Chapter 5

The Pharmaceutical Industry

"It has now been more than fifteen years since Robert Swanson, a young man who understood both finance and science, invited Herbert Boyer, a shy molecular biologist at the University of California, San Francisco, out for a beer. Swanson described his vision to Boyer: that the techniques and ideas that Boyer had devised for manipulating DNA could be translated into products at a private company yet to be established. As a result of that meeting, Genentech, the first well-known biotechnology corporation, was founded; Swanson and Boyer made their fortunes; and profound changes ensued in academic biomedical research, '

Robert Bazell
The New Republic, April 1991.

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INTRODUCTION

The development of biotechnology-based pharmaceutical products is flourishing. Since the early 1970s, independent, dedicated biotechnology companies (DBCs) have been examining the technology's potential for commercial development, and in more recent years, the technology has diffused into research laboratories and the development processes of most major companies in the pharmaceutical industry. Currently, both dedicated biotechnology companies and established, multinational pharmaceutical companies are using the tools and techniques of biotechnology in their drug discovery and development efforts.

Despite the strong barriers to entry, characteristic of the global pharmaceutical industry, there are many DBCs focusing on niche markets and developing biotechnology-based pharmaceutical products. Established pharmaceutical companies use biotechnology as a research tool and are increasingly developing in-house capabilities to complement their conventional research. Strategic alliances and mergers between major, multinational pharmaceutical companies use biotechnology as a research tool and DBCs allow both to compete in the industry and combine their strengths-the innovative technologies and products of the DBCs blended with the financial and marketing power and development and regulatory experience of the major companies.

This chapter examines dedicated biotechnology companies, specifically with respect to human therapeutics and the diffusion of biotechnology into established pharmaceutical companies. The chapter also discusses the dynamics and economics of the pharmaceutical industry as they influence the adoption and commercialization of biotechnology.

RESEARCH AND DEVELOPMENT

Pharmaceutical research and development (R&D) is a risky business. Scientifically, the research and discovery of new drugs is interdisciplinary, involving medicinal chemistry, molecular biology, biochemistry, physics, pharmacology, and other sciences and technologies. Biotechnology has proven to be a source of innovation in pharmaceutical R&D, contributing as both a production technology and a research tool. It is particularly important in drug discovery, as it enables scientists to study the molecular basis for disease and to design drugs that respond to a particular disease process. Once the drug discovery process is completed, the product development process and cycle are virtually the same for biotechnology-derived drugs and conventionally derived drugs. The development process is lengthy and tightly regulated, requiring significant investment in time and money (7). Drug development includes clinical research and trials and the completion of regulatory requirements.

Drug Discovery

Pharmaceutical research began as a chemical science, focusing on chemical structures and corresponding activity, dominated by medicinal and organic chemists. Little was known about the biology, biochemistry, and pharmacology of early products, and drug development in the days following World War II was speculative, based on mass-screening of chemical compounds (56). Since then, the development of physiology, biochemistry, genetics, and other biological sciences—including biotechnology-has provided information at the molecular and cellular level. This has contributed to increased understanding of the relationships between chemical structure and biological activity

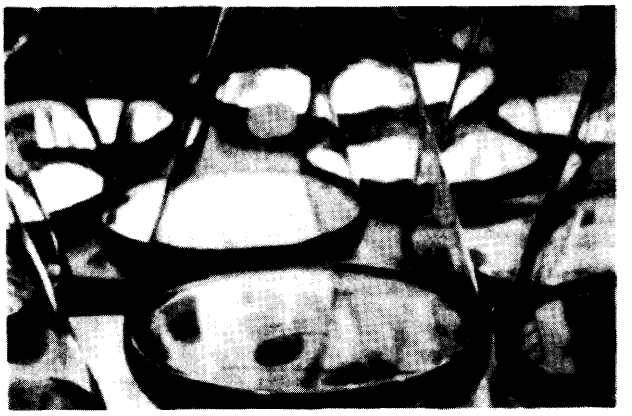

Photo credit: National Institutes of Health

Flasks filled with microbes that have been genetically engineered to produce interferon.

necessary for the discovery and development of new pharmaceutical products (14).

Pharmaceutical R&D is now an interdisciplinary process in which a rational approach to drug design, based on an improved understanding of the biological mechanisms of disease and drug interactions, is increasingly used to complement conventional chemical investigation. Biotechnology is likely to be the principal scientific driving force for the discovery of new drugs as we enter the 21st century, and the impact of biotechnology on the discovery of new therapeutic entities is difficult to underestimate (28).

Conventional Screening

Traditional approaches to discovering new drugs include continued research on existing products, the investigation and characterization of natural products, and the screening of synthetic chemicals and compounds for medicinal and pharmacologic activity (14). Existing drugs will always be researched for possible improvements, be they in terms of dosage, side effects, or increased activity. Screening compounds, both natural and synthetic, for biological and pharmacological activity is the conventional approach to drug discovery (55).

Thousands of natural and synthetic chemicals and compounds are screened every year for biological and pharmacological activity. Natural products have been used to develop many new medicines. Examples include: molds, bacteria, plant products, venoms, and toxins. Penicillins were developed from penicillium mold, and other antibiotics, including streptomycin and bacitracin, were discovered by screening soil samples for biological activity. Plant products often have pharmacological activity and can be used to develop medicines. Morphine and heroin, for example, axe derived from the opium poppy. The study of venoms and toxins has led to muscle relaxants, anticoagulants, and ion-channel blockers. Screening and modification of synthetic chemicals have also resulted in the development of important drugs, including chemotherapeutic drugs, sulphonamide antibacterial, and nonsteroidal anti-inflammatory drugs (14).

Screening is a massive, time-consuming, random, and very risky effort. About 10,000 compounds are screened every year, one or two of which will eventually be marketed as a drug (54). Despite the poor odds associated with conventional screening, these methods have worked well and provided the industry with many drugs. Since the 1950s and 1960s, the most fruitful period of drug discovery using conventional screening, this traditional route toward the discovery of new chemical entities has become more costly and has provided fewer drugs (39).

Rational Drug Design

Conventional screening is increasingly being augmented and complemented by biological sciences that allow a more mechanistic and physiological approach to drug discovery and design. This rational approach to drug design requires close collaboration between many scientific disciplines and is characteristic of drug development efforts of many biotechnology companies and, increasingly, established pharmaceutical companies.

Rational drug design depends on an increased knowledge of cellular mechanisms and control. This contributes not only to the discovery of new drugs, but also improves the understanding of the mode of action of existing drugs (25). Rational drug design focuses on understanding the physiological basis of disease; and research concentrates, in part, on the activity of enzymes, hormones and hormone receptors, cell replication and protein synthesis, and other molecular-level aspects of disease and drug treatment (9,14). The techniques of biotechnology, specifically recombinant DNA (rDNA) and hybridoma technology, are important research tools for rational drug design. Biotechnology can provide information about both the state and mechanism of disease, allowing the discovery aspect of pharmaceutical research to be more specific and targeted. For an in-depth discussion of the use and potential of biotechnology for therapeutic development see OTA's 1988 report, U.S. ***Investment in Biotechnology (48).***

The pharmaceutical industry uses biotechnology for both its products and techniques, and there axe two basic approaches to its use in drug development. First, biotechnology can be a production technology using rDNA techniques to manufacture otherwise unmakeable human proteins, such as human growth hormone. The majority of biotechnology-based drugs currently on the market are natural human proteins that, before rDNA, were not available in sufficient quantities to use as drugs. The second way biotechnology is used is in the rational design of synthetic molecules (33). An example is the use of

biotechnologies to clone and express genes that produce receptors. These receptors are then used to screen for receptor-binding compounds that will either enhance or inhibit receptor-ligand performance. In this case, biotechnology is used to research the disease mechanism and to design drugs to interact in the disease process. The product ultimately derived from this discovery effort will generally be a synthesized chemical, but its discovery depended on biotechnologies (40). This exemplifies the use of biotechnology as a research tool.

Rational drug design has been made possible by the increase in information about the physiological mechanisms of disease--providing additional approaches (aside from conventional screening) to drug discovery. However, there is much more still unknown, and drug discovery remains highly speculative, risky, and uncertain.

Drug Development

Once drug discovery is complete, the development process begins. This is a very lengthy, expensive, and tightly regulated process. Companies spend much of the product development time conducting clinical trials required to prove the safety, efficacy, and quality of the drug (see box 5-A) and waiting for Food and Drug Administration (FDA) review and approval. The actual drug development process, in terms of procedure, regulatory requirements, time, and expense, is very similar for biotechnology-derived drugs and conventional products. However, while the process and the issues are the same for both, the major competitive pharmaceutical companies have the resources, which most DBCs lack, to conduct clinical trials, research new products, and market existing products. Whereas some DBCs have funded and conducted the research and discovery portion independently, the expense, time requirements, and complicated regulatory process lead them to collaborate with established pharmaceutical companies to complete the actual clinical research and product development.

Product development time, for a specific product, has been estimated to be as long as 10 to 12 years (6). In estimating the cost of drug development, an attempt is made to include expenses for products and projects that are not successful and never reach the market. However, the actual cost for developing a new drug is not known and estimates vary.

In the United States, FDA regulates R&D, testing, manufacturing, quality control, labeling, marketing, and postmarketing studies of drugs. Biotechnology-derived drugs must go through the same FDA process as conventional pharmaceuticals, however the actual products are evaluated by different divisions within FDA. Biotechnology-derived drugs, most often classified as biologics, are evaluated by the Center for Biologic Evaluation and Research; conventionally derived drugs are evaluated by the Center for Drug Evaluation and Research. FDA has made its intent to regulate the product, not the process, clear, and has said it sees no need to institute new procedures or requirements for new biotechnology products (46). FDA's final policy statement regarding biotechnology indicated that it would not classify products of rDNA or hybridoma technologies any differently from those produced by traditional techniques and that such products are already covered under existing statutory provisions and regulations for drugs and biologics for human use (48,46).

Drug development requires time, financial resources, and regulatory expertise. DBCs have been extremely successful and innovative in the discovery phase but often lack the resources to independently develop the products. The majority of biotechnology derived drugs, both approved and in development, were discovered by DBCs and are being jointly developed with established pharmaceutical companies.

BIOTECHNOLOGY-DERIVED DRUGS

In 1982, the first biotechnology-based drug, recombinant human insulin, was approved in the United States by FDA. As of August 1991, 15 biotechnology-based drugs and vaccines were on the market (see table 5-l). The drugs are all large proteins which, before advances in biotechnology, were either not available at all, not available in large enough quantities, or not of sufficient purity for wide use as treatments. The exception, insulin, was available from pig and bovine pancreases.

Many new products are in the pipeline, and several are in the final stages of testing. According to the most recent survey of the Pharmaceutical Manufacturer% Association (PMA), there are over 100 biotechnology drugs and vaccines in human testing for a variety of conditions (see

Box 5-A—FDA Clinical Trials

In the United States, new drugs must be approved by the Food and Drug Administration (FDA). Conducting clinical trials and obtaining FDA approval is a rigorous process that can take as long as 10 to 12 years to complete. After completion of preclinical and clinical testing, companies may be required to conduct post-marketing surveillance. The human testing is done on both healthy and patient volunteers. Throughout the process, the drug companies work with FDA to design clinical trials and organize their material and studies. FDA uses expert advisory committees in addition to staff scientists to review new drugs. A brief discussion of the process follows.

