Chapter 4

Financing

"In this entrepreneurial world, the venture capitalist occupies an ambivalent position. Like a gigolo, he's involved, but not involved. He's part entrepreneur, part accountant. He's Santa Claus ***and*** Ebenezer Scrooge."

Robert Teitelman
Gene ***Dreams***

"Interferon is a substance you rub on stockbrokers.'

A scientist quoted in ***Forbes,*** September 1980

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INTRODUCTION

Until recently, genetic engineering was largely commercialized in the United States, mainly in top-notch academic departments and an exponentially expanding troupe of biotechnology entrepreneurial firms. In the last few years, large, established U.S. corporations have increasingly invested in these technologies, both in-house and through a variety of arrangements with dedicated biotechnology companies (DBCs). The markets for new biotechnology-derived medical and agricultural products are worldwide, and now the innovations themselves are starting to be developed throughout all parts of the globe.

Although biotechnology per se is not a single industry but a tool of industry, the financial community has had considerable interest in and effect on the formation and survival of firms commercializing biotechnology. While major corporations, both domestic and foreign, are spending considerable sums to exploit the new techniques, much of the innovation in research continues to come from the smaller firms dedicated to biotechnology. Large, established corporations can rely on revenues from existing operations to fund innovation, but DBCs do not have as wide a comfort zone and, in the absence of product revenues, must rely on equity investors for survival (see box 4-A for a glossary of financial terms). The competitiveness of U.S.-developed biotechnology ***products and processes*** may ultimately depend on broader issues, such as fair trade practices, protection of intellectual property, and the regulatory climate. The competitiveness of U.S. ***innovation,*** however, could very well rely on the ability of DBCs to stay in business. Because biotechnology is capital-intensive, staying in business means raising substantial sums of cash.

This chapter focuses on the current financial status of the leading U.S. DBCs and addresses the ability of new firms to enter the market and raise cash. The status and importance of strategic alliances, both domestic and foreign, and direct foreign investment in U.S. biotechnology also are discussed. Finally, the effects of specific tax policies on the ability of firms worldwide to raise cash are reviewed.

U.S. COMMERCIAL BIOTECHNOLOGY: AN OVERVIEW

The boom for founding DBCs in the United States occurred between 1980 and 1984. During these years, approximately 60 percent of existing companies were founded (54). In a 1988 report, the Office of Technology Assessment (OTA) verified that there were 403 DBCs in existence and over 70 major corporations with significant investments in biotechnology (54). Although these numbers have most likely grown since that time, the areas of primary research and development (R&D) focus of these firms have not changed radically. In 1988, OTA found that human health care was the focus of research for most companies, whether large or small. Agriculture and chemicals were the focus of far fewer firms, and environmental applications of biotechnology were even less well represented (see table 4-l). A 1990 survey by Ernst & Young drawn from a large sample of firms (based on a broader definition of biotechnology) revealed similar segmentation of primary markets (see table 4-2) (19). Companies continue to have a strong focus on human health care products, largely because capital availability has been greater for pharmaceuticals than for food or agriculture, due to the prospect of greater market reward (54,57). Thus,

Table 4-l—Areas of Primary R&D Focus by Biotechnology Companies (1988)

Research area	Dedicated biotechnology companies Number (percent)	Large diversified companies Number (percent)
Human therapeutics	63 (21)	14 (26)
Diagnostics	52 (18)	6(1 1)
Chemicals	20 (7)	11 (21)
Plant agriculture.	24 (8)	7 (13)
Animal agriculture	19(6)	4 (8)
Reagents	34 (12)	2 (4)
Waste disposal/treatment.	3 (1)	1 (2)
Equipment	12 (4)	1 (2)
Cell culture	5 (2)	2 (2)
Diversified	13 (4)	6(1 1)
Other	51 (18)	o (o)
Total	296 (100)	53 (loo)

SOURCE: Office of Technology Assessment, New *Developments in Biotechnology: U.S. Investment in Biotechnology, 1988.*

Box 4-A—A Glossary of Finance and Investment Terms

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

Amortization. Accounting procedure that gradually reduces the cost-value of a limited life or intangible asset through periodic charges to income.

Assets. Anything having commercial or exchange value that is owned by a business, institution, or individual.

Black Monday. October 19, 1987, when the Dow Jones Industrial Average plunged a record 508 points following sharp drops the previous week—reflecting investor anxiety about inflated stock price levels, Federal budget arid trade deficits, and foreign market activity.

Book value. Net asset value of a company's securities, calculated as total assets minus intangible assets (goodwill, patents, etc.), minus current liabilities, minus any long-term liabilities and equity issues that have prior claim. The total net asset figure, divided by the number of bonds, shares of preferred stock, or shares of common stock, gives the net asset value, or book value, per bond or per share of preferred or common stock. Book value can be a guide in selecting stocks and is an indication of the ultimate value of securities in liquidation.

Capital gain. The difference between an asset's purchase price and selling price, when the difference is positive.

Cash burn rate. The rate at which a company uses cash, i.e., cash flow. Biotechnology companies are generally cash users, not generators. Cash burn rates are very high in the years before the first profits are made.

Common stock. Units of ownership of a public corporation. Owners typically are entitled to vote on the selection of directors and other important matters as well as to receive dividends on their holdings. In the event that a corporation is liquidated, the claims of secured and unsecured creditors and owners of bonds and preferred stock take precedence over the claims of those who own common stock. For the most part, however, common stock has more potential for appreciation.

Convertible debt. Debt that is exchangeable in another form for a prestated price. Convertible debt is appropriate for investors who want higher income than is available from common stock, Most commonly, corporate securities (usually preferred shares or bonds) are purchased and later traded for common shares.

Cost of' capital. The rate of return that a business could earn if it chose another investment with equivalent risk-in other words, the opportunity cost of the funds employed as the result of an investment decision or actual debt costs as part of the capital structure of the company.

Equity. Ownership interest possessed by shareholders in a corporation stock as opposed to bonds. Shares can be common or preferred.

(Continued on next page)

Table 4-2—Profile of Market Segmentation (1990)

Research area	Percent of respondents
Human therapeutics	35%
Diagnostics	28%
Agriculture (plant and animal)	8%
Supplier	18%
Other	11%
Total	100%

SOURCE: Adapted from Ernst & Young, *Biotech 97: A Changing Environment* (San Francisco, CA: 1990).

most discussions about the financing of biotechnology tend to be skewed toward companies working in human therapeutics and diagnostics because that is where most of the activity has been (23). And while the methods used by various DBCs to raise cash generally have been similar, DBCs not working in human health have had a more difficult time and have had to follow different routes at different times.

While more companies may have been formed in the early 1980s than the late 1980s, the amount of money invested per company (and dedicated to biotechnology in general) increased significantly. As a result, and despite the lack of private late-stage capital resulting from the market crash in 1987, many of the companies formed late in the 1980s have had somewhat greater staying power than their earlier competitors. In addition, due to having larger amounts of capital at an earlier stage, some of these companies may generate products more quickly (5).

In the early 1980s, fledgling genetic engineering firms would do almost anything to raise cash, often licensing away key first-generation products and

Exit opportunities. A term commonly used by venture capitalists to describe opportunities for investors to realize their investment or pull out of a deal. Examples are the public markets, mergers, and acquisitions.

Liquidity. Ability of an individual or company to convert assets into cash or cash equivalents without significant loss. Having a good amount of liquidity means being able to meet maturing obligations promptly, earn trade discounts, benefit from a good credit rating, and take advantage of market opportunities.

Market capitalization. Valueof a corporation as determinedly the market price of its issued and outstanding common stock. It is calcuated by multiplying the number of outstanding shares by the current market price of a share. institutional investors often use market capitalization as one investment criterion. Analysts look at market capitalization in relation to book or accounting value for an indication of how investors value a company's future prospects.

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

Operating profit (or loss). The difference between the revenues of a business and the related costs and expenses, excluding income derived from sources other than its regular activities and before income deductions.

Preferred stock. A class of stock that pays dividends at a specific rate and that has preference over common stock in the payment of dividends and the liquidation of assets. Preferred stock does not ordinarily carry voting rights.

Royalty. Payment to the holder for the right to use property such as a patent, copyrighted material, or natural resources, Royalties are set in advance as a percentage of income arising from the commercialization of the owner's rights or property.

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

Venture capital, An important source of financing for start-up companies that entails some investment risk but offers the potential for above-average future profits.

SOURCE: Office of Technology Assessment, 1991, adapted from Barren's *Dictionary of Finance and Investment Terms,* 2d ed. (New York, NY: Barren's, 198'7).

vital market segments in order to obtain the necessary cash to survive. Some call this mortgaging the future-more enthusiastic chief executives describe it as leveraging the technology. In any case, front-running companies, like Genentech, Genex, and Biogen, lined up numerous corporate partners with relative ease, only to find later that a deal with a major international corporation did not necessarily prove adequate for survival. Many pharmaceutical firms learned the hard way that biotechnology products represented no magic bullet, and that some of their products would succeed while many others were destined to fail.

As time passed, the term biotechnology lost its ability to turn promises-for-tomorrow into instant cash today. Several changes occurred at the same time. Basic gene-splicing technology became readily available to scientists at large pharmaceutical companies in the United States and overseas. However, unforeseen technical problems in gene expression, in scale-up, and in obtaining meaningful clinical results created a slowing of developments and expectations. Despite technical problems and slower-than-expected product development, the innovative U.S. financial markets supplied the growing number of genetic engineering firms with the increased funding needed to survive. Research and development limited partnerships (RDLPs), both large and small, provided funds between lucrative public offerings, and the venture capital community continued to invest money in new start-up operations.

The 1980s may prove to have been the high water mark for formation of DBCs. A critical event affecting the financial strategies of DBCs came on October 17, 1987, or "Black Monday," when the stock market crashed. Biotechnology companies faced a severe problem: the fabled window for public offerings-particularly initial public offerings-was slammed firmly shut. Although that

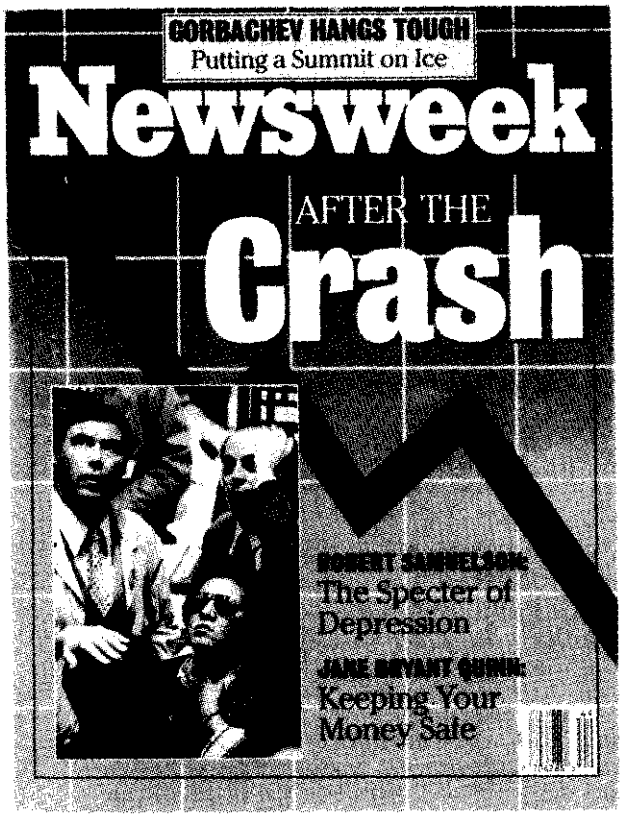


Photo credit: Newsweek, Nov. 2, 1987

Media coverage of the 1987 stock market crash.

window seemed to have slightly opened again by the summer of 1989 (especially for convertible debt issues for the more established companies in the United States and Europe), biotechnology companies had to weather a full 18 months without public financing. Some firms retrenched and focused on their most promising or near-term projects. Others, notably Genentech, had product revenues. Still others, e.g., Cetus, Genetics Institute, and Mycogen, maintained hefty bank accounts accumulated in the early 1980s to carry them through all but the most protracted public equity droughts. But all biotechnology firms reexamined the possibility of alliances with major corporations. As time passed, deals were signed increasingly between DBCs and domestic and foreign pharmaceutical and chemical companies (19). Top-tier DBCs, however, often find themselves on more equal footing with their partners than in the past. These DBCs, having a greater understanding of the powers and limitations of biotechnology have used this knowledge combined with their financial resources to demand clauses securing manufacturing rights or rights to key geographic areas or market segments (31).

