PART II
Firms Commercializing Biotechnology

Chapter 4

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Introduction

Biotechnology has the technical breadth and depth to change the industrial community of the 21st century because of its potential to produce substantially unlimited quantities of:

- products never before available,
- products that are currently in short supply,
- products that cost substantially less than products made by existing methods of production,
- products that are safer than those now available, and
- products made with raw materials that may be more plentiful and less expensive than those now used.

By virtue of its wide-reaching potential applications, biotechnology lies close to the center of many of the world's major problems—malnutrition, disease, energy availability and cost, and pollution. It is because of biotechnology's promise that the developed countries of the world have commenced a competitive battle to commercialize its applications,

Nowhere in the world are efforts to commercialize biotechnology stronger than in the United States. * Large established U.S. companies in industries ranging from pharmaceuticals to petroleum have followed the lead in developing biotechnology that was set by entrepreneurial new biotechnology firms (NBFs) in the United States whose dedication to biotechnology is unmatched anywhere. Major competitive challenges to the United States in current product markets, as well as in new biotechnology markets yet to be defined, will be mounted by established companies in the Federal Republic of Germany, United Kingdom, Switzerland, and France—but the most formidable challenge will come from established companies in Japan. The Japanese consider biotechnology to be the last major technological revolution of this century (58). More immediate than its promise of helping to alleviate some world problems, biotechnology offers Japan an important opportunity to revitalize its structurally depressed basic industries whose production processes are reliant on imported petroleum,

This chapter provides an overview of U.S. and foreign private sector research and development (R&D) and commercialization efforts in biotechnology to help answer the broader question being addressed by this report: Will the United States be able to translate its present technological lead into worldwide commercial success by securing competitive shares of biotechnology-related product markets? The first section of the chapter provides an overview of the types of companies that are commercializing biotechnology in the United States and the five foreign countries expected to be the major competitors in the area of biotechnology. This section briefly examines the four fields where biotechnology is being applied most vigorously —pharmaceuticals, animal health, plant agriculture, and specialty chemicals. The second section analyzes and compares the strength of the U.S. support base with that of the competitor countries, using three important product areas for comparison: biochemical reagents, instrumentation, and software. The third section analyzes the respective roles of the firms applying biotechnology in the United States—NBFs and established companies-in the domestic and international development of biotechnology. It also describes collaborative ventures between NBFs in the United States and established U.S. and foreign companies that are seeking to commercialize biotechnology. The chapter concludes by summarizing major findings with respect to the role of NBFs and established companies in the U.S. commercialization effort.

* For a summary of activities in biotechnology in countries other than the United States, see *Appendix B: Country Summaries.*

Overview of U.S. and foreign companies commercializing biotechnology

U.S. and foreign efforts to develop and commercialize biotechnology differ substantially in qharacter and structure. The manner in which the United States and other countries organize their development efforts is important for two reasons: it can influence their respective commercial capabilities; and it will ultimately shape the character of international competition.

In the United States, two distinct sets of firms are pursuing commercial applications of biotechnology-NBFs and established companies. NBFs, as defined by this report, are entrepreneurial ventures started specifically to commercialize innovations in biotechnology. For the most part, they have been founded since 1976–the same year the U.S. firm Genentech was founded to exploit the recombinant DNA (rDNA) technology patented in the United States by Cohen and Boyer, * Typically, NBFs are structurally organized specifically to apply biotechnology to commercial product development. The established companies pursuing applications of biotechnology are generally processa-iented, multiproduct companies in traditional industrial sectors such as pharmaceuticals, energy, chemicals, and food processing. These companies have undertaken in-house biotechnology R&D in an effort to determine how and where best to apply biotechnology to existing or new products and processes. Table 4 provides a list of NBFs and established companies currently applying biotechnology in the United States and the targeted commercial areas of their research. Figure 10 illustrates the percentage of U.S. firms pursuing biotechnology R&D in specific application areas.

Sixty-two percent (135) of the 219 U.S. companies for whom commercial application areas are known* are pursuing applications of biotechnology in the area of pharmaceuticals; 28 percent are pursuing applications in animal agriculture, and 24 percent in plant agriculture.** In the area of specialty chemicals and food additives, commodity chemicals and energy, the environment, and electronics, respectively, relatively fewer U.S. firms are pursuing commercial applications of biotechnology. In some of these sectors, conventional technologies are working well or existing investments in capital equipment are very substantial. In others, much uncertainty still surrounds the potential of biotechnology or the research needed to develop applications of biotechnology is long term.

In Japan, the Federal Republic of Germany, Switzerland, France, and the United Kingdom, * * biotechnology is being commercialized almost exclusively by established companies. Most European nations and Japan, unlike the United States, tend, for different reasons, to emphasize the importance of large companies instead of small ones. Thus, the development of biotechnology in these countries is biased considerably toward the large pharmaceutical and chemical companies.

It should not be assumed that the small number of NBFs in the European countries or the lack of

● Two U.S. firms, Cetus and Agrigenetics, though established before 1976, are considered to be NBFs. Cetus was founded to capitalize on classical genetic techniques for product development, but showed early interest in biotechnology and began aggressively pursuing product development with the new techniques. Agrigenetics was formed in 1975 to link new genetic research with the seed business. Thus, the behavior and research focus of both Cetus and Agrigenetics place them in the new firm category despite their early founding dates.

● This figure does not include the companies listed that are specializing in bioprocessing, because the bioprocessing R&D may not be associated with specific products. See *Appendix D: Firms Commercializing Biotechnology in the United States* for an explanation of how the list was obtained.

" *These percentages add up to more than 100 percent because many of the firms are engaged in more than one area of commercial application.

●● In the United Kingdom, some NBFs, not including Celltech and Agricultural Genetics, are beginning to form on the periphery of universities. Plant Science, Ltd., for example, is linked to the University of Sheffield; Imperial Biotechnology, Ltd., is linked to the Imperial College in London; IQ(Bio) was formed by some Cambridge University biochemists; Boscot, Ltd., a joint venture between two Scottish institutions, was established by the University of Edinburgh and Heriot-Watt University, and Cambridge Life Sciences pursues biosensors based on work at Southampton University. As an indication of the increased number of NBFs forming in Britain, Biotechnology Investments, Ltd., the venture fund managed by N.M. Rothschild (the bank) now has for the first time since the fund was established more proposals from British firms than from companies in the United States (56).

Table 4.—Companies Commercializing Biotechnology in the United States and Their Product Markets~~[b]

Company (date founded)	Commercial application of R&D[c]	Ph.D.s[d]
Abbott Laboratories	Ph	
Actagen (1982)	Ph	5
Advanced Biotechnology Associates, Inc. (1981)	Ph	
Advanced Genetic Sciences, Inc. (1979)	PA	27
Advanced Genetics Research Institute (1981)	AA	8
Advanced Mineral Technologies, Inc. (1982)	Env	
Agrigenetics Corp. (1975)	PA,SCF	46
Allied Chemical Corp.	PA	
Alpha Therapeutic Corp.	Ph	
Ambico, inc. (1974)	AA	
American Cyanamid Co.	Ph,PA,AA	
American Diagnostics Corp. (1979)	Ph	
American Qualex (1981)	Ph,AA	
Amgen (1980)	Ph,PA,AA,SCF	45
Angenics (1980)	Ph	5
Animal Vaccine Research Corp. (1982)	AA	
Antibodies, inc. (1960)	Ph, AA	Ph,AA
Applied DNA Systems, inc. (1982)	Ph,SCF,CCE,Env	
Applied Genetics, inc. (1981)	AA	
ARCO Plant Cell Research Institute	PA	18
Atlantic Antibodies (1973)	AA	2
Axonics	Ph	
Baxter-Travenol Laboratories, Inc.	Ph	
Becton Dickinson &Co.	Ph	
Bethesda Research Laboratories, inc. (1976)	Ph,AA	
Biocell Technology Corp. (1980)	Ph	
Biochem Technology, inc. (1977)	Bioprocessing	
Bio-con, inc. (1971)	AA	
BioGenex Laboratories (1981)	Ph	
Biogen, inc. (1980)	Ph,AA,CCE,Env	79
Biological Energy Corp. (1981)	CCE,SCF	3
Bio Response, lnc, (1972)	Mass cell culture	6
Biotech Research Laboratories, inc. (1973)	Ph,CCE	11
Biotechnica lnternationa~ inc. (1981)	PA,CCE,SCF,Env, AA,Ph	12
Bio-Technology General Corp. (1980)	PA,AA,Ph	5
Brain Research (1968)	Ph	
Bristol-Myers Co.	Ph	
BTCDiagnostic, inc. (1980)	Ph	3
Calgene, inc. (1980)	PA	21
California Biotechnology, inc. (1982)	Ph,AA	21
Cambridge Bioscience Corp. (1982)	Ph,AA	
Campbell institute for Research & Technology	PA	
Celanese Corp.	CCE	
Cellorgan lnternationa~ inc. (1972)	Ph	
Celtek, inc. (1980)	Ph	5
Centaur Genetics Corp. (1981)	Ph,PA,AA	4
Centocor (1979)	Ph	14
Cetus Corp. (1971)	Ph,AA,CCE	45
Madison (1981)	PA	25
Palo Aito (1980)	Ph	2
Immune (IWO)	Ph	
Chiron Corp. (1981)	Ph,AA	26[e]
Ciba-Geigy	Ph	
Clonal Research (1970)	Ph	3
Codon (1980)	CCE	15
Collaborative Genetics, inc. (1979)	Ph,SCF,CCE	12
Collagen, inc. (1977)	Ph	
Cooper Diagnostics, Inc.	Ph	
Cooper-Lipotech, inc. (1981)	Ph	
Corning Glass Works	SCF	

Table 4.—Companies Commercializing Biotechnology in the United States and Their Product Markets[a]*[b] (Continued)

Company (date founded)	Commercial application of R&D[c]	Ph.	D.s[d]	
Crop Genetics International (1981)	PA			
Cutter Laboratories, Inc.	Ph			
Cytogen Corp. (1981)	Ph			7
Cytox Corp. (1975)	Env			
Damon Biotech, Inc. (1981)	Ph			10
Dairyland Foods Corp.	SCF			
Dart and Kraft, Inc.	SCF			
Davy McKee Corp.	Bioprocessing			
DeKalb Pfizer Genetics (1982)	AA			
Diagnon Corp. (1981)	Ph			
Diagnostic Technology, inc. (1980)	Ph			
Diamond Laboratories	AA			
Diamond Shamrock Corp.	AA,CCE			
DNA Plant Technology (1981)	PA			10
DNAX Corp.	Ph			
Dow Chemical Co.	Ph,PA,CCE,SCF, AA,Env			
Ean-tech, inc. (1982)	E~Env,Ph			3
Eastman Kodak Co.	Ph,Env			
Ecogen (1983)	PA			
E. 1. du Pontde Nemours &Co, Inc.	Ph,PA,CCE,SCF			
Electro Nucleonics Laboratories, Inc.	Ph			
Eli Ltily &Co.	Ph,PA			
EnBio, inc. (1975)	Bioprocessing			
Endorphin, inc. (1982)	Ph			
Engenics, inc. (1981)	Bioprocessing			25
Enzo Biochem, inc. (1976)	Ph,AA,CCE,SCF,PA			
Enzyme Bio-systems, Ltd.	SCF			
Enzyme CenteL Inc.	SCF			
Enzyme Technology Corp.	SCF			
Ethyl Corp.	CCE,SCF,Env			
Exxon Research & Engineering Co.	CCE,Env,SCF			
Fermented Corp. (1978)	Bioprocessing			
FMC Corp.	Ph			
Frito-Lay, Inc.	PA			
Fungal Genetics, inc. (1982)	Ph,SCF			
Genencor (1982)	SCF,CCE			
Genentech, inc. (1976)	Ph,AA,CCE,El			75
General Electric Co.	El,Env,Ph,SCF			
General Foods Corp.	PA			
General Genetics (1982).	Ph			
General Molecular Applications (1981)	Ph			
Genetic Diagnostics Corp. (1981).	Ph			3
Genetic Replication Technologies, inc. (1980).	Ph,AA			
Genetic Systems Corp. (1980)	Ph			14
Genetics Institute (1980)	Ph,PA,SCF,Env			24
Genetics Internationa~ Inc. (1980)	AA,Ph,SCF,CCE, Env,El			17
Genex Corp. (1977).	Ph,AA,SCF,Env			48
Gentronix Laboratories, inc. (1972)	El			
Genzyme (1981).	SCF			6
W. R. Grace&Co.	AA,SCF,Env,PA,Ph			
Hana Biologics, inc. (1978)	Ph			
Hem Research (1966)	Ph,AA			
Hoffmann-La Roche, Inc.	Ph			
Hybridoma Sciences, Inc, (1981)	Ph			
Hybritech, inc. (1978).	Ph			13
Hytech Biomedica~ inc. (1981)	E~Ph			10
IBM Corp.	El			
IGI Biotechnology, inc. (1975).	Ph			
Immulok, inc. (1980).	Ph			

Table 4.—Companies Commercializing Biotechnology in the United States and Their Product Markets~[b] (Continued)

Company (date founded)	Commercial application of R&D[c]	Ph.D.s[d]
Immunetech, inc. (1981)	Ph	
Immunex Corp. (1981)	Ph	18
Immuno Modulators Laboratories, inc. (1982)	Ph	
Immunogen (1981)	Ph	
Immunotech Corp. (1980)	Ph	
Imreg, Inc.	Ph	
Indiana BioLab (1972)	PA,AA,SCF,CCE	
Integrated Genetics, inc. (1981)	Ph	17
Interferon Sciences, inc. (1980)	Ph	7
International Genetic Engineering, inc. (Ingene) (1980)	Ph,PA,CCE	16
International Genetic Sciences Partnership (1981)	PA,AA	
International Minerals &Chemical Corp.	AA,PA,Env,CCE	
International Plant Research Institute (IPRI) (1978)	PA	35
Kallestad Laboratories, Inc.	Ph	
Kennecott Copper Corp.	Env	
Lederle Laboratories	Ph,AA	
The Liposome CoVlnc. (1981)	Ph,AA	
Liposome Technology, inc. (1981)	Ph,AA	
Litton Bionetics	Ph	
3MC0.	Ph	
Mallinckrodt, Inc.	Ph	
Martin Marietta	SCF,PA	
Meloy Laboratories, inc. (1975)	Ph	
Merck&Company, Inc.	Ph,AA	
Microlife Genetics (1981)	SCF,Env	
Miles Laboratories, Inc.	Ph,SCF,CCE,AA	
Miller Brewing Co.	PA	
Molecular Biosystems, inc. (1980)	Ph	7
Molecular Diagnostics (1981)	Ph	
Molecular Genetics, inc. (1979)	Ph,PA,AA	20
Monoclinal Antibodies, inc. (1979)	Ph,AA	7
Monsanto Co.	PA,AA	
Multivac, Inc.	Ph,PA,AA,SCF	
Nabisco, Inc.	PA	
National Distillers &Chemical Co.	CCE	
NPI (1973)	PA,CCE,SCF	25
Neogen Corp. (1981)	PA,AA	
New England Biolabs	Ph	
New England Monoclinal Resources (1982)	Ph	
New England Nuclear Corp.	Ph	
Norden Laboratories	AA	
Novo Laboratories, Inc.	Ph,SCF	
Nuclear&Genetic Technology, inc. (1980)	Ph	
Ocean Genetics (1981)	SCF	
Oncogen (1982)	Ph	
Oncogene Science inc. (1983)	Ph	
Organon, Inc.	Ph	
Ortho Pharmaceutical Corp.	Ph	
Petrogen, inc. (1980)	Env	7
PfizeL Inc.	Ph,PA,CCE,AA, SCF,Env	
Phillips Petroleum Co.	Env,SCF,CCE	
Phytogen (1980)	PA	5
Phyto-Tech Lab	PA	
Pioneer Hybrid International Corp.	PA	
Plant Genetics, inc. (1981)	PA	11
Polybac Corp.	Ph,SCF,Env	
PPG Industries	SCF	
Purification Engineering, Inc.	Bioprocessing	
Quidel Home (1982)	Ph	

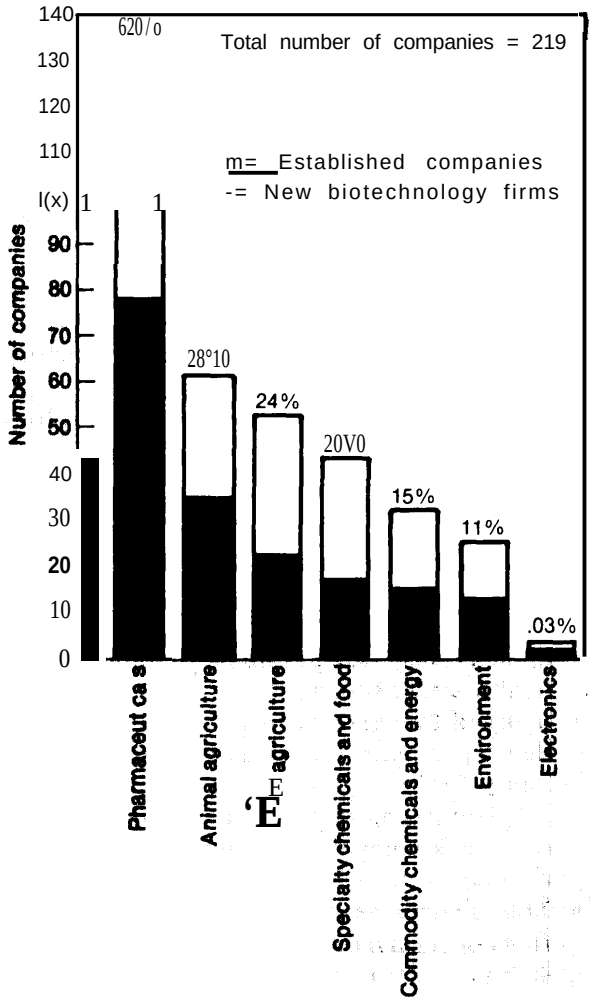
Table 4.—Companies Commercializing Biotechnology in the United States and Their Product Markets~*[b] (Continued)

Company (date founded)	Commercial application of R&D[c]	Ph.D.s[d]
Replicon (1982)	Ph,SCF	
Repligen Corp. (1981)	Ph,AA,CCE,SCF	
Ribi Immunochem Research, Inc. (1981)	AA,Ph	3
Rohm & Haas	PA	
Salk Institute Biotechnology/ Industrial Associates, Inc. (1981)	Ph,AA,CCE	9
Sandoz, inc.	Ph,PA,AA	
Schering-Plough Corp.	Ph,AA	
SDS Biotech Corp. (1983)	AA	
G. D. Searle &Co.	Ph,SCF	
Serono Laboratories, Inc.	Ph	
SmithKline Beckman	Ph,AA	
E. R. Squibb&Sons, Inc.	Ph	
A. E. Staley Manufacturing Co.	AA,PA,SCF	
Standard Oil of California	Env	
Standard Oilof Indiana	Ph,PA	
Standard Oil of Ohio	PA	
Stauffer Chemical Co.	PA	
Summa Medical Corp.	Ph	
Sungene Technololgies Corp. (1981)	PA	4
Sybron Biochemical	Env	13
Synbiotex Corp. (1982)	Ph,AA	
SyncorlnternationaI.	Ph	
Synergen (1981)	AA,SCF,CCE,Env	21
Syngene Products and Research, Inc.	AA	8
Syntex Corp.	Ph,AA	
Syntro Corp. (1982)	AA,CCE	5
Syva Co. (1966)	Ph	
Techniclone international Corp. (1982)	Ph	6
Unigene Laboratories, inc. (1980)	Ph,AA	12
Universal Foods Corp.	SCF,PA	
University Genetics CO. (1980) Genetic Clinics	Ph	
U.O.P v Inc.	SCF,CCE	
The Upjohn Co.	Ph,AA,PA	
Viral Genetics (1981)	Ph	
Wellcome Research Laboratories	Ph	
Worne Biotechnology, inc. (1982)	PA,CCE,Ph,AA, Env,SCF	10
Xenogen, inc. (1981)	Ph,PA	
Xoma Corp. (1981)	Ph	
Zoecon Corp. (1968)	PA,AA	
Zymed Laboratories	SCF,CCE	5
Zymos CorD. (1982)f	PhSCF	

[a] **Does not include support firms.**
%eeApperrdixD:IrrdexofFirmsinthe UnitedStatesCommerciaikingBiotechnology **foradescrlptlonofhowthedatawere collected.**
[c] **ph.pharmaceuticals, pA:plant Agriculture, AA: Animal Agriculture, SCF: Specialty Chemicals ~d Food, CCE:Commodlty Chemicals and Energy, Env: Environmental (Microbial Enhanced Oil Recovery, Microbial Mining, Pollution Contro~ and Toxic Waste Treatement~ El Electronics.**
[e] **AsofMarch1983.**
[d] **M.D.s and Ph.D.s.**

SOURCE: Office of Technology Assessment.