Initially there is preclinical testing that involves laboratory and animal testing to determine the compound's biological activity and safety. This stage takes approximately 1 to 2 years after which the sponsoring company applies for permission to test the compound in humans. The company files an Investigational New Drug (IND) application with FDA that provides information on drug composition, manufacturing data, data on experimental controls, results from laboratory and animal testing, intended procedures for obtaining the consent of subjects and protecting their rights, and an overall plan for human clinical studies. The FDA has 30 days in which to act on the IND application, after which the company can begin human clinical testing.

Human clinical testing is done in three phases, which can take up to 6 years or more to complete. Phase I studies involve safety and pharmacological profiling of the drug. The studies are designed to determine safe dosage range, and how the drug is absorbed, distributed, metabolized, and excreted, as well as its duration in the body. Typically, a small number of healthy subjects, not patients, are involved in Phase I testing, which usually is completed within 1 year. Phase II testing consists of controlled studies in an average of 200 to 300 patients to determine the drug's effectiveness. Additional safety studies are also done on both animals and humans. Phase II testing usually requires 2 to 4 years to complete. Phase III studies require a large number of patients: from 1,000 to 3,000 volunteers are involved. Practicing physicians administer the drug to patients suffering from the indication for which the drug is being tested. Phase III studies are designed to confirm Phase II efficacy studies and identify adverse reactions. These usually take about 3 years to complete.

After the successful completion of the three phases of clinical testing, the sponsoring company submits a New Drug Application (NDA), or a Product License Application (PLA) (in the case of biologic), to FDA that includes all information collected during the trials. The information not only includes all preclinical and clinical test results on the drug's safety and efficacy, but also includes the drug's chemical structure and formulation, manufacturing, production, and labeling details. Average NDA approval time runs 2 to 3 years. After NDA approval is given, companies maintain contact with FDA and provide information on adverse reactions, production, quality control, and distribution records, Post-marketing surveillance is sometimes formalized in what are known as Phase IV studies, which provide the information from studies on the long-term effects fo the drug's use to FDA.

FDA instituted anew process, known as the Treatment IND process, in 1989 for drugs used for life-threatening and severely debilitating diseases, the goal being to reduce approval time. The Treatment IND process allows for broader access to experimental drugs and allows a company to recoup some of its investment while continuing clinical investigation and preparation of its NDA or PLA. Under the plan, if a drug shows particular promise after Phase I clinical trials, then Phase II and Phase III maybe combined, saving several years time.

SOURCE: Pharmaceutical Manufacturers Association, 1990.

table 5-2). Over half of the drugs in development target cancer or cancer-related conditions, and vaccine research is heavily concentrated on finding a vaccine to combat acquired immunodeficiency syndrome (AIDS) (32). A brief description of the types of products in development (see box 5-B) reveals the potential variety of biotechnology-derived therapeutics. Both biotechnology companies and established pharmaceutical companies are involved in the research and development of these products, indicating a commitment by both to use the latest available technology.

Several approved drugs are replacement therapies for patients who lack the biochemical capability to produce or process the necessary proteins. These include insulin for diabetics and human growth hormone for children with growth deficiency. Tissue plasminogen activator (tPA) is used to treat acute myocardial infarction and works to dissolve blood clots, which are causative agents for many heart attacks (56). Other products are approved for specific conditions, and research is continuing to find new indications for their use. Alpha interferon is used to treat hairy cell leukemia, AIDS-related

Table 5-l-Approved Biotechnology Drugs/Vaccines

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

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

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

Table 5-2-Conditions for Which Biotechnology-Derived Drugs Are Under Development

AIDS and AIDS Related Complex (ARC)
Chemotherapy effects
Leukemia
Aplastic anemia
Cancer
Bone marrow transplant
Hematologic neoplasms
Neutropenia
Myelodysplastic syndrome
Infectious diseases
Thermal injury
Reperfusion injury related to myocardial infarction and renal transplantation
Anemia secondary to kidney disease, AIDS, premature infants, chemotherapy, rheumatoid arthritis
Autologous transfusion
Hemophilia
Corneal transplants
Wound healing
Chronic soft tissue ulcers
Diabetes
Wasting syndromes
Nutritional and growth disorders
Venous stasis
Turner's syndrome
Burns
Venereal warts
Herpes simplex 2
Hepatitis-B, non-A, non-B hepatitis
Hypertension
Platelet deficiencies
Septic shock
Pseudomonas infections
Heart and liver transplant rejection
Malaria
Cervical ripening to facilitate childbirth in women experiencing certain implications
Myocardial infarction
Deep vein thrombosis
Acute stroke
Pulmonary embolism

SOURCE: Pharmaceutical Manufacturers Association, Biotechnology Medicines in Development, 1990 Annual Survey.

Kaposi's sarcoma, genital warts, and Hepatitis C. Erythropoietin (EPO) is used to treat anemia associated with end-stage renal disease and AIDS. Many of these drugs also have other potential uses for which they are being tested (see table 5-3) and, if approved, will increase their potential market values.

The market for many biotechnology-derived drugs is potentially large. Much of this drug development is market-driven, with a defined and expectant market. Examples include erythropoietin, human growth hormone, insulin, and tissue plasminogen activator, as well as recombinant Hepatitis B vaccines. All have performed well and are significant and much needed new drugs. Some significantly smaller development is more technology-driven, with a less defined market opportunity (56). An example is alpha interferon, which appeared to be a promising treatment for a variety of diseases because of its antiviral activity. Before biotechnology, it was not possible to isolate enough natural alpha interferon to conduct research to determine its biological activities and potential therapeutic benefits. Using rDNA techniques, alpha interferon is now mass-produced and research is continuing. As research and clinical trials have progressed, however, it has become obvious that much more must be learned about the drug's activity and mechanism of action, with respect to disease, before its use and effectiveness can be better defined.

Table 5-3-Testing for Additional Indications for Approved Drugs

Drug	Approved use	Additional indications
EPO	Dialysis anemia, AIDS related anemia	Autologous transfusion, Premature infants, Rheumatoid arthritis, chemotherapy, pre- and post-surgical use
tPA	Acute myocardial infarction	Deep vein thrombosis, acute stroke, pulmonary embolism
Interferon alpha-2a	Hairy cell leukemia, AIDS-related Kaposi's Sarcoma, Hepatitis C	Cancer, infectious disease, Genital herpes, colorectal cancer, Chronic and acute hepatitis B, Chronic myelogenous leukemia gastric Malignancies, HIV positive ARC, AIDS
Interferon alpha 2b	Hairy cell leukemia, Genital warts, AIDS-related Kaposi's sarcoma	Genital herpes, superficial bladder cancer, basal cell carcinoma, chronic and acute hepatitis B, non-A, and non-B hepatitis, delta hepatitis, chronic myelogenous leukemia HIV

SOURCE: Pharmaceutical Manufacturers Association, Biotechnology Medicines in Development, 1990 Annual Survey.

Interleukin II (several different interleukins, at least 10, have been identified) is another example of a naturally occurring immune system protein with somewhat uncertain actions that is, however, potentially effective in the treatment of cancer (28). Once again, neither the market nor the drug's mechanism of action is as yet particularly well defined, thus its ultimate marketplace success is unpredictable. It is important to differentiate between these drugs (interferon, interleukin, tumor necrosis factor, and others), now being researched, whose development is more technology-driven, and other biotechnology drugs

Box 5-B—Types of Biotechnology Products in Development

According to a 1990 Pharmaceutical Manufacturers Association survey of biotechnology products in development, PMA member companies have over 100 new biotechnology-derived drugs and vaccines in human clinical testing. Many of the products are being developed by multiple companies, and they can be placed in several defined categories. Research continues on several of the already approved products, including erythropoietin, tissue plasminogen activator, growth hormone, and interferon. A brief description of the other types of products in development follows.

Seven different Colony Stimulating Factors are being developed to treat white blood cell disorders including: some cancers, AIDS, aplastic anemia, bone marrow transplants, neutropenia (a condition characterized by a decrease in the number of neutrophilic leukocytes in the blood), and thermal injury. These products stimulate bone marrow to increase blood cell production and restore white cell counts.

Two companies are competing in the development of Superoxide Dismutase indicated for the treatment of conditions related to myocardial infarction and renal transplantation, as well as oxygen toxicity in premature infants.

Hemophiliacs lack the blood clotting protein Factor VIII and are susceptible to severe, life-threatening internal bleeding. Factor VIII can be genetically engineered, resulting in a pure protein in sufficient quantities for treatment. Two companies have applications submitted to the Food and Drug Administration (FDA) and are awaiting final marketing approval.

Growth Factors regulate cell proliferation, function, and differentiation. There are several different types of growth factors that are involved indifferent cellular processes and operate in distinct cells. Several growth factors, including epidermal growth factor, transforming growth factor, fibroblast growth factor, and insulin-like growth factor, are being developed by companies to treat a variety of conditions. Growth factors have many potential uses: including wound healing and the treatment of diabetes, growth disorders, ulcers, wounds, and transplants.

Interleukin is a natural substance that seems to have a wide potential variety of uses but is poorly understood. Interleukins appear to be useful in treating disorders of the immune system. Seven companies have one form of Interleukin or another in clinical testing. Recently, Cetus' Proleukin (interleukin-2) New Drug Application was turned down by FDA. FDA requested more information and additional testing to determine subsets of kidney cancer patients that will benefit from Proleukin treatment. Many of the indications for which interleukins are being tested have no alternative treatment, and thus, interleukin, while mechanistically poorly understood, is the only potential therapeutic treatment.

Monoclinal antibodies are protein molecules produced by white blood cells that can recognize and target foreign matter (antigens) in the cells. As such, there is potential for monoclonal antibodies to be able to target the delivery of drugs to particular cells on the basis of antigen recognition. One monoclinal antibody-based therapeutic, Ortho's Orthoclone OKT-3, is available on the market for treatment of kidney transplant rejection. Eighteen companies have other monoclinal antibody-based therapeutics in clinical trials for a variety of indications, including: treatment of graft-host disease, cancer and, septic shock, as well as prevention of blood clots, pseudomonas infections, rheumatoid arthritis, and diabetes. Centocor's Centoxin and Xoma's Xomen-E5 are both awaiting approval for the treatment of septic shock, and the two companies are already engaged in a patent dispute. A large market is anticipated for these two products in particular. As with interferon and interleukins, the market potential for monoclinal antibodies is promising but somewhat unclear.

Three companies are testing Tumor Necrosis Factor (TNF) for the treatment of cancer, and all are in early stages of clinical testing. TNF is a cellular messenger involved in the triggering of immune defenses. It damages tumor-related blood vessels and interferes with the blood supply and nourishment of the tumor. Again, research continues in efforts to determine exact mechanisms of action, and market potential at this point is relatively unknown as efficacy studies are continuing.

Research and early clinical testing on Recombinant Soluble CD4s for the treatment of AIDS are being conducted by several companies. CD4s are cell surface receptors believed to be involved with the AIDS virus' (HIV) cell surface binding. Research concentrates on creating an analog to the naturally occurring CD4 receptor that will bind to HIV and prevent it from binding to the cell receptor, thus inactivating the virus. CD4 research represents just one use of biotechnology in AIDS research.