FINANCIAL STATUS OF U.S. BIOTECHNOLOGY COMPANIES

To date, most U.S. biotechnology companies have no sales and have been losing money since their inceptions. According to a 1989 survey of 93 biotechnology companies, about one-fourth reported net profits (18). An updated survey in 1990 found that only 21 percent of all companies are profitable, even though overall sales increased by 13 percent (19). Therefore, standard accounting tools, which measure expenses and assets as a function of sales and earnings, are not useful in determining the value or stability of a DBC (46). However, the leading public biotechnology companies have high liquidity and can generate cash once product revenues begin to flow. While most companies are still several years away from profitability and positive cash flow, the top 20 firms could last more than 3 years on current cash levels without raising anymore money (46).

Capital and Market Value

Capital and market value are concentrated in few of the over 400 firms involved in biotechnology. Individual companies that top the list in market values are generally the same ones that lead the industry in total assets, book value, R&D spending, and total employment (see table 4-3). As of early 1990, public market values ranged from less than $5 million to $1.9 billion (only two companies—Genentech and Amgen--had market values of $1 billion or more, while the rest were valued significantly less). In a survey of 42 publicly traded companies, total market capitalization totaled $6.9 billion, and two companies—Genentech and Amgen—together accounted for 42 percent of the total market capitalization (46) (see figure 4-l). The top seven companies have market values ranging from $500 million to $2.5 billion (47).

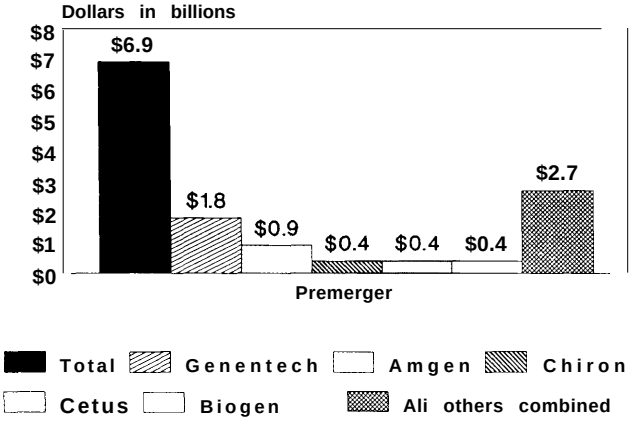
Most of the companies in a Shearson Lehman Hutton survey showed strong cash positions, with 10 having cash balances above $50 million by the end of 1989 (47). Again, only three companies—Genentech, Amgen, and Chiron--produced profits in 1990, leading the industry in revenues as well as R&D spending (5,47). With just two products it markets plus two products from which it receives

Table 4-3-Financial Profile of Leading Public Firms in 1990

	Percent price change in stock performance 6/30/89-6/29/90	Market capitalization ($ million) 6/29/90	Book value ($ million) 12/31/89	Years of cash left at net burn rate	R&D expense (calendar year 1989) ($ million)	Net income (calendar year 1989) ($ million)
Pharmaceuticals						
Genentech*	55%	$2,454	$469	INF	$156.9	$44.0
Amgen	80%	1,526	180	INF	63.6	3.8
Chiron	128%	626	109	INF	46.1	(21.6)
Genetics Institute	41%	520	138	INF	59.4	(28.7)
Cetus	43%	649	92	6.2	52.3	(64.9)
Biogen	112%	546	74	INF	28.5	(0.2)
Centocor	160%	578	133	INF	45.4	(0.1)
XOMA	35%	316	27	INF	25.6	(18.9)
Agriculture						
Mycogen	103%	197	27	INF	7.8	(1.4)
DNA Plant Tech.	49%	143	38	9.9	12.0	(2.9)
Calgene	12%	82	39	10	11.3	(6.6)
Crop Genetics	–11%	37	13	1.3	5.4	(6.1)

*Pre-merger
INF = Infinite
SOURCE: Adapted from Shearson Lehman Hutton, *Bio-Financials: Midyear Supplement*, July 6, 1990.

Figure 4-1—Market Capitalization of 42 Publicly Traded U.S. Firms



SOURCE: ShearsonLehman Hutton, 1990.

substantial royalties, Genentech accounted for more than half of 1989 product sales for the 20 companies reporting sales (50).

What remains remarkable has been the health of biotechnology stocks. While the Standard and Poors 500 advanced 12.6 percent between June 1989 and June 1990, health care biotechnology stocks rose an average of 77 percent and agricultural biotechnology stocks rose 38 percent. The medical biotechnology sector grew by 36.7 percent in 1990 and was the number one stock performer (20,36).

Cash Flow, Product Revenues, and Expenses

Although biotechnology companies have high liquidity (on average, companies have 50 percent of their assets as cash), in their early years they tend to burn more cash than they generate. In 1989, only Genentech and Amgen generated meaningful levels of cash from operations (40,46). One reason that biotechnology companies use their cash reserves so rapidly is the intensity of R&D investment; prior to product commercialization some companies dedicate nearly 65 percent of all expenses to R&D. In 1989, Genentech's R&D expenditures, at 42 percent of sales, were almost as much as those of the next three companies combined (see table 4-3).

Estimates by Wall Street analysts predict that the leading public firms have a mean of just over 3 years and a median of 2.3 years of cash left, at either current or average burn rate (46). Past experience shows that the leading biotechnology companies have been extraordinarily successful at financing virtually all of their cash-flow needs. It is not clear how much longer this success will last, and there is evidence that a two-tiered structure has evolved among DBCs, where leading firms are able to raise cash and the have-nets find sources increasingly unavailable (57). Some analysts believe that only a few biotechnology firms will generate significant annual revenues and thus be able to survive over the longer term (17). This is reflected in a recent trend toward steady financial backing for a few larger

firms and lesser amounts of capital available for smaller, less successful fins.

As would be expected, companies focusing on human health care products have larger cash reserves than those focused on other industries. The average, or mean, cash balance of 34 publicly traded health-based biotechnology companies was $38 million in early 1990; the median was $18 million. The figures were $13 million and $10 million respectively for agricultural companies (46).

Limited product sales hurt cash flows. In 1989, only eight companies had product sales over $10 million (46). A 1989 survey showed that 5-year sales-growth projections had dropped. Yet sales overall are still expected to more than double over the next 2 years (19). Companies continue to survive on cash obtained from R&D contracts, corporate alliances, interest income, and occasionally a common or preferred stock issue. Total industry revenues in 64 public companies reached $1 billion in 1989, up 67 percent since 1987. According to Ernst & Young, which casts a wider net in its survey, product sales in 1990 were $2.9 billion. Genentech and Amgen comprised the bulk of those sales (46).

RAISING CAPITAL

Biotechnology companies in the United States have relied heavily on the investment community for their survival. Despite the relatively high cost of capital in the United States compared to other countries (see table 4-4), U.S. firms have been remarkably successful in attracting investors in the start-up phase. The high cost of capital, however, may put U.S. firms at a disadvantage in the long term. The cost of capital is less important for shorter projects but becomes increasingly important over time. Japanese and German fins, with lower costs, may face fewer risks (22).[1] And, although Japanese corporations are finding it easier than U.S. firms to raise relatively cheap capital (48), U.S. biotechnology companies to date have been able to raise funds through creative financing. This type of financing, however, is very costly in the long term due to the high royalty rates and significant capital required for the companies to buy back the product rights normally transferred to R&D financing vehicles.

It is not clear how long DBCs can go to venture funds and the public markets. According to a 1988 survey, 62 percent of all companies needed major financing of a few million dollars each by the end of 1990, and 90 percent will need financing by the end of 1991 (18). In a 1989 survey, the average company projected a need for $3 million in financing during 1991 and $32 million in total over the next 10 years (19). Some analysts estimate that it will take $5 billion to $10 billion to develop the 100 products now inhuman clinical trials in the therapeutic sector of biotechnology (16,33).

Biotechnology companies continue to be financed primarily through equity (about 75 percent), usually in the form of common stock (46). Debt financing is still relatively rare. In addition to being rare, debt financing has been relatively unsuccessful when used. The convertible debt instruments that were employed counted on appreciation in equity. If this did not occur, the company was forced to service the debt while still operating on a negative cash-flow basis (32). Forty percent of the companies surveyed by Shearson Lehman Hutton had no debt at all.

As biotechnology moves through the 1990s, strategic alliances will be the most reliable, and perhaps sensible, source of needed capital. Strategic alliances may be the only way for some firms to prevent takeover, bankruptcy, or liquidation as they reach the most expensive stages of development.

The following sections cover the current state of private and public equity funds available for biotechnology as well as recent developments in strategic alliances between U.S. firms and between U.S. and foreign fins.

Venture Capital

Venture capital has been the prime source of early stage financing for new and young companies seeking to grow rapidly. It has been a significant source of capital for biotechnology start-ups in the 1980s. The importance of venture capital to U.S. commercial biotechnology reflects the growth, in general, of the venture capital industry. Biotechnology, conveniently, arrived at the right time.

[1] The costs of debt and equity in Germany and Japan are generally lower than that in the United States. This combined with cheaper corporate funding result in a lower cost of funds and a lower cost of capital.

Table 4-4-Cost of Capital for R&D Projects With 10-Year Payoff Lag in Four Countries

	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
United States	12.5	12.9	11.9	12.4	8.3	18.4	15.2	20.3	20.2	16.8	18.2	20.3
Japan	3.9	5.7	6.5	7.3	8.0	8.3	8.7	7.7	9.2	9.4	8.4	8.7
Germany	13.4	13.8	13.3	15.6	15.7	14.7	13.9	14.6	13.9	13.2	14.4	14.8
United Kingdom	18.2	28.4	21.1	33.4	24.2	29.5	28.2	24.4	25.4	18.9	20.6	23.7

SOURCE: Federal Reserve Bank of New York staff estimates, 19S9. The rankings reflect the required real pre-tax rate of return on an investment in plant or equipment.