Figure IO.— Percentage of Firms in the United States Pursuing Applications of Biotechnology in Specific-Industrial Sectors*



● The total percentage of firms exceede W percent bacauea aome compartiasamr applying biotaohnofogy In mom than one industrial 8eotor,

SOURCE Off Ice of Technology Assessment.

NBFs in Japan will retard those countries' development of biotechnology. Varying strategies, organizational differences, and cultural factors all contribute to the competitive strengths of foreign countries' established companies. It is important to note, however, that the complementary efforts of NBFs and established companies in the United States have been a major factor in providing the United States with an early competitive advantage in the commercialization of biotechnology.

Although there are few NBFs outside the United States at present, some European countries are beginning to sense that small firms can make important contributions to innovation, particularly in high-technology fields such as biotechnology. Thus, in contrast to the West German Government, which believes that the development of biotechnology in West Germany is the province of the large chemical companies for which the country is noted and that NBFs are "not in line with the German mentality" (5), the British and French Governments have aided in the establishment of small firms such as Celltech, (U.K.), Agricuhural Genetics (U.K.), and Transgene (France's leading biotechnology venture company).

Efforts in support of small company formation are also being undertaken by organizations elsewhere in Europe. The Organisation for Economic CoOperation and Development, for example, in an effort to spur technological innovations, has made several proposals designed to support small firm development (65). These proposals encompass the promotion of new sources of venture capital, assistance to new startups in developing high quality feasibility studies, and diverse measures to encourage high-technology startups.

Venture capitalization is almost exclusively an American phenomenon (5,69). Many would agree that the formation of venture capital and entrepreneurial drive necessary to start small high-technology firms and vigorously commercialize inventions has been inhibited in much of Europe by a historical labor attitude that gives priority to job security and a predictable business environment rather than to aggressive risk-taking. In Japan, individualism and the creation of small, entrepreneurial and independent high-technology firms appears to be discouraged by cultural traits emphasizing group identity and acceptance. Large, very successful firms typical of Japan provide workers with a group identity and a sense of security, and it is these firms that are commercializing biotechnology in that country.

The biotechnology-related activities of U.S. and foreign companies in the pharmaceutical and animal and plant agriculture sectors are introduced below. Also discussed are foreign companies' biotechnology-related activities in specialty chemi-

cals. Discussion of U.S. private sector activities in specialty chemicals, commodity chemicals, and the environmental and electronics fields is reserved for the chapters in part III. It is important to recognize that there is no "biotechnology industry." Biotechnology is a set of technologies* that can potentially benefit or be applied to several industries.

The industrial sector in which the earliest applications of biotechnology have occurred is the pharmaceutical sector. Because of the rapid diffusion of the new genetic techniques into pharmaceutical R&D programs, the pharmaceutical sector is currently the most active in commercializing biotechnology. For this reason, the pharmaceutical sector serves as a model for the development of biotechnology in this chapter and in much of this report, It is important to recognize however, that the development of biotechnology in other industrial sectors will differ from its development in the pharmaceutical sector. Regulatory and trade barriers and a marketing and distribution system unique to the pharmaceutical sector limit the applicability of the model to other industrial sectors.

Pharmaceutical industry **

The pharmaceutical industry is one of the most successful high-technology sectors of the world economy (80). Because research is the foundation of competitive strength for modern pharmaceutical companies (55), and because pharmaceuticals are the first products to which biotechnology has been applied, the first and perhaps most intense proving ground for U.S. competitive strength in biotechnology will be in the area of pharmaceuticals.

U.S. COMPANIES

The first applications of biotechnology have emerged in the area of pharmaceuticals for several reasons. First, rDNA and MAb technologies were developed with public funds directed toward biomedical research. The first biotechnology products-MAb in vitro diagnostic kits, rDNA-produced human insulin, and interferon—are a direct result of the biomedical nature of the basic research that led to these new technologies. Second, pharmaceutical companies have had years of experience with biological production methods, and this experience has enabled them to take advantage of the new technologies. Finally, since some pharmaceutical products, such as large poly - peptides and antibiotics, can only be produced by biological methods, there are no competing production methods that might inhibit the application of biotechnology to their production.

Pharmaceuticals are profitable products because they are low volume, high-value-added products. * This and other financial considerations such as the following have led many U.S. companies to apply biotechnology to the pharmaceutical field.

- The time required to develop some pharmaceutical applications of biotechnology, in particular MAb or DNA probe in vitro diagnostic products for humans, is much less than that required to develop other industrial applications (except possibly some animal health applications).
- Many of the pharmaceutical products being developed with biotechnology are replacements for or improvements in pharmaceutical products already on the market, and they can quickly generate income to finance the development of additional products.
- The pharmaceutical industry offers high rates of return on both sales and equity and is thus an attractive and profitable industrial sector into which firms might diversify.
- Many of the biotechnology pharmaceutical markets may be relatively small. Small firms with limited production and financial resources are able to compete more equally with large firms in small product markets rather than in large markets, because economies of scale and costs of marketing in small product markets are small.

"See Chapter 3: The Technologies.

" 'Applications of biotechnology to the area of pharmaceuticals are discussed further in *Chapter 5: Pharmaceuticals.*

"Value added is the value that a company adds to goods and services that it purchases from other companies. It is the difference between the sales revenues and the cost of resources that it has purchased from other companies. For a "high-value+ idded" product, therefore, the difference between the resources expended to produce the product and the sales revenues generated by the product is greater than average.

U.S. pharmaceutical companies are quite active internationally. Table 5 illustrates the distribution of sales by the top 20 U.S. and foreign pharmaceutical companies in 1981. Sales by the U.S. companies listed represented almost 60 percent of the total pharmaceutical sales for the top 20 pharmaceutical companies in the world. On the average, almost 42 percent of the sales by these U.S. companies were foreign sales. According to the Institute for Alternative Futures, foreign sales accounted for roughly 43 percent of total U.S. prescription drug sales in 1980 (45), and U.S. pharmaceutical subsidiary sales in foreign countries exceeded $10 billion in 1980. * Given established U.S. pharmaceutical companies' strong export performance in the past, the U.S. posture in world pharmaceuticals markets will be a subject of great interest as biotechnology develops.

Up until about 1976, the average participant in the U.S. pharmaceutical industry could be described as a research-based, integrated, multinational company that spent (and still does) approximately 11.5 percent of its annual pharmaceutical sales on R&D (67). Since about 1976, the profile of the participants has changed considerably. Approximately 70 new US. companies have entered the pharmaceutical field just to apply biotechnology. Many of these NBFs are wagering their existence on the success of commercial pursuits of biotechnology in nascent pharmaceutical product markets. In total, about 135 U.S. companies—78 NBFs and 57 established companies—are known to be pursuing pharmaceutical product and process development using biotechnology. *

Since the early 1960's, the U.S. share of world pharmaceutical research, innovation, production, sales, and exports has declined, as has the number of U.S. companies actively participating in the various ethical drug markets compared to the

• **This figure is from a survey of Pharmaceutical Manufacturers Association member companies that had not been published as this report went to press.**

• **The high level of US. firms' interest in pharmaceutical applications of biotechnology is in part a reflection of the large number of old and new firms producing MAbs.** Many companies included **in table 4 are using** hybridoma **technology to produce MAbs for the markets traditionally addressed by the pharmaceutical industry. In some cases, OTA did not have sufficient information to determine the specific application for MAbs. For example, some companies indicated that they were engaged** in **the production of MAbs, but would not specify their intended use (i.e., research, separation and purification, diagnostic or therapeutic products for humans, animals, or plants). Because a majority of firms producing MAbs are manufacturing MAbs for pharmaceutical use, OTA placed firms for whom data were incomplete in the pharmaceutical sector, even though** hybridoma technology **is also essential to fundamental molecular research on plants, animals, and bacterial systems.**

Table 5.–Distribution of Sales by the Top 20 U.S. and Foreign Pharmaceutical Companies, 1981

Company	Home country	Percent of sales in home country	Percent of sales in other countries	1981 total pharmaceutical sales (millions of dollars)	Share of pharmaceutical sales
American Home Products	Us.	660/0	440/0	$2,303	
Merck	Us.	53	47	2,266	
Bristol-Myers	Us.	71	29	2,190	
Warner Lambert	Us.	55	45	2,045	
Smith Kline Beckman	Us.	59	41	1,782	
Pfizer	Us.	43	57	1,777	
Eli Lilly	Us.	62	38	1,664	580/o
Johnson & Johnson	Us.	56	44	1,308	
Upjohn	Us.	62	38	1,242	
Abbott	Us.	65	35	1,182	
Schering-Plough	Us.	51	49	924	
Hoechst	F.R.G,	28	72	2,555	
Bayer	F.R.G.	24	76	2,400	190/0
Boehringer-Ingleheim	F.R.G.	37	63	1,197	
Ciba-Geigy	Switz.	2	98	1,891	
Sandoz	Switz.	5	95	1,515	160/0
Hoffmann-La Roche	Switz.	3	97	1,629	
Takeda	Japan	94	6	1,195	40/0
Rhone-Poulenc	France	41	59	1,008	3Y0

SOURCE: Adapted from Arthur D. Little, estimates based on publicly available company data.

number of foreign firms (80). At least one study has suggested that substantially fewer U.S.-originated new chemical entities will appear on the market in the mid to late 1980's than are appearing today because of a decline in self-originated investigational new chemical entities since the mid-1970's (83). Table 6 indicates the number of new pharmaceutical products introduced by the United States, four European countries, and Japan in the period 1961-80 and each year since. As the figures in that table show, the United States and France were the leaders in 1961-80, with 23.6 and **18.1** percent of new product introductions, respectively. They were followed by West Germany, Japan, Switzerland, and the United Kingdom. The world leader for the years 1981-83 is Japan, with an average of 27 percent of new product introductions. Although the United States had an average of only 16 percent of new product introductions for the years 1981-83, the drive by NBFs and established U.S. companies to apply biotechnology to the development and production of pharmaceuticals could help reverse the downward trend in U.S. innovation and thereby contribute to the competitive strength of U.S. companies in world pharmaceutical markets.

FOREIGN COMPANIES

Established European and Japanese companies, following the lead of NBFs and established companies in the United States, are now vigorously pursuing pharmaceutical applications of biotechnology. * On average, European companies' biotechnology R&D budgets lag somewhat behind the budgets of established U.S. companies and some U.S NBFs as well (see table 7). As biotechnology processes gain wider acceptance in the pharmaceutical industry, however, European manufacturers-e.g., the West German companies Bayer AG and Hoechst, the Swiss companies Hoffmann-La Roche, Ciba Geigy, Sandoz, and the French company Rhone Poulenc—are expected to challenge U.S. companies, if for no other reasons than their prevailing strength in bioprocessing, their strength in international pharmaceutical markets (see table 5)* and their intentions to maintain this strength,

"Japanese companies are though to have begun making a serious commitment to biotechnology as early as late 1981 (70). West German companies were among the last European companies to begin commercializing biotechnology and did not intensify their R&D efforts in biotechnology until late 1982. Other European countries have paralleled the Japanese in their date of entry into biotechnology.

***Although no British pharmaceutical companies appear in table 5, British companies such as Beecham, Wellcome, Glaxo, and ICI are important international manufacturers of biologically produced products and are applying biotechnology to product development. Additionally, Beecham and Glaxo are among the world's largest producers of biologically made products (48).**

Table 7.–Biotechnoiogy R&D Budgets for Leading U.S. and Foreign Companies, 1982[a]

Company[b]	Biotechnology R&D budget (millions of dollars)
Hoechst (F. R.G.).	$42C
Schering A.G. (F, R. G.)	4.2
Hoffmann-La Roche (Switz.) .	59
Schering-Plough (U.S.).	60
Eli Lilly (U. S.) ... , ...	60
Monsanto (U. S.)	62
DuPont (U. S.)	120
Genentech (U.S.)*	32
Cetus (U.S.)*	26
Genex (U.S.)*	8.3
Biogen (U.S.)*	8.7
Hybritech (U.S.)*	5
Sumitomo (Japan)	6 +
Ajinomoto (Japan)	6 +
Suntory (Japan).	6 +
Takeda (Japan)	6 +
Eif-Aquitaine (France)	4 +

[a] [illegible] R&D figures for British companies not available.
[b] Companies with asterisks are NBFs.
[c] 1983 figure.

SOURCE: Off Ice of Technology Assessment.

Table 6.—introduction of New Pharmaceutical Products by Country of Origin Between 1961 and 1983

Country	Number of new products introduced by year			
	1961-80	1981	1982	1983 (est.)
Japan	155 (10.30/0)	15 (23.10/'0)	9 (23.1 °/0)	17 (35.40!0)
West Germany.	201 (13.40/0)	8 (12.30/o)	1 (2.60/o)	7 (14.60/o)
United States.	353 (23.60/o)	9 (13.9"/0)	9 (23.1 ~0)	6 (12.5Yo)
France	271 (18.1°/0)	3 (4.60/o)	5 (12.80/o)	5 (10,4!40)
United Kingdom	— (—)	3 (4.60/o)	– (–)	3 (6.20/o)
Switzerland	109 (7.3"/0)	6 (9.20/o)	4 (10.2%0)	–( )

[a] Numbers in parentheses indicate share of total number of new pharmaceutical products introduced for the Years indicated.

SOURCE: Nomura Research Institute, "Trends of Biotechnology in Japan," Tokyo, July 1983.

and their increasing shares of worldwide pharmaceutical R&D expenditures as compared to U.S. companies. (Pharmaceutical R&D expenditures by country for the years 1964, 1973, and 1978 are shown in table 8).

The average European company's involvement in biotechnology is largely characterized by research contracts with universities and research institutes rather than by investments in new in-house biotechnology facilities. * Some of the large pharmaceutical companies of Switzerland have, however, begun to make substantial investments in biotechnology facilities. Hoffmann-La Roche, for example, spent $59 million on biotechnology R&D in 1981 (26) and ranks eleventh in worldwide pharmaceutical sales (28). CibaGeigy, which commands 3.1 percent of the global drug market, is building a $19.5 million biotechnology center in Switzerland and a $7 million agricultural biotechnology laboratory in North Carolina (11,12).

West German chemical and pharmaceutical companies have been among the last foreign companies to move into biotechnology. Many of the companies have signed contracts with universities instead of investing in facilities to support their research (10). Some West German companies, including Schering AG and Boehringer Ingleheim, however, are making significant contributions to the German biotechnology effort. Schering AG, for example, in a joint agreement with the State of Berlin is establishing a $10.7 million institute of '(genetic engineering," which is regarded as an important step for biotechnology research in Germany (29).

In terms of total sales, pharmaceutical companies in the United Kingdom are not among the world's top 20, and historically, the United Kingdom has been slow to commercialize the results of much of its basic research. It is important to note, however, that some British pharmaceutical companies (e.g., Glaxo and Beecham) possess substantial bioprocessing knowledge, a capability that may provide them with a competitive advantage as biotechnology develops. Furthermore, some British pharmaceutical companies have made in-house investments in biotechnology. ICI and Wellcome appear to be among the most strongly committed of the British pharmaceutical companies commercializing biotechnology. ICI, for example, has the world's largest continuous bioprocessing plant and is considered an international leader in bioprocessing technology. This company recently developed a new biodegradable thermoplastic polyester, Biopol®, formed by a genetically manipulated microorganism. Although Biopol® is not a pharmaceutical, it does give some indication of ICI's innovative capacity in the biotechnology field.

The pharmaceutical and chemical companies of France appear less aggressive than British companies in developing biotechnology expertise. Three major French companies have R&D programs in biotechnology-Elf Aquitaine (67-percent Governmentawned), Rhone Poulenc (l00)-percent Government-owned), and Roussel Eclaf (40-percent Government-owned and a Hoechst subsidiary). Of these three, Elf Aquitaine has committed the most to biotechnology. It owns Sanofi, a phar-

● **Many of the established U.S. companies have made substantial investments in new in-house facilities. See section below on "Established Companies."**

Table 8.-Pharmaceutical R&D Expenditures by Country: 1984, 1973, and 1978

	1964		1973		1978	
	Level (millions of dollars)	World share (percentage)	Level (millions of dollars)	World share (percentage)	Level (millions of dollars)	World share (percentage)
United States	$282	60%	$640	34%	$1,159	28%
Federal Republic of Germany	40		310	16	750	18
Switzerland ., ...	38	:	244	13	7ooa	17
Japan ... ., .,	27	6	236	13	641	15
France ... ., ...	28	6	166	9	328	8
United Kingdom . .	29	6	105	6	332	8

[a] Estimated

Note Data are in current dollars and represent expenditures for both human and veterinary research

SOURCE National Academy of Sciences, *The Competitive Status of the U S Pharmaceutical Industry* Washington, O C , 1983

maceutical company that is applying biotechnology to human and animal health in areas including diagnostics, neuropeptides, serums, vaccines, and antibiotics, and has established Elf-Bioindustries and E1f-Bioresearch to develop biotechnology in the foodstuffs and agriculture sectors. To support some of its new biotechnology R&D, Elf is currently building a $10 million "genetic engineering" plant (5). Rhone Poulenc is the world's second largest producer of animal health products (84) and is considered to be the second most committed of the three French companies actively commercializing biotechnology (50). To support its biotechnology effort, in 1980, Rhone Poulenc established a small specialty biotechnology subsidiary named Genetica.

Despite the efforts of companies such as Elf and Rhone Poulenc, the initial hesitation France expressed in the early stages of biotechnology development has put French companies at a distinct disadvantage internationally, particularly vis-a-vis U.S. companies. The French Government has a formal policy designed to promote biotechnology, but it is not clear that whatever impetus this policy provides will be great enough to compensate for France's slow entry into biotechnology. Historically, the French Government's plans to promote national champions (e.g., the Plan Calcul, the Concord) have failed. As the pace of biotechnology commercialization quickens, a strong private sector effort may be necessary in order to launch France into a more competitive position.

Overall, Europe is considered to be farther behind the United States in the application of biotechnology to product-related research areas than in fundamental research (23). Strong commercialization efforts by the major chemical companies of West Germany or by the pharmaceutical companies of Switzerland or the United Kingdom, however, could significantly improve West Germany's, Switzerland's, or the United Kingdom's current competitive positions in the commercialization of pharmaceutical applications of biotechnology.

Some would argue that large companies have an inertia that is difficult or impossible to change, making rapid changes in research policy and direction impracticable (5). To the extent that large companies pursuing pharmaceutical applications of biotechnology in Europe lack the dynamism and flexibility to compete with the combined efforts of NBFs and established companies in the United States, Europe could initially beat a competitive disadvantage. If the timing of market entry for therapeutic and diagnostic products becomes the most important factor in competition for market share and market acceptance, however, the marketing strength of the European multinationals could help balance competition in pharmaceuticals between the United States and Europe.

