46] "Biotechnology on the Rebound," *Consulting Resources Corporation Newsletter.*

As a recent Ernst & Young report on biotechnology notes,

> By aligning between and within their sectors—strength to strength and need to need—pharmaceutical and biotechnology companies are equipping themselves to pursue their long term goals . . . state-of-the-art development and delivery of high-quality, cost-beneficial products. The restructuring of the two industries is simultaneous and symbiotic.[47]

Indeed, the link between biotechnology entrepreneurs and larger drug companies, such as Pfizer, Eli Lilly, and Pharmacia & Upjohn, is enduring and complex. *In Vivo* estimates that pharmaceutical firms invested $2.3 billion in smaller biotech companies in 1993. A more recent report placed the value of investments by large firms in the biotechnology industry at about $4.7 billion for 1995; a second report estimated that the number of such alliances increased from 66 in 1994 to 171 in 1995.[48] According to the Institute for Biotechnology Information, such alliances, which range from licensing agreements to straight equity investment, are an important source of revenue for smaller firms.[49] Licensing agreements and research contracts are the primary types of alliances, followed by acquisitions, joint ventures, and marketing agreements.

What have these alliances meant for the competitiveness of the U.S. biotechnology industry? First, pharmaceutical firms have played an important role as sources of capital for biotechnology. Larger companies have provided smaller firms with funding and financial stability at critical times and when all other sources of capital have dried up. Eli Lilly's investment in Centocor was essential to the company's survival after its anti-sepsis compound failed in clinical trials. Today, the Centocor-Lilly alliance is one of the most productive in the industry, and Centocor has several successful products on the market. Similarly, Roche's financial support allowed Genentech to sustain its R&D activities after sales for its clot-dissolving drug, Activase, failed to live up to initial expectations.

Pharmaceutical firms have played an important role as sources of capital for biotechnology.

[47] Ernst & Young, *Biotech 94: Long Term Value, Short Term Hurdles: The Ernst & Young Ninth Annual Report on the Biotechnology Industry* (Palo Alto, Calif. 1994), 21.

[48] *Med Ad News*, July 1996, 31; Ann M. Thayer, "Market, Investor Attitudes Challenge Developers of Biopharmaceuticals," *Chemical and Engineering News*, 12 Aug. 1996, 14.

[49] Mark D. Dibner, "Blood Brothers," *Biotechnology,* 11 (October 1993): 1120.

In addition, pharmaceutical firms provide a combination of product revenues and biotechnology infrastructure that complements the expertise of smaller firms. The biotechnology research facilities of such companies as Pfizer, Lilly, Bristol-Myers Squibb, and SmithKline Beecham are among the largest and best financed in the world. An estimated 30 percent of the R&D funding of all large pharmaceutical firms—nearly $5 billion—goes to investment in biotechnology research.[50] Established drug companies thus provide a potential home for the important research projects of emerging biotechnology companies as well as a steady stream of their own drug development opportunities.

One important trend in strategic biotechnology alliances is the increasing investment by European and Japanese concerns in U.S. biotech companies. While U.S. companies far outpace their competitors in research discoveries and biotechnology innovations, foreign investors are poised to reap significant benefits from the commercialization of products developed from American R&D efforts. In 1994, no less than 47 percent of the research conducted by the U.S. pharmaceutical industry was funded by U.S. affiliates of foreign companies. Examples of foreign companies that have made significant investments in U.S. firms include the Roche Group (Switzerland), Ciba Geigy (Switzerland), Glaxo-Wellcome (U.K.), SmithKline Beecham (U.K.), Rhone- Poulenc (France), Eisai Pharmaceutical (Japan), Yamanouchi Pharmaceutical (Japan), and Pharmacia (Sweden).

Just when biotechnology companies began to recognize the benefits of strategic partnering, the financial markets started to regain their interest in the industry.

Resurgence of Public Market Interest in Biotechnology

Just when biotechnology companies began to recognize the benefits of strategic partnering, the financial markets started to regain their interest in the industry. Announcements from several companies of positive results from clinical trials, together with the prospect of increasing FDA product approvals, buoyed investor interest.[51]

Estimates of the precise amounts raised during 1993 and 1994 vary, but it is clear that the industry's access to capital improved significantly over

[50] Robert Goldberg, "Survey of Pharmaceutical Firm Investment in Biotechnology," Gordon Public Policy Center, Brandeis University.

[51] Analysts have pointed to the number of alliances between biotech companies and pharmaceutical companies, the approvals of ReoPro (a monoclonal antibody produced by Centocor and marketed by Eli Lilly) and Avonex (originated by Biogen for the treatment of multiple sclerosis), and the report of positive clinical trial results for Myotrophin (produced by Chiron and Cephalon and intended for the treatment of amyotrophic lateral sclerosis) as events helping to support investor interest in the industry. Ann M. Thayer, "Market, Investor Attitudes Challenge Developers of Biopharmaceuticals," 16.

that period. The Institute for Biotechnology Information (IBI) estimated that more than $2 billion was raised in 1995 by approximately 61 offerings—a 155 percent improvement over the amount raised in 1994, making 1995 the second best year in the history of the industry. IBI also reported that $2.54 billion was raised in the first five months of 1996, at which point the markets began to cool.[52]

Bioworld reported that a total of $3.965 billion was raised from all sources in 1995, including $2.1589 billion from public offerings.[53] The Biotechnology Industry Organization (BIO) noted that the BioCentury 100 Indicators, a leading measure of market capitalization in the industry, had increased by 80 percent, reflecting an increase in the 1994 market capitalization of the 100 largest biotechnology companies.[54]

Industry analysts interpreted this success in the capital markets as evidence of a new maturity in the industry. Companies were improving their asset management and were learning, through creative partnerships with other companies, to produce new products more efficiently.[55] In addition, both capital markets and regulatory agencies had developed a more sophisticated understanding of the industry and its technical potential. One observer commented, "There may have been some overheating in [biotechnology stocks], but things now seem to be driven more by general macroeconomic issues for technology stocks and not something that is a fundamental issue about biotechnology."[56] Wall Street was pleased by the increasing rate of product approvals and the large number of drugs completing clinical trials, and the federal regulatory agencies appeared to be more at ease with the new technologies and their applications.[57]

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[52] IBI, "Mid-Year Cooling of Hot '96 Public Capital Markets for Biotechnology," *Strategic Developments in Biotechnology*, 6, no. 6 (July 1996): 1. In its most recent report on the industry, Ernst & Young estimates that more than $1.7 billion in public offerings occurred between July 1995 and June 1996, while secondary financing produced $3.4 billion. Kenneth B. Lee and Steven G. Burrill, *Biotech 97.*

[53] *Bioworld Biotechnology State of the Industry Report 1995* (Bioworld, 1995), 31.

[54] The Biotechnology Industry Organization, *Editors' and Reporters' Guide to Biotechnology 1996–1997* (citing Karen Berstein, "Performance Pays Off," Washington, D.C.: BioCentury, 2 Jan. 1996, 1).

[55] Lisa Piercey, "Flush with Cash, Industry Faces a More Stable Future," 1.

[56] Ann M. Thayer, "Market, Investor Attitudes Challenge Developers of Biopharmaceuticals," 16 (quoting Robert Gottlieb of Feinstein Partners, a consulting firm).

[57] "An Industry Coming of Age," in *BioWorld Biotechnology State of the Industry Report 1996*, 1.

Concerns within the health-care system about the use of new products and therapies may pose an obstacle to commercial success.