United States

Despite fluctuations through the 1980s, due, according to some analysts, to excesses and overvaluations in the mid-1980s, the venture capital community is operating in a stable, if not more conservative, environment (57). The pool of funds in the United States managed by organized venture capital exceeds $31 billion (28). Venture funds are still available for biotechnology but have become increasingly concentrated and more readily available to firms or individuals with a proven track record (57,14). Of the over 800 U.S. and Canadian venture capital companies listed in a comprehensive directory of such firms, nearly half indicated a preference for genetic engineering for possible investment (35). A 1989 trade journal listing of venture capital funds with interests in biotechnology showed 86 entries (24). Between 1985 and 1989, about $1.1 billion in venture capital was invested in biotechnology (see table 4-5). Some regions of the United States are particularly well endowed with venture funds for biotechnology. For example, biotechnology companies remained the principal recipients of venture funds in the San Diego area in the last half of 1989, during which time 13 San Diego biotechnology companies raised $113 million (44).

But growth companies, such as biotechnology, require continuing financing, sometimes requiring almost twice as much equity financing between the 3rd and 6th years as required during the frost 3 years (34). Venture capital has been available for biotechnology companies at the founding stage, but it is increasingly difficult to come by during the development stage, which is more expensive than the discovery stage (23). The new conservatism in venture markets has resulted from lower rates of return (30) and lowered likelihood that venture capitalists will support a firm where exit might be difficult. Small companies have been hardest hit by constriction in the venture markets (19).

Opportunities for venture capitalists to realize their return through sale of equity via the public market have been limited since the stock market crash of 1987. Until 1987, the public was willing to play the role of late-stage venture capitalists by buying stocks in companies far from profitable (23). Today, initial public offerings are harder to come by, and many companies are stuck pre-public. One biotechnology executive testified in May 1989 that after the 1987 crash, equity capital was no longer available to small companies, and his company was forced to form limited partnerships with Japanese companies (9). United States firms were not the only ones to suffer the consequences of the October 1987 crash. Foreign firms have also been affected. Acquiring risk capital in Sweden was not difficult prior to that time; Swedish biotechnology firms, comprised largely of small- to medium-sized firms, are now having trouble raising cash (55).

One analyst estimates that public equity became a less favorable strategy for financing for as many as 75 percent of DBCs, whereas strategic alliances gained in favor by as much as 60 percent (l). This does not mean that all biotechnology companies already traded publicly are being hurt. In fact, overall, biotechnology stocks performed well in the last years of the 1980s. Still, the largest source of funding for biotechnology companies is established corporations (20).

Despite positive stock activity, the valuations for the public companies may have peaked as they have finally reached the product stage. For smaller private companies wanting to enter the public market, leveling off of valuation has brought increasing demands for greater maturity before public funds can be raised. One analyst reported that before some firms are willing to underwrite an initial public offering for a health biotechnology company, the company should have positive Food and Drug Administration (FDA) Phase II clinical trial data (4) indicating the product is close to the marketing phase.

Table 4-5-Venture Investments in Biotechnology ($in millions)

	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Venture capital industry											
Total dollars raised	$300	$700	$1,300	$1,800	$4,500	$4,200	$3,300	$4,500	$4,900	$2,100	$2,200
Total capital invested	$458	$608	$1,159	$1,453	$2,584	$2,756	$2,670	$3,230	$3,940	$3,650	$3,260
Total number of companies	375	504	797	918	1,320	1,469	1,377	1,504	1,729	1,472	1,355
Biotechnology industry											
Dollars invested											
New companies	NA	NA	NA	NA	NA	NA	$13.60	$40.15	$54.17	$41.28	$57.83
Total companies	NA	NA	NA	NA	NA	NA	$100.59	$186.18	$255.19	$311.21	$250.85
Percent of total capital invested											
New companies	NA	NA	NA	NA	NA	NA	0.51%	1.24%	1.37%	1.1 3%	*1.77%*
Total companies	NA	NA	NA	NA	NA	NA	*3.77%*	5.76%	6.48%	*8.53%*	*7.69%*
Number of companies	NA	NA	NA	NA	NA	NA	21	25	44	40	*22*
Total companies	NA	NA	NA	NA	NA	NA	65	83	118	110	*97*
Percent of total number of companies											
New companies	NA	NA	NA	NA	NA	NA	1.53%	1.66%	2.54%	2.72%	1.62%
Total companies	NA	NA	NA	NA	NA	NA	4.7P/0	5.52%	6.82%	7.47%	7.16%
Dollars invested Per company											
New companies	NA	NA	NA	NA	NA	NA	*$0.65*	$1.61	$1.23	$1.03	*$2.63*
Total Companies	NA	NA	NA	NA	NA	NA	1.55	2.24	2.16	2.83	2.59

NA = not available

SOURCE: S.P.Galante, *Venture Capital/ Journal,* August 1990.

Internationally

Investment in biotechnology in other countries has been very different from that in the United States. There are few DBCs. Most of the investment has come from large pharmaceutical, chemical, and agricultural corporations spending money on in-house research and strategic alliances with DBCs. It is not clear whether more venture capital availability would result in the formation of DBCs because the culture for innovation and entrepreneurialism is different. The venture phenomenon has been uniquely American, but the past decade has seen an increase in venture activity overseas. In 1988, venture capitalists in the United Kingdom (U.K.) invested over £1 billion, a 27-percent increase over 1987 and more than twice as much as in 1986. United Kingdom investors tend to place their money within the United Kingdom (89 percent), but nearly 10 percent has been invested in the United States. Still, less than 10 percent of venture funds have been invested in biotechnology (2).

The sources of venture funds vary between countries. In the United States, pension funds are a significant source of funds for venture capital. Deregulation of types of investments allowed by pension funds released a large pool of cash for venture use. In general, pension funds are not a source of venture capital in other countries. In the United States, independent private venture capital firms (typically organized as limited partnerships) provide about 83 percent of the total venture capital pool (28). Banks tend to be the main sources of venture capital in the United Kingdom (about 25 percent), Denmark (50 percent), and Germany (56 percent). The government provides as much as 73 percent of venture capital in countries such as Belgium and Luxembourg and nearly 40 percent of the funds in The Netherlands. In France, insurance companies provide 23 percent of venture capital (37). In other European countries, venture capital companies are relatively new. Nearly all of the 40 companies in Germany, for example, are less than 7 years old and have yet to fully realize their investments. Most venture capital investments by European Community (EC) countries have gone to computer-related firms or industrial products. Biotechnology has historically received about 3 percent of the disbursements (37).

The EC has recognized the shortage of start-up and early stage financing across Europe and has recently launched two initiatives: Seed Capital and Eurotech Capital. The Seed Capital project supports 24 new seed capital funds across the EC, seeking to stimulate cross-border investment. Eurotech Capital

attempts to encourage financial institutions to increase their investment in cross-border, high-technology projects by means of investment subsidies ranging from 4 to 50 percent (2).

Some countries' efforts are so new it is impossible to predict how successful they will be. In Taiwan, for example, a venture capital funding system was recently developed to help finance new start-up companies. Government banks led the investment effort, and special income tax exemptions were launched. Thirteen venture capital firms have been established since 1986 under this program (51). In Australia, in an effort to encourage a more healthy venture industry, the government provides tax benefits for those who invest in licensed venture capital companies. This scheme, however, has not been helpful in raising biotechnology venture capital. Of the 44 investment firms listed in a 1988 directory, only 4 stated a preference for biotechnology investment. The average investment of 5 percent is low when compared with a 15-percent investment in the information industries (27).

In Japan, where most of the capital is heavily concentrated in the banking system, venture capital has played a limited role in high-technology financing. Because large companies develop biotechnology, financing traditionally has taken place with debt finance. In the early 1970s, about eight venture capital companies were established, but they functioned more as loan agents than as investors. In the 1980s, venture capital companies were organized in limited partnerships, which provided better exits for investors and changed the tax rate in a favorable way (37).

In general, venture capital sources in Japan are very different from those in the United States. Most Japanese venture capital fund managers lack entrepreneurial management skills and usually operate out of their parent headquarters (which tend to be banks, security houses, or giant corporations such as Kirin or Mitsubishi) and invest conservatively. Most American venture capitalists would claim that Japanese venture capital really isn't venture capital at all. For example, Japanese venture capitalists are willing to accept returns two-fifths of the level that U.S. venture capitalists typically expect. Several other reasons exist for the conservative nature of Japanese venture capitalists-such as the stigma of failure and an emphasis on personal relationships rather than depersonalized sales of equity, which result in sales of equity primarily between cooperating firms. And, although the Nakasone government exempted taxes on capital gains of individual investors, corporations are taxed at a rate as high as 42 percent (37). While the Japanese may be moving rapidly into biotechnology through the efforts of academia, government-supported laboratories, and their major corporations, they have been unable (and perhaps unwilling) to imitate the unique relationships that exist in the United States between DBCs and venture capitalists.

Research and Development Limited Partnerships

Until recent changes in U.S. tax law, research and development limited partnerships (RDLPs) allowed individuals or companies to invest in a fro's R&D and write-off the investment as an expense. Investors became limited partners and were entitled to royalty payments from future sales. But current tax laws effectively prohibit individuals from writing-off the investment as an expense. Investors do not become limited partners until royalty payments are received but technically become owners of the technology to either exploit or sell back to the company for a fixed payment plus royalties. According to some industry executives, the current tax rules governing these partnerships are unclear and further complicate successful transactions (26). This means that RDLPs have to stand on their own merits, and all deals must include equity incentives (32).

Although the dollar amount that can be raised from RDLPs is potentially high, participants at a September 1990 OTA workshop agreed that these partnerships remain a valuable funding vehicle only for established firms with a proven track record and are not widely available (57). In 1989, Genentech raised $72 million in an RDLP to research and develop its CD4-based acquired immunodeficiency syndrome (AIDS) treatment. Even so, executives of Genentech reported difficulties in raising this amount (6), and most biotechnology companies would be fortunate to raise a sum that large (11). RDLPs are not currently a good money raising method--even for established companies (5).

CONSOLIDATION

Consolidation within industries occurs when competition between companies becomes extreme, when marketing of existing products becomes more important than the development of new products,

when the costs for R&D of new products increase faster than the level of sales, or when it is difficult to raise cash. Such consolidations can take the form of buyouts or mergers. Typically, larger companies take over or merge with smaller companies that do not have the marketing power of the larger firms or that have not met the challenges posed by the level of competition. In the 1980s, several industries experienced consolidations, including high-technology areas, such as mainframe computer software, cellular telephones, and semiconductors.

