Chapter 5

U.S. Commercial Biotechnology

"Biotech company officials are spouting projections that have no reality. They whip up the public's imagination every time they rinse out a petri dish."

George Sasic
Thomson McKinnon Securities
Changing Times 6-21-87

"Keep on dancing-—but choose partners carefully."

Peter Drake
Kidder Peabody

"I believe God created stockbrokers so they can tell biotech managers how to promote their companies effectively. "

Richard A Bock
Bear, Stearns & Co.
Bio/Technology, October

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INTRODUCTION

Huge public and private investments have been made in biotechnology since the venture capital community first recognized the potential profitability of Genentech, the first dedicated commercial biotechnology company to go public. Since the formation of Genentech in 1976, several hundred companies have formed, and major U.S. corporations have invested considerable sums in research and development (R&D) in biotechnology.

Biotechnology has captured the interest of the public and Wall Street, yet both have been occasionally disillusioned by the risks and revised time frames for introducing commercial products. Financial markets have reflected the turmoil of regulatory uncertainties, imbalance in the public markets of supply and demand of biotechnology stocks, the high value of the dollar, disinflations, and economic adjustments (25). There is no doubt that biotechnology has arrived as an important tool for industrial innovation; the question remains how the private sector will divide the processes, products, and proceeds of its development and sales. The comparatively smaller biotechnology companies continue to provide many of the innovative new ideas although larger, established corporations are increasingly improving their in-house R&D potential. Mutually beneficial arrangements have been worked out between the two groups,

For the purpose of this report, OTA designates firms as either dedicated biotechnology companies (DBCs) or large, diversified companies employing biotechniques. DBCs (referred to as new biotechnology firms or NBFs by OTA in 1984) are entrepreneurial ventures started specifically to commercialize innovations in biotechnology (35). Because many of these firms are no longer new, and some are quite established, the term "dedicated biotechnology companies" is more likely to stand the test of time than the early term NBF. Largely diversified companies commercializing biotechnology tend to be older and pursue multiple product lines, many unrelated to biotechnology.

This chapter reports on two surveys conducted by OTA in 1987.[1] The original 296 U.S. dedicated biotechnology companies contacted were chosen for their direct and focused involvement in recombinant DNA technology, monoclinal antibodies, and cell culture. The sample was developed from several directories of biotechnology firms compiled annually, including: Sittig and Noyes Directory of Biotechnology Companies; Walton and Hammer Genetic Engineering and Biotechnology Yearbook; Genetic *Engineering News* Directory of Biotechnology Companies; *Bioengineering News* Bio1000; and SCRIP Directory of Biotechnology Efforts in Pharmaceuticals. Of the 296 companies contacted, 136, or 46 percent, responded to the survey questionnaire. Survey data were supplemented, where possible, with press reports, annual reports, and other public information. Companies responded to questions regarding level of R&D investment, number and nature of employees, methods of financing, patent expectations, and product lines. A list of dedicated biotechnology companies, identified by OTA as of January 1988, appears in appendix A. More companies were identified than surveyed.

In 1987, OTA surveyed 53 large corporations known to be investing in biotechnology R&D either in-house or through strategic alliances with DBCs. Companies were selected from previous OTA databases, trade associations, publications, and personal communications with biotechnology industrialists, Companies were asked to report on the level of investment in biotechnology R&D, commitment in terms of full-time employees, sources of innovation, existing and expected biotechnology product lines, patent applications, and

[1]The North Carolina Biotechnology Center conducted a survey, under contract with OTA, of dedicated biotechnology companies. The Center for Survey Research in Boston, MA, under contract with OTA, surveyed large diversified companies.

use of trade secrets. A list of corporations identified by OTA as being involved in biotechnology also appears in appendix A.

The data collected from these two surveys are limited. Ideally, the best way to measure investment would be to first identify, then survey each and every firm involved in biotechnology. Identification of firms is itself problematic. New firms form, and others go out of business or are acquired. Some firms call themselves biotechnology companies when, in fact, they do not meet the OTA definition. Other more traditional firms may be conducting important research in biotechnological areas, but do not consider themselves biotechnology firms, and do not identify themselves as such. Large corporations maybe multinational, with several subsidiaries, making identification of programs and budgets complex.