Vaccine research has been greatly enhanced with the advent of biotechnology. Biotechnology allows for the design and production of subunit vaccines, which are much safer than conventional vaccines that incorporate the actual virus. Subunit vaccines are developed from the viral protein coat, which by itself is incapable of reproducing and infecting the patient. Two vaccines for Hepatitis-B are available on the market, and testing is continuing on a variety of potential AIDS, malaria, and herpes vaccines. The market for these vaccines is very large, and if safe and effective vaccines are produced, their manufacturers should be richly rewarded by a most-welcoming marketplace.

Several other products are in early clinical testing as well. The market potential for many of the drugs described is very large. Infectious disease, cancer, and AIDS all lack effective conventional treatments. If the mechanism of action and the function of the naturally occurring proteins being studied for use as therapeutics are further delineated, a realistic market and demand can be estimated. Right now, some of the products being developed are being pulled by the market, while others are more research driven and their commercial potential is difficult to evaluate as further scientific understanding is still needed.

SOURCE: Pharmaceutical Manufacturers Association% 1990.

Photo credit: Genentech

Since its approval in 1987, Genentech's Activase brand tPA has been used to treat heart attack victims.

(erythropoietin, insulin, and human growth hormone), whose development is both technology and market-driven. The questionable therapeutic potential of the former drugs, along with regulatory uncertainty, make it difficult to predict future sales and success of such biotechnology drugs. It is clear, however, that without biotechnology there would have been no opportunity to study many of these products.

Another way to describe the difference between products that are market-driven and those that are more technology-driven is to think in terms of diseases looking for drugs and drugs looking for diseases. In the case of tPA, human growth hormone, human insulin, and erythropoietin, the action of the protein was fairly well understood, allowing a focus on one or more specific diseases. In the case of Interleukin-2, Tumor Necrosis Factor (TNF), and the like, complicated, multiple biological effects have been exhibited, and researchers have had to search for relevant diseases to address (21).

Estimates of the market value of biotechnology products, including drugs, vaccines, and diagnostics, vary. Revenues in the United States from biotechnology-derived products were estimated to have been $1.5 billion in 1989 and $2 billion in 1990 (50,51). Competitive factors, such as marketing, will play a large role in determining the market share of these drugs. Major, established pharmaceutical companies have primary marketing rights to 8 of the 15 approved biotechnology-derived therapeutics (see table 5-4), and they have licensed development and marketing rights to many of the products under development. Almost all of the 15 approved drugs were invented by DBCs but needed the aid of larger companies' funding and expertise in the development, regulatory, and marketing stages. These agreements were necessitated by the fact that DBCs lacked sales forces in the early 1980s. Now that some companies have the resources to field sales representatives, there will likely be more products marketed, at least in part, by the companies that developed the products (2).

Amgen's EPO and granulocyte colony stimulating factor (G/CSF); Genentech's tPA, human growth hormone, and gamma interferon; Praxis Biologics'(now owned by Lederlee, a subsidiary of American Cyanamid) haemophilus influenza type B vaccine; and Immunex's granulocyte microphage colony stimulating factor (GM/CSF) are, in part, marketed by the biotechnology companies that discovered them. These companies also have agreements with established companies for marketing their products outside of the United States and, in some cases, co-marketing in the United States. Eli Lilly, Hoffmann-La Roche, Merck, Ortho Biotech, Schering-Plough, and SmithKline Beecham--all established pharmaceutical companies-have licensed marketing rights to the other approved products from the DBCs that developed them.

These arrangements demonstrate the aforementioned dependence of biotechnology companies on pharmaceutical companies for clinical development and marketing resources, as well as the established companies' commitments to making biotechnology-derived drugs part of their product portfolios. While

Table 5-4-Marketing of Approved Biotechnology-Derived Drugs

Drug	Marketer
Amgen-erythropoietin	Amgen-United States for treatment of dialysis anemia.
	Ortho Biotech--United States for nondialysis anemia, AIDS related anemia and all other indications awaiting FDA approval. All ex-U.S. market territories except Japan and China for all indications.
	Kirin Brewery Ltd.-Japan and China for all indications.
Genentech-human growth hormone	Eli Lilly
Genentech-human insulin	Eli Lilly
Genentech-tPA	Genentech Boehringer-Ingelheim
Genentech-alpha interferon	Hoffmann-La Roche
Chiron-Hepatitis B vaccine	Merck
Ortho-OKT-3	Ortho
Praxis Biologics-Haemophilus B vaccine	Praxis (bought by Lederlee)

SOURCE: Office of Technology Assessment, 1991.

large companies have demonstrated successful records in conducting clinical trials with drugs discovered elsewhere (in DBCs, universities, and government laboratories for example), they have not historically been as successful in innovation (33). This may change as the established companies continue to develop in-house capabilities in biotechnology and to integrate biotechnology into their R&D programs, while, at the same time, complementing these efforts by collaboration with biotechnology companies.

COMPETITIVE FACTORS

Analysis of the diffusion of biotechnology into the development of human therapeutics and of the United States' competitiveness with respect to global commercialization of biotechnology requires an understanding of the structure and economics of the pharmaceutical industry. The pharmaceutical industry's approach to biotechnology is two-fold and includes efforts by both established pharmaceutical companies and biotechnology companies. Many industry characteristics serve both to determine an established firm's competitiveness and to bar entry by new firms. These include R&D, marketing, and related costs. A description of the structure and economics of the pharmaceutical industry follows. This will illustrate the difficulties faced by small biotechnology companies and will serve to introduce and help explain the different approaches taken toward biotechnology by DBCs and established pharmaceutical companies.

Industry Overview

The modern pharmaceutical industry is a global, competitive, high-risk, and high-return industry that develops and sells innovative, high-value-added products in a tightly regulated process. Competitiveness results from the successful introduction of new products, a dynamic process revolving around innovative R&D in the major global markets. Major industry players are financially strong, vertically integrated firms that control all aspects of the business, from R&D, to manufacturing, to marketing (43). Many of the top firms, especially U. S., Swiss, and British firms, are multinational, with R&D, manufacturing, and marketing operations spread around the globe (see box 5-C). There are also many companies that are more regional, maintaining fully integrated operations only in their home market. The top companies have financial, scientific, regulatory, and marketing resources, enabling them to compete worldwide on the basis of existing products and, importantly, new product introduction.

The industry has faced increased competitive pressure in recent years, leading to a wave of consolidation among established companies. DBCs are trying to enter a high-cost, high-risk, and very competitive industry characterized by lengthy product development schedules and delays between discovery and marketing, which postpone return on investment and require both time and money from participating companies. The costs, risks, and time frame required for drug development can act to bar new companies' entrance into the pharmaceutical industry and affect both DBCs and established pharmaceutical companies with respect to commercialization of biotechnology.

Research and Development

Success and competitiveness in the pharmaceutical business depends on research and new product development, followed by successful marketing. In 1990, the top U.S. pharmaceutical companies spent almost 17 percent of sales on R&D, up from 12 percent in 1980 (44,51). The proportion

Box 5-C—Pharmaceuticals-A Global Industry

When Roche Holdings, Ltd. of Basel, Switzerland bought a 60-percent share of Genentech of San Francisco, CA, concern was raised about the foreign acquisition of the United States' leading biotechnology company. However, Roche, although based in Switzerland, has more operations outside of its small home market than inside. Roche, like most of the top companies in the pharmaceutical industry, operates on a global basis, and has significant U.S. operations, including its wholly owned subsidiary, Hoffman LaRoche, in Nutley, NJ. The head of international drug research and development for Roche operates, not out of Basel, but in the United States, where Roche's worldwide R&D efforts are coordinated. So one may ask, should Roche really be viewed as a Swiss company? How much significance can be attached to the home country of any of the top pharmaceutical companies?

In 1989,4 of the top 10 ranked pharmaceutical companies in terms of sales (see table 5-5) were U.S. companies; two were German, two were Swiss, one was British, and the remaining, SmithKline Beecham, was both a U.S. and a British company created by the merger of SmithKline Beckman of the United States and Beecham of the United Kingdom. All of these companies operate on a global basis with fully integrated operations in countries outside of their home base. These companies do more than just sell their products on a global basis. They conduct R&D, manufacture products, and employ local citizens around the world.

Glaxo, based in the United Kingdom, is the second-ranked company in terms of pharmaceutical sales and is a good example of a company that operates on a global basis. A look at Glaxo's worldwide R&D personnel reveals significant operations outside of the United Kingdom, Glaxo has 3,529 R&D staff in the United Kingdom, 740 in the United States, 353 in Italy, 210 in Japan, 185 in France, 134 in Switzerland, 70 in Canada, 68 in Germany, 54 in Spain, and 379 elsewhere in the world. Glaxo's manufacturing efforts are also multinational, with plants in the U.K., Taiwan, Indonesia, Spain, Scotland, and another being developed in Singapore. Sales are undertaken on a global basis as well, and Glaxo controls approximately 3.5 percent of the world pharmaceutical market. Glaxo's U.S. operations are located in Research Triangle Park, NC, alongside Burroughs Wellcome, which is the U.S. subsidiary of The Wellcome Foundation Ltd. of the United Kingdom, and Ciba-Geigy, whose parent company is Swiss.

Johnson & Johnson, a U.S. company based in New Brunswick NJ, has 175 operating units in 55 countries. Merck & Co., Inc. of Rahway, NJ, has research labs in seven countries, experimental farms in six countries, and manufacturing plants in 18 countries. SmithKline Beecham, of Philadelphia, PA and the United Kingdom, has principal operating units in 28 countries. Syntex Corp. has its head office in Panama, its principal U.S. office in Palo Alto, CA, and production facilities in 11 countries. With an increasing percentage of sales overseas, companies are choosing more often to establish their own sales forces in foreign markets rather than licensing their products to foreign companies for royalties. Having operating units abroad supports companies' efforts to obtain foreign regulatory approval. Investment in pharmaceutical operations, including sales and R&D, in Japan, which is well recognized as being a difficult market to enter, is rapidly increasing.

Conspicuously absent from this type and extent of global pursuit of pharmaceutical operations is Japan. Japan's major companies have begun to internationalize their operations, however, no Japanese companies currently have global representation comparable to the top U.S. and European companies.

SOURCES: Office of Technology Assessment, 1991, based on *'Glaxo Stresses International Presence," *Scrip, No.* 1558, Oct. 17, 1990, p. 14; "Roche's Worldwide Pharmaceutical R&D Will Be Directed From U.S.," *F-D-C Reports*, Sept. 3, 1990, pp. T&G 1-2; *Merck& Co., Inc. Annual Report 1989, SmithKline Beckman Annual Report 1989, Syntex Annual Report 1989;* and M. Freudenheim, "Global Push for Profit at Johnson," *New York Times*, Aug. 3, 1990.

of income spent on R&D has increased over the last 30 years, due, at least in part, to both the increased concern about the safety and efficacy of new drugs (which has promoted increased regulatory scrutiny) and the diminished returns from conventional screening techniques of drug discovery. The latter has resulted in increased time and effort for drug discovery and has led to the development and incorporation of new technologies (38). The spending ratio of R&D to sales is much higher for DBCs, many of which do not currently have products on the market. According to a recent survey conducted by Ernst & Young, therapeutically oriented biotechnology firms spend an average of 69 percent of revenues on R&D (13).