U.S. Health-Care System

FDA has improved its product review process and instituted innovations that have made it easier for the producers of new products to reach their markets. However, concerns within the health-care system about the use of new products and therapies may pose an obstacle to commercial success. The American health-care system has been transformed within the past few years by the concept of managed care, which integrates the delivery and financing of health-care services more closely than more traditional health-care delivery systems. While this integrated approach has been criticized recently for placing cost control ahead of quality care, managed care continues to be the predominant response to the problem of rapidly increasing costs.

The effect that managed care will have on the introduction of the new products and services offered by the biotechnology industry remains unclear, but many are concerned that it may become more difficult to secure industry support for new products. As one executive observed, "For new innovative drugs that fill unmet needs, the focus has shifted much more to having to demonstrate how your drug is cost effective."[58] In the words of another executive, "In most other industrial situations, everybody understands that technology has the effect that you can do more with less. The health-care system is very afraid of the costs of innovation. That's a very big subject that will stay with us and become much more important as the flow of new breakthrough products becomes larger."[59]

Tax Policies

The federal tax code contains provisions designed to encourage investments in new enterprises and corporate investments in research, but the biotechnology industry has found it difficult to claim the benefit of these provisions. Preferential treatment for capital gains income resulting from investments, particularly investments in start-up companies, has been difficult to achieve under existing laws and regulations. In addition, the companies themselves have had difficulty in claiming tax credits for research and new product development because few have had substantial revenues, let alone taxable net income.

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[58] Ann M. Thayer, "Market, Investor Attitudes Challenge Developers of Biopharmaceuticals," 16 (quoting James L. Vincent, CEO of Biogen).

[59] Ibid., 21 (quoting Henri A. Termeer, CEO of Genzyme and chairman of the Biotechnology Industry Organization).

Capital Gains Tax Incentives

As previously stated, the biotech industry depends mainly on equity investments for its funding, and it also makes use of stock options to provide incentives to its officers and employees. In recent testimony, an industry official indicated that "[a]pproximately 78 percent of biotechnology firms provide stock options to all of their employees."[60] For these reasons, the industry has actively supported legislation providing preferential treatment for capital gains.

A particular concern for the industry has been a 1993 provision excluding from taxation gains resulting from the sale of stock of certain small businesses.[61] The industry viewed the regulations issued by the Treasury Department in connection with this provision as severely compromising the intended effect of the legislation. The Treasury Department recently issued a notice of proposed rule making, offering amendments designed to ameliorate some of the antievasion restrictions imposed in the provision. In particular, the proposal provides further guidance concerning the circumstances under which a corporation could redeem *de minimis* amounts of stock without violating the antievasion rules.[62] Representatives of the biotech industry support the rule, but they also seek legislation that would make it much easier to claim the benefits of Section 1202.[63]

Research and Experimentation Credit

The research and experimentation credit provided by the federal tax laws was extended through May 31, 1997, and several new provisions were introduced to increase the number of companies able to claim its benefits.[64] However, the credit will expire shortly, and its provisions were not available during 1995 and 1996. Many biotechnology companies did not qualify for the credit in the past and, even in its amended form, it seems unlikely to benefit the industry now because of its limited life.

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[60] Testimony of Tom Wiggans, president and CEO of Connective Therapeutics, before the Senate Small Business Committee, 19 Sept. 1995, 4.

[61] 26 U.S.C. §1202.

[62] 61 *Federal Register* 28821, 6 June 1996.

[63] Comments of the Biotechnology Industry Organization regarding the IRS proposed "Rules Regarding Stock Redemptions to U.S. Treasury Department," 4 Sept. 1996.

[64] Small Business Job Protection Act of 1996, Public Law 104–188 §1204 (1996).

Orphan Drug Credit

Before January 1, 1995, companies conducting qualified clinical testing of certain "orphan drugs" (drugs for rare diseases or medical conditions) were entitled to a 50 percent tax credit for their expenses. Companies were unable to carry these credits forward to reduce taxes in later years. Since many biotechnology companies lacked current taxable income, they were unable to benefit from the credit. The orphan drug tax credit was extended for the period July 1, 1996, through June 30, 1997. For the first time, companies will be permitted to carry forward unused credits for up to 15 years following the year in which the credit is earned.[65] This new provision should benefit the industry, although the limited period of effectiveness is likely to discourage long-term corporate commitments to developing new orphan drugs.

Regulatory Environment

Regulation is a major factor influencing the development of the biotechnology industry and its international competitiveness, especially for products made from recombinant DNA technology. Health, safety, and environmental regulations affect both the cost and time needed to get biotech products to market and the profits. Other federal regulations, such as those relating to the cleanup of waste sites and to air and water quality, influence the development of the markets served by the bioremediation segment of the biotech industry.

The main regulatory constraints faced by the industry are (1) the necessity of securing approval from U.S. federal and state regulatory agencies (and from foreign countries) to test and market new products, and (2) the need to comply with safety requirements for recombinant DNA research and testing.

New biotechnology products are regulated under the same statutory and regulatory framework used for other food, drug, animal, plant, and chemical products. Because this framework involves several different agencies and has the potential for regulatory overlap and conflict, an effort was made within the executive branch to develop an integrated approach to regulating biotechnology products. This approach is reflected in the 1986 Coordinated Framework for the Regulation of

[65] Ibid., Public Law 104–188 §1205 (1996).

Biotechnology, which clarifies the areas of responsibility of the various federal agencies.[66] The principal responsibilities are shared by three agencies: FDA, the Department of Agriculture (USDA), and the Environmental Protection Agency (EPA). Table 13 outlines the responsibilities of each of these agencies.

In addition to regulating products, the U.S. government regulates the conduct of biotechnology research. The "NIH Guidelines on the Use of Recombinant DNA Molecules" seek to ensure that laboratory experiments on genetically engineered organisms pose no threat to human safety and the environment.[67] Researchers receiving federal funds must follow the guidelines, which have been widely adopted by the biotechnology research community. Finally, under the National Environmental Policy Act, any researcher who receives federal funds, or whose research is subject to federal regulations, may be required to prepare an environmental assessment to determine whether the research will result in a significant environmental impact.

The "NIH Guidelines on the Use of Recombinant DNA Molecules" seek to ensure that laboratory experiments on genetically engineered organisms pose no threat to human safety and the environment.

Food and Drug Administration

The Food and Drug Administration has broad powers to regulate new drugs, vaccines, diagnostics, cosmetics, foods and food additives, new animal drugs, and animal feed additives under the Federal Food, Drug, and Cosmetic Act. The biotechnology industry makes products regulated by four constituents of the FDA. Food products are regulated by the FDA's Center for Food Safety and Nutrition; new animal drugs and feeds are regulated by the Center for Veterinary Medicine; therapeutic drugs are regulated by the Center for Drug Evaluation and Research (CDER); and biologics by the Center for Biologics Evaluation and Research (CBER).[68]

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[66] "Coordinated Framework for Regulation of Biotechnology: Announcement of Policy and Notice for Public Comment," 51 *Federal Register* 23302–23393, Office of Science and Technology Policy, 26 June 1986.

[67] 59 *Federal Register* 34496, amended 59 *Federal Register* 40170, 60 *Federal Register* 20726, 61 *Federal Register* 1482, 61 *Federal Register* 10004. NIH recently revised the structure and role of its Recombinant DNA Advisory Committee with respect to recombinant DNA experiments involving human subjects. 61 *Federal Register* 59725, 22 Nov. 1996. This revision relinquished to FDA the committee's approval responsibilities of recombinant DNA experiments involving human gene transfer, while maintaining the committee's responsibilities for discussion of novel human gene transfer experiments.