Even after compiling a reliable list, there is the additional problem of gathering information from the companies identified. Firms that are privately held–as defined by the Securities and Exchange Commission-often do not wish to divulge financial information, inevitably resulting in undercounting. Some forms of investment by public firms, such as research contracts or licensing agreements, need not be divulged, compounding the problem. Thus, any accounting of total private investment in biotechnology is likely to be an underestimate.

In addition to discussing the results of these surveys, this chapter reports on an analysis of 552 collaborative ventures between U.S. firms and between U.S. and foreign firms that occurred between 1981 and 1986. Collaborative business ventures between U.S. firms have risen steadily over the pasts years, while those between U.S. firms and foreign firms have remained stable.

PROFILE OF COMMERCIAL BIOTECHNOLOGY

While biotechnology has taken on a “trade” status with its own firms, newsletters, investment funds, and regulations, it is not a single industry but a set of enabling technologies applicable to a wide range of industries. Thus, the term ‘(the biotechnology industry” is somewhat of a misnomer. The industry is by no means homogeneous, but comprised of many sectors, each facing its own unique advantages and hurdles.

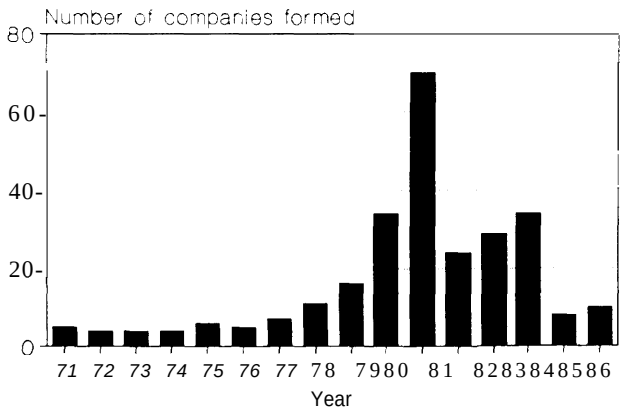
Within the broad categories of DBCs and large, diversified corporations are many traditional industrial sectors: pharmaceuticals, plant and animal agriculture, chemicals, energy, waste management, and ancillary industries that will supply users with equipment, reagents, and information systems. Each sector faces different financial markets, public markets, regulatory requirements, intellectual property issues, personnel needs, and gaps in knowledge needed for commercialization. As the tools of biotechnology are integrated into various sectors, the barriers to commercialization more closely resemble those facing the entire sector or those historically faced by entrepreneurs or multinational corporations-evidence of the growing maturity of biotechnology as an integral part of modern industry. An in-depth discussion of investment and commercialization issues in human therapeutics, plant agriculture, and hazardous waste management appears in chapters 9, 10, and 11.

Formation and Growth of U.S. Commercial Biotechnology

The boom for founding dedicated biotechnology companies occurred between 1980 and 1984. During these years, approximately 60 percent of existing companies were founded. Figure 5-1 illustrates the number of biotechnology companies founded per year between 1971 and 1986. The peak year was 1981, with nearly 70 new firms formed.

OTA verified that, as of January 1988,403 dedicated biotechnology companies are in business and are actually working in the area of biotechnology. In addition to the presence of DBCs, over the past 5 years, major U.S. corporations have increasingly invested large sums in in-house biotechnology research and in joint ventures, acquisitions, licensing, and marketing agreements with smaller

Figure 5-l. -Founding of U.S. Dedicated Biotechnology Companies, 1971-86



SOURCE: Off Ice of Technology Assessment, 1988.

biotechnology companies, and in research contracts with universities. OTA identified 70 major corporations with significant investments in biotechnology (see app. A) of which 53 participated in a 1987 survey. It is important to note that some are subsidiaries of others, and others conduct their biotechnology research solely overseas.

The "biotechnology industry," if measured by the entry of new, small companies in the field, has most likely stabilized. Some analysts would contend that, due to consolidation within the industry and the predominance of a few firms, the number of viable DBCs is actually shrinking. The industry as measured by the amount of money invested by large diversified corporations and DBCs, however, is growing.

Areas of Commercial Application

A human health care focus—therapeutics and diagnostics-continues to dominate both biotechnology R&D and the market in terms of volume. Human health care comprises the primary biotechnology work of 39 percent of DBCs and 37 percent of large, diversified companies. Human therapeutics clearly dominate the focus of most firms, large and small, Among the DBCs, therapeutics represent the primary interests of 21 percent of the respondents; the percent is slightly larger among corporate investors at 26 percent. Human diagnostics rank second as an area of R&D focus by DBCs (18 percent) but fourth by larger companies (11 percent), Therapeutics and diagnostics are considered separately because they tend to be pursued by different industries and are regulated differently by FDA (ch. 9). The strong focus on human health care products by DBCs is not unexpected. Historically, capital availability has been greater for pharmaceuticals than for food or agriculture because of greater market reward (3).