The potential competitive challenge that will be mounted by Japan in the area of pharmaceuticals is more difficult to estimate than the challenge from the European countries for two reasons: 1) Japanese pharmaceutical companies such as Takeda, Sumitomo Chemical, Mitsubishi Chemicals traditionally have not had a significant presence in world pharmaceutical markets (55); and 2) present Japanese commercialization efforts, most being proprietary, are difficult to assess either quantitatively or qualitatively. One set of factors characterizing Japanese efforts to apply biotechnology to pharmaceutical development suggests a rather formidable challenge facing U.S. companies in future biotechnology-related pharmaceutical markets, while a different set of factors suggests less of a future challenge. Each set of factors is discussed in turn below.

Factors that suggest that Japan will have international competitive advantages in the application of biotechnology to pharmaceutical development include the following:

- The application of biotechnology to pharmaceuticals in Japan has stimulated the involvement in pharmaceuticals of many Japanese companies from a broad variety of bioprocess-based industries. Table 9 shows the diversification of Japanese chemical, food processing, and textile and pulp processing companies into pharmaceuticals.

A 1982 Keidanren* survey of 132 Japanese companies using biotechnology found that 83 percent

"Keidanren, the Japan Federation of Economic Organizations, is a national organization composed of about 700 of the largest

Table 9.—Diversification of Japanese Chemical, Food Processing, Textile, and Pulp Processing Companies Into Pharmaceuticals

Company	Pharmaceutical field of entry
Chemical companies:	
Sunstar	Antibiotics, interferon
Hitachi Chemical	Antibiotics, vaccines
Hokko Chemical Industry	Antibiotics
Mitsubishi Chemical Industries	Physiologically active agents, anticancer drugs, diagnostic reagents, monoclinal antibodies
Denki Kagaku Kogyo	Physiologically active agents
Sumitomo Chemical	Monoclinal antibodies, interferon, growth hormone
Daicel	Anticancer drugs
Mitsubishi Petrochemical Industries	Diagnostic reagents
Chisso	Diagnostic reagents
Mitsui Toatsu Chemical	Urokinase
***Food** processing companies:*	
Ajinomoto	Antibiotics
Suntory	Antibiotics, interferon, anticancer drugs, drugs for treatment of high blood pressure
Meiji Seika Kaisha	Antibiotics, interferon
Sanraku-Ocean	Antibiotics
Kikkoman Shoyu	Physiologically active agents, antibiotics, immune suppressors
Takara Shuzo	Physiologically active agents
Meiji Milk Products	Physiologically active agents, interferon
Yakult Honsha	Physiologically active agents, anticancer drugs, diagnostic reagents for liver cancer
Kyowa Hakko Kogyo	Physiologically active agents, interferon
Kirin-Seagrams	Interferon
Kirin Brewery	Anticancer drugs
Sapporo Breweries	Anticancer drugs
Toyo JOZO	Immune suppressors
Morinaga & Co.	Diagnostic reagents for liver cancer, drugs for treatment of high blood pressure
Snow Brand Milk Co.	Interferon
*Textile **and pulp companies:***	
Asahi Chemical Industry	Interferon
Toray Industries	Interferon
Teiji Limited	Interferon
Kirin-Seaarams	Interferon

SOURCE: Office of Technology Assessment.

Japanese companies. It enjoys the regular and active participation of the top business leaders working closely with a large professional staff to forge agreements on behalf of business as a whole. It often surveys its members on issues of economic importance.

of the **60** companies that responded were pursuing applications in the area of pharmaceuticals (70), compared to only 62 percent of U.S. companies (see table 4). Intensified competition is expected to push technical advances in the area of pharmaceuticals along in Japan at a rate that is comparable to or greater than the rate in the United States. Among the companies using biotechnology in Japan, it is already a widely accepted view that Japan can catch up with the United States within 5 years. This point is very well illustrated by the ***Nikkei Sangyo Shirnbun*** (Japan Industrial Daily) survey undertaken in June 1981. According to the survey, 48 percent of the 128 responding firms thought Japan could catch up to the United States in the commercial development of biotechnology in 5 years, and 24 percent estimated that catching up would take only 2 to 3 years (57).

- The Government of Japan, which has targeted the pharmaceutical industry for international expansion, has improved the environment for pharmaceutical innovation, and thus, for the application of biotechnology.

The Japanese Government through targeting of the pharmaceutical industry, changes in patent laws to prevent imitation, and pricing policies in the Government-administered national health insurance system has begun an effort to coordinate trade, pricing, and health care policies to promote pharmaceutical innovation and overseas expansion (74). These Government efforts are expected to facilitate the application of biotechnology in the Japanese pharmaceutical industry.

- Joint pharmaceutical research projects and collaborative arrangements among companies, sometimes in conjunction with Government research institutions, promote biotechnology transfer throughout Japanese industry and accelerate the pace of technical advances. Table 10 provides a list of some Japanese joint ventures in pharmaceuticals derived from the Keidanren survey of 1982.

As early as 1979, the Japanese Ministry of Health set up a study group between Green Cross and Toray Industries to speed the development of interferon, because the Ministry had concluded

Table 10.–Japanese Joint Ventures in Pharmaceutical Applications of Biotechnology

Companies	Product area
Otsuka PharmaceuticalIHayashibara/Mochida Pharmaceutical	Production of alpha, beta, and gamma interferon
Yamanouchi PharmaceuticalIAjinomoto	Large-scale production of thrombolytic agent
Yoshitomo Pharmaceutical/Takeda Chemical	Large-scale production of thrombolytic agent
AjinomotolMorishita Pharmaceutical	R&D on pharmaceuticals
Yoshitomi Pharmaceutical Industries, Ltd./ Yuki Gosei Kogyo Co., Ltd.	Developing rDNA products for circulatory system
Takara Shuzo/Taiho Pharmaceutical	Development of heart drugs using rDNA
Toray IndustrieslKyowa Hakko KogyolGan Kenkyu Kai (Cancer Research Association)	Development of beta and gamma interferon by rDNA
Asahi Chemical IndustrylDainippon Pharmaceutical/Tokyo University	R&D on alpha and gamma interferon
Toray IndustrieslDaiichi Seiyaku Co., Ltd.	Using rDNA to produce gamma interferon
Ajinomoto~akeda Chemical Industries, Ltd.	Development of interleukin-2
Asahi Chemical Industries Co., Ltd./ Dainippon Pharmaceutical Co.	Development of tissue necrotic factor

SOURCE: Office of Technology Assessment.

that the separate approach being taken was costly both in terms of funds expended and time taken (73). Many other examples of technical collaboration in biotechnology in Japan can be cited, and many more Japanese companies have intentions to cooperate with one another in research or development and/or in commercialization in the future. In 1981, a scientist from the Fermentation Research Institute of Japan's Ministry of International Trade and Technology acknowledged that almost half of the companies who work or intend to work in "genetic engineering" will cooperate or have already cooperated in some biotechnology activities (79). Joint ventures such as those listed in table 10 might provide Japanese companies with commercial advantages for two reasons: 1) each firm participating in the venture brings different resources and expertise to the project, thereby making the group effort more efficient; and 2) the intention of some of the joint ventures is to secure patents in fields not yet pre-empted by foreign competition (e.g., new host-vector systems and sophisticated sensors for bioprocessing) or to undertake joint clinical testing (70).

- Japan's share of world pharmaceutical R&D expenditures has been increasing steadily since 1964 (see table 8) as has its share of the worldwide total of newly introduced pharmaceuticals (see table 6).

In 1981, Japanese companies ranked first in terms of the largest number of major new drugs introduced into world markets, being responsible for 15 (23 percent) of the 65 newly introduced pharmaceuticals (see table 6). In 1982, Japanese companies again accounted for roughly 23 percent of the new pharmaceutical products introduced. They also accounted for over 16 percent of all U.S. patents issued for pharmaceutical and medicinal products and for 38 percent of all U.S. pharmaceutical and medicinal patents granted to foreign firms (14).

- Japanese companies applying biotechnology to pharmaceutical development (in contrast to U.S. companies) appear to be dedicating relatively more research effort to the later stages of commercialization (i.e., bioprocessing) and cancer treatment. Seventy-five percent of all Japanese medical and drug companies are engaged in MAb research, and a large proportion of the MAb R&D is targeted toward developing a "magic bullet" for cancer treatment, monitoring bioprocesses, and recovering pioteins (70).

Factors that suggest that the Japanese may not have significant advantages in future biotechnology-related pharmaceutical markets include the following:

- Barriers to entering foreign pharmaceutical markets are high, and Japanese companies at present have neither distribution channels in place nor a sufficient sales force to permit aggressive marketing of pharmaceutical products in Western markets.

Japanese companies' lack of distribution channels in Western pharmaceutical markets is one fac-

tor that has limited Japanese companies' ability to penetrate these markets. It is expected that the mode by which Japanese companies will penetrate these markets in the future will be through joint ventures with U.S. or European companies that allow Japanese companies to take advantage of existing distribution channels. * Although Japanese companies tend to seek opportunities to penetrate foreign markets directly through manufacturing subsidiaries rather than through licensing contracts, only two Japanese companies have established equity joint ventures with U.S. firms * * and only three have established U.S. subsidiaries. * * * However, the international expansion of Japan's pharmaceutical industry has only just begun.

- Almost half of the Japanese companies now using biotechnology expect to "catch up" technologically to the United States in 5 years. These companies therefore intend to set their own R&D and commercialization targets beyond the 5-year catch-up period at considerable commercial risk.

The intention of Japanese companies to catch up to U.S. companies and to set their own R&D targets is a unique phenomenon. In the past, even in high- technology fields such as computers and electronics, the R&D and commercialization targets have been demonstrated in advance by U.S. and Western European companies, so Japanese companies have not had to worry about the marketability of their R&D and commercialization efforts. By selecting the best technology available and refining it, Japanese companies have been able to minimize the time required to catch up with the front runners and sometimes surpass them at the product marketing stage (70). Given the lack of established commercial targets in biotechnology and considering the barriers to entering foreign pharmaceutical markets mentioned above, it cannot be assumed that the Japanese will be major competitors in biotechnology-related pharmaceutical markets.

- Japan's traditional bioprocess-based industries, including pharmaceuticals, rely largely on conventional microbiology, genetics, and bioprocess feedstocks. These traditional approaches in bioprocessing could be challenged by new biotechnology (4 I).

Japan is considered to be behind the United States in fundamental biology. This weakness ***in*** fundamental biology could reduce the potential competitive threat of Japanese companies applying biotechnology to pharmaceutical development.

- Biotechnology R&D investments by Japanese companies are still low in comparison to the investments by U.S. companies.

Although Japan's aggregate investment in pharmaceutical R&D has increased steadily since 1964, investments by individual Japanese companies in biotechnology R&D are still low compared to investments by NBFs and established companies in the United States (see table 7). According to the Nikkei SazIgyo Shiznbun survey (June 1981) and the Keidanren survey (1982), only 5 Japanese companies spent more than $6 million per year , on biotechnology R&D. The average R&D expenditure of 49 of the 60 Japanese companies that responded to the Keidanren survey was under $1 million. Although it is difficult to translate R&D investment into commercial success, on a quantitative basis, Japan falls far behind the United States in terms of industrial expenditures on biotechnology research.

*Animal agriculture industry**

U.S. COMPANIES

The animal agriculture industry encompasses companies engaged in the manufacture of products, the prevention and control of animal diseases, animal husbandry, growth promotion, and genetic improvement of animal breeds. The companies that dominate the production of most animal health products are established U.S. and

• In support of this expectation is a study by the Japanese Productivity Center in *1982* of the potential for Japanese drug firms in the United States. The study estimated that the establishment of a U.S. subsidiary by a Japanese company would require an investment of about *$80* million over a 4-year period. The study recommended that Japanese companies form joint ventures with U.S. companies rather than establish a Japanese company or purchase a U.S. company (75).

* *Takeda with Abbott (U. S.) and Fujisawa with SmithKline (U.S.).

* •*The three U.S. subsidiaries are Daiichi Pharmaceutical **Corp.,** Otuska Pharmaceutical, and Alpha Therapeutics (subsidiary of Green Cross),

• Applications of biotechnology to animal agriculture are discussed further in *Chapter 6: Agriculture.*

foreign pharmaceutical and chemical companies. ” Most of these companies have global marketing and distribution networks and undertake animal drug production as a diversification of their principal activities. In recent years, the advent of biotechnology, the rising industrialization of animal agriculture, and changing dietary habits in foreign countries have increased the demands for improvements in old products and for completely new products. NBFs may have a major role to play in expanding animal health markets.

Sixty-one companies in the United States are known to be pursuing animal health related applications of biotechnology, as shown in table 4. Thirty-four (56 percent) of these companies are NBFs. Of special note is the role new firms appear to be playing in three major segments of the industry-diagnostic products, growth promotants, and vaccines. possible explanations for why some NBFs might be interested in these three animal health markets include the following:

- Recombinant DNA methods used to make human vaccines are suited to making safe and effective animal vaccines against both viral and bacterial infections, just as the MAb or DNA probe technology used to produce human products is suited to making passive vaccines or diagnostic products for animals. * *
- The markets for many animal health products (e.g., vaccines or diagnostic products) are relatively small and therefore allow NBFs to compete equally with larger companies without suffering from scale disadvantages.
- The commercial introduction of veterinary vaccines can generally be achieved more quickly than can that of human therapeutic products. The regulatory process allowing veterinary vaccines to enter the market typically can be completed in about 1 year (17). Thus, the lower costs of commercialization for veterinary vaccines in comparison to human pharmaceuticals and the potential for short-term product revenues may reduce NBFs’ financial need to collaborate extensively with established companies. *
- Some veterinary vaccine research (e.g., on feline leukemia vaccines) could serve a~ a model for developing human vaccines for similar viruses that could launch some NBFs into the more profitable human pharmaceutical markets.

The fact that 34 of the 61 U.S. companies pursuing applications of biotechnology in animal agriculture are NBFs suggests the evolution of an expanding animal health market in which NBFs such as Molecular Genetics, Inc. (MGI), Amgen, Chiron, Bio-Technology General and Cetus perceive opportunities. In contrast to human pharmaceutical products, animal vaccines and diagnostic products are in many cases being developed by NBFs independently of established U.S. or foreign companies.

In the development of animal growth promotants, however, established U.S. companies are more involved. The market for animal growth promotants is the second fastest growing market in the animal health field, and because it may be the most significant commercial development area (26), it is also one of the most competitive. Global sales for growth promotants are expected to reach $515 million by 1985 (84). Several established U.S. companies, including American Cyanamid, Eli Lilly, Monsanto, and Norden (a subsidiary of SmithKline Beckman), have displayed interest in the field by sponsoring research contracts with NBFs such as MGI, Biotechnica International, Genentech, and Genex. Other established U.S. companies have shown interest by conducting initial evaluations of growth promotants developed by NBFs, as Eli Lilly did in the case of a product developed by the NBF Biotechnology General.

In an effort to expand their own technical capabilities and reach new product markets, some es-

● **Major U.S. producers of animal health products include Syntex, Pfizer, Eli Lilly, Upjohn, SmithKline Beckman, American Cyanamid, Merck, Johnson & Johnson, Tech America, and Schering-Plough. Major foreign producers include Burroughs-Wellcome (U.K.), Rhone-Merieux (France), Hoechst AG (F.R.G.), Bayer AC (F.R.G.), Connaught** (Canada), Beecham (U.K.), Solvay (Belgium), Boehringer Ingleheim (F. R.G.), Intervet (Netherlands), and **Elf Aquitaine (France).**

• ***The NBFs Chiron and Cetus both became involved in the veterinary products business as extensions of their research in the field of human health care (17,20). The NBF Monoclinal Antibodies, Inc., as a spinoff from research on detection kits for human pregnancy and ovulation, is developing an ovulation detection kit for large animals which will be useful in animal breeding management.**

“Collaborative ventures between NBFs and established U.S. and foreign companies are discussed further below.

tablished pharmaceutical and chemical companies have contracted with NBFs for animal health projects including the development of animal growth promotants and vaccines for foot-and-mouth disease, rabies and colibacillosis (a diarrheal disease that kills millions of newborn pigs and calves each year). Norden, for example, funded research by the NBF Cetus to develop a vaccine to prevent colibacillosis in hogs. This vaccine received the US. Food and Drug Administration's (FDA's) approval in 1982. As other examples, American Cyanamid and Merck have both contracted with NBFs for projects involving bovine growth hormone and a vaccine for foot-and-mouth disease. Many of the products under joint development are already undergoing testing.

Several NBFs are in a strong competitive position vis-a-vis established U.S. and foreign companies in animal-related biotechnology. Most of the established U.S. companies have made relatively small investments in this area-equal to or less than investments in animal health by most of the leading NBFs (54), As established U.S. companies in the animal health field increase their biotechnology investments, the U.S. competitive position in domestic as well as foreign animal health markets should strengthen.

FOREIGN COMPANIES

Established U.S. and European companies control world animal health product markets, but collectively, European companies' efforts to produce new or replacement animal vaccines or growth promotants using biotechnology do not appear to be as strong as the collective efforts underway in the united States. European companies appear on the basis of reported research projects almost exclusively dedicated to the development of products for the world's two largest animal vaccine markets, rabies and foot-and-mouth disease. U.S. companies dominate the world market for animal growth promotants, and few European animal health companies have indicated an interest in entering the growth promotants product market. Furthermore, few European companies have established R&D joint ventures with the leading U.S. NBFs engaged in growth promotant R&D.

Japanese companies have exhibited relatively little commercial interest in the area of animal health, probably because meat does not constitute as large a portion of the Japanese diet as it does of the diets in Western European countries and the United States. Recently, however, the Japanese chemical company Showa Denko and the U.S. company Diamond Shamrock set up a biotechnology joint venture, SDS Biotech Corp., in Ohio exclusively for animal health research (13).

*Plant agriculture industry**

U.S. COMPANIES

The plant agriculture industry encompasses companies engaged in R&D activities to modify specific plant characteristics (e.g., tolerance to stress, nutritional content, yield, and growth rate) or to modify traits of micro-organisms that could be important to plant agriculture (e.g., nitrogen fixation, disease suppression, and insecticide production). The importance of plants as a food source and renewable resource and the potential of biotechnology to alter plant characteristics has attracted a diverse set of firms to the plant agriculture industry. Fifty-two U.S. firms listed in table 4, 30 established companies and 22 NBFs, are applying biotechnology to plants. Table 11 provides some examples of the diverse application areas that NBFs are pursuing.