[68] Biologics includes blood, vaccines, human tissues, and many drugs derived from living organisms.

Table 13. Federal Biotechnology Regulatory Framework

Regulatory Authority	Products Regulated
Food and Drug Administration	
Federal Food, Drug, and Cosmetic Act	Human drugs Human diagnostics Human foods and food additives Animal drugs Animal feed additives Cosmetics Color additives
Public Health Service Act	Human biologics
U.S. Department of Agriculture	
Virus-Serum-Toxin Act	Animal biologics Transgenic animal-health issues
Federal Plant Pest Act Plant Quarantine Act	Plants and micro-organisms that may be plant pests
National Environmental Policy Act	
Environmental Protection Agency	
Federal Insecticide, Fungicide, and Rodenticide Act	Microbial and plant pesticides, insecticides, and fungicides
Toxic Substances Control Act	Chemical and environmental uses of micro-organisms not covered by other authorities

Source: Office of Science and Technology Policy, Executive Office of the President, *Coordinated Framework for the Regulation of Biotechnology* (1986).

Food Regulation

FDA issued a policy statement in 1992, that explained its oversight of foods derived from new plant varieties, including varieties developed through genetic engineering.[69] FDA stated that engineered foods must meet the same stringent safety standards under the Food, Drug, and Cosmetic Act that apply to all foods. Noting that purveyors bear a legal duty to ensure that foods are safe and wholesome, FDA issued comprehensive scientific

[69] 57 *Federal Register* 22984, 29 May 1992.

guidance to help developers to meet their legal duty. Substances added to food through genetic engineering are required to undergo premarket review and approval by FDA as food additives, unless the substances are generally recognized as safe (GRAS). Substances that have been safely consumed as components of food or are substantially similar to such substances will be assumed to be GRAS and exempt from premarket clearance. FDA's guidance to industry focuses on (1) the safety of new substances in food and their digestibility and potential toxicity or allergenicity; (2) nutritional alterations or changes that affect processing, storage, or preparation of food; and (3) unintended changes in the composition of food, especially in regard to important nutrients, antinutrients, and toxicants. FDA requires that a food be labeled by its common or usual name, and significant alterations in the nutritional content of the food may necessitate a new common or usual name or other labeling to disclose the alteration. Labeling is also required if a new allergen is present in the food. It is prudent practice for developers to consult with FDA on safety and regulatory issues prior to market distribution. The agency has established informal procedures to facilitate industry-FDA consultations.

Regulation of Drugs and Biologic Products

The most important sources of regulation are CBER and CDER, which monitor all aspects of drug development, including safety and efficacy, labeling, marketing, and advertising, for the products under their control. CBER derives its regulatory authority from the Public Health Service Act, while CDER's authority lies in the Federal Food, Drug, and Cosmetic Act.

Industry Concerns with Drug Approval Process

Industry is particularly concerned with FDA's process for testing and reviewing new drugs for domestic marketing. This concern relates to both the time the process requires and its cost. Another concern is the relative speed of U.S. regulatory process compared with that of other industrialized countries with developing biotech industries.

The industry had expected biotechnology products to complete the FDA drug approval process more quickly than conventional drugs because of reduced safety and toxicity concerns. Industry reports estimated that the average development time for biopharmaceuticals, from isolation of a gene or monoclonal antibody to marketing approval of the product, would be 7 years, compared with 12 years for conventional drugs and traditional biologics.[70] However, although biotechnology products demonstrate fewer

[70] Brigittas Bienz-Tadmore and Jeffery S. Brown, "Biopharmaceutical and Conventional Drugs: Comparing Development Times." *BioPharm* 7, no. 2 (March 1994): 48.

safety and toxicity problems, they are experiencing the same development costs and regulatory complexity as other new products.

In addition, in recent years biotechnology products have experienced the same general increases in the cost and complexity of clinical trials as other products. According to industry sources, between 1989 and 1993, the cost of tests and related procedures per patient increased by 69 per-cent, 118 percent, and 51 percent for phase I, phase II, and phase III trials, respectively. In addition, the time between filing an investigational new drug (IND) application (to seek permission to conduct human clinical trials) and submitting an approval application has increased from two and a half years in the 1960s to six years in the 1990s.

Some evidence suggests that new U.S. biotechnology products are granted marketing approval in Europe before receiving approval in the United States, although many were developed and clinically tested in the United States. Between 1982 and 1992, 82 percent of all new biotech products were developed in the United States, 14 percent in Europe, and 4 percent in Japan. The United States also took the lead in clinical testing. Eighty-six percent of new biotech products were first tested in the United States compared with 14 percent in Europe.[71] However, Europe received the drugs first 75 percent of the time and, on average, one to two years sooner than the United States.

Some evidence suggests that new U.S. biotechnology products are granted marketing approval in Europe before receiving approval in the United States.

A survey presented at the 93rd annual meeting of the American Society for Pharmacology and Therapeutics showed that through early 1992, 93 monoclonal antibodies had been approved in Europe, compared with only 8 in the United States. Forty-two vaccines had been approved in Europe, 8 in the United States. By mid-1992 there had been 64 European approvals of recombinant DNA products and only 21 U.S. approvals.[72] According to industry sources, approximately 100 anticancer agents have been approved over the past 30 years; less than 50 percent are available in the United States, but more than 60 percent are available in Japan and Germany.

[71] Kenneth I. Kaitin and Jeffery S. Brown, "A Drug Lag Update: White Paper on Four Areas of Relevance to New Drug Development" (Boston, Mass., 1994), 12.

[72] George B. Rathman, "Regulatory Problems Are Slowing Approvals of Biotechnology Drugs" (speech given at the Pharmaceutical Research and Manufacturers of America, January 1995).

A further industry concern had to do with FDA's regulation (and frequent restriction) of the exportation of unapproved drugs to foreign countries. FDA's approach to this issue, coupled with the apparent delays in approvals of new products, was said to have made it more effective for biotechnology companies to manufacture and market their innovative products overseas than in the United States.

Recent FDA Reforms to Biotech Drug Regulation

In the past four years, FDA has taken a number of steps to address these concerns. As a part of the Clinton administration's Reinventing Government Initiative, FDA has proposed six different reforms aimed at protecting public health through innovative, common-sense oversight of industry activities. One of FDA's top priorities has been to reduce product review time while maintaining high standards of safety and effectiveness. FDA has expanded access to promising therapies and has set up a process of accelerated approval for drugs developed to treat serious or life-threatening diseases. New programs such as Treatment IND (TIND) give seriously ill or dying patients access to therapies before they are approved for marketing, while the "parallel track" program provides HIV-infected patients who are unable to join controlled trials access to experimental drugs.[73] In addition, Congress provided FDA with additional resources to expedite drug and biological reviews without sacrificing quality by enacting the Prescription Drug User Fee Act, which permitted the agency to assess fees for its regulatory work.

One of FDA's top priorities has been to reduce product review time while maintaining high standards of safety and effectiveness.

In April 1995, FDA announced a complex set of proposals to "reinvent" drug and medical device regulation. These proposals included the following:

- Allowing manufacturers of drugs and products made from biologic materials to change their manufacturing processes without FDA preapproval when the risk was negligible.
- Permitting manufacturers of biological drugs to begin producing new products in pilot facilities in order to lower their start-up costs and bring new drugs to market more quickly.
- Allowing greater flexibility in the labeling of biological products.
- Eliminating special requirements for insulin and antibiotics manufacturers.