Animal health and agriculture are the focus of 14 percent of DBCs and nearly 21 percent of large, diversified companies. Chemicals (commodity and specialty such as polymers, enzymes, and additives) are the focus of 7 percent of DBCs, but 21 percent of the corporate sample. It is not surprising that pharmaceuticals and chemicals rate first and second as the areas of application pursued by the latter, since the pharmaceutical and chemical sectors have been the most active in terms of R&D investment in biotechnology. Table 5-I

Table 5-1 .—Areas of Primary R&D Focus by Biotechnology Companies

Research area	Dedicated biotechnology companies Number (percent)	Large, diversified companies Number (percent)
Human therapeutics	63 (21)	14 (26)
Diagnostics	52 (18)	6 (11)
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)	1 (2)
Diversified	13 (4)	6 (11)
Other	51 (18)	o (o)
Total	296 (100)	53 (loo)

SOURCE: Office of Technology Assessment, 1988.

compares the fields of commercial application pursued by both groups.

The production of biotechnology reagents, such as restriction enzymes and recombinant DNA vectors, also ranks high among DBCs (12 percent). It is possible that the number of biotechnology suppliers will grow as routinization and standardization of many biotechnology processes occurs. Several small firms may find their niche as the supplier of specialized reagents. The same is true for equipment. Equally likely is the possibility that companies will turn in-house for these services, requiring less dependency on outside interests.

Most DBCs that responded to the OTA survey reported that 100 percent of their efforts are biotechnology-related. On the average they report that recombinant DNA technologies assist them in approximately 44 percent of their work, use of monoclinal antibodies underlies 36 percent of their work, and cell culture contributes to 31 percent of their work,

Anticipated product Lines of Corporations Investing in Biotechnology

Table 5-I lists the areas of application invested in by U.S. corporations investing in biotechnology. Eighty-nine percent expect that they will develop product lines in those areas within the next 5 years. Interestingly, nearly half of the corporate representatives stated that the anticipated product lines were different from current product lines. Twenty-eight percent indicated that the biotechnologically derived product lines were not at all like current products, indicating a trend in using biotechnology as a means of diversification. Forty percent felt that anticipated products developed from biotechnology were similar to existing products.

R&D Investment in Biotechnology

Biotechnology companies, more than others, are driven by R&D, relying on eventual conversion of the R&D into revenues. Funding and building R&D will remain a key component of the business strategy of DBCs until they have products requiring heavy financial commitments to regulatory review, manufacturing, and marketing. Established corporations have either created new biotechnology R&D initiatives in-house, redirected existing R&D efforts, or invested in biotechnology R&D conducted by other firms or university-based scientists.

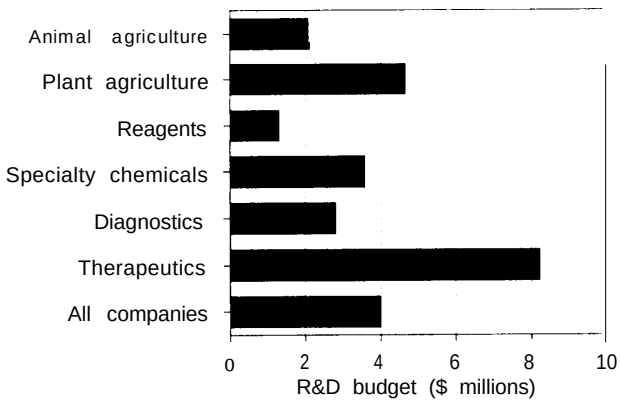
Based on responses to a 1987 survey, OTA estimates that 403 DBCs invested about $1.2 billion in biotechnology R&Din 1987, and major corporations invested more than half that amount or $0.8 billion. Because there is a good possibility that some double counting may occur due to collaborative ventures between the two groups, the combined industrial investment in biotechnology R&D is most likely in the range of $1.5 to $2.0 billion in 1987. This estimate approximates that generated by the National Science Foundation where biotechnology R&D performance by industry was estimated to be $1.4 billion in 1987 (29). Industrial investment in biotechnology R&D, therefore, is roughly two-thirds that of Federal spending.