Pharmaceutical R&D is very risky and companies are not guaranteed any return for several years, if at all. There is no assurance that any project will lead to a marketable product (42). Only 1 drug in 10 that enters clinical trials will make it to market, and only

30 percent of marketed drugs recover their R&D costs (6). Due to the high risk involved, companies must have diverse R&D capabilities to ensure product differentiation (16,1). In 1989, worldwide pharmaceutical R&D spending was estimated to be $16 billion (37). The U.S. pharmaceutical industry invested an estimated $8.3 billion on R&D in 1990, up from $7.3 billion in 1989 (50,51). Seven countries-the United States, Japan, the United Kingdom, Germany, Switzerland, France, and Italy—accounted for approximately 80 percent of R&D spending (37).

Barriers to entry in the pharmaceutical industry related to R&D are not so much a result of the demands for resources to conduct research, but rather, for development. DBCs can usually secure enough initial or first-round financing to conduct at least the research part of the R&D. With no sales contributing revenue, when full-scale development begins, many companies find themselves in financial straits with neither enough money nor experience to conduct the necessary clinical trials (47). At this point, many DBCs turn to pharmaceutical companies for joint product development.

Marketing

Marketing is an extremely expensive aspect of the pharmaceutical business. Companies have increased spending in recent years as they increased the size of their sales forces to cover world markets. Large, multinational companies have the resources to market their products in each major market. Foreign markets can differ from domestic markets in many ways, including cultural differences, distribution, pricing, payment, and regulatory requirements. Penetrating a foreign market often requires local expertise and local sales forces (22). Companies access foreign markets by licensing marketing rights to products, acquiring local companies, and/or locating new facilities abroad (l).

Drug companies tend to make the bulk of their profits from only a few products, which adds to the riskiness of R&D and the need to spread money into many areas and compounds with the expectation that only a few will bring big results. The dependence on a few products makes effective marketing, including advertising and promotion, important. Pharmaceutical companies market to doctors, which requires office visits by salespeople. In 1989, representatives of pharmaceutical companies made nearly 30 million visits to U.S. doctors' offices. Marketing costs

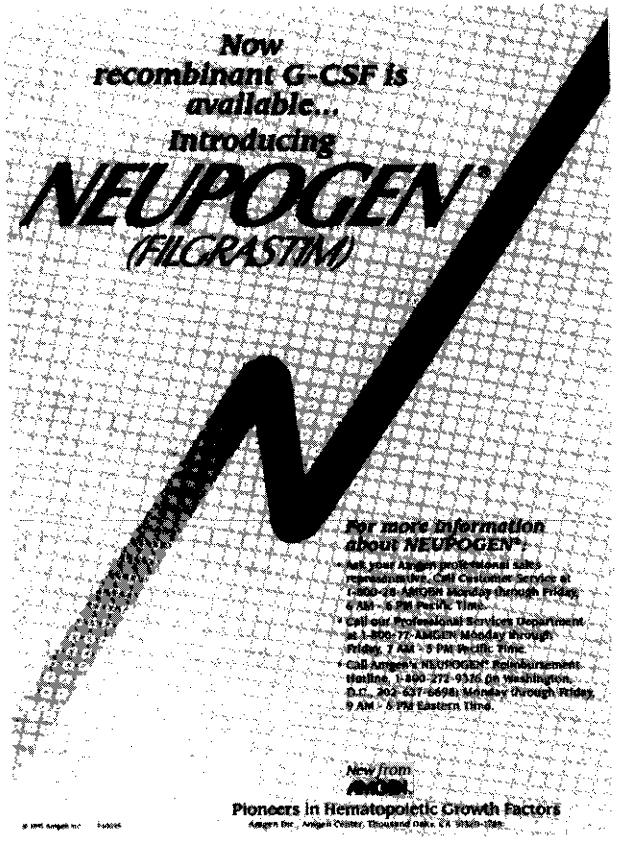

Photo credit: **Amgen**

Advertisement for recombinant G-CSF.

represent about 24 percent of drug revenues, twice what was spent 10 years ago (11). The pharmaceutical industry, in the United States alone, spends over $5 billion a year on promotional activities (49).

The industry is unique in that companies do not market directly to the consumer; rather, there is an indirect relationship between the company, the prescriber (the doctor), and the payer (patient or third party.) The industry markets to hospitals and doctors that prescribe drugs but do not pay for them. This has, historically, allowed companies to focus on the quality and efficacy of a drug--not on the price (20). However, with the increased worldwide emphasis on health care cost containment, and the increased presence and control of third-party payers in the purchasing decision—insurance companies and Medicare in the United States and national health policies in other countries-pharmaceutical companies are being pressured to develop cost-effective therapies, and price has become a sensitive issue (see box 5-D).

Box 5-D--Price and Cost Containment

Pharmaceutical companies and DBCs are operating in an increasingly cost-conscious environment. Governments worldwide are trying to decrease health care expenditures and are cutting reimbursement prices on drugs. Governments are increasingly looking (at least indirectly) at drugs' economic benefits, in addition to their therapeutic benefits, and are becoming more discriminating in their payment decisions. Price controls are used to contain escalating costs of health care, but they also raise the level of financial risk involved in new drug development. Should they excessively hinder return on investment, price controls have the potential to deter investment, and thus, decrease innovation.

Many countries control the prices of prescription pharmaceuticals under their national health policies and insurance programs. Several countries, including Brazil, Japan, and Canada, impose strict price controls on pharmaceuticals, resulting in both unprofitable production and decreased investment by companies. There are several different approaches taken to cut the cost of pharmaceuticals. Some countries, including Denmark and France, do not include all drugs under their national health policies. They exclude particularly costly drugs from reimbursement. The creation of formularies, lists of specific drugs that qualify for reimbursement, is also being considered by Medicaid and Medicare programs in the United States, with the latest step taken being the passage of the Medicare Pharmaceutical and Prudent Purchasing Act by the 101st Congress. Other cost-cutting measures included price freezes in The Netherlands, Greece, and Italy; the allowance of higher prices in return for increased R&D spending in Australia; and higher prices allowed for innovative drugs in Japan to stimulate R&D. The United Kingdom controls pharmaceuticals, not by price controls but by profit controls, limiting the amount of profit made by pharmaceutical manufacturers.

Pricing and reimbursement policies by third-party payers have already been an issue with biotechnology-derived drugs, many of which are very expensive. Amgen's erythropoietin, used to treat dialysis and AIDS patients' anemia, costs approximately $5,000 per year for dialysis patients. Human growth hormone, used to treat human growth hormone deficiency in children, costs approximately $10,000 per year. Genentech's recombinant tissue plasminogen activator (Activase), used to treat acute myocardial infarction, costs $2,200 per dose.

If companies cannot expect to charge reasonable sums for their products or cannot be guaranteed third-party reimbursement, the incentive for further efforts is decreased and the viability of the firms maybe compromised. The downward pressure on pricing affects both large, multinational pharmaceutical companies and DBCs. In response to pricing pressure and cost-containment efforts, companies developing pharmaceuticals will increasingly be conducting cost/benefit analyses along with R&D to justify the expense of product development and the high prices they charge and to determine the potential for return on investment.

SOURCES: Derived from: "The New World of Drugs," *The Economist*, vol. 310, No. 7588, Feb. 4, 1989; pp. 63-64; "Managing R&D—No Easy Solution," *Scrip, No.* 1502, Apr. 4, 1990, pp. 4-6; *Scrip* review issue, 1989; Ernst & Young, *Biotech 91: A Changing Environment (San* Francisco, CA: 1990); G. Omenn, dean, School of Public Health and Community Medicine, University of Washington, Seattle, WA, personal communication, 1990.

In recent years the trend has been to increase the size of the marketing forces by adding new sales representatives in all the major markets. In addition, co-promotion has been a new phenomenon in which companies share the responsibility for marketing each other's products. This allows sales representatives to market more products using established contacts with doctors and hospitals. In addition, access to a familiar market and success in the domestic market is extremely important. Sales are easier in this market than in foreign markets because there is no language or cultural barrier and domestic sales can support international sales (2).

Few DBCs, perhaps only Genentech (S. San Francisco, CA), Centocor (Malvern, PA), and Amgen (Thousand Oaks, CA) have marketing staffs and established distribution routes for their products. At the same time, many of the biotechnology-derived drugs on the market are entirely new therapeutic products. For these drugs, including erythropoietin, alpha interferon, Interleukin II, and others, doctors must be educated about entirely new classes of products, their uses, and their potential for effective treatment. This can be accomplished most effectively by very large marketing organizations (23). Most DBCs with approved products have licensed marketing rights to established pharmaceutical companies.

There are obvious advantages to teaming up with an established pharmaceutical company for marketing purposes. For example, Centocor (Malvern, PA) and Xoma (Berkeley, CA) both have products in

development to treat gram negative sepsis septic shock. Centocor plans to market its product, Centoxin, with its own sales force consisting of 75 sales representatives in the United States and 45 in Europe. Xoma plans to market its product, Xomen-E5, under a licensing agreement with Pfizer's Roerig subsidiary using the latter's 750 sales representatives. Xoma is benefiting from an established sales force and distribution network and Roerig's familiarity with the medical community. The obvious disadvantage of licensing agreements is that DBCs retain only a portion of the profits from the drug's sale (4) (see ch. 4).

Table 5-5-Company Rank by Pharmaceutical Sales 1989

Company	Sales($miilions)
Merck (U. S.)	$5,405.5
Glaxo (U. K.)	$4,679.5
Bristol-Myers Squibb (U. S.)	$4,442.0
Bayer (Germany)	$4,237.8
Hoechst (Germany)	$4,200.5
Eastman Kodak (U.S.)	$4,009.0
Ciba-Geigy (Switzerland)	$3,775.9
SmithKline Beecham (U. S./U.K.)	$3,668.8
Sandoz (Switzerland)	$3,464.1
American Home Products (U. S.)	$3,276.5

SOURCE: "Merger Effect on Top Pharma Firms," *Scrip*, No. 1570, Nov. 28, 1990, p. 13.

Market

The size of the global pharmaceutical market was estimated to be $150 billion in 1989 (50). The United States is the largest drug market, accounting for approximately 30 percent of the world market (3). The European Community (EC) is the second largest total market. Japan is the second largest single-country market, with an approximate 17.6 percent market share (57). Pharmaceutical products are marketed globally and, in 1989, 34.4 percent of the $51.2 billion in sales by U.S. drug companies were overseas (8,6). The main competitors for the world pharmaceutical market are principally U.S. and European companies (see table 5-5), more specifically the multinational firms based in Switzerland, the United Kingdom (U.K.), and Germany, which are huge, multinational organizations with research, manufacturing, and marketing operations worldwide. Focus on penetrating world markets, not only domestic markets, is crucial to success in the pharmaceutical industry (18).