[73] Statement of David Kessler, Commissioner of Food and Drugs, Committee of Labor and Human Resources, U.S. Senate, 6 Apr. 1995.

- Exempting certain low-risk medical devices from premarket review.
- Exploring the use of outside organizations to review low- to moderate-risk medical devices.
- Speeding the review of devices by charging user fees.
- Committing to strict performance goals for such reviews.
- Working to harmonize international standards for the review of drugs and medical devices.[74]

In November 1995, the Clinton administration announced a reinvention initiative intended to streamline the regulation of biotech drugs used for therapy.[75] The proposed initiative is expected to save biotechnology companies millions of dollars and to cut drug development time by months without diminishing drug safety and effectiveness. The initiative calls for eliminating differences between the regulatory requirements imposed by CBER and CDER on "well-characterized" biotech drugs—a definition expected to include most biotech drugs. The report includes the following proposed initiatives:

- Eliminate the requirement that manufacturing facilities be separately licensed.
- Eliminate the policy under which CBER evaluates and releases individual lots of biotech drugs after the drugs have been approved.
- Replace with 1 form the 21 approval application forms for biotech drugs, blood, vaccines, and other drugs.

For all biologicals, including biotech drugs regulated by CBER, FDA will

- Eliminate the requirement that promotional labeling be approved prior to the launch of a biological and for the 120 days following its approval.

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[74] "Reinventing Drug and Medical Device Regulation," *FDA Backgrounder*, 5 Apr. 1995.

[75] "Reinventing the Regulation of Drugs Made from Biotechnology," U.S. Food and Drug Administration, Nov. 1995.

- Decide within 30 days whether newly submitted information supports the initiation or continuation of a human investigation that the agency has put on hold.

- Permit a corporation to designate more than one person to act as a "responsible head" in dealings with CBER.

More recently, FDA announced a plan for improving the regulatory framework for products derived from cells and tissues. Recognizing the rapid development of therapies involving the manipulation and use of human cells and tissues, HHS secretary Donna Shalala said, "Now that science is providing even more new ways of using tissues, FDA has developed an innovative regulatory approach to allow these novel products to benefit patients as soon as possible."[76] Under the new framework, the level of regulation would be proportionate to the degree of risk arising from the processing of the tissue. Little or no regulation would be imposed on some products, such as cells and tissues removed from and transplanted into the same person in a single surgical procedure. The degree of oversight would increase with potential risks. For example, tissues that were processed to alter their biological or functional characteristics would be required to undergo controlled clinical trials and premarket approval to demonstrate their safety and effectiveness.

The proposed changes are the most significant reforms to be undertaken by the FDA for regulating biotech drugs. As part of this effort, FDA committed itself to eliminating the backlog of overdue drug applications.[77] It also undertook to reduce or eliminate the requirement for companies to provide a manufacturing supplement to their original approval application for minor changes in the content or manufacturing process of a drug or biological. FDA intends to specifically reduce the number of supplements for biologicals by 50 percent.

Administrative burdens on the export of drugs have been eased under the provisions of the Federal Food, Drug, and Cosmetic Act and the Food and Drug Administration Export Reform and Enhancement Act of 1996.[78] The laws make it easier to export drugs authorized for marketing in certain foreign countries even if they are not authorized for sale in the United States. FDA is also working closely with other countries to harmonize the

[76] "Reinventing the Regulation of Human Tissue," *HHS News*, 28 Feb. 1997.

[77] Ibid.

[78] Public Law 104–134, codified at 7 U.S.C. §§ 2101 et seq.

Information collected by FDA on its internal operations shows that substantial progress has been made in improving the speed with which new drugs are reviewed.

regulatory requirements for drugs and to develop international standards for devices, foods, and veterinary medicine products.

Information collected by FDA on its internal operations shows that substantial progress has been made in improving the speed with which new drugs are reviewed. FDA's study indicates that in 1995, 82 new drugs were approved in a median time of 16.5 months, compared with 62 new drugs approved in 19 months in 1994. Of the 1995 approvals, 28 were for new molecular entities (NMEs) approved in a median time of 15.9 months, compared with 22 NME approvals in 17.5 months in 1994. During 1995, 15 "priority" drugs were approved in a median time of 6 months, compared with 17 priority drugs approvals in 15 months in 1994.[79] Industry sources also indicate that the time for product approval has decreased—from an average of 2.3 years in the early 1990s to 1.6 years in 1995.[80]

FDA has also offered evidence showing that its processes are at least keeping pace with those of foreign regulatory agencies. FDA performed its own analysis of a group of new drugs launched between January 1990 and December 1994. The study, which focused on drugs approved in both the United States and another country, indicated that "[i]n every case . . . , the U.S. was the first to approve more of the drugs that eventually became available in both countries."[81]

The edge over the United Kingdom was slight, with 30 of 58 drugs approved first in the United States. With respect to Germany, 31 of the 44 drugs approved by both countries were approved first in the United States. With respect to Japan, the United States approved 10 of the 14 drugs first. The study also looked at drugs approved in other countries but not in the United States. David Kessler, commissioner of Food and Drugs, stated that "only a small handful" offered therapeutic advances over existing products or could be used to treat conditions for which no therapy now exists.[82]

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[79] "FDA: A Record of Accomplishment," *FDA BG*, 1 May 1996.

[80] Ann M. Thayer, "Market, Investor Attitudes Challenge Developers of Biopharmaceuticals," 16 (citing data from the Pharmaceutical Research Manufacturers' Association).

[81] Statement by David A. Kessler, Commissioner of Food and Drugs, before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies of the Committee on Appropriations, U.S. House of Representatives, 12 Mar. 1996, 4.

[82] Ibid.

Environmental Protection Agency

EPA's effect on the domestic industry is complex. On one hand, it has regulatory authority that it intends to use to regulate aspects of the industry's activities and that industry fears will result in new regulatory burdens. On the other hand, its responsibilities for overseeing the cleanup of polluted sites give it the power to create or enhance important new markets for the industry.

Industry Response to Proposed EPA Rules

On the basis of its regulatory authority under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA has proposed several initiatives for regulating different types of biotechnology products. The biotechnology industry has generally supported these efforts but has offered suggestions on how to improve several aspects of the proposals.[83]

Pursuant to FIFRA, pesticides may not be sold or distributed unless they are registered with EPA (or exempted from registration). Such registration can occur only when it is shown that the product, "when used in accordance with widespread and commonly recognized practice, . . . will not generally cause 'unreasonable adverse effects on the environment.'" The FFDCA gives EPA the authority to set tolerances for (or exempt from such tolerances) pesticide residues in raw agricultural commodities and to regulate the presence of such residues in processed foods. In November 1994, EPA published a proposal for addressing "pesticidal substances produced by plants" pursuant to FFDCA.[84]

EPA proposed that under FIFRA, it would regulate "those plant-pesticides that have the greatest potential for new environmental exposures and adverse effects to nontarget organisms." Industry representatives, although generally supportive of EPA's approach, offered suggestions to

[83] Comments of the Biotechnology Industry Organization on EPA's proposed "Policy on Plant Pesticides Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act," 23 Feb. 1995; Comments of the Biotechnology Industry Organization on EPA's proposed "Rule to Regulate Certain Microbial Products of Biotechnology under the Toxic Substances Control Act," date unspecified.