Established U.S. companies from industries ranging from oil and chemicals to food and pharmaceuticals appear to be dominating the U.S. investment in biotechnology R&D in plant agriculture (25). U.S. chemical companies that have made considerable in-house investments in plant-related biotechnology research include American Cyanamid, Dow, Allied, DuPont, and Monsanto. These companies already produce chemical pesticides and herbicides and already have research using plant cell and molecular biology techniques directed toward increasing the resistance of crop plants to these chemicals (15). American Cyanamid, which has the expertise to synthesize herbicides, and the NBF MG1, which has the expertise to develop novel corn strains tolerant to new herbicides, have a joint program to develop herbicide-resistant corn. New corn strains developed for herbicide resistance might make it possible

* Applications of biotechnology to plant agriculture are discussed further in ***Chapter 6: Agriculture.***

Table 11.—Applications of Biotechnology to Plant Agriculture for Seven New Biotechnology Firms

Advanced Genetic Sciences, Inc.:
—Development of plant varieties with increased resistance to disease, stress, herbicides and pests, and tolerance to extreme weather conditions
—Development of antagonistic bacteria that do not contain ice nucleation properties to optimize frost protection
Biotechnica International:
—Improvement of nitrogen-fixing capability of *Rhizobium*
—Introduction of nitrogen-fixing capability in plants that rely on fertilizer
—Herbicide resistance in selected plants
—Improved protein content in alfalfa
Bio-Technology General Corp:
—Development of a biofertilizer, *Azospirillum*
—Development of several strains of trichoderm, a micro-organism that controls soil-borne fungi that cause damage to many plants.
International Genetic Engineering (Ingene):
—Modification and production of bacteria that are lethal to four specific weeds and three groups of insects
—Production in micro-organisms of plant growth regulators—hormones that affect many biological functions including flowering, fruit ripening, and water loss.
—Modification of organisms that are responsible for ice nucleation in an effort to interfere with the organisms' ability to adhere to plants
Cetus Madison:
—Development of soybean and corn hybrids to increase vigor
—Development of microbial inocculant for corn, soybean, cotton, wheat, and rice to protect plants against fungal and insect diseases and to increase plant growth through nitrogen fixation and other biological processes
—Exploration of ways to add genes to make plants unpalatable to insect pests and to make plants resistant to diseases
Ecogen, Inc.:
—Development of microbial and viral pesticides
Molecular Genetics, Inc.:
—Development of herbicide-resistant corn and nutritionally enhanced field corn

SOURCE: Company prospectuses and annual reports.

to develop markets for broad-spectrum herbicides that might not otherwise be used. Some U.S. chemical companies may be investing in plant-related biotechnology to compensate for possible reductions in future sales due to the development of plants that do not require chemicals (e.g., plants that fix nitrogen, plants that produce pesticides) or due to competition from microbial insecticides or nonchemical treatments (30). Some pharmaceutical companies may invest in plant-related biotechnology, for example, to seek new sources of therapeutically active substances or to develop a commercial process for producing secondary products from plants (e.g., morphine and codeine).

One route by which some established U.S. companies have entered the plant agriculture field is through the acquisition of seed companies. Seed companies provide both an in-place marketing system and high-quality, commercially successful gene pools, often representing as much as 10 to 20 years of R&D. Through their ownership of seed companies and investments made both in-house and through sponsored research with NBFs, some established companies are assuming active roles in the modern research impetus for seed improvement. By assuming stronger roles in basic plant science research, U.S. companies like ARCO, Shell, Allied, Monsanto, and DuPont hope to play a leading role in the development of future agriculture markets.

FOREIGN COMPANIES

The commercialization of plant-related biotechnology is occurring more slowly in the European competitor countries than in the United States. For example, most West German plant tissue culture research is going on in universities (6). Some of the large European pharmaceutical companies are reportedly interested in plant tissue culture, but only Boehringer Mannheim (F.R.G.) and the Society for Biotechnology Research (GBF, Gesellschaft für Biotechnologische Forshung) have made their interests public. Boehringer Mannheim is also engaged in research to produce digitalis using immobilized plant cells (10). Although excellent basic research is conducted in centers such as the Max Planck Institute for Plant Research in Cologne,* few commercial pursuits are known.

Great Britain possesses some of the strongest basic research in interdisciplinary plant sciences and recently a new firm launched by the British Technology Group, Agricultural Genetics, was established to exploit discoveries made at the Agricultural Research Council. Whether or not the basic research will be commercialized successfully is difficult to predict.

*Bayer signed a 3-year agreement with the MaxPlanck Institute for research in plant cultivation with special attention to rDNA to improve plant resistance to phytotoxins.

The Japanese are very interested in the development of amino acids and high-value compounds by selecting and engineering plant cells to produce secondary metabolizes in vat culture. MITI has identified secondary compound synthesis as a major area for commercialization, and this area of plant-related biotechnology research will receive approximately $150 million from MITI during the next 10 years (15). With their experience in large-scale bioprocessing, the Japanese are well ahead of the United States in this aspect of plant biotechnology. Japanese companies have already reported repeated success in growing plant cells in 15,000 liter batches (68). The upper limit in the United States is only 300 liters (68).

Although biotechnology is not expected to provide foreign countries with an ability to reduce U.S. dominance in world grain markets, it may provide foreign countries with opportunities to seize specific agricultural markets. In both France and Italy, for example, there are major commercial activities in plant tissue culture techniques for eliminating viruses and propagating fruit and nut trees (15).

*Specialty chemicals industry**

The specialty chemicals industry promises to be a particularly competitive industry as biotechnology develops, because large chemical companies from both Japan and the Federal Republic of Germany as well as the United States are hoping to switch from the stagnant commodity chemicals industry into the more profitable specialty chemicals industry.

The general chemical and petrochemical firms of Japan are leaning strongly to biotechnology, and some of them are making rapid advances in R&D through their efforts to make biotechnology a key technology for the future. Japanese companies are expected to be especially strong competitors in future specialty chemical markets for reasons including the following:

- Japanese bioprocess-based companies are known to possess highly developed enzyme technology, a prerequisite for efficient biological production.
- Japanese chemical companies view specialty chemicals as a profitable area in which to diversify. Showa Denko, a leading chemical company in Japan, is expecting to become a major world producer of the amino acid tryptophan, first by using a new low-cost semisynthetic production method, and second by rDNA production.
- Two Japanese companies, Kyowa Hakko and Ajinomoto, are currently the world's major producers of amino acids. Both companies have operating production plants in the United States, and both have strong biotechnology R&D programs in Japan. Ajinomoto, for example, has succeeded in improving the production of the amino acid threonine by rDNA technology using E. ***coli,*** and Showa Denko has cut in half the production cost for tryptophan through a semisynthetic production process.

The commercialization of biotechnology will require many small, incremental improvements in bioprocess technology, superb quality control, and mass production to progress along the learning curve. As biotechnology development reaches large-scale production stages, well-developed bioprocessing skills will be necessary to compete in world product markets. Nowhere is the art of bioprocessing better refined than in Japan. Certainly Japan's expertise in this area will provide competitive strengths in many future biotechnology product markets.

Two West German companies that have experienced declining profits for the last 10 years because of poor chemical sales are Hoechst and Bayer, the world's largest chemical exporters and the world's two largest pharmaceutical companies (see table 5). These two companies spend more on R&D than any other pharmaceutical companies. Both these companies have targeted specialty chemicals as an area where biotechnology might increase corporate sales and profits (10). Bayer has a longstanding collaboration with its two U.S. subsidiaries, Miles and Cutter, and these two subsidiaries help keep Bayer informed of biotechnology developments in the United States. Much

Applications of biotechnology to specialty chemicals are discussed further in *Chapter 7: Specialty Chemicals and Food Additives.

of Bayer's specialty chemical research is taking place in the United States through these two subsidiaries. Bayer has opted for specialty chemicals as its main R&D focus; Miles is important in the enzyme and organic acid field using bioprocessing, and Cutter is expanding its R&D activity in purifying enzymes and proteins on a large scale (10). Two other German companies, Schering AG and BASF AG, are also actively applying biotechnology to the production of specialty chemicals. Schering's main research focus is on the genetic manipulation of micro-organisms to produce amino acids such as lysine (10), and BASF is building a $24 million "Biotechnicum)" a combination of research laboratory and pilot plant with a product focus on optically active intermediate chemicals and vitamins. Schering has also signed two research agreements with Genex, one of which involves the development of a genetically manipulated microbe to produce an amino acid.

U.S. and foreign support firms

Companies engaged in biotechnology research have increased and expanded the demands placed on the infrastructure that has traditionally supplied biochemical reagents, instrumentation, and software for biological research and production. As "scaled-up" production of biotechnology products comes on line, the demand for these supplies as well as for new production instrumentation is likely to increase further.

The United States, with an assortment of companies supplying biochemical reagents, instrumentation, and software, has the strongest biotechnology support sector in the world. The U.S. biotechnology support sector is characterized by a large number of small specialty firms that compete in small specialty product markets such as biochemical reagents used in rDNA research (e.g., BioSearch, Vega, P-L Biochemical (a subsidiary of the Swedish company Pharmacia), Bethesda Research Laboratories, * Collaborative Research, New England BioLabs, Applied Biosystems, Creative Biomolecules, and Intelligenetics) and several medium-sized to large firms that produce analytical and preparative instrumentation as well as bioprocess equipment* * for larger, more diverse product markets (e.g., Beckman, Perkin Elmer, Varian, Hewlett Packard, Waters, New Brunswick).

In most support areas, European and Japanese support sectors are underdeveloped compared to that of the United States, although both are expanding quickly. Two factors might account for weak support sectors in Japan and Europe as compared to that of the United States:

- The United States is a recognized leader in basic biomedical research, and over the years, public funds, notably from the National Institutes of Health, have created a large well-defined market for specialty products used in biological research (l).
- Because so many large and small U.S. companies are currently applying biotechnology, the specialty research product needs are greater in the United States than in any other country, and opportunities exist for many small manufacturers. In fact, the U.S. market for custom oligonucleotides (DNA fragments) and biochemical reagents for synthesis of DNA is equal to that of the rest of the world (51).

In Europe and Japan, there are few biotechnology support firms supplying biochemical. Thus, European and Japanese companies developing biotechnology generally have to manufacture oligonucleotides and other biochemical reagents in-house. Consequently, the expense for biochemical in European countries and Japan is often greater than in the United States, where many support firms have achieved significant economies of scale (51). The alternative to in-house production of support materials in Europe and

"Bethesda Research Laboratories was recently purchased by Dexter Corp.'s GIBCO division. The new name for the merged company will be Life Technologies, Inc.

*** ● See *Chapter 3: The Technologies* for a discussion of bioprocess equipment.**

Japan is reliance on a foreign supplier. Such reliance could impede technical advances (21) and retard commercialization in the short run. Although there are Japanese and European instrumentation manufacturers, U.S. instrumentation is considered superior to both Japanese and European instrumentation and dominates the European market (51). The Japanese instrumentation market is supplied by Japanese manufacturers, which have not made significant inroads in foreign markets (52).

Important product areas

For purposes of analysis, OTA examined three product areas thought to have significant short-term implications for research developments and technical developments in the biotechnology field:

- biochemical reagents used specifically in rDNA research (e.g., oligonucleotides and restriction enzymes);
- instrumentation used in product R&D (e.g., DNA and peptide synthesizers) and separation and purification instruments such as high-performance liquid chromatography (HPLC); and
- software designed to drive the microprocessors that automate instruments as well as software designed to analyze DNA and protein sequence data in data banks.

The United States is a world leader in all three product areas. If adequate supplies of the above products and services can sustain the present rate of growth of biotechnical advancement, the United States could possess a short-term advantage in bringing biotechnology products to international markets.

BIOCHEMICAL REAGENTS

The availability of quality biochemical reagents such as oligonucleotides (DNA fragments) and restriction enzymes (enzymes used to cut DNA) is crucial to sustaining the rapid development of the new biotechnology field and making it viable on a large scale. Between 1980 and 1990, sales of biochemical for DNA and peptide synthesis in the United States are expected to increase at an annual rate of 20 percent (81). As more research is undertaken in plant agriculture, sales are expected to rise further. The total synthetic DNA market for 1983 to 1984 is estimated at $3 million to $4 million, and demand is expected to increase 25 to 30 percent a year (36).

Until rather recently, most oligonucleotides were made in-house in the United States; however, as demand for these materials has increased, small specialty support firms have been started to exploit these small markets. One source believes that the evolution of small support firms in the United States is gradually shifting many skilled biochemists in U.S. companies commercializing biotechnology from routine laboratory duties to basic research and that the net result has been an increase in the progress of biotechnology research in the United States (51).

Small U.S. support firms are estimated to supply about 25 percent of the total reagents used in biotechnology research in the United States at present (51). Some expect this figure to increase to about 50 percent as small firms achieve economies of scale, and their prices become lower than those of in-house manufacture. others believe an estimate of 50 percent might be somewhat high, because some of the major users of reagents, in order to control availability, quality, and cost, are opting for in-house manufacture rather than purchase (40). In-house manufacture may in fact limit the growth of the reagent market. The Canadian firm Bio Logicals no longer manufactures oligonucleotides at all, because the market is smaller than was originally estimated, and the business is becoming one of low profit margin (4).

The unavailability of specific DNA sequences will clearly slow any research development on those sequences. Research at the U.S. firm Genentech was slowed, for example, when the company had to wait weeks for a reagent that is only available from Sweden (43). In the United States, the existence of many small custom reagent suppliers makes delays of this kind rare, In Europe, however, delays of 1 to 2 months occur more often. Nonetheless, there is little competition in Europe among firms making custom synthesized fragments, because European researchers are willing to wait a couple of months for special reagents (51). DNA probes (small pieces of DNA that recognize specific genes) are not even manufactured there (21).

The biochemical supply situation is somewhat different in the United Kingdom, a nation strong in basic research but weak in commercial applications (51,69). As early as 1980, a well-known British Government biotechnology report, the Spinks' report, recognized that the United Kingdom had a shortage of suppliers of suitable equipment and reagents for biochemical laboratories (2). The number of new small British suppliers of biochemical reagents and restriction enzymes is increasing, but British firms using these products as well as instrumentation still purchase much of them overseas. * British firms' reliance on foreign biochemical suppliers could be reduced as an increasing number of small supply companies are beginning to form in the United Kingdom.

The demand for support materials in Japan has increased significantly since MITI designated biotechnology a priority area for the 1980's. In anticipating the increased demand for research supplies, the Science and Technology Agency (STA) sponsored an industrial research team** whose objective is "DNA extraction, analysis, and synthesis technology development" (70).

Until recently, oligonucleotides were produced in Japan only on an experimental basis and foreign products were used for domestic consumption. Now, three Japanese companies and their affiliated trading firms produce and market synthetic DNA in Japan, * * * and two of them are members of the MITI research team. Only two Japanese companies, Nippon Zeon Co, and Takara Shuzo, produce restriction enzymes for the estimated $4.5 million Japanese market (35). Nippon Zeon Co., a subsidiary of Kongo Pharmaceutical Co., is manufacturing 35 kinds of restriction enzymes and 87 different synthetic DNA fragments mostly for research institutes in Japan (37). Takara Shuzo, in addition to supplying enzymes to the Japanese market, is exporting them to the United Kingdom. Because of the increasing rate at which biotechnology research is being carried out in Japan, and because of the underdeveloped support industry there, the current supply of oligonucleotides and restriction enzymes for biotechnology research in Japan is inadequate. In fact, Japanese distributors are still looking for U.S. suppliers (40).

The biotechnology support structure in Japan is expected to develop differently from that of the United States, because most companies commercializing biotechnology in Japan will continue to manufacture or import their own specialty biochemical supplies. In order to meet their own needs, Japanese companies have integrated vertically and are increasing their efforts to develop products such as reverse transcriptase and other enzymes that will reduce the cost and speed up the rate of biotechnology R&D. This pattern of vertical integration and in-house manufacture is not likely to change in the short term. The Japanese supply structure could retard research and create an early commercial disadvantage for Japanese companies in the short run.

INSTRUMENTATION

The instrumentation field includes all the instrumentation used in biotechnology from the analysis and synthesis of DNA molecules to the monitoring and control of large-scale separation and purification of commercially important biological compounds. of particular importance to the pace of biotechnical development is the newly designed or recently modified instrumentation that is meeting the special needs of biotechnology research and production. Two of the most important instrument areas are DNA and peptide synthesizers and bioprocessing separation and purification instruments such as HPLCS.

Automated DNA and Peptide Synthesizers.—Automated DNA and peptide synthesizers significantly reduce the number of persomel and the amount of time required for synthesis. Such synthesizers will have significant impacts on the timing of research outputs and technical developments in biotechnology in the United States (61). An increased availability of specifically synthesized gene fragments arising from automated

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"The British firm Amersham recently launched new product lines to meet the growing need for restriction enzymes in the United Kingdom, but rather than manufacturing the enzyme itself, Amersham will be supplied with 22 restriction enzymes by the Japanese firm Takara Shuzo Co. (9). Typically, Japanese companies do not pursue small foreign markets; in this case, however, Amersham's distribution network provided easy access to the European enzyme market.

• ● Ajinomoto, Wakinaga Yukuhin, Yamasu Shoyu, Yuki Gosei Yakuhin Kogyo, Toyo Soda Manufacturing Co., Ltd.

• * ● Nippon Zeon Co.-Mitsui Trading Co., Yamasa Shoyu-Sumitomo Shoji, Yoshitomi-Yuki Gosei.

synthesis may give researchers more flexibility in the manipulation of genetic information. Automated synthesizers can, among other things, expand the availability and variety of linkers and adapters* for cloning DNA, provide probes for finding messenger RNA and DNA gene sequences, or manufacture whole genes themselves.

The United States leads the world in synthesizer technology. The support companies that manufacture DNA and/or peptide synthesizers in the United States include Vega Biotechnologies, BioSearch, Beckman Instruments, Sys-Tee, Applied BioSystems, P-L Biochemical, Syncor, Genetic Design, and Sequemat. Generally, these companies have very good communication with the U.S. companies and laboratories they supply. BioSearch customers, for example, keep BioSearch continually informed of their needs so that automation can be designed based on these needs. Communication networks between European instrument suppliers and their European customers are not so well developed.** US. companies might, therefore, gain some competitive lead time in biotechnology, because they will be among the first to benefit from automation developments in the United States.

There are no Japanese companies actually manufacturing DNA or peptide synthesizers for commercial use (21)81), but some U.S. manufacturers of DNA and peptide synthesizers have established distribution agreements in Japan.*** The reasons given most often for the dearth of Japanese manufacturers are the high risks of bringing synthesizers to market and the small size of the Japanese synthesizer market. A 1982 market survey by American Commercial Co. (Vega Biotechnoloy's Japanese trading company) found the Japanese market at that time to be approximately 150 machines (81). Without automation to synthesize the genes or fragments necessary for research, the Japanese may find it difficult in the short run to keep pace with American research advances. Additionally, if future markets develop for total gene synthesis, Japanese research could be slowed because Japanese companies have not developed their own automation.

The only two DNA synthesizer manufacturers in Europe are Celltech and Cruachan Chemicals Co., Ltd. (U.K.). However, companies in France, the Federal Republic of Germany, Switzerland, and the United Kingdom have introduced peptide synthesizers to the market or plan to soon. Sempa (France) is not aggressively marketing its machine in the United States. The relatively small size of the European market discourages many potential large European manufacturers from entering the market. The inherent risks of introducing a new product might also discourage small European companies from entering the market as well.

Over the next 5 years, the U.S. market for automated DNA synthesizers is expected to grow to between approximately 500 (81) and 1,000 units (21). Since March **1983,** Applied BioSystems (U. S.) has shipped 30 synthesizers, and in just over a year, BioSearch (U. S.) has shipped about 50 (37). Some observers expect that the largest biotechnology support markets in the near term will be those for synthesized whole genes and purification systems (2 I). Though some firms doubt that a market for whole genes is developing, other firms, including Creative BioMo]ecules (U.S.), have aIready begun to market whole genes. Creative BioMolecules' synthetic gene for human pancreatic growth hormone releasing factor.

New developments in continuous-flow peptide synthesizers have led to an upsurge in interest in this different type of instrument technology. The U.S. market for peptide synthesizers 5 years from now is expected to be 500 units—the same size market that is forecast for DNA synthesizers (81).

In a situation of rapidly changing technology, the United States is at a clear advantage in the short run because of the supply of automated instrumentation, an automated synthesis instrument supply standpoint, because many small U.S. companies are willing to address these small, high-risk markets, In Europe, few small or large firms are willing to do the same.

***Short nucleotide sequences that encode restriction enzyme sites.**
• "See the Spinks' report recommendations.
•• "A U.S. synthesizer manufacturer contacted by OTA was not aware of any Japanese companies that manufacture synthesizes (40).