The Japanese market has, historically, been difficult to enter without a Japanese partner; thus, U.S. and European companies, to ensure market presence, have collaborated with Japanese companies that dominate their domestic market. For many years U.S. and European companies increased their presence in Japan by establishing their own marketing forces. In recent years, in a few cases, they built research facilities, e.g., Roche, or acquired a Japanese company, e.g., Merck, which bought Banyu Pharmaceutical in 1983 (56,12). Currently, 24 U.S. pharmaceutical companies operate in Japan and account for about 15 percent of the $33 billion Japanese market. The domestic market is still dominated by Japanese companies, and no American or European company is among the top 10 in Japan (29). At the same time, Japanese companies, which for the most part are not multinational, are now pushing to increase their export markets and are beginning to globalize their operations (41) (see box 5-E).

The pharmaceutical industry, despite high-entry barriers, is not particularly concentrated. No company holds even a 5-percent share of the world market (26,30). In 1987, the largest 10 firms held only 27.6 percent of the world market (38). The four largest firms in the PMA account for only 25 percent of sales in the United States; the top 8 account for under 50 percent, and the top 21 for only 75 percent (29). However, it is important to recognize that there is neither a central product in the pharmaceutical market nor a long-term product leader (27). Availability of financial resources can serve both to determine existing fins' competitiveness and to bar new entrants, including biotechnology companies. Because comparatively few drugs maintain large market shares for extended time periods, companies must aggressively market approved products and develop innovative new ones in order to compete. Competition is both static and dynamic. In the static sense, competition is based on product differentiation, but not price. Dynamic competition is derived from R&D and new product introduction. Market share, which changes with new product introduction, also is a measure of competition (16,38).

Consolidation

In recent years, the industry has experienced two rather opposite phenomenons: consolidation and the development of small startups focusing on biotechnology derived therapeutics. Together, these illustrate the increased resources demanded by the competitive nature of the industry and the need

Box 5-E—Japan's Pharmaceutical Industry

Japan is the second largest pharmaceutical market in the world behind the United States. The domestic market is dominated by Japanese companies that are relatively big, although smaller than the top U.S. companies, and profitable at home, but that lack a significant global presence. Historically, the Japanese pharmaceutical market was protected by the government, and foreign penetration was very difficult. Since the mid-1980s, this has begun to change, increasing the competitiveness of the Japanese pharmaceutical market and driving Japanese companies toward globalization.

Before 1986, foreign drug companies were required to conduct clinical trials in Japan, on Japanese, and submit the data in Japanese. Companies were not allowed to apply directly to the Japanese Government, specifically the Ministry of Health and Welfare, for drug approval (shonin) and license (kyoka), but were required to have a Japanese partner. These requirements were changed and foreign companies are now allowed to apply directly to the government for new drug approvals. However, the changed laws applied only to new products, so firms had to maintain their contracts with Japanese partners for old products. After the 1985 Market-Oriented Sector-Selective (MOSS) talks, bilateral trade negotiations between the United States and Japan, some of the problems related to market access and regulatory processes were resolved and the Japanese market opened significantly to foreign entrants.

There are several significant differences between the pharmaceutical industry in Japan and that of other countries, aside from language and cultural differences. In the United States, doctors prescribe, but do not sell drugs to patients, and they do not earn money by prescribing any particular drug. In Japan, pharmaceutical companies sell the drugs to doctors or hospitals, which often have in-house pharmacies, at prices below the government's official price. The doctor or hospital then sells the drugs to patients at the government price, thus making a profit from the sale of the drugs. Another difference is the research intensity of Japanese firms vis-a-vis American and European companies. Japanese pharmaceutical companies historically conducted little basic research and were not known for their R&D capabilities. They tended to license new drugs from foreign firms that needed a partner to penetrate the market.

The direct entrance of foreign firms into the Japanese market, combined with efforts, since 1980, to control pharmaceutical prices in Japan, resulted in increased competition. The domestic firms that dominated the market had, until this point, been protected from foreign competition by the Japanese Government. Japan now reduces the government price for pharmaceuticals biennially. Japanese companies also export few drugs, selling abroad only about 2 percent of the total domestic pharmaceutical production. In the face of increased competition, Japanese companies have sought export markets and have begun to globalize their operations.

Japanese companies are now seeking to penetrate global markets, through both increased export and by locating operations outside of Japan. Japanese companies have established joint ventures with foreign companies and are establishing sales forces in Europe and the United States. Japanese companies are also investing in U.S. biotechnology companies and licensing the Japanese and Far East marketing rights to new biotechnology-derived drugs. To increase their R&D capabilities, Japanese companies are funding research at American universities and biotechnology companies. Japanese companies maintain significantly smaller R&D budgets than their U.S. and European counterparts.

A recent Japanese survey examined Japanese pharmaceutical companies' representation in foreign countries. The survey counted joint ventures, research centers, and subsidiary companies, but not local distributors or licensees. Thirteen Japanese companies had a total of 24 offices, research centers, joint ventures, or wholly owned subsidiaries in the United States. Sixteen companies had direct representation in Taiwan; nine in Germany; eight in the United Kingdom; seven in Thailand; six in Indonesia; and five in South Korea. This demonstrates Japanese companies' efforts to globalize their businesses and 1ocate operations at sites around the world. However, these efforts do not nearly meet the already established global operations of the top U.S. and European companies, some of which operate at fully integrated levels in 20 or more countries.

The Japanese market is becoming more competitive and so are Japanese pharmaceutical companies, which are increasing their presence in international markets. While the pharmaceutical market in Japan is still dominated by domestic firms, foreign firms are now able to establish their own facilities and sales forces in what was previously a tightly protected market. The increase in foreign competition, along with increased cost-containment pressure, have driven the historically domestic Japanese companies to seek foreign markets in order to increase their competition with U.S. and European companies.

It is important to note that while Japanese companies are entering the global marketplace, significant differences remain between them and their international competitors. U.S. and European companies maintain a significant scientific and technological edge over their Japanese counterparts and are more R&D-intensive. Japanese companies face a significant reorganizational challenge by trying to improve their research capabilities and globalize their operations at the same time, and globalization is sure to be more difficult and slower than it has been in other Japanese industries.

SOURCES: Office of Technology Assessment, 1991 derived from: A. Yoshikawa, "The Other Drug War: U.S.-Japan Trade in Pharmaceuticals," *California ManagementReview,* vol. 31, No. 2, winter 1989; "Japanese Pharma. Firms Overseas," *Scrip*, No. 1535, July 27,1990, p. 23; G. Mossinghoff, statement before the International Trade Commission, Jan. 17, 1991; D. Swinbanks, "Huge Profit From Drugs," Nature, vol. 342, No. 23, November 1989, p. 333.

Table 5-6-Merger and Acquisition Activity in the Pharmaceutical Industry

1988	Eastman Kodak (U.S.)--Sterling Drug (U.S.)
	American Home Products (U.S.)--Robins (U.S.)
1989	SmithKline Beckman (U.S.)--Beecham Products (U. K.)
	Novo (Denmark)--Nordisk (Denmark)
	Merrell Dow (U.S.)--Marion Laboratories (U.S.)
	Bristol-Myers (U.S.)--Squibb (U.S.)
1990	Rhoune-Poulenc (FR)--Rorer (U.S.)
	Hoffmann-La Roche (Switz)--Genentech (U. S.)
1991	Kodak (Sterling Drug) (U. S.)-Sanofi (FR)
	Chiron (U.S.)-Celvs (U.S.)

SOURCE Office of Technology Assessment, 1991.

for innovative R&D and new products. In the last several years, there has been significant merger and acquisition activity between established firms (see table 5-6) (11). Consolidation strengthens the scientific base, expands the technology and product portfolios of the companies, and reflects the increased costs of doing business-especially R&D and marketing.

By pooling R&D budgets, companies can ensure a broad R&D program, covering many therapeutic categories, and a more complete product portfolio. With the increased resources of what used to be two separate R&D budgets, companies can ensure the breadth of R&D necessary to develop products for the many therapeutic submarkets and spread risk, increasing the chances of developing a successful product (43). These mergers have, in some cases, resulted in more than doubling the size of companies' sales forces and providing an economy of scale. The larger sales forces enable companies to reach more doctors and hospitals, further penetrate markets, and enter markets in which they previously had no representation. This is especially true of foreign markets (19).

Dedicated Biotechnology Companies and the Pharmaceutical Industry

DBCs are almost exclusively a U.S. phenomenon. No other country has a remotely comparable number. Biotechnology companies are created specifically to exploit the commercial potential of biotechnology. These companies start as research institutions with science and technology but without products. They do not undertake R&Don nearly as broad a scale as established companies. Instead, they pursue niche markets by focusing either in specific technologies (e.g., drug delivery) or particular products (e.g., growth factors). The companies must fund the initial costs of infrastructure development, including buildings, plants, equipment, and people (scientists, managers, salespeople, and lawyers), without the benefit of internally generated revenues. They depend on venture capital, stock offerings, and relationships with established pharmaceutical companies for their financing needs.

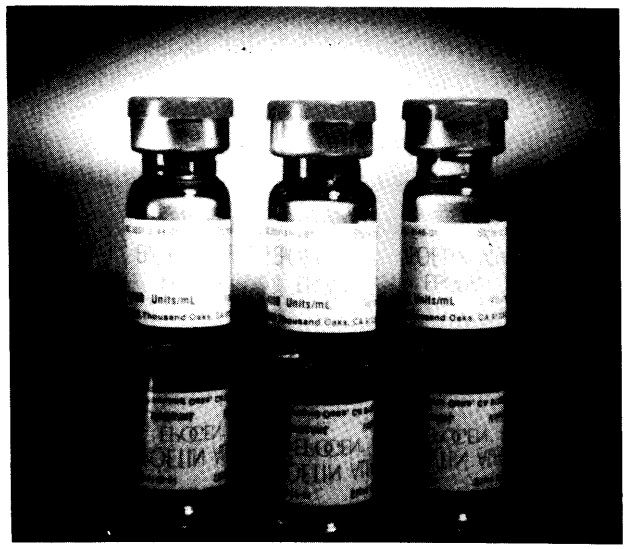

Photo credit: Amgen

Since FDA approval in 1989, more than 90,000 patients have used EPOGEN brand recombinant EPO, the best selling biotechnology-derived drug to date.

Biotechnology companies are fully capable and competitive when it comes to research and applications of technologies. However, the very fact that their expertise is focused in biotechnology and related niche areas of pharmaceutical research illustrates the difference between them and large pharmaceutical companies. Established pharmaceutical companies maintain a greater breadth of R&D, work to penetrate multiple therapeutic markets worldwide, and devote major resources to product development and, at the same time, can integrate and implement newer aspects of biotechnology to complement their conventional research capabilities. Biotechnology is being introduced into the pharmaceutical industry as it proves itself, as products are developed and technologies perfected, and as their potential for use in the industry is observed (9).

DBCs are attempting to break into an industry marked by high costs and risks, in which successful, established pharmaceutical companies with large R&D budgets and marketing clout feel pressure to consolidate to be competitive. While some companies have been successful operating at all levels,

from R&D to manufacturing to marketing, none compete head-to-head with major established companies except in niche markets and on a product-by-product basis (21). DBCs that are able to vertically integrate their operations, as Genentech and Amgen have done, are likely to continue to concentrate on niche markets.