[84] "Proposed Policy, Plant Pesticides Subject to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act, (FFDCA)," 59 *Federal Register*, 23 Nov. 1994.

improve the rule. The part of the proceeding related to the agency's authority under FFDCA may have been affected by recent passage of the Food Quality Protection Act, which alters some of the agency's responsibilities in the area of food purity.

Another EPA initiative was made under TSCA, which authorizes the agency to acquire information on chemical substances and mixtures of chemical substances in order to identify and regulate potential hazards and exposures. In a proposed rule published in September 1994, EPA suggested that micro-organisms should be regarded as new chemical substances under TSCA.[85] EPA proposed that this TSCA authority provided the basis for the agency to screen micro-organisms before they are introduced into commerce and set out proposed notification procedures, as well as exemptions from this new procedure, for certain micro-organisms.

Industry representatives expressed a number of concerns about the proposal, although their comments were generally supportive. One concern was that EPA "focused too much on genotypic changes that can be brought about by genetic engineering and neglected whether these can bring about distinct microbial phenotypes that may require health and safety review. The central focus as to newness should be on whether there has been an intergeneric transfer of a new phenotypic trait." Industry was also concerned because EPA's proposal would set up a procedure to regulate certain R&D activities. While recognizing that "some research activities raise scientific uncertainties and may require EPA review," the industry representatives urged that the agency bore "a substantial burden" to justify its proposal in view of an exemption for certain research activities contained in TSCA.[86]

EPA's broad responsibilities for cleaning up hazardous wastes sites give rise to important market opportunities for companies offering bioremediation technologies and services.

Market for Bioremediation Technologies and the Superfund Program

EPA's broad responsibilities for cleaning up hazardous wastes sites under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA) give rise to important market opportunities for companies offering bioremediation technologies and services. EPA has identified 35,000 potentially hazardous waste sites and determined that 1,400 require immediate remediation under the CERCLA Superfund program. EPA estimates that more than 5,000 facilities will require corrective action

[85] Proposed Rule, 59 *Federal Register* 45526, 1 Sept. 1994.

[86] Section 5(h)(3) of TSCA permits manufacturers to manufacture or process small quantities of materials for the purposes of research and development.

under RCRA and that the costs of these actions will be between $7 billion and $42 billion.

Many in the biotechnology industry believe that bioremediation technologies offer the most cost-effective means for accomplishing remediation under these programs. But the application of bioremediation technologies within the CERCLA Superfund and RCRA programs has not proceeded as far or as fast as the industry had hoped it would. A primary reason for the limited use of bioremediation is that its effectiveness depends on many site conditions. Despite the limitations, EPA has selected bioremediation for 69 source control (primarily soil) remedies at sites on the CERCLA National Priority List. Bioremediation accounts for 10 percent of all treatment technologies selected for source control. EPA has also selected in-situ bioremediation to clean up groundwater at 15 sites.

The industry has pointed to several aspects of the Superfund program and other cleanup programs that may discourage use of bioremediation technologies. For example, CERCLA provides for the selection of a specific remedy for each site through a complex process leading to a record of decision. Industry believes that this procedure creates a predisposition to use better known technologies and makes it difficult to consider new technologies that may emerge after the record of decision has been completed. However, EPA asserts that it has taken several initiatives to promote bioremediation and to inform site managers of the technology's capabilities.

The industry is also concerned about the use of extremely demanding "applicable or relevant and appropriate requirements" (ARARs) to judge the results of a cleanup. ARARs discourage the use of innovative technologies by posing the threat of further treatment if exacting standards are not met. EPA and the states may require responsible parties to use a more traditional remedy if a new technology fails to meet the cleanup standards. EPA offered some regulatory relief for conducting bioremediation treatability studies under the 1994 Treatability Study Sample Exclusion Rule. The rule increased the quantity limits of contaminated media for treatability studies that may be conditionally exempt from RCRA permitting and manifest requirements over a two-year period, allowing an additional two years to conduct bioremediation studies.

EPA has initiated proceedings to reexamine its approaches to its cleanup responsibilities, and many within the biotechnology industry hope the

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review will lead to more opportunities for using bioremediation technologies in the RCRA and Superfund programs. EPA proposals relate to the appropriate strategy for corrective actions and to the management of hazardous contaminated media under RCRA.[87] The proposals appear to reflect a broad commitment to rethinking the agency's approach to corrective actions under all of its statutory authority.

The biotechnology industry, through its trade association, BIO, filed comments that supported EPA's proposals and that focused primarily on the need to promote innovative remediation technologies. The comments pointed out a number of specific aspects of EPA corrective- action practices that might be modified to eliminate disincentives for the use of innovative technologies.

Possible Regulatory Gaps and Overlapping Regulatory Oversight

Under the 1986 Coordinated Framework for Regulation of Biotechnology, the responsibility for regulatory oversight for releases of genetically modified animals and fish is unclear. As a result, review of transgenic animals and fish are dealt with on a case-by-case basis through interagency consultations among FDA, USDA, and EPA.

Some biotechnology products are subject to regulation by several federal agencies, although interagency procedures are in place to coordinate reviews to reduce duplication and minimize delays. For example, transgenic plants expressing a pesticide are regulated by both USDA and EPA. If the plant is edible, it is also regulated by FDA. Transgenic animals used as living factories to produce drugs, biologics, or other products are subject to review by FDA, USDA, and EPA (if industrial products are produced).

Department of Agriculture

USDA's Animal, Plant Health, and Inspection Service (APHIS) regulates animal vaccines under the Virus-Serum-Toxin Act, plant pests under the Plant Pest Act, and genetically engineered plants under the Plant Quarantine Act. Its Food Safety and Inspection Service has regulatory oversight over genetically engineered livestock intended for human consumption. As USDA has gained experience in reviewing applications, it has gradually streamlined its regulations. In August 1995, APHIS

[87] EPA, "Corrective Action for Releases from Solid Wastes Management Units at Hazardous Waste Management Facilities," 61 *Federal Register* 19, 432, 1996; EPA, "Requirements for Management of Hazardous Contaminated Media (HWIR-media); Proposed Rule," 61 *Federal Register* 18, 780, 1996.

published proposed procedures stating that it would allow field testing of most genetically engineered plants to occur following notification rather than after the granting of a permit. Pursuant to this proposal, if APHIS does not object within 30 days of notification, the test can proceed.[88] The proposal has not been finalized.

USDA's authority intersects in many areas with those of FDA and EPA. FDA has broad authority to regulate the introduction of new food crops, whether conventionally grown or genetically modified. Specifically, FDA requires that genetic modifications that substantially alter the nutritional value of the host, use genetic material from outside the traditional food supply, or use known allergens be subjected to strict premarketing testing, regulatory oversight, and labeling requirements. FDA also has the authority to order questionable products off the market.

USDA and EPA both have performance standards for the development of pesticides, herbicides, and genetically modified test crops. They control the introduction of any potentially hazardous materials into the environment. Ag-biotech products awaiting FDA clearance include three delayed-ripening tomatoes, a virus-resistant squash, a beetle-resistant potato, and herbicide-resistant cotton and soybeans.

The ag-biotech industry is making progress toward meeting these regulatory challenges. And the regulatory agencies are generally striving to establish standards that assess genetically engineered organisms and novel foods by the same criteria used for foods modified by conventional methods. This approach is grounded on the beliefs, also reflected in the framework for federal biotechnology regulation, that crop and animal breeding is safe and that organisms modified through biotechnology do not pose unexpected risks. This premise is more widely accepted in North America than in Europe, where members of the Green movement take an opposing stance. The favorable North American climate could change, however, if unexpected health, environmental, or socioeconomic risks result, leading to a reevaluation of regulatory requirements.