R&D Budgets of Dedicated Biotechnology Companies

The R&D budgets for dedicated biotechnology companies surveyed by OTA had a mean of $4 million per firm, or more than 40 percent of the expected revenues. The range of responses from 108 companies was $10,000 to $45 million. The median response was $1.5 million. Genentech, for example, spent $80 million on R&D in 1986 (18). Skewing of the OTA data could be caused by the therapeutics firms, which tend to have, on average, R&D budgets of close to $9 million, higher than firms in other sectors. Differences in the size of R&D budgets are illustrated in figure 5-2.

R&D budgets are more than four times larger in public companies than in private companies. As would be expected, R&D budgets in dollar terms increase with company size, but consume the largest portion of expenditures for medium-size firms. This is most likely due to the high administrative start-up costs of small firms, the diversion of funds to other activities in large companies, and economics of scale for R&D activities. In any event, there are numerous complexities involved in measuring R&D budgets at the firm level, and it is difficult to conclude whether R&D activity, as opposed to budgets, really varies uniformly with firm size (23).

Figure 5-2.-Mean R&D Budgets for U.S. Dedicated Biotechnology Companies



SOURCE" Office of Technology Assessment, 1988

R&D Investment by Major U.S. Corporations

Based on the responses of the 53 major corporations responding to the OTA survey, OTA extrapolates that corporate investment in biotechnology R&D approximated $0.8 billion in 1987. These companies dedicate 20 percent of their total R&D expenditures to work specific to biotechnology. Responses ranged from annual R&D expenditures of $10,000 to $150 million. The mean annual biotechnology R&D budget for these companies was $11 million in 1987.

Ninety-six percent of the respondents indicated that at least some of this R&D was conducted in-house, but 83 percent indicated that some of the research is conducted by outside firms or universities. only four percent of the companies responded that none of their biotechnology R&D is conducted in-house. Thus, major corporations are building their in-house R&D capabilities while simultaneously complementing their research with outside sources of innovation. Collaboration between DBCs and major corporations is discussed later in this chapter.

Sources of Revenues

Gathering reliable information about actual sources of revenue in biotechnology companies is a difficult task, given the small number of products being marketed and the multiple sources of revenue available to firms. Numbers concerning products and sales can be deceiving. Plant agriculture seemingly leads in expected revenues because firms in this area are most probably also seed companies that rely on sales of seeds to fund their R&D. Diagnostics receive only about 10 percent of the overall R&D investment but account for about 55 percent of product sales (25). Revenues for diagnostics also currently lead therapeutics in sales due to the longer testing and approval process for therapeutics.

Besides being difficult to determine whether revenues have increased due to bigger research agreements or sales, it is often not entirely clear to what extent biotechnology products account for those sales being reported. Many companies are selling services or related products but have not yet sold a product directly derived from their biotechnology R&D. To date, no biotechnology company has been able to report a profit solely from the sale of biotechnology products (6).

Calgene is a case in point. In July 1986, Calgene forged agreements with Procter & Gamble and Philip Morris Co. and expanded its contracts with Campbell Soup and Rhone-Poulenc Agrochimie. It also acquired Agro Ingredients, a marketer of specialty plant oils and ingredients to industrial users and food processors. Calgene also signed an agreement with Ciba-Geigy. As a result of these new contracts, Calgene's product development revenues jumped 217 percent. Sales, which were zero the year before, totaled $882,000 as a result of the Agro Ingredients acquisition. Overall, Calgene's total revenues rose 465 percent to $2.1 million while their net loss narrowed to $329,000 from a previous year deficit (38).

Sales projections for the total industry are remarkably different, even one year into the future. One analyst predicts total industry product revenues to be about $75 million in 1987 (31). Another projects industry sales to approach $1 billion in 1987 (25). Presumably, the difference in projections can be attributed to what is being counted. For example, firms might include in their revenue totals the sale of non-biotechnology items or the sale of instrumentation, equipment, and supplies essential to biotechnology R&D.