Bioprocessing Separation and Purification Instrumentation.—Technical advances in separation and purification as well as monitoring will affect both laboratory research and commercial production and ultimately the U.S. competitive position in biotechnology (61). * The use of rDNA technology to produce low-volume, high-value-added products as well as high-volume products has greatly increased the need to develop more economic bioprocesses. As large-scale production draws closer, the ability to isolate and purify large quantities of desired products will be a determinant in how fast companies can reach international product markets. Those countries that possess the most advanced technology to separate and purify commercially important compounds might gain some commercial advantages in the early stages of production. Without more economic production, financial and commercial success in biotechnology may be difficult to achieve.

In the United States, Europe, and Japan, there is intense competition in R&D to develop improved large-scale separation and purification methods for biological compounds as well as methods for monitoring and controlling a bioproc - ess itself.** There is widespread effort to apply HPLC, continuous-flow electrophoresis, and flow cytometry to bioprocesses to decrease the manufacturing costs of compounds such as proteins. Increasingly, R&D efforts are being undertaken to scale-up analytical instruments, particularly HPLCS, for use in larger volume production processes. The United States is a recognized leader in analytical instrumentation used in biological research and thus stands at the forefront of many of the technical innovations being made in the bioprocess field. As automation and the use of sophisticated instrumentation to monitor and control the production process begins to transform bioprocessing from an art to a science, thereby making production more economic, U.S. companies will be in a strong competitive position.

HPLC is one of the most commonly used separative techniques and also one of the fastest growing instrumentation fields in the world (76). The growing sales are due in part to its expanded use in both analytical and preparative areas. HPLCS are considered standard analytical tools in the laboratory to accurately isolate and purify organic molecules, drugs, and some peptide hormones. More recently, HPLCS have been scaled-up successfully to monitor bioprocesses and purify large quantities of proteins such as leukocyte interferon.

Half of the $300 million worldwide HPLC market belongs to U.S. producers, and the European HPLC market is dominated by three U.S. companies, Varian, Beckman Instruments, and Waters. Japanese and European companies have tried with little success to penetrate segments of the U.S. instrument market. Pharmacia, a Swedish company, is the only exception. Large American companies such as Hewlett Packard, Perkin Elmer, and Beckman are so firmly entrenched by virtue of their service and applications networks that foreign firms (e.g., Shimadzu, a Japanese company) are having a difficult time making inroads. An absence of major foreign companies in the U.S. market and the dominance of American companies abroad highlights the prominent U.S. position in instrumentation markets.

Although U.S. companies dominate world HPLC markets, the Swedish company Pharmacia is a major competitor in separation and purification technology, especially chromatography (52). In fact, it is the only company in the world doing large-scale industrial chromatography. Waters and Beckman are thought to be catching up (52). According to John McTaggart of Tag Marketing, U.S. companies are catching up to Pharmacia in procedures for reducing the bulk of material at initial stages of isolation and purification (52), The gap is narrowing, because U.S. companies strong in hardware support (i.e., advanced solid matrix, membrane, and hollow fiber design) such as Millipore, Amicon, and Nuclepore are making advances in product recovery through ultrafiltration. The United States is considered the technological leader in hollow fiber and membrane technology.

*The reader is directed to *Chapter 10: Bioelectronics* for a discussion of sensor technology.

**See the discussion of bioprocess technology in *Chapter 3: The Technologies.*

SOFTWARE

The United States holds a commanding position in software designed for molecular biology and bioprocessing. with a superior capability to analyze and manipulate sequence data or to purify large quantities of valuable products, for example, the United States might gain some commercial lead by hastening research in some product development areas.

Automation will be necessary to develop more efficient bioprocesses and to lower the costs of biological production. U.S. instrumentation and software manufacturers such as Perkin-Elmer and Fisher Scientific are designing a wide range of software for use in biological research and production processes. The United States is the recognized leader in software design in general and in sophisticated computer applications to biological research specifically. Because of the dominant role U.S. companies play in instrumentation markets, and because of the increasing importance microprocessors and automation are having in biological research and production, the United States is expected to gain some short-term advantages in the commercialization of biotechnology.

Software controls all processes automated by microprocessors. Current software applications in biotechnology are wide ranging and include the manipulation of DNA sequence data contained in data banks, the automatic ordering of nucleotide bases to synthesize pieces of DNA, the modeling of protein structures, and the monitoring and control of large-scale bioprocessing. on the analytical level, purification of peptides and DNA fragments, for example, is expected to become more sophisticated through technical advances in automation (40). on a preparative level, the utility of FIPLCs, for example, is being increased by interfacing HPLCS with other instruments (e.g., infrared and mass spectrometers) and computers.

The availability in the United States of software designed to analyze the data in the private and public DNA and protein data banks that have been created worldwide may give U.S. companies commercializing biotechnology some competitive advantages. Both public and private DNA sequence banks exist in the United States. The two largest private and public banks respectively are: the Nucleic Acid Sequence Database (1,200,000 nucleotide bases), operated by the National Biomedical Research Foundation, Georgetown University Medical Center; and the Genetic Sequence Data Bank (GENBANK) (1,800 DNA sequences totaling 2 million nucleotide bases) founded on data collected, organized, and annotated by the Los Alamos National Laboratory and developed through funding from the U.S. National Institutes of Health. The latter data bank will be a repository for all published nucleic acid sequences of more than 50 nucleotide base pairs in length. Georgetown also operates the world's largest protein sequence data base, which currently contains 2,100 sequences and about 360,000 amino acids.

The United States is not unique in its creation of such data bases; however, in terms of size, there are no foreign equivalents. The Europeans have their own nucleic acid data base, the Nucleotide Sequence Data Library (operated by the European Molecular Biology Laboratory, EMBL), and the Japanese will have their own equivalent soon. In addition to these foreign DNA data bases, small private foreign protein data banks exist for the exclusive use of the institutions with which they are affiliated.

A research advantage for the United States is expected to arise not only from the availability of data bases, but also from the software being designed by academic institutions, nonprofit research foundations, and private companies to analyze the data in the banks. Since GENBANK's development was made possible through public money, the data are available to the public, domestically as well as internationally. Additionally, subscribers to Georgetown's Nucleic Acid Database can use the accompanying programs to access both the GENBANK and EMBL's bank. With equal international accessibility to the data bases, competitive advantage will flow to the country that has the ability to perform sophisticated sequence manipulation through specially developed software. In fact, the utility of the data bases will be defined by the available software.

The U.S. company 1ntelligenetics is specializing in the application of data processing and artificial intelligence techniques to biological problems, and this company has created specific software pack-

ages to assist researchers with molecular genetics analysis. Some of the subscribers include SmithKline Beckman, DNAX, Hoffmann-La Roche, Biogen, and Pfizer.

Conclusion

The U.S. support sector provides competitive as well as commercial advantages to U.S. companies developing biotechnology through: 1) the timely and sufficient supply of biochemical such as oligonucleotides and restriction enzymes for rDNA R&D, 2) new or modified instrumentation such as DNA and peptide synthesizers as well as large-scale purification instruments such as HPLCS, 3) the design of new software for research and production, and 4) a continuous exchange of information between suppliers and companies using biotechnology that results in the creation of new products and in constant improvements in existing instrumentation, equipment, and software used in biotechnology R&D.

The first advantage, timely and sufficient supply of biochemical reagents for rDNA R&D, can affect the rate at which some biotechnology research is carried out. An increasing number of small U.S. companies specializing in custom DNA synthesis has made available sufficient supplies of reagents in the United States that are priced lower than European or Japanese supplies. In Europe, although the number of companies supplying custom reagents has increased, supplies still are not adequate and delivery is slow, especially when reagents are imported (43).

The second and third advantages, new or modified instrumentation and new software design, may provide U.S. companies with a short-term advantage through more efficient research methods and production processes. DNA and peptide synthesizers, for example, are beginning to automate the long and tedious manual task of assembling DNA and peptides, thereby creating greater efficiency in the early stages of research. The scale-up of HPLCS for use in purification of commercially important compounds may also provide greater production efficiency. Software used to drive the microprocessors used in synthesizers or bioprocessing equipment, or to manipulate sequence data in data banks, or to direct computer modeling of proteins may also give U.S. companies short-term advantages in the earlier stages of commercialization. It should be noted, however, that these materials can be exported without difficulty, and that any U.S. advantage derived from their manufacture in the United States is short term.

The fourth advantage, information exchange between support firms and the companies developing biotechnology, promotes technology transfer within the United States and stimulates improvements in instrumentation and software design for biotechnology application. Not only do support companies constantly improve on the products that they themselves manufacture, but the companies that they are supplying in turn strengthen the U.S. support base by developing customized and automated instrumentation and equipment for in-house use, which they may then make available to other companies once their proprietary position has been secured. Examples of companies in the latter category include Genentech, Cetus, and Bio Logicals (Canada). Bio Logicals' DNA synthesizer grew out of in-house technology to produce oligonucleotides for itself. Cetus recently established a new subsidiary, Cetus Instrument Systems, to capitalize on the commercial value of novel instrumentation and computer systems developed for its own in-house R&D. Genentech and Hewlett Packard started a joint venture company, HP Genenchem, to develop for themselves and other companies automated instrumentation for use in biotechnology R&D. Genentech will provide the joint venture with instrumentation already developed and add early insights for research and commercial instrument opportunities (37). Possible areas of automation include DNA and protein sequencers and synthesizers and industrial-scale HPLC and flow cytom - eters for bioprocess monitoring and control.

In the current stage of biotechnology development, there is considerable interaction between suppliers and potential users, particularly in the area of sophisticated instrumentation. Ideas for new products are developed through in-depth conferences with customers and potential customers to determine or anticipate what kinds of R&D problems they might have. Also, in response to customers' needs, U.S. support firms are constantly upgrading and modifying instrumentation to maximize its utility. These interactions and

tailoring of instrumentation and equipment to meet industrial needs will be critical to surmounting the numerous problems anticipated in the design, scale-up, control, and optimization of industrial biotechnological processes (22).

The U.S. biotechnology support sector currently provides a sufficient and ***timely*** supply of biochemical, instrumentation, and software to U.S. firms using biotechnology. By virtue of its support strength, the United States holds research advantages over other countries-advantages that may or may not be translated into commercial products. For the United States to retain these advantages in the future, U.S. support firms must remain poised to meet the immediate and expanding supply needs of the U.S. firms commercializing biotechnology.

U.S. firms commercializing biotechnology and their role in competition

As noted at the beginning of this chapter, the commercial development of biotechnology in the United States is being advanced by two types of firms: NBFs and large established US. companies. It is important to keep in mind throughout this report the organizational nature of the U.S. biotechnology development and commercialization effort and the strength that the present NBF-established firm competition and complementarily lends to this effort. NBFs and established U.S. companies both have important roles to play in the present phase of biotechnology development. Not until the technology is more fully developed will the parameters of responsibility for each group of firms be more clearly defined.

New *biotechnology firms*

The development of biotechnology is still at an early stage, and competition at present, both in the United States and abroad, is largely in research and early product development (e.g., vector selection and gene expression). Development and commercialization have not yet progressed to a point where competition for market shares is of immediate concern. In the present research-intensive stage of biotechnology's development, NBFs are providing the United States with competitive advantages in biotechnology through contributions to innovation. In the early stages of a new technology, small firms in the United States tend to dominate an industry and contribute most to product innovation. As a group, it is the small companies that have most "quickly and successfully taken new technologies from the laboratory and adapted them for large-scale production" (78). Small firms move much more aggressively to market than do established companies that have built-in disincentives to advance the state-of-the-art quickly because of existing investment in established product lines and production processes. * As a technology matures, many established companies, as later entrants, begin to play a larger role in innovation, as well as production and marketing.

That small firms contribute significantly to technological innovation is widely accepted, although there is disagreement over the amount of their contribution. Some U.S. studies suggest that small businesses play a more important role in technological innovation than do large firms. A recent study prepared for the Small Business Administration by Gellman Research Associates, Inc., for example, holds that: 1) small firms produce 2.5 times as many innovations as large firms, relative to the number of people employed; and 2) small firms bring their innovations to market much more rapidly than do large firms (32). Another study undertaken by Human Services Research for the National Science Foundation found that small firms (i.e., firms with fewer than 1,000 employees) pro-

***For example, a pharmaceutical firm with a vested interest in symptomatic treatment of colds may have little incentive to develop a vaccine against the cold-causing viruses, since it would diminish the company's sales of decongestants.**

duced 24 times as many major innovations per R&D dollar as did large firms and 4 times as many as did medium-sized firms (44). Finally, an Office of Management and Budget study concluded that small firms (i.e., firms with fewer than 1,000 employees) had a ratio of innovations to employment in R&D 4 times as great as that of larger firms (19). In combination, the results of these studies suggest that small firms appear to be more efficient than large companies in the way they use the R&D funds available to them (32).

THE EMERGENCE AND FINANCING* OF NBFs

Since 1976, more than 100 NBFs have been formed in the United States. The founders of many NBFs recognized early that most developments in biotechnology would flow from basic research carried out in academic institutions. For this reason, they formed their companies around a nucleus of talented university scientists, frequently using nonproprietary technology. Several NBFs (e.g., Genentech, Centocor, Genetic Systems) got started by placing R&D contracts with academic researchers for the commercial development of a laboratory discovery.

The character and record of the chief scientists in a new firm is important for several reasons: the amount of venture capital made available to the firm might be determined by the scientist's reputation in the scientific community; the scientist may have some influence over the flow of other well-respected scientists and skilled technicians to the company; and his or her reputation might attract the endorsement of established companies which provides valuable reinforcement to the NBF (e.g., Genentech's early relationships with the U.S. company Eli Lilly and the Swiss company Hoffmann-La Roche).

NBFs must be able to attract and retain qualified personnel if they wish to attract venture capital,** develop marketable products, and maintain their domestic competitive position. Competition in the United States for skilled personnel is intense.*** According to the First Annual Technical Staffing Survey conducted by Scherago Associates in New York, the average biotechnology firm* in the United States more than doubled its staff of scientists between 1980 and 1982 from 3.1 to 7.3 (72). Scherago expects the number of Ph.D.s to almost double again by 1984. The results from the OTA/NAS survey of firms' personnel needs** substantiate the Scherago survey findings, but they also show that the average number of scientists per firm might be growing at a faster rate than originally estimated. The average number of Ph. D.s for the NBFs listed in table 4 as of March 1983 was already 15. 7.* * *

NBFs, by virtue of their size, incentive plans, and innovative and academic-like environment have been able to attract many talented scientists. It is expected that NBFs will continue forming, in part because new firms will continue to be able to attract good scientists.

The formation of the loosely organized and highly competitive structure within which biotechnology is developing in the United States has been shaped largely, but not exclusively, by the availability of venture capital and the willingness of scientists to pursue commercial gain through small, newly formed entrepreneurial companies. The emergence and growth of venture-capital-backed NBFs in the United States began around 1976. As shown in figure 11, not until late 1982, when venture capitalists had satisfied much of their portfolio requirements for biotechnology stock (42) and over 100 new companies had been formed, did startup activity begin to taper off.†

Many of the first NBFs (e.g., Genentech, Genex, Cetus) financed their own proprietary research by providing large established U.S. and foreign companies with research services for initial product development or by entering into licensing agreements with such companies that would re-

● **The financing of NBFs is discussed in detail in *Chapter 12: Financing and Tax Incentives for Firms.***

●● **Because most NBFs are unable to meet many of the standard int'ester requirements for such things as earnings, sales, rate of growth, etc., sometimes potential investors use the number of Ph. D.s per firm as a measure of future earning power.**

●" ● **See *Chapter 14: Personnel Availability and Training* for a more detailed discussion of personnel needs and availability in the United States.**

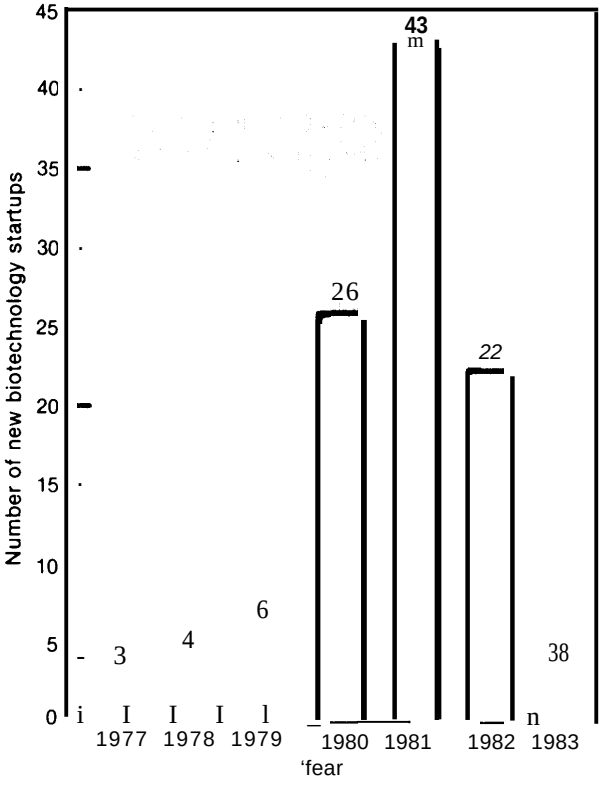
•Scherago **defines a biotechnology firm as a gene manipulation company.**

●***See *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.***

*●***This average is based on the firms in table 4 for whom Ph. D. figures are given.**

†**The pace of new biotechnology startups may also have been slowed because many of the top university scientists who wanted to join new firms probably had already done so. A year or two ago a survey done by an investment company looking for an unaffiliated molecular biologist reportedly approached 20 researchers before it found one without a commercial tie (16).**

Figure 11 .–Emergence of New Biotechnology Firms, 1977-83



[a]As of November 1983.

SOURCE: **Off Ice of Technology Assessment**

suit in future product royalty income. Product development contracts between NBFs and established companies generally provide for periodic cash payments from the established company to the NBF during the stages of research and early product development and for additional payments to the NBF (royalties income) following product sales. Following early product development by the NBF, the established company is generally responsible for obtaining the necessary regulatory approvals, manufacturing, and marketing of the product.

In the last couple of years, more and more NBFs have begun shifting away from developing products for larger companies for reasons including the following:

- NBFs have decided to concentrate more on proprietary research,
- profit margins from licensing technology to established companies are low and may not provide sufficiently substantial earnings (26), and
- most NBFs do not want to be dependent on another company for financial survival.

Instead of relying on contract revenues many NBFs are now obtaining financing through R&D limited partnerships, public stock offerings, or private placements. By retaining the rights to produce and market some of the products they develop (rather than developing products for established companies), some NBFs are seeking to become fully integrated producers and marketers. Genentech, for example, is hoping to manufacture and market four new products (human growth hormone, tissue plasminogen activator, and two types of interferon), and a large portion of Genentech's capital expenditures since 1981 has gone into a production plant for these products (24). Similarly, the NBF Amgen is building a $10 million pilot plant in Chicago for preclinical and clinical studies, and the NBF Genex has just purchased a manufacturing plant in Kentucky to produce phenylalanine and aspartic acid (the two amino acids used to produce the sugar substitute aspartame).

COMMERCIAL PURSUITS OF NBFS

Most NBFs are applying biotechnology to the development of pharmaceutical products or products for use in animal and plant agriculture. For several reasons, the most popular area of commercial pursuit among NBFs at present is the development of MAbs for research and in vitro diagnosis of human and animal diseases. *

- MAb in vitro diagnostic products require much shorter development times than do many rDNA-produced pharmaceutical products, because the technological development of MAb products is less complex. Furthermore, FDA's premarketing approval process is less costly for in vitro products than for products intended for internal use.

Pharmaceutical applications of MAbs are discussed in *Chapter 5: Pharmaceuticals.* The applications of MAbs in the diagnosis, prevention, and control of animal diseases are discussed in *Chapter 6: Agriculture.