The original intent of many of the early DBCs was to become fully integrated, competitive pharmaceutical companies, but the economics of the pharmaceutical industry may very well deny this opportunity to most. Perhaps in recognition of those barriers, many of the newer companies were founded with the intention of developing one idea or targeting a niche market and, perhaps, being acquired. The latter was true for Hybritech, which was acquired by Eli Lilly, and Genetic Systems, which was bought by Bristol-Myers (now Bristol-Myers Squibb) and recently sold to the Sanofi of France. According to a recent Ernst & Young survey, 39 percent of all companies surveyed expect to be acquired by a large firm within the next 5 years, and 32 percent expect to merge with an equal-size firm in the same period (13).

Strategic Alliances

DBCs have been able to secure initial financing and certainly have excellent scientific and technological capabilities, but they often lack other important resources. The vast majority of DBCs lack the money to fund clinical development and to successfully market their products worldwide. It is for these reasons that DBCs team up with major pharmaceutical companies (19). Biotechnology companies that do not turn to larger drug companies for help are usually forced to hold special public offerings to raise the capital for clinical development. Such public financing has been in the form of R&D limited partnerships, debt offerings, or new stock offerings (2).

There are several reasons for companies in the pharmaceutical industry to collaborate, be it with another established pharmaceutical firm or a biotechnology company. Collaboration creates access to markets, access to technological skills and competences that may not be developed in-house, and an opportunity to share the costs and risks associated with the development of new drugs and the use of new technologies. When DBCs were first created in the 1970s, the risks were very high as the potential for commercial development and profits was unproven. It was not known if biotechnology could be successfully used to develop and produce new drugs, and the costs of scaling-up biotechnological production methods were unknown. Due to these unknowns, many pharmaceutical companies did not choose to pursue the development of biotechnology, at least in-house, until the early 1980s when the initial uncertainties about the technology were resolved. Another reason for this delay was that most established firms did not have the personnel or interdisciplinary expertise required to use and develop the technology. Pharmaceutical companies needed to restructure their research departments and programs and hire skilled personnel before they could integrate biotechnology into their drug development efforts (38).

Strategic alliances are often established after DBCs have conducted significant research and development on particular products. The pharmaceutical company uses its established resources to further develop the drug and conduct clinical trials, thus gaining new products without having to make the initial investment and assume the entire risk inherent in new product development. DBCs receive necessary financing and development, regulatory, and marketing expertise, while pharmaceutical companies are able to complement their in-house R&D activities and add innovative new products to increase the breadth of their product portfolios. Often, the pharmaceutical company will take full responsibility for putting the drug through the regulatory process (the U.S. FDA and foreign regulatory approval) and for introducing the drug in foreign markets. Increasingly, the more successful biotechnology companies maintain U.S. marketing rights to their products, allowing both DBCs and established firms to receive revenues from product sales.

There are many types of strategic alliances between DBCs and pharmaceutical companies. They include agreements to exchange technology, joint ventures, equity arrangements, and R&D contracts (38). At the current level of commercialization, the most common type of agreement is licensing, which can include joint development of specific products as well as the exchange of marketing rights for financial support. Examples of U.S. pharmaceutical companies' alliances with DBCs include Ortho Biotech, a subsidiary of Johnson & Johnson, which has agreements with Xoma (Berkeley, CA) and Amgen (Thousand Oaks, CA), among others; Pfizer's subsidiary, Roerig's, agree-

ment with Xoma; Merck & Co.'s agreements with Genentech (S. San Francisco, CA), California Biotechnology, Inc. (Mountain View, CA), Immunomedics, Inc. (Warren, NJ), Repligen, Inc. (Cambridge, MA), and Chiron (Emery vine, CA); Hoffmann-La Roche's licensing agreements with Cetus Corp. (Emeryville, CA) and Genetics Institute, Inc. (Cambridge, MA); SmithKline Beecham PLC's agreements with Nova Pharmaceutical Corp. (Baltimore, MD), and T Cell Sciences, Inc. (Cambridge, MA) and others (13).

European companies tend to depend both on strategic alliances and, more so than U.S. companies, on in-house capabilities in biotechnology. There are few European DBCs with which to collaborate, and the majority of European companies' strategic alliances are with U.S. DBCs. Some recent strategic alliances include Sandoz's $30 million investment in Cytel (La Jolla, CA), Ciba-Geigy's investment in Texas-based Tanox Biosystems (Houston, TX), and Glaxo's $20 million investment in Gilead Sciences (Foster City, CA) (34). In addition, many European pharmaceutical companies have licensed European marketing rights from U.S. DBCs. Examples include Boehringer Mannheim's agreement with Genetics Institute to market EPO in Europe and Boehringer Ingelheim's arrangements for marketing Genentech's tPA.

European companies, such as Bayer, Ciba-Geigy, Roche, and Sandoz have developed significant in-house capabilities in biotechnology and maintain large biotechnology R&D budgets. Bayer has a biotechnology research budget of $100 million and Ciba-Geigy recently spent $60 million on a new central biotechnology research unit. Roche, in addition to acquiring Genentech, spent between $130 million and $140 million on biotechnology in 1989. Sandoz expects to invest $150 million in biotechnology in 1991 and a total of $1 billion by 1995 in biotechnology R&D, including both in-house and collaborative activities. European companies' expenditures for biotechnology are global. Roche, for example, funds R&D not only in its native Switzerland but also in the United States, the United Kingdom, and Japan. Sandoz conducts research in Switzerland, the United States, the United Kingdom, and Austria (17,36).

Japanese companies, in addition to increasing exports and their presence overseas, are also investing in U.S. DBCs. Examples include the following: Chugai Pharmaceutical's deals with Genetics Institute and Upjohn and its $110 million acquisition of Gen-Probe (San Diego, CA); Tokyo's Institute for Immunology's $20 million investment in IDEC Pharmaceuticals (La Jolla, CA); and Genetics Institute's collaboration with Japan's Yamanouchi Pharmaceutical Co. (34).

Competitive Influence of Government Policies

At the current level of commercialization, most of the factors influencing the competitiveness of U.S. pharmaceutical and dedicated biotechnology companies with respect to biotechnology are market forces and general economic variables. There are many U.S. Government policies that influence businesses based on health and life sciences without addressing biotechnology specifically. Federal funding for biomedical research, regulatory policies, and intellectual property protection are important public policies that affect the commercialization and competitiveness of U.S. biotechnology.

Federal Funding for Basic Research

The United States' lead in biotechnology is due in large part to strong government support for basic research in biological and biomedical sciences. The vast majority of Federal research support in the biological sciences goes to university scientists conducting basic research, whereas applied research and development has always been considered the responsibility of industry (48). Industry worldwide, including DBCs and pharmaceutical companies, has benefited from the strong research base funded by the U.S. Government (see app. C). Technology transferred between government laboratories, universities, and industry enables applied research and commercial development of biotechnology. Continued funding for basic research in biological sciences will be important for the future of biotechnology.

Regulation

The regulatory component of the human therapeutic development process is perceived, by both entrepreneurial and established companies, as the major factor influencing the time required to develop a pharmaceutical product. The debate over the rigorous and lengthy drug regulatory process has gone on for years. Arguments have been made that when too strict, regulation becomes prohibitive to pharmaceutical development. Overly stringent regulation could impede international competitiveness

and compromise human health by reducing the availability of therapeutic products. However, the importance of protecting the public from unsafe or ineffective drugs is stressed (48).

The FDA, its mission, responsibilities, and structure, is currently under review by an advisory committee of the U.S. Department of Health and Human Services (U.S. DHHS) which is addressing many of the concerns of industry, government, and the public (52). Representatives of the pharmaceutical industry and biotechnology firms, testifying before the advisory committee's drugs and biologics subcommittee, raised several issues of concern, including: the increased workload and resources of the Center for Biologics Evaluation and Research, responsible for reviewing biotechnology-derived therapeutics, the use of advisory committees, and the need for sufficient resources in terms of both personnel and equipment (15).

The regulatory process is a burden for both established pharmaceutical companies and DBCs. The time delay and lack of regulatory approval can be damaging to both DBCs and established companies, but, arguably, perhaps more so to a DBC. Very few DBCs benefit from product sales and profits to support R&D, and for many, FDA approval is the first positive sign of potential earning power—an important characteristic required for financing. Companies have expressed concern that FDA delays have negatively affected their ability to gain financing, especially from Wall Street (see box 5-F). However, thus far, the experience with biotechnology drugs has been mostly positive, with many biotechnology-derived drugs experiencing significantly shorter approval times than conventional drugs. According to the FDA Office of Biotechnology, marketing approval times for new biotechnology products have averaged about half of the mean 32 months (for approval of the New Drug Application which is fried after all clinical trials have been completed) required for approval of nonbiotechnology products (46).

In order to introduce products in markets worldwide, pharmaceutical companies and DBCs must obtain regulatory approval h-em each individual country in which they choose to market a drug. The drug approval process is different in each major market, and attempts are being made to harmonize regulatory procedures. Drug approval often takes longest in the United States. Of the 135 new drugs approved by FDA during the period 1984 to 1989, 106 were first approved abroad; in 1990, 18 of 23 drugs approved in the United States were frost approved abroad (29,5 1). Until 1986, with the

Box 5-F—Effects of Regulatory Decisions on Wall Street

A lack of regulatory approval is a setback for any drug developer, but for biotechnology companies it is potentially devastating, Wall Street, a primary source of financing for many biotechnology companies, places great importance on the Food and Drug Administration's (FDA) actions and often uses the administration's decisions as a basis for their stock recommendations for biotechnology companies, in lieu of product performance. Thus, a negative reaction from FDA leaves biotechnology companies, seeking their first product approval, much more vulnerable than an established company with a significant product portfolio currently generating revenue.

For example, in May 1987 an FDA advisory committee recommended against approval of Genentech's tissue plasminogen activator (tPA) (later approved and now on the market). Genentech's stock dropped 14 points in 2 days and lost 25 percent of its value. A more recent example is FDA's 1990 recommendation against Cetus' Interleukin-2 for the treatment of kidney cancer. In the 2 weeks surrounding FDA's decision, Cetus' stock dropped over 40 percent. After FDA's decision, Cetus' stock price fell from its 52-week high of $22.50 to $8.63. Since Wall Street cannot evaluate companies without products on the basis of sales, revenues, and profits, it must value them on the basis of research, people, potential, and scientific promise. FDA approval, or lack thereof, reflects on a company's scientific and product development ability; thus, when FDA approval is not granted, the value given the company by Wall Street drops.

SOURCES: R, Baum, "Biotech Industry Moving Pharmaceutical Products to Mark%," *Chemical and Engineering News, vol. 65, No. 29, July 20, 1987, pp. 11-14, 20, 28-32;* "Cetus *Lass* Widened in Fiscal 4th Quarter; Drug Costs Are Cited," *Wall Street Journal,* Aug. 8, 1990, p. B4; L. Christensen, "Cetus Considers Strategic Options After the Delay in FDA's Approval of Proleukin IL-2," *Genetic Engineering News,* vol. 10, No, 9, October 1990, pp. 1, 40, 48; B. Culliton, "Cetus's Costly Stumble on IL-2, "Science, vol. 250, No. 4977, Oct. 5, 1990, pp. 20-21; U.S. Congress, Office of Technology Assessment, "Financial issues Affecting Biotechnology: At Home and Abroad," transcript of a workshop held Sept. 13, 1990.