Patent and Trademark Office and Intellectual Property Rights

The ability to control discoveries through the establishment of intellectual property rights is fundamental to the competitiveness of the biotechnology industry. As companies bring more products to market and revenues increase, these rights, and the prompt resolution of disputes concerning them, will become increasingly important. The Patent

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[88] 60 *Federal Register* 43567, 22 Aug. 1995.

and Trademark Office (PTO) of the Department of Commerce plays a pivotal role in establishing intellectual property rights through its decisions concerning the patentability of biotechnology products and processes under U.S. law. The unique characteristics of biotechnology research and product development have raised some special issues under the patent laws. The recent resolution of several of these issues seems likely to prove helpful to the patentability of genetic information.

PTO's Changes to Its Utility Guidelines

In June 1995, PTO established new guidelines on the means of establishing the "utility" of a biotechnology invention—one of the fundamental requirements for issuance of a patent. The biotechnology industry had expressed concern over the high expenses associated with human clinical trials, which were previously required in many cases to demonstrate utility. The new guidelines eased the evidentiary burden of the patent applicant by indicating that animal and in vitro studies could demonstrate utility without clinical tests involving human subjects. The guidelines are expected to streamline the patenting process.[89]

Biotechnology Process Patent Act

The biotechnology industry had expressed concern about the standards used to evaluate the patentability of biotechnology processes. In a 1985 case, *In re Durden*, involving the patentability of a chemical manufacturing process, the United States Court of Appeals for the Federal Circuit held that a process could not meet the legal requirement of being "unobvious" simply because it involved a starting material or a resulting compound that was unobvious.[90] Many products of the biotechnology industry were produced through the recombinant expression of known proteins, and the resulting protein might not be patentable because it occurred naturally. However, the company might seek patents for both the starting product (e.g., a recombinant gene or host cell) and for the process used to produce the end product. While the patent for the starting product might be granted, the industry felt that claims for the patentability of processes were being unfairly denied on the basis of *Durden*—by characterizing the recombinant expression of the protein as an obvious process.

The lack of a patent covering the process by which biotechnology products were produced could be particularly significant when companies faced import competition. The foreign product might be made using the

[89] Kenneth B. Lee and Steven G. Burrill, *Biotech 96.*

[90] *In re Durden*, 226 USPQ 359 (Fed. Cir. 1985).

domestic company's starting materials and production process, but the domestic patent on the starting material would be of no help in preventing the sale of the resulting product. The Process Patent Amendments Act, contained in the Omnibus Trade and Competitiveness Act of 1988, gave process patent holders the right to exclude imports and sales or use of a product made abroad using a domestically patented process. However, the biotech companies were not generally in a position to use this remedy because of the lack of a process patent.[91]

In November 1995, President Clinton signed into law the Biotechnology Process Patent Act, P.L. 104-41, which amended the patent law to enhance the protection for biotechnology processes.[92] The act focuses on the question of the obviousness of a biotechnology process, providing a fairly concrete standard for when such a process should be deemed unobvious. Under this standard, a biotechnology process (a term defined by the law) is unobvious if it makes or uses a composition of matter that is novel and unobvious. Two recent decisions by the federal circuit court have also emphasized that the *Durden* ruling should not result in the automatic rejection of claims that a generally known process using new materials is unobvious.[93] On the basis of the guidance provided by the new legislation and recent judicial decisions, PTO has issued guidelines for considering process claims involving the making or use of unobvious products.

Foreign Competitors

The rapid growth in industry alliances and the industry's maturing relationship with capital markets are the hallmarks of America's global leadership in biotechnology. The creation of multidimensional research partnerships has been critical to achieving commercialization of products, while the industry's recent success in introducing new products to market has provided a more objective basis for access to capital. Approximately one-half of all biotech companies worldwide are based in the United States, and these companies far outpace their competitors in innovation. In 1995, U.S. companies received 81 percent of the 150 genetic engineering health-care patents issued in the United States. U.S. companies received 122 genetic engineering patents, while companies from the

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[91] *Amgen, Inc. v. U.S. International Trade Commission*, 14 USPQ 2d 1734 (Fed. Cir. 1990).

[92] Codified at 35 U.S.C. § 103(b).

[93] *In re Ochai*, 71 F 3d 1565 (Fed. Cir. 1995); *In re Brouwer*, 37 USPQ 2d 1663 (Fed. Cir. 1995).

European Community received 11, followed by Japanese companies, which received 6.[94]

European biotech and pharmaceutical firms, like their American counterparts, are building alliances and seeking to improve their access to financial markets. While the U.S. industry is substantially larger and more dynamic by most measures, the European industry has begun to grow larger and stronger in important ways. With the support of the larger drug companies and the European Union (EU), centers of research excellence near universities in Britain, Benelux, France, and Germany are being established. Also, larger pharmaceutical firms are becoming increasingly interested in linking up with small biotech firms.

The European Union constitutes the world's largest accessible market for medical products.

The European Union constitutes the world's largest accessible market for medical products, boasting 370 million consumers and $50 billion in annual drug sales. To help European firms tap this unparalleled market, the EU recently created the European Agency for the Evaluation of Medicinal Products (EMEA). EMEA will coordinate the approval and regulation of new medical products across national borders. Based in London, the agency has developed a compulsory, centralized procedure for approving medical products developed from biotechnology. In the past, if a firm wanted to launch a new product in the European market, it had to file a separate application for approval in each of the European Union's 15 countries. According to one expert, it could take a new product five or six years to penetrate the market under this system. In contrast, under the new protocol, a firm must submit only one application per product, and the application is reviewed within 300 days of receipt. If approved, the product can be marketed throughout the European Union.

In this new environment, the European industry is beginning to increase in both size and financial strength. A recent Ernst &Young report revealed that the number of biotechnology firms in Europe increased from 486 in 1994 to 584 in 1995, while the number of employees increased 7 percent, from 16,100 to 17,200.[95] The report indicates that for the same period corporate revenues improved by 20 percent (to $1.522 billion), spending on R&D increased by 21 percent (to $795 million), and the industry's total net loss decreased by 49 percent (to $189 million).

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[94] Pharmaceutical Research and Manufacturers of America, "Biotechnology Medicines in Development" (Washington, D.C., 1996).

[95] Ernst & Young, *European Biotechnology 96: Volatility and Value* (1996); M. Ward, "European Entrepreneurs Earn $1.5 billion in 1995," *Nature Biotechnology* 14 (May 1996): 565.

A number of firms, particularly in the United Kingdom, raised money through public offerings (on the London Stock Exchange, other European markets, or the NASDAQ), and the industry as a whole raised $394 million from all sources of capital. Favorable results from clinical trials of several British companies aided companies there in their financing efforts, and the market capitalization of biotech companies listed on the London Stock Exchange increased by 150 percent during the year.

Significant differences between the European and American industries remain, however. The Ernst & Young report showed that in 1995 there were twice as many start-up companies in the United States as in Europe (although the rate of new company formation appeared to be on the increase in Europe). R&D in the U.S. companies was funded at 10 times the European level and, because of the U.S. industry's lead in product development, revenues were 9 times those of the European companies.