- Relatively short development times and modest capital requirements for MAb in vitro diagnostic products afford NBFs opportunities to generate short-term cash flow from these products with which to fund the more time-consuming and costly R&D on pharmaceutical products intended for internal use. *
- Entering the MAb in vitro diagnostic products market is relatively easy for NBFs, because the diagnostic market is highly fragmented and the individual diagnostic markets relatively small. Thus, NBFs are likely to encounter few scale disadvantages in competition with large established companies.
- The markets for in vitro MAb diagnostic products are growing, thus providing expanding opportunities for entry by NBFs. The clinical immunodiagnostic market has grown at an annual rate of approximately 20 percent for the past few years, and this rate of growth is expected to continue or increase in the future (63). The 1982 market was valued at $5 million to $6 million (77). Table 12 provides 1982 and 1990 estimates for the size of various MAb markets in the United States.

Oppenheimer & Co. expects the clinical immunodiagnostics market to be the most important source of revenue to NBFs in 1983 (63). Many of the in vitro MAb diagnostic products now being developed or sold are replacement products that offer improved (more accurate) detection, shorter test times, and lower production costs (63)—and as might be expected, competition for market shares and scientific and financial resources is intense. Since 1980, more than 12 new U.S. companies (e.g., Xoma, Quidel, Techniclone, New England Monoclinal Resources) have formed specifically to exploit hybridoma technology, and most of them either already have MAb diagnostic kits on the market or are seeking FDA's approval. In 1982 alone, FDA approved some 30 in vitro MAb diagnostic kits (26).

To increase their chances for commercial success, NBFs solely dependent on MAb-based diagnostic products must find market niches. Although, a focused strategy such as MAb production could bring NBFs financial success with a smaller investment of dollars and scientific expertise in a shorter time frame than a more diverse strategy typical of some of the more heralded, multipurpose companies, such a strategy could also limit their growth potential (26). The worldwide diagnostic market represents only $2 billion out of the $80 billion annual human drug market (24). Until NBFs are capable of entering the larger drug markets, however, diagnostic products may prove crucial in supporting the high costs of pharmaceutical development.

Some NBFs are developing MAb therapeutic and in vivo diagnostic products, although the number of NBFs developing these products is less than the number developing in vitro MAb diagnostic products. " In addition to MAb therapeutics to treat cancer, MAb therapeutic products are being developed to treat bacterial infections that are sometimes difficult to treat with antibiotics and viral infections for which no antibiotics exist. As will be discussed in the section below entitled "Collaborative Ventures Between NBFs and Established U.S. Companies)" the regulatory environment for pharmaceuticals imposes heavy long-term financial burdens, which many NBFs may be unable to bear alone. Since many of the new firms aspire toward short-term earnings and independent production and marketing, it is not surprising that in vitro MAb diagnostic products are the area of application most widely chosen by NBFs.

Many small markets exist for NBFs in animal agriculture, and for replacement as well as new products, the barriers to market entry are low. Furthermore, the costs of obtaining regulatory approval for most animal health products are lower than those for human pharmaceuticals. However, in order to market some animal health products, including vaccines, a large and highly

*Cetus Corp. (U.S.), for instance, is developing diagnostic products for detecting blood-borne pathogens such as hepatitis B virus with funding from Green Cross of Japan and for detecting cytomegalovirus. Cetus is also developing readily marketable biotechnology products for animal agriculture until its more profitable products, particularly anticancer drugs, are developed. Likewise Hybritech (U. S.) and Genetic Systems (U.S.) are producing MAb diagnostic products to support other longer range R&D activities such as MAb therapeutics.

• An even smaller number are developing MAbs for use in separation and purification.

Table 12.—Estimates of U.S. Monoclinal Antibody Markets, 1982 and 1990 (1981 dollars **in millions)**

Application	1982 market size	1990 market size
Diagnostics:		
In vitro diagnostic kits	$5 to $6	$300 to $500 ($40)"b
Immunohistochemical kits (examination of biopsies, smears, etc.)	Nil	$25
In vivo diagnostics (primarily imaging)	Nil	Small to $lOO[b,d]
Therapeutics (includes radiolabeled and toxin-labeled reagents)	Nil	$500 to $l,ooob"
Other		
Research	Small	$10
Purification	Small	$10

[a]High number indicates market for total kit, number in parentheses indicates value of antibody alone for kit (includes patent licensing fees).
[b]Variation depending on industry source, although the range has been corroborated by at least two sources.
[c]This number could be much higher or lower depending on regulatory process
[d]Based on current pricing (19S1 dollars) for diagnostic tests of the **same type.**

SOURCE: Office of Technology Assessment.

specialized sales force may be necessary. Some NBFs do not expect to hire their own marketing force. Genentech, for example, does not expect to market its own animal vaccines. Some NBFs hope to use existing distribution networks for animal health products instead of developing their own specialized marketing force,

NBFs pursuing plant agriculture applications of biotechnology seem to have found sponsors for longer term research in areas such as enhanced protein content and nitrogen fixation, but a number of new firms are conducting proprietary research in areas such as the regeneration of inbred crop lines from tissue culture. NBFs pursuing plant biotechnology are already using cell culture technologies rather successfully to introduce new plants to the market. One firm, Ecogen, has been formed to focus exclusively on microbial and viral pesticides and other novel pest control methods. As the more frontier techniques such as gene transfer are developed, they can be incorporated into ongoing product lines (15).

FUTURE PROSPECTS OF NBFs

Almost 2 years ago, skeptics forecast a '(shake-out" among the NBFs (18,31,60,66). Even though the commercialization of biotechnology now may be more time-consuming, more expensive, and less profitable than was initially hoped, such a shake-out has not yet occurred. A shakeout will occur, however, when new markets develop and present trends in financing, established firm involvement, and technical capability change.

NBFs were formed to exploit research advantages in biotechnology, and many NBFs still possess such advantages. Given their research advantages, and assuming good management and adequate financing, many NBFs may continue to compete successfully with both larger companies and other NBFs as long as competition in biotechnology remains focused in research. Eventually, however, perhaps within 2 or 3 years, most NBFs will have to manufacture and market their own products in order to finance future growth and achieve some level of commercial success. A change from a research-oriented strategy to a more production-oriented strategy will mark a new stage in development for the average NBF, because in the past (and to some extent even now) NBFs out of need for capital have sold their processes to established companies.

NBFs that are wholly dependent on biotechnology for revenues cannot spread the risk of product development over a broad range of products made by traditional methods (unlike the established companies that have several product lines to generate revenues). Many NBFs will fail if markets for the biotechnology products now being commercialized do not develop. Furthermore, many NBFs will fail if capital for production scale-up, clinical trials (if necessary), and marketing is not available when markets develop.

The commercialization of biotechnology in the United States and other countries at present is characterized by a large number of companies, many small, some medium, and many *large,* applying biotechnology to a very narrow range of products. * Most of the products are rDNA-pro-

"Examples **of such products are interferon,** interleukin-2, **human growth hormone, tissue** plasminogen **activator, and** MAb-based diag-

duced pharmaceuticals and MAb-based diagnostic products. Because of the large number of companies and small range of biotechnology products, most of the initial product markets are likely to be very crowded, costly to enter, and highly competitive. The sharp decline in the formation of NBFs in 1983 might be explained in part by the currently high levels of competition. How many producers the initial biotechnology product markets might ultimately accommodate is uncertain. Thus, the factors likely to affect the future commercial success of the NBFs most immediately are the timing of market introduction, product performance, and product quality. Price, and hence production costs, will be of greater importance later.

The major determinant to the commercial future of NBFs, assuming they are able to maintain a research advantage, will be their ability to obtain financing and their ability to enter the newly developing product markets. NBFs must manufacture and market their own products not only to generate sufficient revenues to fuel growth but also to be in control of the timing of their own product introduction. It remains unclear whether NBFs will have the financial resources and marketing strength to enter some of the new markets. Large established pharmaceutical companies, for example, normally employ some 500 people just to market their drugs (24), while Genentech, one of the largest NBFs, has a total of about 500 employees.

Some of the most difficult markets for NBFs to enter will be those for human therapeutics, in part because of the regulatory costs associated with product approval and in part because of the market competition posed by established U.S. pharmaceutical companies, which could control some of the early channels of distribution. Entering the markets for in vitro diagnostic products, as mentioned earlier, is relatively easy and does not require large capital investments, but because these markets are currently very crowded, survival may be difficult.

The specialty chemicals market appears relatively easy to enter, both because little competition exists at present and also because the regulatory environment does not impose high costs on product development. Research is near term for many of the products, 3 to 5 years, and an NBF would experience few production scale disadvantages in competition with larger companies.

The safety regulations applicable to animal health products are significantly less stringent than those applicable to pharmaceutical products intended for internal human use, and many market niches exist for small firm entry. Additionally, relatively little competition from established companies exists at present. However, the need for an extensive sales force to market some of the products might pose a considerable barrier to some NBFs wishing to enter animal health markets.

The availability of venture capital and financing for NBFs has been sufficient thus far to fuel the growth of many NBFs. The public market, particularly for new issues, and R&D limited partnerships continue to provide capital to NBFs for use in further research, pilot plant construction, clinical trials, and product development. From August 1982 to May 1983 alone, NBFs raised $200 million through R&D limited partnerships (6). One analyst estimates that R&D limited partnerships will raise a total of $500 million in 1983 (7). The public stock market has also been receptive to NBF issues. Between March and July 1983, 23 NBFs raised about $450 million (39). As long as the public market and R&D limited partnerships make financing available to NBFs, they can continue developing independent strategies, thereby reducing their reliance on established companies.

Paralleling the emerging desire by some NBFs to become integrated producers and marketers is an apparent reduction from 1982 to 1983 in the number of research contracts sponsored by established U.S. companies * and an increase in the amount of capital established U.S. companies

nostic products for detection of venereal diseases and pregnancy. Tables 18 and 23 in *Chapter 5: Pharmaceuticals* provide a list of firms engaged in cloning projects for interferon and human tissue plasminogen activator, respectively, and exhibit a rather high level of competition for the two products. Additionally, at least eight NBFs are cloning interleukin-2 (Chiron, Genex, Biogen, Cetus, Genetics Institute, Immunex, Interferon Sciences, and Quidel).

• It is impossible to quantify the number and value of all established company sponsored research contracts because not all of

are devoting to in-house biotechnology programs. Although the pattern is beginning to change, research contracts sponsored by established companies still provide a large portion of the NBFs' revenues. * If the decline in number of research contracts sponsored by established companies continues, which is likely, NBFs must begin finding other sources of revenue. Increases in the amount of capital established U.S. companies are devoting to in-house biotechnology programs portend greater competition in R&D from the larger companies. Equipped with greater financial and marketing resources, more regulatory and, in some cases, production expertise, many U.S. established companies will be formidable competitors in the long run as biotechnology product markets develop. Not all NBFs will survive the competition of the established companies; provided they have adequate financing, however, some NBFs will be able to commercialize their early research advantages before the established companies commercialize theirs.

As biotechnology continues to emerge, and further technical advances are made, new generations of NBFs undoubtedly will evolve to develop the technologies. Within the next several years, a second generation of NBFs is likely to emerge as the result of developments such as the following:

- intensified competition that forces some firms out and creates new opportunities for more entrants,
- a major technological advance in some area of biotechnology such as computer-assisted protein design, which encourages the entry of more new companies,
- the diffusion of advances in bioprocessing, which enables small firms to assume responsibility over their own production, and
- the development of the technologies to the point where scientists from present companies or young scientists from universities will start their own companies.

public. However, on the basis of those that have been reported, most observers would probably agree that the number of new outside research contracts sponsored by established companies in 1983 has dropped significantly from 1982 levels.

***See *Chapter 12: Financing and Tax Incentives for Firms* for further discussion of the sources of NBF revenues.**

ROLE OF NBFS IN U.S. COMPETITIVENESS IN BIOTECHNOLOGY

The development of biotechnology is still at an early stage, and competition at present is predominantly in the areas of research and early product development. This early stage of biotechnology development is precisely where NBFs are playing the largest role in competition. Later, however, as the technology develops further and enters a large-scale, capital-intensive production stage, the science may become less important vis-a-vis production expertise, and the dominant role NBFs currently play in the US. biotechnology effort may diminish.

The launching of embryonic high-technology industries by entrepreneurial firms is a phenomenon unique to the United States. Historically, small new firms in the United States have had a major role in shaping the competitive position of the United States in emerging technologies. * As discussed further below, NBFs have thus far assumed a similar role in biotechnology:

- by contributing to the expansion of the U.S. basic and applied research base for future biotechnology development,
- by transferring the technology to several industries through joint agreements with other companies,
- by decreasing investment risk by advancing learning curves for later entrants, such as established companies or other NBFs,
- by developing markets, and
- by increasing the level of domestic competition in the United States and thereby accelerating the pace of technology advance.

The formation in the United States of over 110 NBFs that have various links to the network of university biology, chemistry, and engineering departments has extended the basic research base beyond the universities and has expanded the applied research base beyond just a few companies. While the basic and applied research base is being broadened for future biotechnology development, joint agreements and licensing arrangements between NBFs and large established U.S.

● ***See Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology.***

companies are effectively diffusing biotechnology across many industrial sectors.

With the help of venture capitalists, NBFs started much earlier to evaluate the commercial potential of biotechnology than did large established US. or foreign companies. As early as 1976, NBFs were willing to risk their very existence on the undemonstrated potential of biotechnology. A survey conducted by OTA indicated that most established U.S. companies did not begin in-house biotechnology R&D until 1981 or later. * This finding suggests that the early burden of risk was carried by NBFs. Although many established U.S. companies have now made substantial commitments to biotechnology through investments in plant and equipment for in-house biotechnology R&D programs, others are still hesitant to make such investments and many NBFs continue to function as a litmus test for the new technologies. In Europe and Japan, most companies did not make major investments in biotechnology until after 1981. Thus, it might be suggested that the early R&D activity of NBFs has given the United States a competitive lead in the early stages of biotechnology's commercialization.

The NBF initiative to commercialize biotechnology not only has spurred the development of new product markets but also is expected to expand existing markets through the introduction of products with increased effectiveness and decreased cost. For example, diagnostic kits using MAbs and DNA probes are being developed to detect venereal diseases (e.g. chlamydia and herpes) that are difficult and time~onsuming to detect by existing methods. Vaccines are being developed for diseases that now have no reliable prevention (e.g., hepatitis and herpes in humans and colibacillosis in calves and pigs).

The NBFs' entry into the traditional markets served by established companies, where NBFs have taken the risks of developing new products or potentially reducing the production costs of existing ones, has prompted many established U.S. companies to explore potential applications of the new technologies. The market uncertainty created by the new firms and the perceived competition they represent to the established companies is healthy in a competitive context, because it increases the aggregate level of industrial R&D in the United States. The perceived competitive threat that NBFs pose to established companies could become even greater as NBFs such as Biogen, Genentech, and Genex begin to shift away from developing products for large corporate clients and begin to turn toward independent production and marketing of their own products.

Because of their technological expertise and early role as contract research companies, the NBFs have helped established U.S. companies evaluate the feasibility and suitability of using the new technologies in their existing lines of business. They have also helped the established companies evaluate new avenues for diversification, Frequently, the established U.S. companies maintain multiple research contracts with the NBFs to evaluate several applications simultaneously or to evaluate the same application from different perspectives. In this way, the established companies can "ride along" the NBF learning curves while minimizing expenses and risk. In a competitive context, this relationship between NBFs and established U.S. companies is important because it may help to position both types of U.S. firms in international product markets.

From the standpoint of U.S. competitiveness, the innovative lead taken by NBFs in the United States might seem to be a handicap because of the potentially adverse consequences from the transfer of technology from the United States to foreign countries. But the United States, at first through the new firms and now with the combined effort of the established companies, has the ability to maintain its lead by continuing to innovate and develop at a pace equal to or faster than its competitor countries. While competition remains mostly in research, the ability of the United States to remain competitive and in the forefront of biotechnology development rests heavily on NBFs, As biotechnology reaches production stages, the bioprocessing, regulatory, and marketing experience of the established companies will be crucial to a strong US. position.

● **The survey questionnaire is reproduced in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.***

Established U.S. companies

The proliferation of many NBFs and the developments in biotechnology that have been made thus far have prompted many established U.S. companies to re-evaluate the competitive and technological environments in which they have been operating. To some extent, U.S. corporate investment in biotechnology has been both an aggressive and defensive response to the potential market threat represented by NBFs such as Biogen, Genex, Cetus, and Genentech. Although a few pharmaceutical and chemical companies such as Monsanto, DuPont, and Eli Lilly have had biotechnology research efforts underway since about 1978, most of the established U.S. companies now commercializing biotechnology did not begin to do so until about 1981. *

INVESTMENTS IN BIOTECHNOLOGY BY ESTABLISHED U.A COMPANIES

The motivations underlying established U.S. companies' decisions to invest in biotechnology and the forms that each investment takes vary from company to company. When biotechnology first began to receive commercial attention, many established U.S. companies, particularly those without a major in-house biotechnology program, elected to gain in-house expertise by obtaining technology through research contracts with NBFs or universities, * * R&D contracts with NBFs, * * * or equity investments in NBFs. For some established U.S. companies, contracts with or equity positions in NBFs are still a major route by which to expand their knowledge of biotechnology.1 However, several of the established U.S. companies that initially entered the field through R&D joint ventures are now increasing their commitment to biotechnology through internal expansion.

Since 1978, equity investments in NBFs, often accompanied by research contracts, have been a popular way for established U.S. companies to gain expertise in biotechnology. Table 13 lists many established U.S. companies that have made equity investments in NBFs and the NBF in which they have taken the equity position. * Although only individual corporate strategies can specifically explain why established U.S companies have taken positions in NBFs, some of the investments may have been viewed by the established companies as:

- a defensive strategy against market share losses to unknown technologies,
- an avenue for diversification and greater return on investment, and
- a means of gaining a '(window on the new technology."

Figure 12 provides the aggregate equity investment figures for 1977 to 1983 based on table 13. Review of table 13 and figure 12 shows that:

- equity investments in NBFs range from $0.5 million to $20 million;
- some established companies have made multiple investments in the same NBF;
- a number of established companies have made investments in more than one NBF;
- equity investments, in some cases, have led to the formation of another firm (e.g., Genentech and Corning Glass formed Genencor, and Diamond Shamrock and Salk Institute/ Biotechnology Industrial Associates formed Animal Vaccine Research Corp.); and
- equity investments have tapered off since 1982.