Box 5-G—The Drug Export Amendments Act of 1986

The Drug Export Amendments Act of 1986 allows the export of new drugs not yet approved by the Food and Drug Administration (FDA) for use in the United States. Export is restricted to 21 countries that have sophisticated drug approval processes and is dependent on the individual country's approval. The importer must sign a written agreement guaranteeing that they will not re-export the drug to countries other than the 21 approved.

FDA approval often takes longer than approval outside the United States. Before the act was passed, export of unapproved drugs was not allowed, and companies were forced to manufacture drugs abroad or license their technology to foreign firms in order to enter the marketplace. The amended act allows companies to recoup research and development costs and generate income sooner than if they had to wait for FDA.

The act holds particular importance for biotechnology companies, which in the early stages of development often lack the resources to establish manufacturing facilities abroad. Before the act was passed in 1986, biotechnology companies had to forfeit the proprietary rights to their technology to multinational partners overseas in order to ensure supply of the product and guarantee access to foreign markets and return on investment. Although many companies still license technology and marketing rights abroad, since 1986 many biotechnology companies have been able to preserve the right to supply their products from the United States. This change in the law is of considerable significance to international trade. Cetus has taken advantage of the act by exporting Proleukin (Interleukin-II) to several European countries, which have approved the drug, while waiting for FDA approval in the United States.

The Drug Export Amendments Act of 1986 applies only to human drugs. The export of drugs not registered in the United States for use in animals is not permitted. This maybe of significance to biotechnology in the future, as biotechnology has applications to veterinary medicine and animal health.

SOURCES: Drug Exports Amendments Act of 1986, Public Law 99-660; B. Andrews, vice president, Agricultural Division, Cyanamid International, Wayne, NJ, personal communication Aug. 6, 1990; G. Rathmann, chairman emeritus, Amgen Inc., Thousand Oaks, CA, personal communication Aug. 3, 1990.

passage of the Drug Export Amendments Act, it was against the law to export drugs from the United States not approved by FDA (see box 5-G).

Inconsistent **worldwide** regulations and the lack of acceptance of foreign clinical trial test data in particular, have caused problems for the pharmaceutical industry. The latter has, in the past, been a significant problem in Japan, where the U.S. Trade Representative concluded in 1989 that this, along with the difficulty of obtaining regulatory approval for drugs, increases the cost of doing business in Japan. The industry is somewhat protected by both the Standards Code, and the Technical Barriers to Trade Code of the General Agreement on Tariffs and Trade (GATT), which refers to the application of technical standards to products, including testing, labeling, and certification. It requires that standards are applied so as not to discriminate against imported products (45). This code is very important in ensuring that health and safety regulations are not used as trade barriers to discriminate against imported products (53).

Governments' approach to pharmaceutical regulation, including both the lengthy approval times and the inconsistency of worldwide regulations, influence the competitiveness of pharmaceutical fins. Attempts to harmonize regulations and improve the current drug approval processes will benefit all companies, independent of national origin, in their introduction of new products in global markets.

Intellectual Property Rights Protection

Patent protection has been judged to be of substantial importance to innovation, new product development, and new product introduction in several industries-including pharmaceuticals (24). Intellectual property protection, in the form of patents and orphan drug market exclusivity (see box 5-H), is critical to the pharmaceutical industry for two primary reasons:

- It can provide the temporary market monopoly necessary to recoup the high costs of R&D.
- Drugs with new therapeutic values depend on patent protection in order to capture and hold a significant market share. Patent expiration allows competing products, either generics or brand names from other companies, to enter the market (43).

Patents contribute to market success by denying market access to those products that will infringe a

Box 5-H—The Orphan Drug Act

The 1983 Orphan Drug Act seeks to induce the development of drugs for rare diseases. Rare diseases are defined by the legislation as conditions that affect fewer than 200,000 people in the United States. The act offers incentives to invest in orphan product development that, due to the small patient population, is not likely to offer a full return on investment to the company. The government offers grants, tax breaks, and most importantly, 7 years of market exclusivity to the first manufacturer to gain the Food and Drug Administration's (FDA) approval for a product with orphan designation. The market exclusivity provision is a form of intellectual property protection and has proven to be controversial.

Since the act was passed in 1983, over 375 products have received orphan designation from FDA, and over 40 orphan drugs are on the market. Nine of the 15 biotechnology-derived drugs on the market have orphan drug status, as do 19 additional biotechnology-derived drugs currently under development. Controversy was raised in the 101st Congress over three orphan drugs that turned out to be very profitable: 1) aerosol pentamidine, 2) erythropoietin (EPO), and 3) human growth hormone. The latter two are biotechnology-derived drugs. Arguments were made that these drugs would have been developed without the Orphan Drug Act incentives because there was great opportunity for profit.

The U.S. House of Representatives and the Senate passed amendments to the Orphan Drug Act that would have removed orphan drug status if the patient population exceeds 200,000 and also would have allowed for shared market exclusivity if another company could prove it was developing the same orphan drug simultaneously to the first company that received FDA approval. After much debate, and divided industry lobbying, the final bill applied only to new orphan products and not to the three drugs that spurred the debate. The bill, as passed, would have allowed market competition for products that proved to be particularly profitable. The President vetoed the legislation, claiming the shared exclusivity provision would remove incentive for developing orphan products.

The case of EPO is particularly controversial and complicated. Amgen (Thousand Oaks, CA) received FDA approval in June 1989 to market its EPO to dialysis patients suffering from anemia associated with end-stage renal disease, a patient population of under 200,000. EPO, paid for mostly by the government's Medicare program that covers dialysis patients, costs about $5,000 per patient per year, and Amgen has sold over $300 million worth of the drug. Amgen received 7 years of marketing exclusivity, under the Orphan Drug Act, for EPO used to treat chronic kidney failure. Genetics Institute (Cambridge, MA) also has developed EPO as an orphan drug, but the company has yet to receive FDA approval due in large part to Amgen's orphan drug claims.

SOURCE: Office of Technology Assessment, 1991.

patent position during the lifetime of the patent. A U.S. patent provides 17 years of protection, but since the patent is usually applied for prior to broad testing, several of the initial 17 years of protection granted are lost during the years of clinical development. The regulatory process reduces the effective patent life to approximately 9 to 10 years, resulting in shorter protected market time and increased difficulty in obtaining return on investment (5).

In the 1980s, legislation was passed in the United States and Japan, and draft legislation is now being considered by the EC to extend patent protection to make up for at least some of the years lost during clinical development (see box 5-I). This extension of effective patent life recognizes the importance of patent protection, the effect of the regulatory process on new product development, and the need for public policies to provide incentives for companies to continue investing in R&D.

Intellectual property protection has historically been a problem for the pharmaceutical industry. Many countries, particularly newly industrializing countries (NICs) such as India, Argentina, and other South American countries, do not provide patent protection for pharmaceuticals. Their reasoning includes the desire to protect domestic industries from competition, to encourage domestic production without the need to pay hard currency royalties to other countries (10), and to reduce or control retail prices (31). Copying pharmaceuticals is relatively easy, and companies have lost significant sales and revenues to patent infringers and markets where patent protection is not available or effective (37).

Until recently, neither Brazil nor Canada granted pharmaceutical patents. Brazil is working on a draft

Box 5-I—Patent Term Extension for Pharmaceuticals

Drug companies usually secure patent protection early in drug development, before the drug enters the regulatory process. Regulatory approval for new drugs takes, on average, 7 to 10 years to complete. This translates into a 7- to 10-year reduction in patent protection for pharmaceutical products when they reach the market, leaving such products with, on average, 9 years of protected life. In response, the United States and Japan passed legislation allowing the extension of patent terms for pharmaceuticals. Similar legislation in being considered by the European community (EC).

In 1984, the Unites States passed the Drug Price Competition and Patent Term Restoration Act of 1984. The act restores part of the patent life lost due to lengthy regulatory approval The act allows extension of the patent term for up to 5 years, but it does not allow extension beyond 14 years of effective patent life. The actualextension granted is equal to the total time taken by the Food and Drug Administration (FDA) to review the New Drug Application, plus one-half of the clinical testing time. In addition, the act promotes generic competition by providing FDA with an Abbreviated New Drug Application (ANDA) process. This process facilitates the approval of generic drugs by eliminating the need for costly clinical studies. An ANDA does require the sponsoring company to demonstrate its generic's bioequivalence to the pioneer drug. This is much less costly and time-consuming than complete clinical trials and facilitates the market entrance of generic drugs.

Japan also allows similar patent term extension for pharmaceuticals. In 1988, revisions were made to Japanese patent law to allow for an extension of the patent term for pharmaceutical products. Extension can be granted for periods up to 5 years, on the basis of time lost during the required drug approval procedures.

Pressure has been put on the European Commission to amend its patent law to allow for patent term extension similar to that offered by the United States and Japan. France and Belgium provided the first draft legislation to the commission, which responded with a proposal for a supplementary protection certificate (SPC). It was adopted in 1990 and currently is in front of the European Parliament. The proposal would provide effective protection for 16 years by granting a supplementary certificate to holders of a basic European patent. The guaranteed 16-year monopoly is longer than that created by the U.S. and Japanese patent term extensions.

The formula for deriving the extension is somewhat complex. The SPC takes effect the day after the basic patent expires and will be equal to the time elapsed between the filing of an application for a basic patent and the date of the first marketing approval in the EC, minus 4 years. The term for a European patent is 20 years, thus SPC will guarantee a monopoly of 16 years after marketing approval in almost all cases. The maximum length of an SPC is 10 years, thus for all cases in which marketing authorization is given up to 15 years after the basic patent application is filed, the company will be granted a 16-year monopoly. If 15 or more years pass, the company will not be given a 16-year monopoly, but it will receive a maximum SPC of 10 years.

Patent term extension in the United States and Japan and the proposed legislation in Europe recognize the importance of patent protection and market exclusivity for pharmaceutical producers, and acknowledge the burden of regulation.

SOURCES: H, Grabowski and J. Vernon, "Longer Patents for Lower Imitation Barriers: The 1984 Drug Act," *American Economic Review*, vol. 76, No. 2, May 1986, AEA Papers and Proceedings, pp. 195-198; R. Whaite and N. Jones, "Supplementary protection Certificates—Restoration of the Patent Term for pharmaceutical, The European Commission's proposed Regulation," Linklaters & Paines, 199& M. Fujii, "Government's Support for Pharmaceutical Industry," *Business Japan*, vol. 33, Issue 7, July 1988, pp. 80-83.

law that will provide both product and process patents for pharmaceutical products and which may be approved in 1991. In response, the United States has lifted sanctions against Brazilian pharmaceutical products, levied in 1988 in response to Brazilian companies' infringement on U.S. pharmaceutical patents. Canada has tied patent protection to an increase in R&D within the country. Bill C-22, passed in 1987, provides 10 years of patent protection to companies in return for an increase in their R&D spending in Canada as a percentage of sales: from 4.9 percent in 1986, to 8 percent in 1991, 9 percent in 1994, and 10 percent in 1996. The incentive has worked, with Merck Frosst (Canadian subsidiary of Merck & Co.), Glaxo, and Sandoz, among others, making substantial R&D investments in Canada (35).

SUMMARY

Biotechnology has found its place in the research-based pharmaceutical industry, both as a production technology and a research tool. Biotechnology is

particularly important for research and drug discovery as it allows for a molecular- and cellular-level approach to disease, drug-disease interaction, and drug design. Biotechnology is likely to be the principal scientific driving force for the discovery of new drugs as we enter the 21st century, and the impact of biotechnology on the discovery of new therapeutic chemical entities is difficult to overestimate.