Some of the most interesting differences described in the report relate to the companies' commercial objectives. In the United States, 42 percent of the companies chose to focus on therapeutic products requiring intensive R&D, compared with only 19 percent in Europe. Setting aside the U.K. companies, the market focus of the European companies tended to be much more service oriented; 18 percent concentrated on the role of industry supplier and another 18 percent focused on contract manufacturing or research services. Analysts link this difference to the relative ease with which American companies can access capital markets compared with the European companies. One writer observed that "restricted capital raising opportunities mean that most European firms have little choice but to try and balance the books. This means, in general, they cannot afford to invest in risky, yet potentially more rewarding, opportunities."[96]

To date, there have not been any significant product approvals in Japan. The Japanese biopharmaceuticals industry is years behind that of the United States; there are fewer than 10 independent biotech companies in Japan. However, demand for biotechnology-derived products in Japan is substantial. Japan is the second largest pharmaceutical market in the world; it accounts for 19 percent of the world market for ethical (patented, not generic) drugs, with sales in excess of $37 billion.[97] In addition,

[96] "European Bioscience Firms Add Value in Volatile Market," *BioBusiness*, 20 (April 1996): 3.

[97] European Parliament, Directorate General for Research, "Working Paper: American and Japanese (Bio)Pharmaceutical Presence in Europe" (1996), (citing OECD health data, 1992).

increased competition in its home market and several other factors are causing the Japanese industry to increase its investment in research and to expand its participation in foreign markets.[98] These new directions seem likely to increase the role of the Japanese industry in the evolution of the international biotechnology industry.

Trade Issues

The net U.S. trade balance in biotech-related products, royalties for technology licenses, and payments for contract R&D services is clearly positive.

The net U.S. trade balance in biotech-related products, royalties for technology licenses, and payments for contract R&D services is clearly positive. Most biotech-derived products on the market are of U.S. origin. For example, the top-selling biotech-derived biopharmaceuticals, the largest market component of the biotechnology industry, were developed by U.S. companies and are largely produced in the United States for export (see table 7).

Access to global markets is essential to obtaining returns on investment and maintaining the competitiveness of the American biotechnology industry. Trade in biotechnology is in its infancy, and the performance of biotech-derived products outside of health care is largely untested. The main barriers to trade in biotechnology products are nontariff barriers, including insufficient protection and enforcement of intellectual property rights and health, safety, and environmental regulations.

Tariffs and import quotas on biotech-derived products are generally not significant barriers in the U.S. industry's major export markets; tariffs and quotas will decline further in importance as tariff cuts, negotiated under the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) and the North America Free Trade Agreement (NAFTA), are phased in over a 5- to 15-year period. The United States, the European Union, Japan, Canada, and Korea agreed under the Chemical Tariff Harmonization Agreement to reduce pharmaceutical tariffs to zero and other chemical tariffs to between 0 to 6.5 percent. Other import barriers that often arise to replace falling tariffs, such as import quotas, will be replaced by tariffs and subject to reduction commitments.[99]

Many American biotechnology companies consider the inadequacy of foreign protection for biotechnological and pharmaceutical inventions to

[98] Ibid.

[99] Executive Summary on the results of the GATT Uruguay Round of Multilateral Trade Negotiations (The White House, Washington, D.C., 1993) 2.

be the most serious nontariff trade problem. This issue is discussed in detail in a later section.

Safety and Environmental Regulations

Products of biotechnology are all subject to health and safety inspection, certification, or marketing approval. Differences among national regulatory systems can delay or prevent the introduction of biotech-derived products in foreign markets. Such differences have not posed significant new hurdles for foreign approval of U.S. biopharmaceuticals. National health authorities have been gaining experience in reviewing biopharmaceuticals since the first products were developed in the early 1980s and, as noted earlier, some biotechnology companies have reported that marketing approval times are faster in Europe than in the United States.[100]

However, differences in national health, safety, and environmental regulations for biotechnology products are particularly important for agricultural products. Even though new biotech-derived foods and agricultural products are rapidly approaching commercialization (see tables 8 and 9), some countries do not have regulatory policies in place. Disagreement among EU nations on the labeling of genetically engineered foods and seeds delayed the European Commission's novel food and seeds directives.[101] Some countries, including Germany, Austria, Denmark, and Sweden, favored strict labeling of all genetically engineered foods, while other countries did not. The European Union's parliament and council of ministers voted in January 1997 to accept a conciliation proposal on the labeling of genetically modified foods and food ingredients under the Novel Food Directive. The regulation will be effective in May 1997 and will require labeling of products that consist of living genetically modified organisms and foods that are no longer equivalent to existing foods.

The European Commission is also rewriting its directives on the contained use and environmental release of genetically modified organisms. Those directives are widely held by industry and regulators to be overly restrictive.[102] All EU nations are party to a European Council directive

[100]"Should the FDA Emulate Europe's EMEA?," *BIO/TECHNOLOGY* (July 1995): 636.

[101]"Novel Food Regulation Set for July," *Biotechnology Business News*, 23 June 1995; "More Delays for EU Seed Legislation," *Biotechnology Business News*, 31 (May 1995).

[102]"EU Plans to Streamline GMO Regulations," *BIO/TECHNOLOGY* (September 1994): 864.

entitled the "Deliberate Release of Genetically Modified Organisms," which governs field trials of plants and microbes and the marketing of products made from genetically modified organisms for subsequent release into the environment, and to the European Council directive entitled the "Contained Use of Genetically Modified Microorganisms." Proposed changes to these directives would make it easier to introduce genetically modified organisms or products derived from them by streamlining approval requirements and ensuring that the classification of risk categories for such organisms are appropriate.

Ag-biotech products will also face social and economic trade barriers. Resistance from consumers may affect potential markets. While biopharmaceutical products find ready acceptance in foreign countries, it remains to be seen whether consumers will accept genetically engineered foods.

According to national polls, novel foods have a higher degree of acceptance in the United Kingdom and France than in Germany, where a recent study reported that 80 percent of respondents would not buy genetically engineered foods.[103] Many countries have agricultural trade policies, including high quotas and tariffs, that restrict foreign imports and protect the livelihood of farmers. Products that enhance agricultural productivity could swell commodity surpluses and increase government support payments to farmers.

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The United States has an enormous stake in how foreign governments regulate agricultural biotechnology products. One example relates to American exports of soybeans to European markets, valued at $1.6 billion a year. A group of countries, led by Denmark, opposes the importation of soybeans produced from seed genetically engineered to tolerate the Roundup™ (glyphosate) herbicide. The countries demand that the products be clearly labeled before importation is allowed. A mandate to label genetically engineered crops would require segregation of the variety throughout the food chain, imposing costs so high that it is unlikely that genetically engineered crops could be introduced.[104] The "Roundup Ready™ Soybean" was approved by FDA, USDA, and EPA in 1994. Monsanto planned to introduce it to U.S. farmers in 1995. The

[103] "German Consumers Skeptical about Novel Foods," *Biotechnology Business News*, 18 Aug. 1995.

[104] Council for Agricultural Science and Technology, "Labeling of Food Plant Biotechnology Products." Issue Paper (July 1994); Karen Bernstein, "Contemplating Agbiotech's Future," *BioCentury*, 4 Dec. 1995.

soybean was expected to account for about 10 percent of the 1996 U.S. soybean crop, with which it would be mixed.[105]

Political Barriers to Trade: The Case of BST

Ag-biotech products will also face political trade barriers, as the case of recombinant bovine somatotropin (BST) demonstrates. In November 1993, after extensive testing, FDA approved BST, a growth hormone that enhances milk production in cows, for use in the United States. BST is now used in about 30 percent of dairy cows in the United States.[106] The European Union has had a ban on the use and marketing of BST since 1990. Even though the European Union's Committee on Veterinary Medicinal Products found in 1993 that BST satisfies the essential authorization criteria of safety, quality, and efficacy, the European Union has imposed a moratorium on use of BST until 2000.[107] The decision was influenced by concerns that BST use would increase surpluses of dairy products, causing farmers to reduce dairy herds and thereby increasing the European Union's already massive beef stocks. Both impacts would swell the costs of the European Union's Common Agricultural Policy which pays farmers for surplus milk and beef. In a concession to BST producers, the European Union agreed to allow limited test trials under veterinary supervision to proceed in countries that permit the use of BST to enhance milk production in cows.