The years 1978 and 1979 appear to have marked the beginning of general US. corporate

● **This statement is based on the responses to a survey conducted by OTA and the National Academy of Sciences. The survey questionnaire is reproduced in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.***

●● ***Major* university contracts in biotechnology appear to have been declining over time. University/industry relationships in biotechnology are discussed in *Chapter 11: University/industry Relationships,***

*●● For **a more detailed discussion of R&D joint ventures, see the section below entitled "Collaborative Ventures BetweerNBFs and Established U.S. Companies. "**

†In 1982, **Monsanto, for example, committed approximately $40 million to outside contracts in biotechnology; however, the overall number of newly formed research and licensing agreements is waning as more and more established companies commit large amounts to in-house staff and facilities.**

● **A much smaller number of foreign established companies have taken equity position in American NBFs. They are not included in table 13. The notable foreign investors are Sandoz (in Genetics Institute), Novo (in Zymos), a group of Japanese and Swedish investors (in Genentech), C. Itoh (in Integrated Genetics), and Bayer in Molecular Diagnostics).**

●● **The percentage of NBFs purchased by the established companies listed in table 13 range from 1.6 to *100* percent, with 10 *to* 30 percent being the most common.**

Table 13.—Equity Investments in New Biotechnology Firms by Established U.S. Companies, 1977=83"

Date	U.S. established company	New biotechnology firm	Equity (millions of dollars)
1980	Abbott Laboratories	Amgen	$5
1981	Allied Corp.	Calgene	2.5
1983		Genetics Institute	10
1981	American Cyanamid.	Molecular Genetics, Inc.[b]	5.5
		Cytogen	6.75
1981	ARCO	International Genetic Engineering, inc. (lNGENE)	0.75
1982	Baxter-Travenol	Genetics Institute	5
1982	Beatrice Foods	International Genetic Engineering, inc. (lNGENE)	3.0
1980	Bendix	Engenics	1.75
1982	Bendix/Genex	Proteins Association	16.5[c]
1983	BioRad	International Plant Research Institute(lPRI)	1
1981	Campbell Soup..	DNA Plant Technologies	10
1981	Continental Grain	Calgene	1
1981	Cooper LabslLiposome Tech. Corp.	Cooper-Lipotech	2.7
1982	CorninglGenentech	Genencor	20
1983	Cutter Laboratories	Genetic Systems	9.5
1982	DeKalb	Bethesda Research Laboratories	0.6
1980	Dennison Manufacturing Corp.	Biological Technology Corp.	2
1983	Diamond Shamrock/Salk Institute Biotechnology Industrial Associates.	Animal Vaccine Research Corp.	N.A.*
1981	Dow	Collaborative Research	5
1981	Dow	International Genetic Engineering, Inc. (lngene)	N.A.
1981	Ethyl	Biotech Research Labs	0.95
1981	Fluor	Genentech	9
1981	FMCICentocor.	Immunorex	4.9
1980	General Foods	Engenics	0.5
1982	Getty Scientific Corp.	Synergen	4
1982	Gillette	Repligen	N.A.
1983	Hewlett-Packard Co./Genentech	HP Genenchem	N.A,
1978	INCO, inc.	Biogen[e]	0.35
1979	INCO, Inc.	Biogen	1.25
1980	INCO, Inc.	Biogen	4.61
1981	INCO, Inc.	Biogen	2.5
1981	INCO, Inc.	Immunogen	1
1981	INCO, Inc.	Plant Genetics	N.A.
1981	INCO, Inc.	Liposome Co.	N.A.
1977	Innoven [f]	Genex; Genentech	2
1981	Johnson & Johnson	Quadroma	0.7
1982	Johnson & Johnson	Enzo Biochem	14
1983	Johnson & Johnson	Immulokg	18
1982	Kellogg	Agrigenetics	10
1979	Koppers	Genex	3
1980	Koppers	Genex	12
1981	Koppers	Engenics	1.25
1981	Koppers	DNA Plant Technologies	1.7
1982	Eli Lfliy	International Plant Research Institute (IPRI)	5
1979	Lubrizol	Genentech	10
1980	Lubrizol	Genentech	15
1982	Lubrizol	Sungene	4
1980	McLaren Power &Paper Co.	Engenics	1.25
1982	Martin Marietta..	Molecular Genetics, Inc.	9.7
1982	Martin Marietta	NPI	5
1982	Martin Marietta.	Chiron	5
1983	Martin Marietta	Chiron	2
1980	MeadCo.	Engenics	1.25
1980	Monsanto	Biogen	20
1980	Monsanto	Collagen	5.5

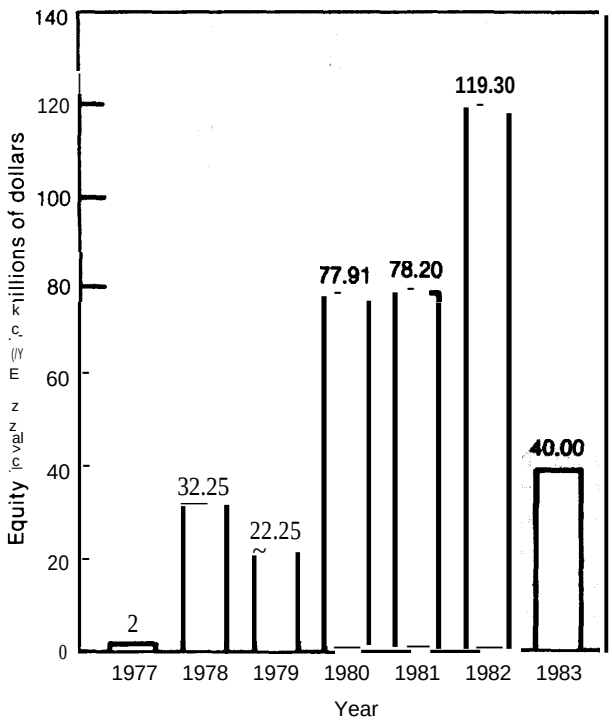
Table 13.–Equity Investments in New Biotechnology Firms by Established U.S. Companies, 1977-83[a] (Continued)

Date	U.S. established company	New biotechnology firm	Equity (millions of dollars)
1978	National Distillers	Cetus	5
1980	National Patent Development Corp.	Interferon Sciences	0.6
1980	Nuclear Medical Systems	Genetic Replication Technologies	0.95
1981	Phillips Petroleum	Salk Institute BiotechnologyIIndustrial Associates	10
1981	Rohm & Haas ... ,	Advanced Genetic Sciences	12
1979	Schering-Plough .,	Biogen	8
1980	Schering-Plough	Biogen	
1982	Schering-Plough	DNAXQ	2 :
1978	Standard Oil of California.	Cetus	12.9
1978	Standard Oil of Indiana	Cetus	14
1982	SyntexhlGenetic Systems	Oncogen	9.5
1982	SyntexlSyva	Genetic Systems	9.5
1980	Tosco	Amaen	3.5

[a] As of May 1983.
[b] American Cynamid sold 375,000 shares of MGI to Moorman Manufacturing in 1983.
[c] Investment over a 6-year period.
[d] N.A. = Information not available.
[e] Biogen is only 80 percent U.S.-owned.
[f] Monsanto & Emerson Electric.
[g] Acquisition.
[h] Incorporated in Panama.

SOURCE: Office of Technology Assessment.

Figure 12.—Aggregate Equity Investments in New Biotechnology Firms by Established U.S. Companies, 1977-83[a]



[a] As of May 1983

SOURCE: Off Ice of Technology Assessment.

interest in biotechnology, with equity investments made by a number of oil and mining companies in the NBFs Biogen, Cetus, Genex, and Genentech. By 1980, commercial applications of biotechnology were advancing in industrial areas where some established companies had no prior R&D commitment, and from 1979 to 1980, there was a dramatic increase in the number and size of equity investments. Equity investments in NBFs have been made by U.S. companies from a variety of industrial sectors: Monsanto (chemicals), for example, invested $20 million in Biogen and $5.5 million in Collagen; Lubrizol (chemicals) made a second equity investment in Genentech totaling $15 million; Fluor (engineering) invested $9 million; and Koppers (mining) expanded its equity position in Genex by investing $12 million.

In 1981, the amount of equity capital invested in NBFs barely exceeded the amount invested the previous year, but in 1982, equity investments soared to a record high of $119 million, an increase of 52 percent over 1981, and the highest level of equity investments in biotechnology ever made. In 1983, the level of equity investments in NBFs dropped significantly. A growing commitment among established U.S. companies to in-house R&D programs in conjunction with pre-

viously made equity investments may have contributed to the sharp decline.

In 1982, established U.S. companies not only increased their equity investments in NBFs but they also dramatically increased their in-house investments in biotechnology R&D programs. Capital investments for in-house R&D programs generally reflect the highest level of commitment to biotechnology, as new facilities and employees are often needed to start the new effort. Several U.S. pharmaceutical companies are spending large amounts on new facilities: G.D. Searle, for example, is building a $15 million pilot plant to make proteins from rDNA organisms; DuPont is building an $85 million life sciences complex; Eli Lilly is building a $5o million Biomedical Research Center with emphasis on rDNA technology and immunology and a $9 million pilot plant and lab for rDNA products; Bristol Myers is building a new $10 million in an alpha interferon production plant in Ireland. * Companies from other sectors have also made substantial investments in biotechnology. See table 7 for a list of the 1982 biotechnology R&D budgets for some of the established U.S. and foreign companies most actively supporting biotechnology.

The product areas in which established U.S. companies have directed their biotechnology R&D efforts are as diverse as the industrial sectors they represent. Established companies, however, appear to be playing a dominant role in the development of biotechnology in the areas of plants (25) and commodity chemicals–two rather long-term and costly research areas (see table 4).

ROLE OF ESTABLISHED COMPANIES IN U.S. COMPETITIVENESS IN BIOTECHNOLOGY

Many established U.S. companies manufacture several product lines and are therefore concurrently evaluating different biotechnology application areas. DuPont, for example, is evaluating applications of biotechnology to food production, health care, and renewable resources. Broad strategies such as DuPont's will have a positive effect on the development of biotechnology in the United States by diffusing applications throughout many industrial sectors.

Unlike the many NBFs that have taken a relatively short-term approach to biotechnology in order to generate income for longer term research, many established U.S. companies have several product lines and are taking a longer term approach to biotechnology research; some established companies are not expecting commercial development for 10 to 20 years (27). The long-range research orientation of established U.S. companies will be very important to the long-term competitive position of the United States.

Established U.S. companies will play a major role in the first biotechnology product markets. Because many NBFs have licensed technology to established U.S. companies hoping to finance future growth from the royalties received from the future sale of the products, the established companies will be responsible for the production and marketing of many early biotechnology products. For example, two NBFs, Petroferm and Interferon Sciences, have already solicited the production expertise of Pfizer and Anheuser Busch, respectively, Pfizer's chemical division is the foremost producer of biopolymers and xanthan gums and will produce Petroferm's new bacterial oil emulsifier. Anheuser Busch, through beer production, has accumulated years of experience using yeast and will produce interferon using Interferon Science's genetically manipulated yeast.

The most important element in competition for pharmaceutical market acceptance and market share might be the timing of product entry. Although some NBFs have recently begun funding their own clinical trials and product development, most NBFs still have rather limited financial resources. Most NBFs also have limited production, marketing, and regulatory experience. Such limitations may hinder the ability of NBFs to become major participants in early pharmaceutical product markets. Although the U.S. competitive position in pharmaceutical markets has been declining since the mid-1970's, established U.S. companies appear strategically positioned to compete effectively in international biotechnology product markets as such markets develop.

● Schering-Plough **is expected to spend more than $40 million on interferon R&D alone in** 1983.

Established U.S. companies also have a competitive role to play in research, because continuous technical advances will be necessary to maintain the present competitive strength of the United States. As the established U.S. multinational companies, along with the other later entrants, expand their in-house research and production facilities they will undoubtedly make substantial contributions to the U.S. commercialization of biotechnology.

Collaborative ventures between NBFs and established U.S. companies

As suggested previously, the development of biotechnology in the United States is unique from the standpoint of the dynamics of the interrelationships between NBFs and the large established U.S. companies, NBFs and established U.S. companies not only compete with one another, but they also, through joint ventures of many kinds, complement one another's skills. In addition to delaying a "shakeout" among NBFs, joint ventures between NBFs and established companies have allowed NBFs to concentrate on the research-intensive stages of product development, the area in which they have an advantage in relation to most established U.S. companies.

A joint venture is a form of association between separate business entities that falls short of a formal merger, but that unites certain agreed upon resources of each entity for a limited purpose. * Joint ventures between NBFs and established companies are attractive for at least three reasons:

- they assist NBFs and established companies in overcoming resource limitations which may prevent them from developing or marketing a product themselves;
- they offer established companies and NBFs less costly methods by which to develop expertise in areas in which they lack in-house capability; and
- they provide established companies with an opportunity to achieve economies of scale in R&D for complex technological problems that might not otherwise be obtainable.

Considerable expenditures in time and money are required to research, develop, and market biotechnologically produced products. The NBFs, started exclusively to exploit innovations in biotechnology, have initially concentrated their activities on research. As a rule, therefore, NBFs have limited financial resources with which to fund production scale-up activities beyond the laboratory or pilot plant stage, not to mention the financing required for regulatory approval and marketing should their research activities in biotechnology yield pharmaceuticals and to a lesser extent, animal drugs and biologics, food additives, chemicals, or microorganisms for deliberate release into the environment. Established companies have an advantage over NBFs in that they have relatively more financial strength, regulatory experience, and product distribution channels that are already in place, although many established companies are at a disadvantage compared to NBFs with respect to the possession of technical expertise in biotechnology. R&D joint ventures and contracts between NBFs and established companies, therefore, reflect a mutual search for complementary skills and resources,

Examples of the collaborative agreements that are taking place between NBFs and established U.S. and foreign companies are shown in table 14. * R&D contracts accompanied by product licensing agreements form the basis for most joint ventures between NBFs and established U.S. companies in the area of pharmaceuticals. Furthermore, equity investments in NBFs by established companies are often accompanied by R&D contracts. Equity joint ventures wherein equity capital is provided by both partners (e.g., Genencor) for R&D or marketing are less common. Since research contracts and product licensing agreements characterize most joint ventures, three points should be kept in mind throughout this section:

- Licensing agreements and future royalties provide NBFs with financing to do their proprietary research.

● ***Chapter 18: Antitrust Law*** **explores some of the legal considerations surrounding R&D joint ventures, and** ***Chapter 12: Financing and Tax incentives for Firms*** **highlights joint ventures from a financial perspective**

"The large proportion of pharmaceutical joint agreements presented in table 14 reflects the commercial emphasis by companies on pharmaceutical development.

Table 14.-Some Collaborative Ventures Between New Biotechnology Firms and Established U.S. and Foreign Companies[a]

New biotechnology fhn—Established company	*New biotechnology f!rm—Established company*
Biogen N.V. (Netherlands Anti//es)%	*Cetus:*
—Meiji *Seika Kaisha, Ltd.* (Japan) has license and development agreement with Biogen N.V. for the scale-up of a still unnamed agricultural chemical which Meiji could bring to market by 1984-85.	—*Roussel Uclaf* (France) has a contract with Cetus under which Cetus produces vitamin B12. Cetus is receiving royalties.
—International Minerals Corp. has exclusive marketing rights to Biogen's rDNA-produced swine and bovine growth hormones. Biogen will receive royalties.	—*TechAmerica* has a contract with Cetus under which Cetus will develop a rDNA antigen to be used as a vaccine against calf bovine diarrhea. TechAmerica will perform clinical research, manufacture, and market.
—*Shionogi & Co., Ltd.* (Japan) will conduct clinical trials and pursue the commercial development in Japan of Biogen's gamma interferon for human therapeutic use.	—*Norden Labs, Inc.* has a contract with Cetus under which Norden will produce and market rDNA colibacillosis vaccine. Cetus receives royalties.
—*Merck* is developing Biogen's hepatitis B vaccine.	—*Cooper will* market a MAb from Cetus Immune that is used in tissue typing for organ transplants.
—*Shionogi* (Japan) has a license from Biogen to develop and market Biogen's human serum albumin in Japan and Taiwan.	—*Shell Oil Co.* gave a research contract to Cetus under which Cetus will develop human beta-1 (fibroblast) interferon.
—*Shionogi* (Japan) has a license and development agreement with Biogen to develop interleukin-2. Shionogi will conduct Japanese clinical trials.	***Chiron:***
—1/VCO has a contract with Biogen to do studies of the feasibility of bioextraction of nonferrous metals from low-grade ores and other sources of minerals.	*Merck* possesses option for exclusive worldwide license for the use, manufacture, and sale of Chiron's hepatitis B vaccine.
—*Fujisawa Pharmaceutical Co.* (Japan) has an agreement to develop and produce Biogen's tissue plasminogen activator in Japan, Taiwan, and South Korea.	***Collaborative*** *Genetics:*
—*Monsanto* will fund Biogen's developments of a technique to produce and purify tissue plasminogen activator.	—*Akzo N.V.* (Netherlands) gave Collaborative Genetics a research contract to develop genetically manipulated micro-organisms to produce bovine growth hormone.
—*KabiVitrum* (Sweden) is collaborating with Biogen **in the development of commercial products based on Factor Vlll. Biogen intends to market the products in the United States and Canada, and KabiVitrum will have the right to market** such products in certain other countries.	—*Green Cross* (Japan) has licensed from Collaborative and Warner-Lambert the process by which urokinase is microbially produced.
—*Green Cross* (Japan) has a license from Biogen to manufacture hepatitis B vaccine. Green Cross has exclusive license to market in Japan,	—*Dow* has given a research contract to Collaborative under which Collaborative will produce rennin via genetically manipulated micro-organisms.
—Suntory, *Ltd.* (Japan) has an agreement with Biogen under which Biogen will develop rDNA micro-organisms to produce tumor necrosis factor, to scale-up production, and to support clinical trials, and Suntory will have exclusive marketing rights in Japan and Taiwan.	***Cytogem***
—*Teijin, Ltd.* (Japan) has a license to develop and market Biogen's Factor Vlll in Japan, South Korea, Taiwan, Australia, and New Zealand.	—*American Cyanamid* has an agreement with Cytogen to develop a MAb that will deliver a chemotherapeutic agent to cancer cells.
Calgene:	***Damon Biotech:***
—Allied Chemical *Corp.* has a contract with Calgene under which Calgene will do research in nutrient efficiency in plants.	—*i+offmann-La Roche* (Switz.) has contracted Damon to apply its microencapsulation system to the production of MAbs. Hoffmann-La Roche will retain the marketing rights to the interferon produced by this process.
Cambr/dge Bioscience:	***Enzo Biochem:***
—*Virbac,* a French animal health care company, has a contract with Cambridge Bioscience under which Cambridge Bioscience will develop feline leukemia virus vaccine.	—*Meiji Seika Kaisha* (Japan) obtained worldwide marketing rights to products based on Enzo's hybridoma technology, including a newly developed pregnancy test.
Cenbcoc	***Genentech:***
—FMC *Corp.* has 50/50 joint venture to develop human-derived monoclinal antibodies (MAbs).	—*Monsanto* is testing Genentech's bovine and porcine growth hormones. Commercialization and production will be joint effort.
—*Toray/Fujizoki* (Japan) have signed an agreement to manufacture and market Centocor's hepatitis diagnostic in Japan.	—Genentech has **a** joint development contract with *Hoffmann-La Roche* for the production of leukocyte and fibroblast interferon. Hoffmann-La Roche will conduct testing to determine its effectiveness. Genentech will supply part of Roche's requirements and receive royalties on sales.
	—*KabiVitrum* (Sweden) has worldwide (except in the United States) marketing rights for Genentech's human growth hormone.
	—*Fluor* will develop commercial production operations for Genentech to scale-up new biotechnology products.