A general trend in high-technology-including biotechnology-is that the basic technology is relatively inexpensive for firms to develop. Several factors may contribute to this phenomenon. First, the Federal Government supports basic research through grants to universities-the results of which become public knowledge. Second, there are few regulations affecting basic research. Small companies with innovative ideas can compete successfully by exploiting their narrow specialty. However, as ideas approach the market, the capital required to make improvements and start production increases dramatically. Undoubtedly, the cost of developing biotechnology products is rising rapidly; enough to concern the largest DBC. Although start-up companies will continue to play a crucial role in the development of biotechnology, mergers and takeovers will become more common as the market limits capital availability and the costs of developing and marketing new products increases while cash supplies become limited.

Mergers will allow large corporations to lead in the effort to develop commercial biotechnology products immediately, without having to engage in basic research that is often not applicable to a commercial product. Because of the relatively low cost at which technology can be acquired, large foreign- and domestic-based pharmaceutical and pesticide firms will likely be active in takeovers and mergers of biotechnology firms in the United States. Moreover, foreign multinationals view U.S. firms as particularly attractive, given the size, affluence, and openness of the U.S. market, as well as the foundation of basic research techniques and knowledge that many companies possess. To date, there have been no hostile takeovers in biotechnology, largely because the assets (people) have no obligation to stay and many takeover opportunities exist elsewhere (40).

The recent $660 million merger of Chiron and Cetus is symptomatic of the consolidation beginning to occur among companies involved in biotechnology. One of the frost takeovers of a biotechnology company occurred in 1982 when Schering-Plough Corp. acquired DNAX (Palo Alto, CA) for $29 million (3). In 1986, two important buyouts of biotechnology companies took place. Hybritech (San Diego, CA) was bought by Eli Lilly for $500 million, and Genetic Systems was acquired by Bristol-Myers for nearly $300 million (3). A few buyouts have occurred between foreign and U.S. fins. For example, in 1988, Denmark's Novo-Nordisk purchased a Seattle-based biotechnology firm, Zymogenetics. In 1989, Gen-Probe, Inc. (San Diego, CA) was sold to Japan's Chugai Pharmaceutical for $110 million (39), and Seradyn, Inc. was bought by Mitsubishi Kasei. In 1990, Schering AG purchased Codon Corp. and Triton Biosciences. A sampling of acquisitions can be found in table 4-6. Further consolidation is inevitable.

Foreign Participation in Mergers and Acquisitions

Relationships between U.S. biotechnology companies and foreign corporations have taken virtually every form and combination of forms imaginable, including: acquisition, merger, equity investment, joint venture, co-marketing, technology licensing, product licensing, and research sponsorship. Obviously, mergers and acquisitions are the most extreme interactions that can take place between two companies. The case of Genentech and Hoffmann-LaRoche is the most notable (see box 4-B). Other consolidation occurring today within the pharmaceutical industry is illustrated by Eastman Kodak's purchase of Sterling Drug, the trans-Atlantic merger between SmithKline Beckman and the Beecham Group, the union of Squibb Corp. and Bristol-Myers, the Marion Laboratories merger with Merrell-Dow, and the Rhone-Poulenc acquisition of Rorer. But these are big companies merging with other big companies. While drug companies are teaming-up for potential synergies and improved competitiveness in an increasingly global marketplace, traditional reasoning has long proposed that financial pressure would eventually force biotechnology companies to sell out in order to survive. Financing has been particularly tight ever since the stock market crash of 1987, and the majority of biotechnology concerns have nervously watched

Table 4-6-Acquisitions of U.S. Biotechnology Companies, 1989-90

Acquirer	Target company	Transaction form	Date
Abbott Laboratories	Damon Biotech, inc.	Acquisition	Oct. '89
American Cyanamid Co.	Praxis, Inc.	Acquisition	Nov. '89
American Vaccine Corp.	IAF BioChem	Merger	Oct. '89
Applied Bioscience International, Inc.	Environ Corp.	Merger	May '90
Baxter International, Inc.	Bio-Response, Inc.	Acquisition	Jan. '90
Biomedical Technologies, Inc.	Flow Labs	Acquisition	Nov. '89
Biopool International, Inc.	inter-Haemaol, Inc.	Acquisition	Mar. '90
Cambridge Bioscience Corp.	Angenics, Inc.	Acquisition	Aug. '89
Cambridge Bioscience Corp.	Biotech Research Labs,	Merger	Apr. '90
Carter-Wallace, Inc.	Hygenia Sciences	Acquisition	May '90
Chugai Pharmaceuticals, Inc.	Gen-Probe, Inc.	Acquisition	Nov. '89
Collagen Corp.	SummaCare, Inc.	Acquisition	Apr. '90
Eastman Kodak Co./Cultor Ltd.	Genecor, Inc.	Acquisition	Jan. '90
Eli Lilly & Co.	Pacific Biotech, Inc.	Acquisition	Apr. '90
Hoffman-LaRoche, Inc.	Genetech, Inc.	Acquisition	Jan. '90
Genentech, Inc.	Genentech Canada	Acquisition	Jan. '90
Genzyme Corp.	Integrated Genetics.	Acquisition	Aug. '89
Immucor, Inc.	Immucor, GmbH.	Acquisition	May '90
Immunotech Pharmaceuticals	Dura Pharmaceuticals	Acquisition	Jan. '90
Institut Merieux.	Connaught Biosciences,	Acquisition	Dec. '89
Life Sciences International, Inc.	International Equipment	Acquisition	Apr. '90
Life Technologies Inc.	Waitaki International, Inc.	Acquisition	July '89
Microgenics Corp.	Bioautomated Systems, inc.	Acquisition	Mar. '90
Mitsubishi Kasei	Seradyn, Inc.	Acquisition	Oct. '89
Moleculon, Inc.	Kalipharma, Inc.	Acquisition	Nov. '89
Murex Clinical Technologies Corp.	Dominion Biological	Acquisition	Jan. '90
Orion Pharmaceutical, Inc.	KSV Lipids	Acquisition	Aug. '89
Porton International, inc.	Hazelton Biologics, Inc.	Acquisition	Dec. '89
Porton International, Inc.	Sera-Lab, Ltd.	Acquisition	Dec. '89
Quidel Corp.	Monoclonal Antibodies, inc.	Merger	July '90
Sanofi Pharma SA.	Genetic Systems, Inc.	Acquisition	Apr. '90
Schering AG	Codon Corp.	Acquisition	May '90
Schering AG	Triton Biosciences	Acquisition	June '90
Synbiotics Corp.	Cryschem, Inc.	Acquisition	Feb. '90
Transgenic Science, Inc.	Mason Research	Acquisition	Dec. '89
Institute Union Carbide Corp.	Vitaphore Corp.	Acquisition	May '90
Ventrex Labs, Inc.	Cambridge Medical Technology	Acquisition	Aug. '89
Xoma Corp.	Ingene Corp	Merger	Nov. '89

NOTE: The information displayed was gathered from publicly available sources (industry journals, newspapers, press releases, etc.) As such, it is not meant to be an all encompassing list but rather, a reasonable sample of the activity during the past year. No confidential survey data was used for this list.

SOURCE: Ernst & Young, 1990.

their bank accounts dwindle since then. For many such start-up companies the choice has been one of cutting R&D or turning to corporate sources for various types of financial assistance.

The North Carolina Biotechnology Center (NCBC) maintains a database that monitors public literature citations to take a much broader approach to biotechnology agreements. The center includes a deal if either one of the firms involved has some biotechnology activities. As a result, more agreements are included within the NCBC database, which tracks more than 550 small and large firms that work with recombinant DNA (rDNA), monoclonal antibodies, or new cell culture technologies.

For the years 1982 to 1988, a total of 33 biotechnology-related acquisitions involved a firm from the United States and a firm from Europe, while only three involved combinations of U.S. and Asian companies. Many of these deals consisted of multinationals on both sides of the Atlantic exchanging divisions, with biotechnology often an unimportant part of the buyouts. In the three Asian acquisitions, for example, biotechnology played virtually no role whatsoever (31).

The long-awaited biotechnology consolidation has been less than dramatic so far, but ***worldwide*** acquisitions were on the rise in 1989 and 1990 (see table 4-6). Of these deals, few involve a foreign

Box 4-B—The Genentech/Hoffmann-LaRoche Merger

In February 1990, the biotechnology community was stunned when the Swiss pharmaceutical company Roche Holdings, Basel, announced that it was acquiring **60** percent of Genentech for **$2.1** billion. Roche Holding Ltd. is the parent company of Hoffmann-LaRoche. In principal, the arrangement is a merger rather than a takeover and Roche's investment represents a much greater interest in biotechnology than it has previously taken. Hoffmann-La Roche has joint ventures to develop specific products with at least 13 other companies and owns 4 percent of Cetus. The announcement was met with dismay by some because of rising concern about foreign investment in the U.S. economy; Japanese firms were actively purchasing U.S. assets, including Sony's highly publicized acquisition of Columbia Pictures 4 months prior to Roche's announcement.

The merger agreement was overwhelmingly approved by Genentech shareholders and passed Federal Trade Commission (FTC) review in September 1990. Under the terms of the agreement, Roche Holdings will exchange every two shams of Genentech stock for $36 cash plus one share of Genentech redeemable stock. Roche has the right to buy all of the redeemable stock at various dates between December 1990 and June 1995 at prices ranging from $38 to $60 per share.

Genentech was the largest and most successful independent U.S. biotechnology company and had become symbolic of American superiority in the field. The biotechnology-based pharmaceutical company was founded in 1976 using venture capital. In October 1980, Genentech was able to capitalize on the biotechnology hype during the public offering of its shares. During the first 20 minutes of trading, the stock rose from the initial offering price of $35 to $89. This was especially surprising given that investors' decisions were based on expected profits from products that were not yet developed, approved, or marketed. Nevertheless, investors were lured to Robert A. Swanson's dream to ''build a fully integrated, independent pharmaceutical company. Swanson hoped that Genentech would achieve a billion dollars in annual sales by 1990.

Genentech's success is considered extraordinary because it pioneered four of the first six genetically engineered pharmaceutical products available on the market. The first three commercial successes for Genentech were human growth hormone, human insulin, and alpha interferon. Genentech's largest effort was in the development of tissue Plasminogen Activator (tPA). By 1989, Genentech's product and licensing royalties revenues had grown to $400 million from its products-the aforementioned human insulin, human growth hormone, alpha interferon, and tPA. While revenue increased steadily, costs of research, development, and litigation also rose. In 1989, Genentech spent 40 percent of its revenues on research and development, amounting to $155 million.

Genentech was the primary company to develop Activase (the brand name for tPA). Sales of Activase, Genentech's main product, were much slower than expected because of delays in Food and Drug Administration (FDA) approval, scientific studies questioning its effectiveness, and the availability of an inexpensive, low-technology competing product. The inability of Activase to live up to original expectations combined with increased costs of bringing new products to the market may have spurred Genentech's efforts to find a partner.

Genentech executives report that they looked for a U.S. partner before approaching Roche Holdings. Roche was deemed suitable because, among other things, it took a long-term view on the merger, it needed to take a major step forward with its comparatively slow-moving internal biotechnology efforts, and was apparently less concerned with quarterly performance. In addition, Genentech wanted to expand the sale of its products overseas very quickly.