Dedicated biotechnology companies and established pharmaceutical companies are pursuing the commercial development of biotechnology independently and through joint efforts. While the future of the technology itself is bright, that of the pioneering, innovative DBCs is less clear. The pharmaceutical industry is highly competitive, global, and risky and requires significant resources. The markets are global, the R&D and marketing are expensive, the regulatory requirements axe strict, and the financiers of biotechnology companies are becoming more discriminatory in their funding.

DBCs and pharmaceutical companies often work in concert, each contributing valuable assets required for new drug development. DBCs' strengths include innovative research and technological capabilities which, when combined with the monetary, regulatory, and marketing strengths of established pharmaceutical companies, translate into new pharmaceutical products. The majority of DBCs, which focus exclusively on the commercialization of biotechnology, could not survive without strategic alliances. Pharmaceutical companies, which are increasingly integrating biotechnology into their in-house research programs, use biotechnology to complement traditional approaches to drug discovery and depend on strategic alliances for innovative new products and technological know-how.

At this point in the commercialization of biotechnology, much of the success or failure rests on economic and market forces, in addition to scientific and technological feasibility. Government policies that affect these conditions contribute to, but are not likely to independently determine, the success or failure of either the companies or the technology itself. Several government policies that are affecting the successful commercialization of biotechnology and the competitiveness of the U.S. pharmaceutical industry as a whole have been identified. These policies include:

- government support for basic research in biological and biomedical science,
- regulatory policies for the approval of new drugs and biologics, and
- intellectual property rights protection.

Continued support for basic research in biological and biomedical sciences is essential to maintain the strong scientific base that has given the United States the acknowledged lead in biotechnology. Improved intellectual property protection at home and abroad and efforts to harmonize worldwide patent polices will benefit both DBCs and pharmaceutical companies in their drug development efforts. Scrutiny and improvement of regulatory policies, especially the length of time required to obtain FDA approval, will contribute to increased competitiveness of U.S. industry. Action on these points would likely contribute to U.S. competitiveness in the commercialization of biotechnology, which, at this stage, is highly dependent on market forces.

CHAPTER 5 REFERENCES

1. "An Anti-Depressant for Americans Drug Industry," *The Economist,* vol. 294, No. 7376, Jan. 12,1985, pp. 70-71.
2. Beier, D., vice president, Governmental Affairs, Genentech, Inc., personal communication, Dec. 6, 1990.
3. Business Technology Research, Inc., *Drug Delivery Systems* (Wellesley Hills, MA: Business Technology Research, 1988).
4. "Centocor Still Awaiting Centoxin FDA Advisory Committee Review," *F-D-C Reports, Inc.,* vol. 52, No. 49, Dec. 3, 1990, p. T&G-1.
5. Cocks, D.L., "Economic and Competitive Aspects of the Pharmaceutical Industry," in M.C. Smith, Ph.D., *Principles of Pharmaceutical Marketing,* 3d ed. (Philadelphia, PA: Lea & Febiger, 1983).
6. Copmann, T., Pharmaceutical Manufacturers Association, personal communication, December 1990.
7. Crombie, L., "Sugared Pill," *Nature,* vol. 347, No. 6289, Sept. 13, 1990, p. 137.
8. Cutaia, J.H., "In the Pink-Except for a Case of Nerves," *Business Week, No. 3140,* Jan. 8, 1990, p. 102.
9. Dart, E. C., "Exploitation of Biotechnology in a Large Company," *Phil. Trans. R. Soc.* Lond. B 324, 1989, pp. 599-611.
10. Ditzel, R., director, University of California Technology Management, personal communication, December 1990.
11. "The Doctor's Dilemma," *The Economist,* vol. 314, No. 7639, Jan. 27, 1990, pp. 69-70.

12. Eisenstodt, G., "A Different Kind of Drug Problem (Inroads Into American Market by Japanese Pharmaceutical Companies)," ***Forbes,*** vol. 145, No. 2, Jan. 22, 1990, pp. 4041.
13. Ernst & Young, ***Biotech 91: A Changing Environment (San*** Francisco, CA: Ernst & Young, 1990).
14. Ganellin, C.R., FRS, "Discovering New Medicines,' ***Chemistry and Industry, No.*** 1 (London, 1989), pp. 9-15.
15. Godown, R.D., president, Industrial Biotechnology Association, statement before the Subcommittee on Drugs and Biologics of the Advisory Committee on the Food and Drug Administration, U.S. Department of Health and Human Services, Nov. 8, 1990, La Jolla, CA.
16. Grabowski, H.G., "AnAnalysis of U.S. International Competitiveness in Pharmaceuticals," ***Managerial and Decision Economics, special*** issue, spring 1989, pp. 27-33.
17. Hodgson, J., "European Biopharmaceutical Culture,'' ***Biotechnology,*** vol. ***8, No. 8,*** August 1990, pp. 720-723.
18. Hoff, L. C., "External Factors Will Shape Pharmaceutical Industry Future," ***Financier,*** vol. 11, Issue 12, December 1987, pp. 3640.
19. Howells, J., "The Globalisation of Research and Development: A New Era of Change?" ***Science and Public Policy,*** vol. 17, No. 4, October 1990, pp. 273-285.
20. Jadlow, J.M., "A Summary and Critique of Economic Studies of the Ethical Drug Industry: 1%2-1968," R.I. Chien (cd.), ***Issues in Pharmaceutical Economics*** (Lexington, MA: Lexington Books, 1979).
21. Klausner, A., director of research, Domain Associates, personal communication, November 1990.
22. Layman, P.L., "Global Pharmaceutical Industry Undergoing Major Shifts," ***Chemical and Engineering News,*** vol. 66, No. 35, Aug. 29, 1988, pp. 16-17.
23. Macek, K., president, TMS Management, Duxbury, MA, personal communication, December 1990.
24. Mansfield, E., "Patents and Innovation: An Empirical Study," ***Management Science,*** vol. 32, No. 2, February 1986, pp. 173-181.
25. Marsh, P., "Biotechnology and the Drug Industry," ***British Medical Journal,*** vol. 300, No. 6718, Jan. 20, 1990, pp. 146-147.
26. Merck& Co., Inc., Rahway, NJ, 1989 Annual Report.
27. Miller, W.R., "Productivity and Competition: A Look at the Pharmaceutical Industry," ***Columbia Journal of WorldBusiness,*** vol. *23,* Issue 3, fall 1988, pp. 85-88.
28. Montague, M., research operations director, Monsanto Co., personal communication, December 1990.
29. Mossinghoff, G.J., president, Pharmaceutical Manufacturers Association, statement at hearings before the International Trade Commission, Jan. 17, 1991.
30. ''The New World of Drugs," ***The Economist, vol. 310, No. 7588,*** Feb. 4,1989, pp. 63-64.
31. Omenn, G., dean, School of Public Health and Community Medicine, University of Washington, personal communication, December 1990.
32. Pharmaceutical Manufacturers Association, Washington, DC, "Biotechnology Medicines in Development, 1990 Annual Survey."
33. Raines, L., director, governmental relations, Industrial Biotechnology Association, personal communication, Nov. 27, 1990.
34. Ratner, M., "The Year in Review: Perspectives on Biobusiness 90," ***Biotechnology,*** vol. 8, No. 10, October 1990, pp. 913-914.
35. Reisch, M.S., ''Canada's Merck Frosst Plans Major Pharmaceutical R&D Expansion," ***Chemical and Engineering News,*** vol. 67, No. 49, Dec. 4,1989, pp. 16-17.
36. "Sandoz 'Innovascan' Biotechnology Discovery Initiative," ***F-D-C Reports, Inc.,*** vol. 53, No. 6, Feb. 11, 1991, pp. T&G-7-8.
37. ***Scrip,*** Review Issue 1989.
38. Sharp, M., "Collaboration and the Pharmaceutical Industry-Is it the Way Forward," DRC discussion paper No. 71, Science Policy Research Unit, University of Sussex, May 1989.
39. Sharp, M., ''Technological Trajectories and Corporate Strategies in the Diffusion of Biotechnology," DRC discussion paper No. 74, Science Policy Research Unit, University of Sussex, paper for Royal Swedish Academy of Engineering Sciences and OECD conference on Technology and Investment: Crucial Issues for the 1990s, Stockholm, Jan. 21-24, 1990.
40. Stucki, J., vice president, pharmaceutical research, retired, Upjohn Co., personal communication, November 1990.
41. "Surviving the Changes of the '90s," ***Scrip, No.*** 1523, June 15, 1990, pp. 16-17.
42. Syntex Corp., Palo Alto, CA, 1989 ***Annual Report.***
43. Temin, P., ''Technology, Regulation, and Market Structure in the Modern Pharmaceutical Industry," ***Bell Journal of Economics, vol.*** 10, autumn 1979, pp. 426446.
44. Thayer, A., "Many Biotech Companies Enter '90s With Sharply Higher Revenues," ***Chemical and Engineering News,*** vol. 68, No. 14, Apr. 2, 1990, p. 9-11.
45. U.S. Congress, Congressional Budget Office, ***The GATT Negotiations and U.S. Trade Policy*** (Washington, DC: Congressional Budget Office, June 1987).
46. U.S. Congress, Office of Technology Assessment, "Biotechnology in a Global Economy: Options for

U.S. Strategy," transcript of a workshop held May 2, 1989.
47. U.S. Congress, Office of Technology Assessment, "Financial Issues Affecting Biotechnology: At Home and Abroad," transcript of a workshop held Sept. 13, 1990.
48. U.S. Congress, Office of Technology Assessment, New ***Developments in Biotechnology: U.S. Investment in Biotechnology, OTA-BA-360*** (Springfield, VA: National Technical Information Service, July 1988.
49. U.S. Congress, Senate Committee on Labor and Human Resources, ***Hearings on the Advertising, Marketing, and Promotional Practices of the Pharmaceutical Industry, Serial No. 101-1217,*** December 1990.
50. U.S. Department of Commerce, International Trade Administration, 1990 ***U.S. Industrial Outlook*** (Washington, DC: U.S. Government Printing Office, January 1990).
51. U.S. Department of Commerce, International Trade Administration, 1991 U.S. ***Industrial Outlook*** (Washington, DC: U.S. Government Printing Office, January 1991).
52. U.S. Department of Health and Human Services, Advisory Committee on the Food and Drug Administration, "Interim Progress Report to the U.S. Department of Health and Human Services,' September 1990.
53. United States Office of the U.S. Trade Representative, 1989 National Trade Estimate Report on Foreign Trade Barriers (U. S., GPO).
54. Warden, W.M., "The History of Drug Discovery, Development, and Regulation," R.I. Chien (cd.), ***Issues in Pharmaceutical Economics*** (Lexington, MA: Lexington Books, 1979).
55. Werner, R.G., ''Biobusiness in the Pharmaceutical Industry," ***Arzneimittel-Forschung,*** vol. 37 (II), No. 9, 1987, pp. 1086-93.
56. Wolnack, B., president, Wolnack & Associates, personal communication, December 1990.
57. "World Pharma Market Estimates," ***Scrip, No. 1555,*** Oct. 5, 1990, p. 20.