The United States is concerned that the European Union's decision to withhold BST from the market could set a precedent. The United States government continues to pursue a solution with the European Union in bilateral talks. To avoid similar cases in the future, the United States is seeking harmonized, science-based regulations for biotech food products in the Codex Alimentarius Commission, a joint body of the World Health Organization and the Food and Agriculture Organization. The commission is recognized by the World Trade Organization as the authority on food standards for international trade. It was reported in July 1995, however, that the commission, at the request of the European Union, had delayed consideration of BST for two years. The most recent battle over BST in Europe took place in mid-1996, when the European Commission rejected a request from Eli Lilly & Co. to include BST in the list of substances that may be used in veterinary medical products intended to treat

[105]"Biodiversity: U.S. Mutant Soybeans Targeted at Jakarta Meeting," *Inter Press Service*, 7 Nov. 1995.

[106]"Wider Use of Cow Drug Is Reported," *New York Times*, 1 Feb. 1995.

[107]"EU Agrees on Patents but Nixes BST for 5 Years," *BIO/TECHNOLOGY* (March 1995): 212.

food-producing animals. This action reaffirmed the European Union's position on BST.[108]

Biodiversity Treaty

The purpose of the United Nations Convention on Biological Diversity ("the Biodiversity Treaty"), signed at the Earth Summit in Rio de Janeiro in 1992, is to promote the conservation and sustainable use of the earth's biological diversity and the fair and equitable sharing of benefits arising from the use of genetic resources.[109] The United States initially opposed the treaty, in large part because of concerns about wording on technology transfer, intellectual property rights, and biosafety.[110] However, after clarifying its positions in interpretive statements on these issues, the United States signed the treaty in 1993.[111] The biotechnology industry supported that decision and has participated actively in the subsequent proceedings under the treaty.[112]

Proceedings under the treaty have focused on two principal issues—the treatment of genetic resources and the safety of biomaterials. The first issue involves questions about the compensation to be paid by firms in industrialized countries for using genetic resources in developing countries to create products to be patented and sold in global markets. The United States has supported the principle that benefits should flow back to the countries that provide access to their genetic resources.[113] The benefits could include monetary compensation, training, cooperative work programs, and improved access to information. The United States

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[108] *BioBusiness*, 24 May 1996.

[109] The Earth Summit was organized by the United Nations Conference on Environment and Development (UNCED). The Biodiversity Treaty came into force on December 29, 1993, and has been ratified by 134 countries. President Clinton signed the treaty on June 4, 1993. The Senate has not given its advice and consent for ratification. The United States is not entitled to a vote but has participated as an observer to international proceedings under the treaty.

[110] "U.S. Refuses to Ratify Rio Treaty on Biodiversity," *Genetic Engineering News* (15 June 1992): 12.

[111] "Message from the President of the United States Transmitting the Convention on Biological Diversity with Annexes," Treaty Document 103-20 (U.S. Government Printing Office, Washington, D.C., 1993).

[112] "Administration Gets High Marks on Interpretation of Biodiversity Treaty," *Biotechnology Newswatch*, 6 Dec. 1993; "Biotech Helps Salvage Biodiversity Treaty," *BIO/TECHNOLOGY* (August 1993): 878; "Biotechnology Industry Endorses Administration Interpretation of Treaty," *Daily Report for Executives*, 26 Nov. 1993.

[113] "Message from the President of the United States," Treaty Document 103-20.

has maintained that the most effective way to achieve these objectives is through contracts between the developing countries and the firms using the genetic resources. Some countries have already entered into agreements with U.S. government agencies and pharmaceutical and biotechnology firms to provide access to their genetic resources under a benefit-sharing arrangement. Adequate protection for intellectual property rights in these agreements is essential if the genetic resources are to be developed commercially; the Biodiversity Treaty requires that all parties ensure that access to, and transfer of, technology is consistent with the protection of intellectual property rights.

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With respect to questions of safety, the treaty required the parties to consider the need for a protocol or international standards on the safe transfer, handling, and use of genetically modified organisms. In November 1995, the parties agreed to draft a protocol on the transborder movement of these organisms by 1998.[114] However, there have been significant differences between the parties concerning the nature of the protocol. While the parties have agreed to consider requiring notification of countries importing organisms that have been genetically modified, there has been considerable disagreement over the scope of the requirement. The question of whether any such obligation would extend to commodity products shipped in international commerce has been discussed, as has the effect that the notification requirement would have on the regulatory systems already in place in major importing and exporting countries. Countries with experience in handling biomaterials prefer to continue to develop biosafety standards at the national level, while many developing countries wish to rely on multilateral forums like the Biodiversity Treaty proceedings to sort out these issues.

GATT and the TRIPS Agreement

The biotechnology industry benefits from fair international trade and thus supported the U.S. negotiating positions in the Uruguay Round negotiations of GATT. The industry will profit from the near elimination of pharmaceutical tariffs agreed to in those talks and is a strong supporter of the protection for intellectual property provided by the Trade Related Aspects of Intellectual Property (TRIPS) agreement.

One aspect of the TRIPS agreement that concerns industry is the possible impact of the new domestic laws in shortening the period of protection provided by domestic patents. Prior to the TRIPS agreement, a U.S. patent was granted for 17 years following the date of patent issuance.

[114] "Accord on Biosafety Protocol Reached at U.N. Conference," *Daily Report for Executives*, 20 Nov. 1995.

Extensions of the patent term were possible under the Drug Price Competition and Patent Restoration Act of 1984; these extensions compensated for delays in the premarket regulatory approval process. As a result of domestic implementation of TRIPS, the U.S. patent law has been modified: The patent term is now 20 years from the date of filing. However, because biotech patents are usually processed more slowly than the average patent, the implementation of the 20-year term could actually shorten the effective life of a patent.

Remedies for this problem, in addition to the remedies provided by the Drug Price Competition and Patent Restoration Act, are possible on several fronts. The U.S. Patent and Trademark Office has been working closely with industry to continue to speed regulatory review of biotechnology patents. In addition, Congress is considering amendments to the GATT implementation law that could add five years to the term of a patent when there were undue delays in the patent's issuance.[115]

The industry is also concerned that foreign governments may use TRIPS to limit the issuance of biotechnology patents. TRIPS allows parties to exclude from patent protection several technologies, including diagnostic, therapeutic, and surgical methods for treating humans or animals, as well as plants and animals (other than micro-organisms) and processes for making plants and animals (other than nonbiological or microbiological processes). These exceptions may limit the kinds of inventions that the biotechnology industry and other segments of the pharmaceutical industry can protect under foreign law. Under the current legislation, the TRIPS agreement will be reviewed in four years, and this issue could be elevated to the World Trade Organization should circumstances require.

[115]S. Sternberg, "House Judiciary Committee Agrees to Amendments Extending Patent Protection," *BioWorld Today* (17 May 1996): 1.