During the next few years, the daily management of Genentech is expected to change little. Roche Holdings has said that Genentech will continue to have a high degree of flexibility and independence; Roche will appoint only 2 of the 13 members of Genentech's board of directors. How long this relationship will last is unclear. The main benefit for Genentech appears to be an immediate infusion of $492 million. Genentech executives noted that the company simultaneously gained the capital to finance its long-term drug development plans and reduced its need to worry about volatility in quarterly profits. Kirk Raab, CEO and President of Genentech, implied that fluctuations in eamings were hurting Genentech's ability to conduct its programs and secure financing. In essence, Genentech is gaining a degree of security that will offset its lost independence. In addition, Genentech will have access to Roche's large international sales staff. Sales of Genentech's products are likely to show strong growth, especially overseas; currently only 20 percent of Genentech's revenues originate from sales outside the United States.

Nearly all of Genentech's 1,850 employees hold stock options. The day the merger was completed, Genentech gave its employees a cash windfall of approximately $120 million, or $60,000 each. Kirk Raab stands to gain $7.9 million in stock options while Chairman and cofounder, Robert Swanson, would receive $4.2 million in cash on top of stock options. Herbert Boyer, cofounder and co-patentee on the most famous recombinant patent, will collect $36 million in cash for turning in his 2 million shams.

SOURCES: Office of Technology Assessment, 1991, based on Associated Press wire story, Sept. 9, 1990; *Business Week*, ''Roche's Big Buy May Set Off a Shopping Frenzy," Feb. 19, 1990; M. Chase, ''Genentech Plans To Sell 60 Percent Stake to Roche Holdings for $2.1 Billion" *Wall Street Journal,* Feb. 5, 1990; M. Ratner, "New Era for Genentech, and So It Goes," *Biotechnology,* March 1990; R.A. Swanson, "Remarks Before the Vice President's Council on Competitiveness," February 1990.

acquisitor. In fact, in the case of Genzyme's proposed takeover of Integrated Genetics, it was the small U.S. acquisitor outbidding the large Italian pharmaceutical concern, the Ares-Serono Group. Rather than demonstrating any international trend, 1989 and 1990 proved to be the years of the teamup ***between*** U.S. biotechnology companies: the years' deals involve U.S. biotechnology companies on both sides of the contracts. A 1990 survey of biotechnology companies revealed that within the next 5 years nearly half expect to acquire another company and 39 percent expect to be acquired (19).

With such a small number of acquisitions by foreign firms it is difficult to identify temporal trends. It seems certain, however, that overall buyout activity is heating up, with half the total number of biotechnology acquisitions being made (or being proposed) within the past 2 years. Nevertheless, it would seem that if an onslaught of biotechnology-hungry multinationals acquiring cash-strapped biotechnology companies was going to occur, the trend would likely have become quite evident by now. The key is, if American biotechnology companies remain willing to arrange deals for single products or product lines at reasonable prices, why should a foreign firm go through all the trouble and expense of making a complete acquisition (25). In a 1990 survey, three-quarters of the companies surveyed believe it does not matter whether an acquirer is foreign or domestic (19).

Analysts expect that many struggling, cash-short American biotechnology firms will command some of the richest takeover premiums in the years ahead (15). The Premiums paid for recent acquisitions have been high. Hoffmann-LaRoche acquired 60 percent of Genentech at a 40-percent premium over its market valuation. Chugai paid a 92-percent premium for Gen-Probe, and American Cyanamid paid a 175-percent premium for Praxis Biologics (19).

Many industry observers disagree, however, on the likelihood of a spate of foreign biotechnology takeovers (57). One argument proposes that the major assets of U.S. genetic engineering firms are their young, energetic scientists. These assets walk out of the building every night, and they would likely move to another start-up company if they didn't like the corporate atmosphere following a takeover. That reasoning may carry somewhat less weight today than previously, however, as a number of biotechnology companies are beginning to show product revenues and operating profits and therefore have tangible worth in addition to their scientific expertise. But, with companies spending 70 percent of their revenues on research, this argument is still relevant (40).

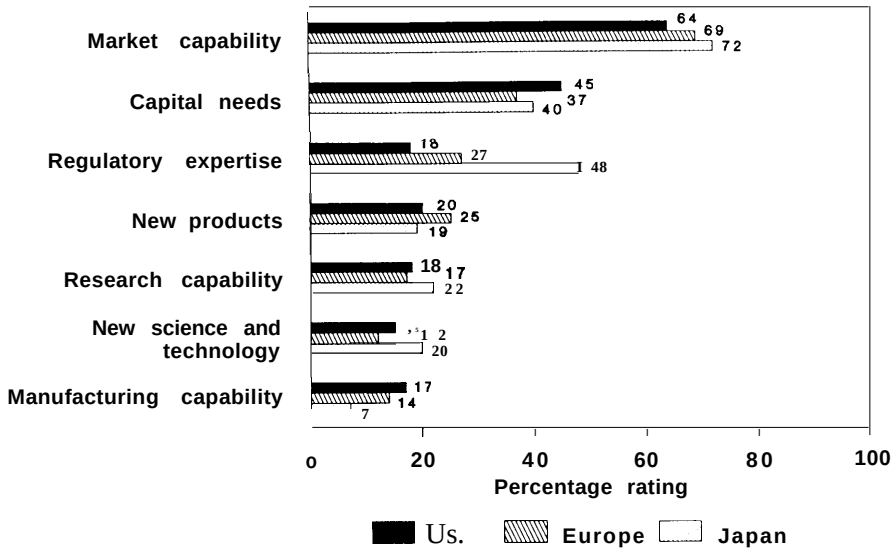
With any takeover, be it foreign or domestic, the new parent is likely to put in place new management and infrastructure. An action that could have negative consequences on an entrepreneurial, research-based biotechnology fro-these problems are multiplied if the parent company is headquartered overseas. This may be one reason why Japanese firms prefer strategic alliances over total acquisition. In general, strategic alliances expose the parent company to less risk than acquisition.

STRATEGIC ALLIANCES

As venture funds become more conservative and the public market more difficult to penetrate, U.S. companies increasingly rely on strategic alliances with both domestic and foreign firms to raise much-needed cash. While policymakers may be concerned about asymmetrical deals wherein the foreign firm gains more than the U.S. firm, U.S. companies enter into alliances that offer the most cash with the greatest flexibility. A 1989 survey examined the reasons that biotechnology companies turn to foreign partners for strategic alliances in the first place (19). United States firms cite marketing expertise as the prime reason for foreign ties, followed by the availability of capital and the regulatory expertise necessary to market products in foreign countries (see figure 4-2).

It is surprisingly difficult to define exactly what constitutes an alliance between a U.S. biotechnology company and a European or Asian partner. For example, the research collaboration that Cetus signed with Hoffmann-La Roche in early 1990 covering human diagnostics based on polymerase chain reaction (PCR) technology is really with the New Jersey-based Hoffmann-La Roche, Inc. subsidiary of the Swiss-based parent. Nevertheless, researchers at Roche's world headquarters in Basel probably have a much better handle on PCR technology than if Cetus' deal was with a totally unrelated company. Similarly, if Nova Pharmaceutical's major collaboration with SmithKline Beckman was an all-American deal when it was first signed, does anything change now that SmithKline has merged with England's Beecham Group?

Figure 4-2—Reasons for Geographic Strategic Alliance



SOURCE: Ernst & Young, *Biotech 91: A Changing Environment* (San Francisco, CA: 1990).

Keeping track of new alliances is often a relatively straightforward procedure because of the publicity surrounding such announcements. Monitoring the termination of such deals, however, is much more difficult. For example, 46 publicly held biotechnology companies tracked by Shearson participated in 65 deals that terminated during 1988. European partners were involved in eight of those teruminations; Asian partners participated in four. Reasons for ending agreements include a change in focus on the part of one of the partners, unsatisfactory R&D progress, or the planned conclusion of R&D contracts for better or worse. For example, in Pharmacia's termination of agreements with Biotechnology General and Chiron, analysts point to major corporate restructuring going on within the Swedish company (46).

A further difficulty with deal-counting is that one agreement may cover just a single protein while another may involve a whole range of products. For example, Chiron Corp. 's joint venture with Switzerland's Ciba-Geigy includes a variety of biotechnology-derived vaccines; by comparison, Amgen and Kirin have actually made three separate agreements (plus one more between Amgen and the Kirin-Amgen joint venture) with each covering a specific therapeutic product obtained using a DNA technology.

Despite these difficulties and limitations, it is instructive to step back and examine the overall numbers of agreements forged between U.S. biotechnology companies and European and Asian partners. The investment bank Shearson Lehman Hutton has kept track of the various domestic and foreign alliances currently in place for 46 publicly traded U.S. biotechnology fins. It lists transactions that have taken place from the inception of the biotechnology companies through February 1,1989. Biotechnology firms have an average of six corporate partners each. The average number of foreign alliances for each U.S. biotechnology company is 3.5, which includes an average of 2.1 European alliances and 1.4 deals with Asian companies, almost always Japanese firms (see table 4-7). These figures have been confirmed in a separate survey by Ernst & Young (1990).

A half-dozen biotechnology companies have forged an extraordinary number of foreign ties; Chiron, Biogen, and Genentech lead the way (see table 4-8). The data reveal several different strategies for foreign strategic alliances: some U.S. firms have emphasized European accords (e.g., Chiron and Immunex), others have stressed Asian over European alliances (e.g., Amgen, Bio-Technology General Corp., and The Liposome Co.), and still others have opted for a balanced approach (e.g., Biotech Research Labs, Genentech, Integrated Genetics, and Mycogen).

'Timing the tables and examining the situation from the perspective of the foreign partners reveals

Table 4-7—Breakdown of the Number of Alliances With 46 Publicly Held U.S. Biotechnology Companies With European or Asian Partners

Total number of alliances	Number with European firms	Number with Asian firms
1	28	18
2	9	11
3	4	2
4	0	3
5	0	0
6	0	1
7	3	0
8+	1	0

SOURCE: Teena Lerner, Shearson Lehman Hutton, 1990.

that 62 percent of European firms that have made deals with U.S. biotechnology companies have made just one such accord, while 91 percent have made three or fewer; the average number of deals per European company is two. The European outliers are Switzerland's Hoffmann-La Roche (13 deals), Ciba-Geigy (7 deals), Sandoz (7 deals), and Germany's Hoechst (7 deals). Although these represent a large number of alliances, the European corporate dealmakers have struck nowhere near the number of biotechnology accords as the most active of U.S.-based multinationals, such as Johnson & Johnson (23 deals) and Eastman Kodak (20 deals) (46). A country-by-country analysis of strategic alliances appears in box 4-C.

As for Asian firms, the overall pattern is similar. Some 51 percent of those companies that do have strategic alliances with biotechnology companies have only one agreement, with all but one Asian company having four deals or fewer. The one Asian outlier is Kirin Brewery, which has six agreements (four with Amgen and the remaining two with Plant Genetics, Inc.). Other major Japanese corporations entering into alliances are Green Cross, Mitsubishi Chemical, and Yamanouchi Pharmaceutical, each with four agreements.