Table 14.—Some Collaborative Ventures Between New Biotechnology Firms and Established U.S. and Foreign Companies[a] (Continued)

New biotechnology firm—Established company	*New biotechnology firm—Established company*
—*Eli Lilly* has been granted exclusive worldwide rights to manufacture and market Genentech's human insulin. —*Corning* and Genentech have a joint venture (Genencor) to manufacture and market rDNA-produced enzymes for food processing and chemical industries. Corning provides expertise in immobilization of enzymes. ***Genetics institute:*** —*Sandoz* (Switz.) is funding research by Genetics institute to clone monokines and lymphokines in bacteria, i.e., interleukin-2. ***Genetic Systems Corp.:*** —*Cutter Labs* and Genetic Systems have a $2.5 million joint venture to develop human MAbs for the diagnosis and treatment of *Pseudomonas* infections. For other MAb products, Genetic Systems will do R&D and market the diagnostic products, and Cutter will market therapeutic products. —Syva has a research, development, and marketing agreement with Genetic Systems which will finance some of Genetic Systems' R&D activities related to diagnostic tests for sexually transmitted diseases such as herpes, gonorrhea, and chlamydia. Genetic Systems receives 5 percent royalties on sales. —*Daiichi Pure Chemicals Co., Ltd.* (Japan) (a subsidiary of Daiichi Seiyaku Co.) entered into an agreement with Genetic Systems to collaborate on the R&D of a diagnostic test kit for blood disorders in the human immune system. Daiichi will receive the exclusive manufacturing and marketing rights in Japan, Taiwan, Mainland China, and Southeast Asia, for the products for treating blood disorders. Genetic Systems will receive royalties. —A separate marketing agreement with Daiichi grants the exclusive right to purchase and sell, for research products only, in Japan and other Asian countries, certain MAbs developed by Genetic Systems. —A joint venture between *Syva Co.* (a subsidiary of Syntex Corp.) and Genetic Systems to develop MAbs for the diagnosis and treatment of human cancer. –New *England Nuclear* (E. 1. du Pent de Nemours & Co,) has the rights to market Genetic Systems' MAbs for the identification of different types of human blood cells to the research market throughout the world, with the exception of Japan, Taiwan, People's Republic of China, and Southeast Asia, which are covered by Daiichi Pure Chemicals Co., Ltd. Genex: —*Yamanouchi Pharmaceutical Co.* (Japan) will manufacture and sell a biological product developed by Genex which dissolves fibrin. Yamanouchi will market the product for 15 years, paying Genex a licensing fee of 8 percent of sales for development and scale-up. Genex will retain the patent rights. —*BristoLMyers Co.* has a contract with Genex under which Genex will develop genetically modified micro-organisms that will produce leukocyte (alpha) and fibroblast (beta) interferon. Bristol-Myers owns all rights. Genex receives royalties. —A Japanese company (proprietary) has a contract with Genex under which Genex will develop a genetically modified micro-organism to produce L-try ptophan. All discoveries will be the sole property of the Japanese customer. —*Vineland Laboratories* and Genex have a joint development project to produce a vaccine against coccidiosis. —*Koppers* has a contract with Genex under which Genex will develop genetically modified micro-organisms to do biocatalytic transformations of aromatic chemicals from coal distillate derivatives. All micro-organisms and research findings are the sole property of Koppers. Genex will receive royalties. —*Schering AG (F. R. G.)* has a contract with Genex under which Genex will develop a microbe that will produce a blood plasma protein. Schering AG will receive worldwide exclusive license. —*Green Cross* (Japan) has a contract with Genex under which Genex will develop a microbial strain that produces human serum albumin (HSA). Green Cross will receive an exclusive license to sell, for at least 15 years, all microbially produced HSA under the contract in Japan, Southeast Asia, India, China, Australia, New Zealand, North America, and South America. Genex receives royalties. —*KabiVitrum* (Sweden) has a contract with Genex for HSA similar to that of Green Cross except Kabi's rights are limited to Africa, Europe, and the Middle East. —*Yoshitomi Pharmaceutical Industries* (Japan) has a contract with Genex under which Genex will develop genetically modified micro-organisms to produce interleukin-2. —*Mitsui Toatsu Chemicals Inc.* (Japan) contracted Genex to develop a microbial strain that produces human urokinase. Genex will retain the patent and Mitsui Toatsu will receive an exclusive license with the right to make, use, and sell the product for the royalty period, about 15 years. —*Mitsubishi Chemical Industries, Ltd.* (Japan) will develop and market Genex's HSA. —*Pharmacia* has a contract with Genex under which Genex will develop a nonpathogenic strain of bacteria that would produce a protein with potential therapeutic applications. ***Hana Biologics, inc.:*** —*Recordati S.p.A.* (Italy) has an agreement with Hana under which Hana will develop and distribute biomedical research and MAb diagnostic products. —*Fujizoki Pharmaceutical Co.* (Japan) has a joint venture with Hana under which Hana will develop new immunodiagnostic tests. Also, Fujizoki has a distribution agreement with Hana under which Fujizoki will market Hana products in Japan. ***Hybritech:*** —*Teijin, Ltd.* (Japan) has an agreement with Hybritech under which Hybritech will develop human MAbs for treatment of lung, breast, colorectal, prostate, and certain leukemia-lymphoma type cancers. The goal of the

Table 14.—Some Collaborative Ventures Between New Biotechnology Firms and Established U.S. and Foreign Companies[a] (Continued)

New biotechnology firm-Establishect company	New blotechnobgy firm-Established company
joint venture is to combine Hybritech's MAb manufacturing technique and Teijin's unique technique of binding a cytotoxic substance to an antibody for cancer therapy. —*Travenol Laboratories, Inc. will* provide $1 million for research and $1.9 million for stepwise benchmark payments to Hybritech to develop MAbs for treating major bacterial infections. Hybritech will receive royalties on Travenol's worldwide sales. ***Immunex:*** —Diamond Shamrock has a license to commercialize Immunex's lymphokines for use in animals. ***Integrated Genetics, Inc.:*** –Connaught Laboratories, Ltd. (Canada) has an R&D agreement with Integrated Genetics to produce hepatitis B surface antigen in yeast or mammalian cells. ***Interferon Sciences:*** —*Bristol-hfyers* has a licensing and supply agreement with Interferon Sciences under which Bristol-Myers will commercially develop interferon for the treatment of herpes zoster. –*Green Cross* (Japan) has a $2.5 million R&D and supply agreement with Interferon Sciences under which interferon Sciences will supply Green Cross with gamma and alpha interferon. —*Collaborative Research* is synthesizing interferon in yeast. Collaborative provides Interferon Sciences with the alpha-interferon producing clones. Interferon Sciences is involved in the product end and plans to optimize the bioprocess. ***Interferon Sciences, IncJCo/laborative Genetics:*** —Both companies have a license agreement under which *Green Cross* shares results of a study evaluating application of rDNA technology to the production of interferon by yeast or other micro-organisms. ***Molecular Genetics, Inc.:*** —*American Cyanamid* has an R&D contract and licensing agreement with Molecular Genetics under which Molecular Genetics will develop bovine growth hormone. Cyanamid is conducting scale-up and testing. —*American Cyanamid* has sponsored an R&D contract and formed a licensing agreement with Molecular Genetics to select herbicide-resistant corn in tissue cult ure.	—American **Cyanamid sponsored an** R&D contract and formed a licensing agreement with Molecular Genetics under which American Cyanamid will conduct human testing, secure regulato~ approvals, and manufacture and market any products developed from Molecular's human herpes simplex vaccine research. *Ledede* has begun preclinical testing. —*Philips-Roxane* (subsidiary of Boehringer-Ingleheim (F. R.G.)) sponsored research and has exclusive license to manufacture and market bovine papilloma virus vaccine developed by Molecular Genetics. Philips-Roxane is responsible for obtaining government approval. ***Monoclinal Antibodies:*** —*Ortho Pharmaceuticals* has an agreement with Monoclinal Antibodies under which Monoclinal Antibodies will develop and manufacture an innovate diagnostic product that will be marketed by Ortho. ***Petrogen, Inc.:*** —*Magna Corp.* has a 10-year joint venture with Petrogen under which Magna will field test micro-organisms developed by Petrogen for use in shallow, low-pressure stripper wells. ***ARCO Plant Cell Research Institute:*** ***—H. J. Heinz*** and ARCO Plant Cell Research institute have a joint venture to develop a tomato with high solids content. ***Schering-Plough:*** —*Yamanouchi* (Japan) will manufacture alpha interferon using Schering-Plough's technology. ***Unlvers/ty Genetics:*** —*Kureha Chemical Industry* (Japan) has a license to develop bovine interferon based on University Genetics' technology. ***Worne B/otechno/ogy:*** —*Ornni Biotech* (Canada) and Worne are in a joint project to extract usable petroleum from Canadian oil sands using micro-organisms. ***Zymos, Inc.:*** —*Cooper Laboratories* funded research and has the rights to alpha-1 antitrypsin developed by Zymos for possible treatment in emphysema.

aMaj$_{or}$ Public contracts, agreements, and ventures.
b$_{Biogen}$ is only about so-percent U.S. owned

SOURCE: Office of Technology Assessment.

- NBFs in many cases are still reliant on established companies for working capital, whether it be through research contract revenue or equity investments.
- Licensing agreements diffuse technology to different industrial sectors and promote the development of biotechnology in the United States.

Typically, an NBF will enter into an R&D contract, joint venture, or licensing agreement with an established U.S. company to secure funds for proprietary R&D, or, in the case of some pharmaceutical products, to obtain a partner to do clinical evaluations, obtain regulatory approvals, and undertake marketing. Furthermore, the revenues make the new firm attractive to investors if and

when the firm wants to use the public market as a source of financing. Typically, the research objective of the NBF in many R&D joint ventures is to develop a micro-organism and the related bioprocessing, extraction, and purification processes needed to produce the desired product in quantities sufficient to proceed with testing. The established company then organizes and implements clinical trials (if necessary) and takes responsibility for the production and marketing of the product. Joint venture partners are usually sought by NBFs to share the risk in new technological areas that appear to have significant commercial applications but that require large investments and have long development times. Joint venture partners are usually sought by established companies because they can provide a "window on the new technology" in addition to oftentimes providing products. Corporate equity investments in NBFs, in addition to providing "windows on the new technologies," can also provide the corporate investor with the possibility of a large return on its investment when (and if) the NBF goes public, or, if the NBF is aIready publicly held, with potential profit if the stock increases in value.

NBFs in general retain the rights to any patents resulting from the contract research performed, and should the product be marketed, the NBF obtains income through the royalties, which over a range of products may enhance the NBF's financial position so as to enable it to later enter future markets independently. The established company often obtains an exclusive license to the technology developed through the contract and also gains access to that specific product market. If the contract has been preceded by an equity investment, the established company might serve as a marketing partner to the NBF in diverse product areas.

R&D contracts also enable the established company to minimize the risks and costs associated with biotechnology R&D. Should the research not produce desirable results, the contract can be canceled and someone else has paid for the infrastructure. By sponsoring several companies at one time, as Schering-Plough, Koppers, and Martin Marietta have done, the sponsor can spread the risk of not finding the most relevant technology-in essence, portfolio diversification. Additionally, the research effort can be either short or long term depending on the desire of the contracting firm. By minimizing the front end costs and the risk, contracts serve as a kind of feasibility study (49), Successful contracts with NBFs or universities can lend credibility to the commercial potential of the new technology and can help obtain the corporate support necessary to fund future projects in the same field.

Established companies suffer no disadvantages in joint ventures with NBFs except a loss of risk capital should the research be unsuccessful. In fact, as the only buyers of the technology and the major group with the financial resources to commercialize it, established companies exert a great deal of control over the rate at which biotechnology is being developed in the United States.

NBFs do suffer disadvantages as a consequence of their own resource deficiencies, which necessitate their reliance on established companies. These financial reliances of NBFs on established companies will play a crucial role in the future viability of the entire NBF sector for three reasons:

- The low profit margins from licensing technology do not generally provide IVBFS with adequate financing for growth and expansion.
- Contract relationships, and thus revenues, are very likely to be transitory. There is a strong economic incentive for established companies to exercise a high degree of "control" over their own product development efforts and to bring their own work in-house.
- The commercial success of many NBF products is reliant on the amount and timing of resources that licensees and partners (established companies) devote to clinical testing (when necessary), obtaining regulatory approval, and marketing.
- Some of the contracts with established companies are tightly written, making it difficult for some NBFs to pursue interesting research findings which might occur in the course of the contracted work.

NBFs with a heavy reliance on contract revenue could face uncertain futures unless their own proprietary research yields marketable products in

the near term. Most NBFs are not assured that operating revenues from established companies will be sufficient to fund projected product development. The reliance on established firms for manufacturing and royalty incomes could also jeoprdize the future earning power of many small firms. Those NBFs that have licensed to established companies the right to manufacture and market their products do not control the timing of market entry for these products. If royalties are expected to be the major source of an NBF's operating revenue, then the NBF's correct choice of a marketing partner is crucial for financial success. It might not be wise, for example, for an NBF to choose a marketing partner whose own products stand to be displaced by the new product.

The NBF Genentech, for example, licensed Eli Lilly to produce the new human insulin product Humulin" On the one hand, because Lilly controls the insulin market in the United States, an effective distribution network is already in place and Humulin® sales could be substantial. On the other hand, Humulin" is a competitor of Eli Lilly's animal-derived insulins, and Eli Lilly holds about 85 percent of the U.S. insulin market. In other words, the pace of market development for Humulin® is controlled by the very company whose monopoly position Humulin® sales otherwise might challenge. For example, Eli Lilly could be threatened by the introduction of the new product, and delay the marketing of Humulin®, or if the costs of producing Humulin® are not competitive with Eli Lilly's existing insulin product, then Eli Lilly could also delay the market introduction of Humul.in®. Other arrangements of this kind between NBFs and established companies could slow the market entry of new products and reduce the flow of royalties to NBFs. *

An obvious disadvantage common to all NBFs is the sale of technology to ensure survival. By transferring technology to established companies, some NBFs could be canceling the comparative advantage they currently possess in domestic markets. If the competitive pressures arising from the technology transfer to established companies grow too strong, many NBFs will not survive. Additionally, since the most important factor in market acceptance and market share competition may be the timing of market introduction of competitive therapeutic and diagnostic products, the correct choice of partners could be crucial to the U.S. competitive strength.

Collaborative ventures between NBFs and established foreign companies

The observations made concerning NBFs' reliance on established U.S. companies apply equally to R&D arrangements between NBFs and established foreign firms. But the same situation has greater implications for U.S. competitiveness when viewed in the context of international technology transfer. *

Joint ventures between NBFs and established foreign companies are motivated in part by a foreign need for American technology and in part by NBFs' desire to retain U.S. marketing rights– rights often ceded in joint ventures with established U.S. companies. Most observers would agree that the United States is currently the leader in developing commercial applications of biotechnology. Reflecting the strong technological position of some U.S. companies is the increasing number of established foreign companies that are seeking R&D contracts with NBFs. Between 1981 and 1982, for example, the NBF Biogen experienced a 948-percent increase ($520)000 to $5.5 million) in R&D fees from Japanese companies (3), while Genentech experienced a 504-percent increase ($2.6 million to $15.7 million) (33). NBFs often seek joint marketing agreements with established foreign companies for access to foreign markets. on the basis of publicly available R&D joint venture agreements, it appears that the United States is a net exporter of technology.

Foreign companies' joint ventures with NBFs generally take the form of licensing agreements for R&D, and few foreign companies seem to be taking equity positions in the NBFs. From the NBFs' point of view, the same advantages (e.g., the

*See ***Chapter 5: Pharmaceuticals*** **and** ***Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology*** **for a more general discussion of the Eli Lilly -Genentech joint agreement.**

***There are enormous difficulties in assessing the degree of technology inflow and outflow because of the many ways technology can be transferred; however, most observers would probably agree that the current net flow of biotechnology is outward from the United States.**

revenues) and disadvantages (e.g., reliance on royalty income instead of product sales and a loss of technological advantage) are associated with licensing agreements with foreign companies as are associated with licensing agreements with U.S. companies. From the standpoint of the U.S. competitive position in biotechnology, however, the advantages and disadvantages of such agreements are not at all the same. In the case of domestic-domestic licensing agreements, technology is diffused within the United States and U.S. biotechnology development is promoted. In the case of domestic-foreign agreements, technology is transferred out of the United States and thus contributes to the foreign development of technology.

Agreements in the pharmaceutical industry between established U.S. and foreign companies are more difficult to evaluate than agreements between NBFs and established foreign firms. Licensing in the pharmaceutical industry is standard practice to overcome the complexities of clinical testing, registration, and marketing in foreign countries. It is common for licensers to barter, so that they can obtain privileges to market in their territories some products developed by the licensee. The established U.S. companies applying biotechnology are in a position to be able to barter without a loss to their competitive position. The' NBFs, if in need of financing or in pursuit of foreign markets, are not in such an advantageous position. The only bargaining chip they have is their proprietary research.

NBFs that because of their initial inability to finance development and clinicaI trials license some of their proprietary research to foreign companies may be ceding an indirect advantage to foreign companies. However, the licensing strategy and future royalty income may also provide some NBFs with the needed working capital to commercialize other research advantages. At this time, it remains unclear both how technology export will affect the commercial success of the NBFs and how it is likely to influence the U.S. competitive position in biotechnology.

Findings

U.S. efforts to commercialize biotechnology are currently the strongest in the world in part because of the unique dynamism and complementarily that exists between NBFs and established U.S. companies in developing biotechnology for wider commercial application and in part because of a strong U.S. support sector that supplies reagents, instrumentation, and software to the companies applying biotechnology. At present, most NBFs are still specializing in research-oriented phases of product and process development, precisely the commercial stage where they excel. The established companies, on the other hand, have assumed a major share of the responsibility for producing and marketing, and, when necessary, obtaining regulatory approval for, many of the earliest biotechnology products, the commercial stages where their resources are strongest.

Whether the dynamism arising from the competition and complementarily between NBFs and established companies will continue giving the United States a comparative advantage in the context of product introduction remains unclear. Since the established U.S. companies, through production and marketing agreements with NBFs, control the later stages of commercialization for many new products being developed, they will have considerable control over the pace at which these new products reach the market. Some established companies may have disincentives to market the new products that might compete with products they are already producing,

Biotechnology is still in an early stage of commercial development, and competition remains largely in research and early product development. In the current research-intensive phase of development, the new entrepreneurial firms founded specifically to exploit innovations and research advantages are providing the United States with a competitive edge in the commercial development of biotechnology. Through their R&D efforts, NBFs are contributing to biotech-

nology's commercial development in the United States through innovation, technology diffusion, product market development, and encouragement of technical advances because of the increased domestic competition they generate.

The financial constraints faced by the NBFs in the United States have led NBFs into R&D joint ventures and licensing agreements that are diffusing NBF-generated innovations to established U.S. and foreign companies. The collaborative ventures between NBFs and established U.S. companies, by broadening the U.S. technology base for future biotechnology development, in the short run have promoted competitive vigor among U.S. companies commercializing biotechnology. Increasing domestic competition arising from established company R&D, however, stands to threaten the survival of many NBFs and, consequently, the source of much of the current innovation in biotechnology. Since the established U.S. companies now have some control over the later aspects of product development, they can control the rate at which some of the early products are introduced to the marketplace. It is not clear what this situation may do to the U.S. competitive position.

Although NBFs have assumed much of the risk associated with biotechnology's early development, established U.S. companies are making substantial contributions to the U.S. commercialization effort. Through equity investments and licensing and contract agreements with NBFs, established U.S. companies are providing many NBFs with the necessary financial resources to remain solvent. Through joint development agreements with NBFs, many established companies will also provide the necessary production and marketing resources to bring many NBF products to world markets. These resources, in turn, are helping to sustain the rapid pace of technical advance spurred by NBFs. Recently, more and more established U.S. companies have been increasing their in-house investments in biotechnology research and production facilities, so the role of established U.S. companies in the U.S. biotechnolo~ commercialization effort is expanding.

US. competitive strength in biotechnology will be tested when large+cale production begins and bioprocessing problems are addressed. The Japanese have extensive experience in bioprocess technology, and dozens of strong "old biotechnology" companies from a variety of industrial sectors in Japan are hoping to use new biotechnology as alever to enter profitable and expanding pharmaceutical markets. Japanese companies, which already dominate biologically produced amino acid markets, are also major competitors in new antibiotic markets; in the future, they could dominate other specialty chemical and pharmaceutical markets as well.

Pharmaceutical markets will be the first proving ground for U.S. competitive strength. International competition will be intense, and the American drug and chemical companies, as well as some NBFs, will be competing against not only the Japanese companies but also the major pharmaceutical and chemical companies of Western Europe, all of whom expect to recover their biotechnology investments through extensive international market penetration. Although there seem to be fewer European companies than Japanese companies commercializing biotechnology, the potential of European pharmaceutical companies such as Hoechst (F.R.G,), Rhone Poulenc and Elf Aquitaine (France), ICI, Wellcome, and Glaxo (U.K.), and Hoffmann-La Roche (Switzerland) is impressive. Thus, to remain competitive internationally and to compete effectively in the future, it is crucial for U.S. companies to rely on rapid innovation made possible by NBFs, rapid product development made possible by established companies, and the accumulated and combined experience of both groups of firms.

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