The Shearson data are useful as far as they go, but they were constructed specifically to track and evaluate publicly held biotechnology companies, rather than monitoring the actual technologies involved. With over 400 U.S. companies dedicated to biotechnology, the Shearson figures clearly leave out small, public biotechnology companies as well as privately held concerns. In addition, established U.S. pharmaceutical, chemical, and other companies with significant in-house biotechnology expertise are also ignored.

Table 4-8-Number of Agreements With European and Asian Partners for 46 Publicly Held U.S. Biotechnology Companies As of 1989

U.S. company	Number of European deals	Number of Asian deals	Total number foreign deals
Amgen	1	4	5
Bio-Response	0	0	0
Biogen	8	7	15
Biotech Research Labs	0	0	0
BioTechnica International	2	0	2
Bio-Technology General	0	4	4
Calgene	4	1	5
California Biotechnology	3	2	5
Cambridge Bioscience	1	1	2
Centocor	4	4	8
Cetus	3	1	4
Chiron	12	4	16
Collaborative Research	2	1	3
Crop Genetics	0	0	0
Cytogen	1	0	1
Damon Biotech	1	0	1
DNA Plant Technology	4	0	4
Ecogen	0	0	0
Enzo Biochem	0	0	0
Epitope	2	1	3
Escagenetics.	1	1	2
Genentech	7	6	13
Genetics Institute	6	3	9
Genex	3	1	4
Genzyme	2	2	4
Gen-Probe	4	1	5
Immunex	5	0	5
Imre	0	2	2
Integrated Genetics	3	4	7
Ingene	0	1	1
Invitron	0	0	0
Lipsome Technology, Inc.	1	0	1
Molecular Genetics	2	0	2
Monoclonal Antibodies..	1	0	1
Mycogen	0	1	1
NeoRx	0	0	0
Nova Pharmaceutical	0	0	0
Oncogene Sciences	0	0	0
Plant Genetics	1	3	4
Repligen	4	1	5
Synergen	1	0	1
Syntro	1	1	2
T Cell Sciences	0	3	3
The Liposome co.	0	5	5
Vestar	3	0	3
Xoma	3	0	3

SOURCE: Teena Lerner, Shearson Lehman Hutton, 19S9.

The NCBC data that were sorted under contract specifically for this report show that from 1982 to 1989 both European and Japanese firms have had significant interactions with U.S. companies. Ap-

Box 4-C-Country-by-Country Analysis of Strategic Alliances

Analysis of the countries involved in U.S.-Asian alliances shows Japan involved in 94 percent of the 195 deals made from 1982 through 1988. In 1988, there was a record 52 U.S.-Japanese deals struck; but some of the other Asian countries also signed agreements with U.S. firms. The half-dozen non-Japanese deals signed last year involved companies from China, Israel, Singapore, Korea, and Pakistan.

Alliances between biotechnology companies from Western countries and the Soviet Union are also becoming more common of late. In one such arrangement, Monsanto agreed to contribute $500,000 toward joint research at the U. S. S.R. 's Shenyakin Institute for Bio-Organic Chemistry involving neurobiological processes, human and animal growth hormones, and plant genetic engineering. In another 1989 pact, Millipore and the Soviet Institute of Genetics opened a joint R&D facility in Moscow that will initially develop separation processes for alpha-interferon and the amino acid L-threonine.

The leading players in U.S.-European alliances are the United Kingdom (74 deals), Switzerland (63), and Germany (45). Even though companies from each of these countries posted a record number of trans-Atlantic biotechnology accords last year, the United Kingdom and Germany have clearly boosted their participation, while Switzerland's presence has been more steady throughout the 7-year period. This may have something to do with far-sighted Swiss pharmaceutical giants like Hoffmann-La Roche, Sandoz, and Ciba-Geigy having played such active partnership roles from the beginning.

The European countries that make up the second-tier in terms of U.S. alliance activity are Sweden (28 deals), France (28), Italy (25), and The Netherlands (24). French, Italian, and Dutch accords are clearly on the rise, while Swedish participation has been more evenly spread over the analysis years.

Belgium and Denmark, with 10 agreements apiece, make up a third tier of countries when it comes to U.S.-European deals; Czechoslovakia, Finland, Ireland, Norway, and Spain represents the fourth tier, with companies from each country having signed between one and three pacts.

In Germany, industry invests heavily in R&D-58 percent of the national total-and the pattern extends to biotechnology. The majority of biotechnology activities are being conducted by large firms including: Bayer, BASF, Boehringer Ingelheim, Hoechst, and Schering. Some of the firms, such as Bayer and Hoechst, are funding biotechnology R&D at the rate of $70 to $100 million a year—amounts equivalent to U.S. companies, such as DuPont and Monsanto. Licensing agreements, strategic alliances, and even acquisitions involving U.S. firms (e.g., BASF's $1 billion acquisition of Inmont) may help German firms gain access to cutting-edge technology. In addition, German firms are locating biotechnology facilities in the United States, such as BASF's production facilities in Massachusetts. Wellcome has a joint venture manufacturing facility in the United States with Genetics Institute.

In Switzerland, where the pharmaceutical industry is very strong, industry accounts for 75 percent of all R&D investment (approximately US $3.25 billion annually). Commercial investment in biotechnology goes toward basic research. Because of production costs and a small internal market, most Swiss companies prefer to produce products abroad.

SOURCE: Office of Technology Assessment, 1991, adapted from data obtained from the North Carolina Biotechnology Center; Decision Resources, *Selected Company Liaisons in Biotechnology, First Quarter 1989* (San Francisco, CA: Arthur D. Little, 1989).

proximately 366 European-U.S. biotechnology accords and some 266 Japanese-U.S. biotechnology deals were struck during the 7-year period.

Equity Arrangements

Biotechnology companies are always looking for money; selling equity to major U.S. and foreign corporations has always been an important part of this fundraising, often accompanying strategic marketing or distribution deals. Using data on 46 publicly traded U.S. biotechnology companies show seven instances of equity participation in a U.S. biotechnology firm by an overseas investor (table **4-Y).** This means that foreign firms accounted for 18 percent of the total 38 equity investments listed. As with outright acquisitions, the small number of these deals indicates that this mute has not been an important one for European and Asian companies as they try to compete in biotechnology. A General Accounting Office (GAO) report confirms the relatively minor part that foreign direct investment has played in U,S. biotechnology (52).

The NCBC databases reveal 25 cases of U. S.-European equity arrangements and 12 cases of

Table 4-9-Equity Participations in 46 Publicly Held U.S. Biotechnology Companies by European and Asian Partners

U.S. firm	Partner	Description
Cetus	Hoffmann-LaRoche	Purchased 950,000 Cetus shares (3.6%) in Jan. 1989 for $15 per share
Chiron	Ciba-Geigy	Paid $20 million for 1 million Chiron shares in Dec. 1988
DNA Plant Tech.	Adron AB	Owns 2.3% of DNAP
DNA Plant Tech.	Hilleshog Research AB	Owns 6% of DNAP
Imre	Takeda Chemical	Takeda increased its equity ownership to 10% in Aug. 1988
Nova Pharm.	Celanese	Celanese, which was acquired by West Germany's Hoechst, purchased $10 million Nova shares in 1987
Plant Genetics	Kirin Brewery	in 1986 Kirin purchased a total of almost 95,000 shares of various classes of preferred stock

SOURCE: Teena Lerner, Sheareon Lehman Hutton, 1990.

U.S.-Japanese deals. The European data show a recent increase in this activity, with 13 deals being made in the last 2 years; however, the U.S. firm was acting as the equity ***purchaser in*** more than half of these 13 instances. Four deals involving equity buy-ins into U.K. biotechnology companies Celltech and British Biotechnology Ltd. clearly illustrate the fact that recognized genetic engineering expertise is no longer limited to U.S. shores.

Of 25 U.S.-European equity arrangements, five contain an explicitly mentioned marketing or distribution agreement. Interestingly, however, of the 15 deals made in the last 3 years, only 1 involves such a dual function, indicating, perhaps, U.S.-European equity investments are now being made for their own sake, rather than as part of a window on technology or market access approach. On the Japanese side of things, 6 of 12 equity deals explicitly mention marketing or research funding with no trend away from dual agreements in the last few years. This seems indicative of the fact that the Japanese market is still inaccessible to most biotechnology companies by any route other than teaming up with a large Japanese corporation.

Joint Ventures

With the exception of complete acquisition, the most intimate relationship two companies can have is a joint venture. In most cases, these arrangements consist of both parties contributing a corporate strength. In biotechnology, the genetic engineering company invariably contributes the necessary technology; and the partner contributes financing, perhaps some development skills, and marketing capacity down the line. For most biotechnology companies, joint ventures are almost always preferred over licensing arrangements as they give the start-up firm opportunity to finance internal infrastructure consistent with becoming vertically integrated and a share in profits rather than receiving only a small royalty on eventual sales.

Joint ventures now account for most international alliance activity in terms of dollars, while marketing arrangements are still number one in terms of overall numbers of deals made (58). Many of these agreements, especially in the early years, involved major American companies, such as Squibb, Corning Glass, Abbott Laboratories, and DuPont; but as time passed, the biotechnology companies began to play a growing role, especially the larger, big-name companies like Genetics Institute, Chiron, Amgen, and, of course, Genentech. Whether the U.S. biotechnology company is dealing with Europe or Japan, the more the firm can bring to the partnership the better are its chances of negotiating a full-scale joint venture, as opposed to a limited and less valuable licensing or marketing arrangement. Although it would seem that U.S. biotechnology companies would be maturing over the last year or two to the point where more of them could pull their own weight in a joint venture involving an overseas partner, the evidence does not point to any large increase in such joint ventures.

If one particular joint venture were to be singled out as a model for biotechnology companies to examine, the Kirin-Amgen venture would be a good place to start. According to Amgen president Harry Hixson, it took the two companies just 8 weeks in 1984 to arrange the deal from beginning to end (29). Kirin put up $12 million and Amgen contributed patent rights, technology, and (somewhat unusually) $4 million in its own funding. Research took place on both sides of the Pacific, and the companies divided up worldwide marketing rights as follows: Amgen kept U.S. rights, Kirin took Japanese rights, and the Kirin-Amgen joint venture itself held onto rights for the rest of the world. Johnson & Johnson later bargained for European marketing rights from Kirin-Amgen as well as rights to certain U.S.

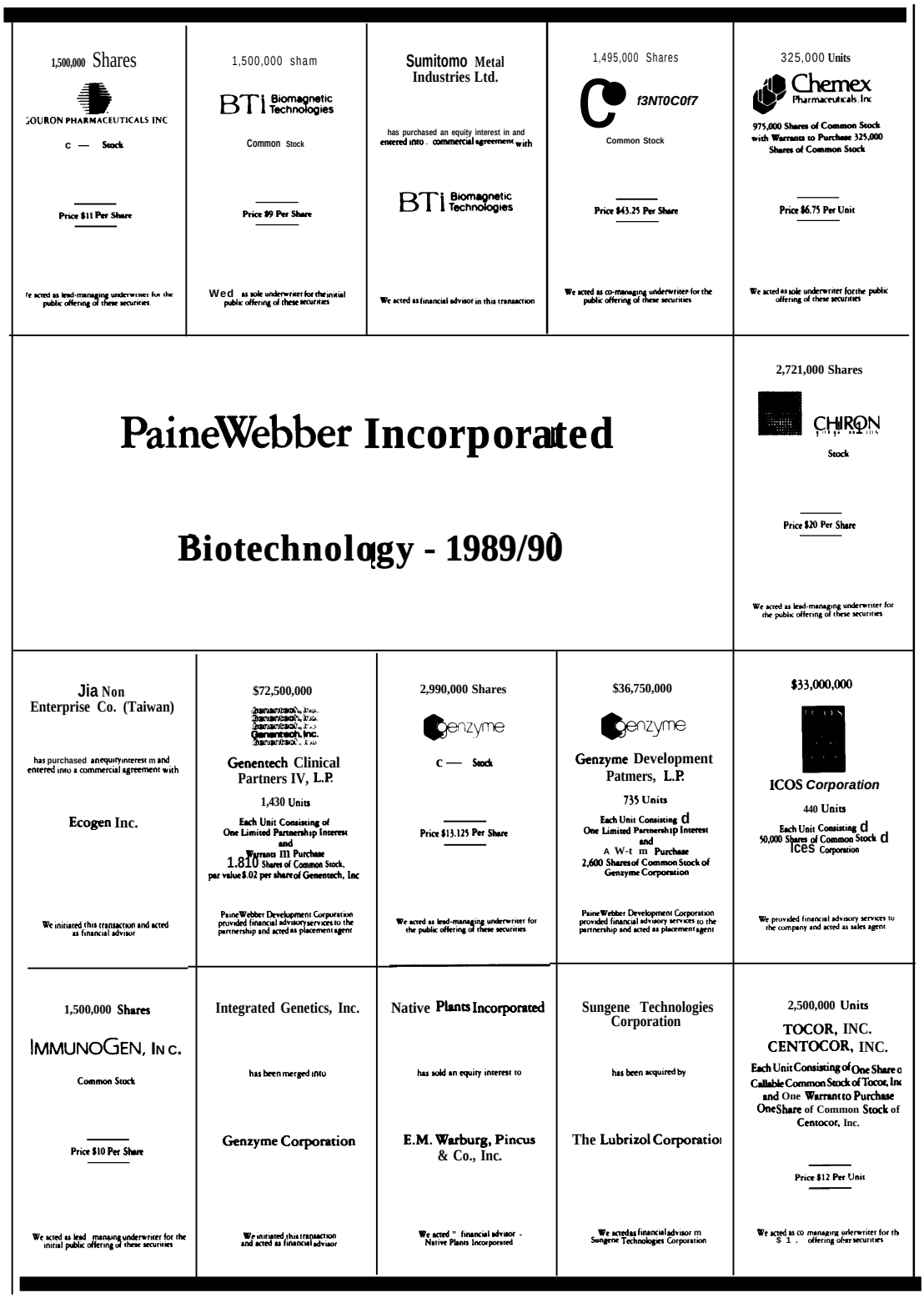


Photo credit: PaineWebber Inc.

Advertisement, financial services for biotechnology companies.

markets from Amgen. The key factor in making the arrangement a success was the potential success of the product, erythropoietin (EPO), a protein that stimulates the production of red blood cells. Erythropoietin is approved for use in close to a dozen European countries. In June 1989, EPO received marketing clearance from the U.S. FDA for treatment of renal dialysis patients who suffer anemias due to their inability to produce red blood cells.

Even this joint venture wasn't perfect. For example, one of the reasons that Amgen was able to negotiate such a favorable arrangement was that Kirin sells a lot more beer than it does drugs, so this company would not immediately be considered the best of marketing partners for a biotechnology-derived therapeutic. In fact, this marketing weakness probably played a role in the joint venture's eventual decision to license European rights to EPO.

Licensing and Marketing Deals

Licensing, whether it involves technology itself or the marketing rights to eventual products that result from R&D, has been an important source of funds since the inception of commercialized molecular biology.

Despite their popularity in terms of numbers of deals, licensing agreements do not receive raves from biotechnology executives. These arrangements, if made with a large pharmaceutical company, provide the large pharmaceutical company very good downside protection with milestone payments often eliminated if the research is not going well. The biotechnology companies, however, gain somewhat limited upside potential from these deals, because if the product is successful it will be the pharmaceutical company that reaps the lion's share of the profits (41).

So why are there so many licensing deals? The problem, according to one executive, is that partnerships and joint ventures cannot be completed until a company has financed its own risk capital and has come up with a product or service in which someone has an interest. If the primary objective is to raise cash, a company is at a negotiating disadvantage from the beginning (9). Mycogen, an agricultural biotechnology company, was able to raise $18 million in its initial public offering and has been able to add about that much again in funding from three major international collaborations. These were with Kuboto (covering bio-insecticides in Japan), Royal Dutch Shell (for bioinsecticides in the rest of the world, except North America), and Japan Tobacco (for bioherbicides worldwide) (8).

As for new trends, some companies are now actually more willing to give up certain enabling technology as part of an agreement than in previous years. In this scheme the technology per se is not so valuable, but rather, the products; the technology is seen as something that will become available anyway (42). The key, however, is when a company licenses out the use of tools, such as specific promoters and transformation systems, it does so for clearly restricted areas of research.

Another trend developing as biotechnology companies grow, have product sales, and develop their own sales forces is some of the marketing agreements can switch direction. For example, in 1987 the Japanese pharmaceutical firm Mitsubishi Kasei selected Genentech to develop and market some of its products in the United States. However, Genentech was one of the few DBCs that had developed a major marketing staff in the United States. While companies such as Amgen, Immunex, and Cetus have developed smaller sales forces, it is unlikely that many similar agreements will be developed in the near term (59).

Co-Marketing Agreements

In order for biotechnology companies to participate in co-marketing agreements, they need two key, but relatively rare, components--a product and a marketing staff. Marketing is expensive and requires a sales force, something most DBCs do not have. Not surprisingly, then, only a few such deals have been struck. Each deal is different, but all involve the larger, more advanced biotechnology firms. Because Genentech and Amgen have the highest market capitalization and are widely considered bellweather biotechnology companies, their deals are worthy of a closer look as they may predict future activity.

As an example, Amgen created Kirin Amgen as a joint venture with Kirin Brewery in Japan to develop EPO and subsequently elected to include granulocyte-colony stimulating factor (G-CSF). This time, Amgen held onto markets in the United States, Canada, Australia, New Zealand, and Europe, while Kirin took the marketing rights in Japan, Korea, and Taiwan; with the rights to the rest of the world assigned to the joint venture. Later, Kirin forged a co-marketing arrangement with the Sankyo Co. for

Japanese distribution of G-CSF, and in 1989 Amgen and Hoffmann-La Roche agreed to a 10-year co-promotion deal in Europe under which the product will be sold under Amgen's name. After this 10-year period, Amgen has the right to take over exclusive European sales and marketing.

As for Genentech, under a co-promotion agreement signed in February 1989 with Boehringer Ingelheim Pharmaceuticals, Boehringer's 475-person U.S. sales force joined Genentech's sales force in promoting Activase, tissue plasminogen activator (tPA), to office-based physicians in the United States. Boehringer Ingelheim Pharmaceuticals is the Connecticut-based affiliate of Germany's Boehringer Ingelheim International GmbH, which is Genentech's tPA licensee for all countries except the United States, Canada, and Japan. The co-promotion agreement was to run through the end of 1991 but was eventually bought out by Genentech.

TAX POLICY AND ITS EFFECTS ON FINANCING R&D

Biotechnology companies require higher levels of R&D investment than companies in other industrial sectors. Tax relief is one of the methods the Federal Government uses to reduce the financial burden on R&D-intensive industries. The justification for tax relief programs is based on the premise that such investment results in public benefits and in a greater rate of industrial innovation than would have occurred otherwise. Taxes and effects on investment in biotechnology were discussed in detail in a 1988 OTA report (54). More general discussion of the relationships between tax policy and innovation can be found in a 1990 OTA report (56). Tax issues that have emerged since 1988 and are specific to biotechnology are discussed in the following section. In addition, tax policies of other countries are examined.

Capital Gains

Capital gains are profits obtained from the sale of capital assets, such as stocks and real estate. Capital gains are taxed in most industrialized countries, albeit to differing extents. In fact, most Western European countries and Japan have systems of capital gains taxation that are more complicated and differentiated than that in the United States (38).

After the Tax Reform Act of 1986, these gains in the United States were taxed at a maximum of 28 percent in 1987 and at ordinary income rates starting in 1988. Substantial capital gains are rare for most people. In 1988, Americans filed 109.8 million tax returns; only 7.8 million returns accounted for all $159 billion of capital gains, equivalent to 7 percent of the tax returns filed (43). Debate during the fiscal year 1991 budget negotiations focused, in part, on a proposal to cut the top rate for capital gains taxes. While lowering the rate would likely stimulate stock trading, past experience with lowering the rate has shown that it does little to induce savings and thus capital investment (43). One argument for cutting the tax rate has been to encourage venture capital. But venture capital accounts for only a small fraction of total capital gains. Most of the venture capital comes from investors not subject to taxes anyway, such as foreigners, pension funds, and college endowments (7).

The tax rate on capital gains is only one factor driving venture capital. The total amount of professionally managed venture capital is an extremely small factor in the overall economic picture, even if it is critically important to biotechnology start-ups. Nonetheless, should the capital gains rate be lowered, the rise in investment in both RDLPs and venture funds will no doubt have a beneficial effect on biotechnology companies seeking capital.

R&D and Investment Tax Credits

The R&D tax credit lowers the cost of investment in research activities by providing a 20-percent tax credit on incremental R&D spending. The statutory rate of 20 percent is calculated based on the excess of qualified research over a base amount which is linked to R&D spending in a specific historical period. The base amount is figured by multiplying a freed-base percentage by a firm's average gross receipts over the preceding 4 years. The effective rate of the credit is much lower than 20 percent as it is based only on incremental spending, and the amount of the credit is disallowed as a tax deduction. The effective rate of the credit is, therefore, approximately 5 percent (26). The incremental nature of the credit ties it to increasing research expenditures rather than total expenditures made in a year, thus encouraging companies to increase their R&D commitment. Several other countries have similar tax incentives (see box 4-D).

To date, the R&D tax credit has been of little use to many U.S. biotechnology companies, be-

Box 4-D—R&D Tax Incentives of Selected Foreign Countries

Australia. In Australia, biotechnology firms can avail themselves of the benefits of several industry-wide programs, including an R&D taxation incentive (companies undertaking appropriate research can receive a tax break at 150 percent of the value of the research), grants, and a range of consulting services through the National Industries Extension Service.

Canada. In Canada, immediate expensing of costs for both current and capital expenditures for R&D purposes is allowed. Canada provides for an indefinite carry-forward of excess R&D deductions. Canada also offers a 20-percent flat rate tax credit for R&D activities based on a firm's total R&D spending. Canada's R&D credit is unique in reducing R&D deductions correspondingly on a dollar-for-dollar basis.

France. French tax law provides for the full deduction of current R&D expenses in the year in which they are incurred. Until recently, buildings used solely for scientific and technical research were eligible for a special accelerated depreciation allowance, under which 50 percent of the cost of the building was deductible over the remaining useful life of the asset. In 1983, the special depreciation allowance was replaced by a 25-percent incremental tax credit (very similar in structure to the U.S. R&D credit). France has adopted a generally applicable system of accelerated depreciation in the first year of service of the assets. Finally, France also maintains a system of cash grants for R&D, under which companies creating or expanding scientific or technical research departments may be entitled to a taxable cash grant of 15 to 20 percent of the value of such expenditures to a maximum of 25,000 francs per-job created.

Japan. Japanese corporations undertaking R&D in Japan may deduct their current R&D expenses in full in the year in which such expenses are incurred, with a carryover of unused deductions for up to 5 years. Since 1966, Japan has had an R&D tax credit for current R&D expenditures equal to 20 percent of the excess of current R&D expenditures over the largest amount of such expenditures incurred in any single prior tax year since 1966. In addition, Japan allows a special deduction of up to 40 percent of corporate income for firms that derive some portion or all of their income from "overseas transactions in technical services." Small firms which export products are allowed special reserves, deductible at rates ranging from 0.25 to 1.4 percent of income from exports, for the development of overseas markets.

Taiwan. In Taiwan, current expenditures on R&D are deductible in the year in which they are incurred. R&D equipment is eligible for accelerated depreciation as well as an investment tax credit of 15 percent (in the case of domestically produced equipment) and 5 percent of the acquisition cost (in the case of imported equipment). Technology-intensive industries are eligible for a special reduced corporate income tax rate of 22 percent. A 20-percent incremental credit is available over the highest credit of the past 5 years. If no R&D was conducted during the past 5 years, a tax credit for R&D in excess of 5 percent of current year revenues is available.

United Kingdom. In the United Kingdom, current expenditures on R&D are fully deductible in the year they are incurred. In addition, capital expenditures incurred in R&D activities are fully allowable as a deduction in the year such expenditures are incurred. Unused deductions may be carried forward for a period of up to 5 years.

Germany. The Federal Republic of Germany provides for the deduction of current R&D expenditures from taxable income in the year they are incurred. While capital expenditures on R&D, generally must be depreciated over the economic life of the assets, accelerated depreciation of R&D assets at rates up to 40 percent over the first 5 years are permitted with respect to personal property,

SOURCE: E. Palmer, "Antitrust, Capital Gains, and Research and Development Tax Benefits in Several Industrialized Nations," European Law Division, Law Library of Congress, April 1990.

cause they are not profitable enough to generate a credit. The credit, however, can be carried forward for 15 years and provides a strong incentive as it increases earnings over the long term by reducing the tax burden. The tax reductions come at a critical time, when a company starts earning money and selling products (26). The lower tax rate provides a company needed earnings. Still, smaller, newer companies are at a disadvantage, because the government is, in effect, subsidizing R&D of larger companies but not of smaller ones (10). And, when considering the time-value of money carried-forward tax benefits are less valuable than tax benefits rendered in the current year.

The investment tax credit was one of the first specific tax incentives that the Federal Government established to encourage investment in physical plants and equipment, allowing the company to

deduct a 10-percent credit for the cost of qualified property that was either constructed or purchased. The credit was eliminated in 1986 in favor of an overall reduction in the corporate tax rate, as it was unclear how effective the tax credit was at stimulating capital investment. In addition, the costs were deemed greater than the benefits (56). Several studies have attempted to measure the benefits of the investment tax credit; estimates of the additional investment range from $0.12 to $0.80 for each dollar not collected in taxes (56). Estimates of the actual increase in R&D spending from 1981 to 1985 as a result of the tax credit, range from $500 million to $2.9 billion annually (53). The investment tax credit, therefore, resulted in lost revenue of between $13 billion and $37 billion to the government over a 5-year period (56).

One of the most controversial tax-related issues has been whether or not R&D tax credits and investment tax credits induce more investment. And, if the tax credits encourage investment, does this additional investment activity have any measurable effect on the U.S. economy? Following the introduction of the R&D tax credit, private R&D spending doubled from 1980 to 1986, amounting to nearly $60 billion (45).

The R&D tax credit remains controversial to a Congress constantly faced with a budget deficit. The total amount of revenue lost as a result of the subsidy was approximately $700 million in 1985 (56) and as high as $1.8 billion in 1989 (53). The Treasury Department projected that a permanent extension of the credit would reduce Federal revenues by $500 million in fiscal year 1992,$1 billion in 1993, $1.3 billion in 1991, $1.6 billion in 1995, and $1.8 billion in 1996 (21). Estimates on the effect of the credit indicate that between $0.35 and $0.99 of additional R&D spending is generated for every dollar not collected in taxes. The main obstacle to the enactment of a permanent R&D tax credit is that it is very difficult to measure its effectiveness. And, although available since 1981, the R&D tax credit is not a permanent part of the tax code. Most recently it was extended through December 31, 1991, by the Omnibus Budget Reconciliation Act of 1990. Thus, companies are unable to take full advantage of the program because of the uncertainties. Despite the obvious popularity of the R&D tax credit, Congress has not yet made it a permanent part of the tax code. Many biotechnology companies feel that a permanent R&D tax credit would allow companies to plan, rather than to guess, what their financial commitments will be when investing in long-term, high-risk endeavors (9). The President's budget request for fiscal year 1992 included a provision to make the credit permanent and expand it to cover 100 percent of applicable research expenses.

Tax Credits and the Orphan Drug Act

Prior to 1983, U.S. pharmaceutical companies had little incentive to invest in developing drugs likely to yield only limited financial profit. Small biotechnology companies developing innovative new techniques were even less likely to invest any of their limited R&D budgets in any potentially unprofitable human therapeutic. Drugs available or to be made available for such rare afflictions as Huntington's disease, that affect only a small population, are commonly known as "orphan drugs" (see ch. 5 for further discussion of orphan drugs). In 1983, Congress amended the Federal Food, Drug, and Cosmetics Act with the Orphan Drug Act (Public Law 97-414) to provide incentives for developing drugs for rare diseases that would otherwise not be developed. A 50-percent tax credit for the cost of conducting clinical trials and 7-year market exclusivity were the key incentives provided in the act. The 7-year market exclusivity provision of the act was designed to protect companies selling drugs that were ineligible for product or use patents, were off patent, or had little patent term outstanding. The act has been amended twice, and there is momentum in the direction of another amendment.

A 1984 amendment (Public Law 98-551) defines a rare disease or condition as that which affects fewer than 200,000 persons in the United States--or more than 200,000 persons when it is clear that the cost of developing the drug will not be recovered by sales of the drug in the United States. A 1985 amendment (Public Law 99-91) authorizes 7 years of exclusive marketing approval for all orphan drugs, regardless of their patentability, with the intention of encouraging private pharmaceutical companies to invest more in orphan drug development.

In late 1990, Congress approved a measure that would tighten the requirements under which companies will be eligible for this 7-year market exclusivity-withdrawing orphan drug status for drugs when the patient population grows beyond 200,000. This provision came amidst charges that some companies

were earning unexpectedly high profits from the sale of orphan drugs. The House-approved bill also would allow more than one company to market different versions of a drug granted orphan status in instances where the companies developed the drug simultaneously. A similar version of the bill passed the Senate in fall 1990 but was vetoed by the President in December 1990.

Amortization of Goodwill

If company A has tangible assets valued at $2 million and company B is willing to pay $3 million to acquire company A, the excess $1 million company B is willing to pay is treated as an intangible asset, or goodwill, on company B's balance sheet. Goodwill is generally understood to represent the reputation of the firm and the continuing loyalty of their customers. Because this intangible asset has no independent market or liquidation value, generally accepted accounting principles promulgated by the Financial Accounting Standards Board require that goodwill (the differential between the purchase price of an acquired company and its book value) be amortized through their earnings stream over a period of time. Some analysts believe this requirement hurts the competitive status of American companies wanting to acquire firms (23). These analysts believe it penalizes companies by lowering their earnings enough to upset Wall Street. This is particularly true since there is no tax deduction for the writeoff of goodwill. Thus, earnings are penalized for the total amount of the goodwill writeoff rather than the tax-effected amount of the writeoff (26). This contrasts with the rules in England. A British firm, for example, can write-off goodwill immediately and get a tax deduction. Participants at a September 1990 OTA workshop on financing biotechnology, raised the concern that the current requirement, that goodwill be amortized, could lead to the sale of major assets overseas.

SUMMARY

Commercial activity in biotechnology in the United States has led the world because of excellent science and the ability of entrepreneurs to finance their ideas. The U.S. venture capital pool is unparalleled, and the magnitude of the federally funded research base that fuels the DBC research agenda is unique. Despite long delays in product development and considerable regulatory hurdles, start-up firms have been able to raise cash in the initial stages of operation. While the venture community has become more conservative in where it chooses to invest, there appears to remain viable opportunities for entrepreneurs with good ideas. Where there is a choke point, however, is in the ability of start-up companies to move forward into development, testing, and marketing of their products—the expensive part of the process. As much as $30 billion may be needed just to develop the 100 biotechnology products currently in human clinical trials.

Some private firms are caught pre-public, as the public market is less likely to play the role of risk-taker since Black Monday. This has left most firms cash poor and unable to move into development. The companies fortunate enough to have gone public well before 1987 are, on average, able to generate cash when needed through limited partnerships, secondary public offerings, and strategic alliances. The top 20 firms will most likely remain stable, surrounded by an ever-changing backdrop of DBCs. Start-ups will continue to appear, but these companies will likely face the reality of merger or acquisition. Only a dramatic surge in the public markets will dislodge some of these companies from this fate.

Consolidation of existing companies is inevitable and most likely necessary. What concerns some observers is the role that foreign acquisition and investment will play in the fate of many of these vulnerable fins. Although it is true that the amount of joint activity between U.S. firms and foreign firms has been on the rise, much of this activity is necessary to conduct business in a global market, i.e., licensing, marketing, and co-marketing agreements. To date, there is insufficient evidence to state that U.S. commercial interests in biotechnology are currently threatened by foreign competition. Acquisition is a costly and risky means to acquire a technology, and most corporations have avoided this mechanism. As U.S. DBCs move closer to product reality, however, foreign corporations with large pools of cash may be more willing to pursue acquisition to obtain and ensure manufacturing rights. Executives of DBCs tend to feel that manufacturing rights will be crucial for the viability of their companies.

While some foreign firms-usually the big companies such as Kirin, Ciba-Geigy, Hoffmann-LaRoche, and Hoechst—are actively investing in

U.S. DBCs, so are American firms such as Lilly, Monsanto, Johnson & Johnson, and Eastman Kodak. United States corporations are slightly disadvantaged when it comes to acquisition, however, because American accounting and tax practices prevent them from deducting the full expense of acquisition in the year it occurs. Some analysts feel this practice allows foreign corporations to move more rapidly toward acquisition. In addition, the relatively high cost of capital in the United States makes it harder for U.S. corporations to save the sums needed for acquisition and for DBCs to raise the cash needed to take biotechnology products to market.

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