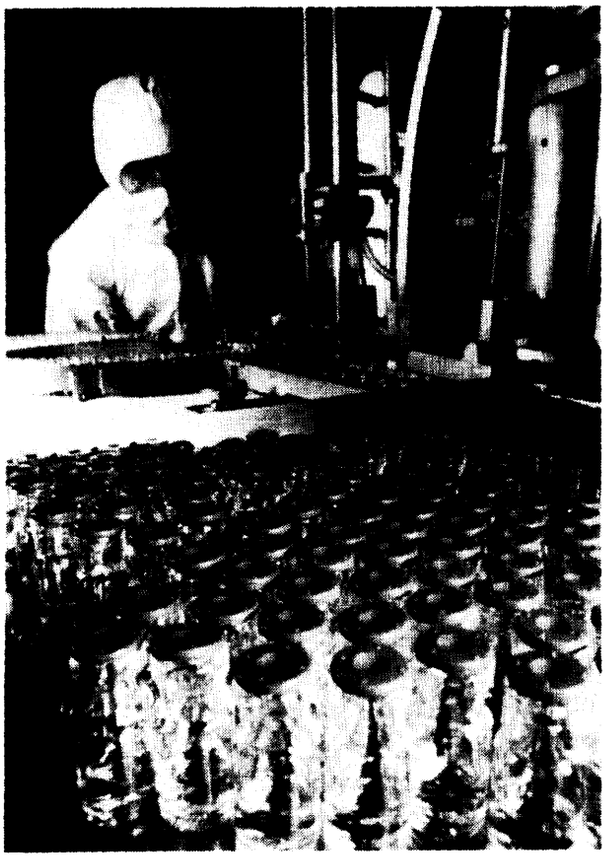


Photo credit: Amgen

Industrial biotechnology manufacturing facility.

In calculating the worth of commercial biotechnology, most financial analysts limit their estimates primarily to biotechnology-based human health care products. No good data are yet available on sales in other sectors. The current list of human therapeutics derived from biotechnology approved for sale is still very short: human insulin, human growth hormone, alpha-2 interferon, a monoclinal antibody for reversing kidney transplant rejection, a hepatitis B subunit vaccine, and tPA. Most biotechnology products so far have been monoclonal antibody diagnostic test kits and gene probes; there are almost **200** monoclinal-based diagnostic kits. Kit sales were **$150** million in **1985 (1).**

Again, aggregate revenue figures can be skewed by the performance of a few firms. In the first quarter of 1987, revenues increased sharply and losses narrowed at the leading four or five DBCs. Rises were related to either increased product sales or more extensive collaborative arrangements with other companies. In 1985, Genentech posted revenues of $90 million and Cetus posted at $57 million, but sales of products accounted for only $5.1 and $1 million, respectively. Most other companies were far behind in reported revenues (less than $10 million) (l).

Even one company can skew the market averages. For example, of 18 companies analyzed in one study, total industry losses in the first quarter of 1987 were $15.3 million, but $5.4 million of those losses belonged to Monoclinal Antibodies (33), Firms record net losses as they increase their operating costs associated with proprietary research and product development.

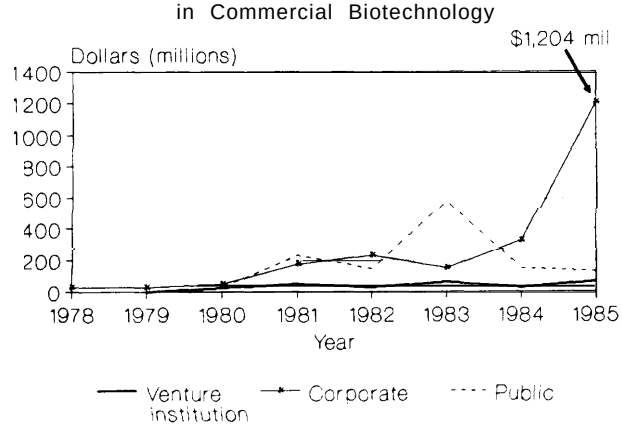
FINANCING OF DEDICATED BIOTECHNOLOGY COMPANIES

Investors have staked more than $3 billion on biotechnology between 1976 and 1986 (11). It is significant, however, that 80 percent of the dollars have been raised by 10 companies (2). Financing of biotechnology, in terms of DBCs, is quite concentrated.

Dedicated biotechnology companies have relied heavily on two funding mechanisms to finance their research and development: equity investments and joint ventures. Equity investments in DBCs maybe by individuals, small financial institutions, or corporations trying to gain a foothold in the technology. The corporate source of invest - ment is the fastest growing, rising steadily since 1983 (see figure 5-3).

The OTA survey of major corporations found that 83 percent invest in R&D conducted outside the company, either by DBCs, universities, or both. Corporations can invest in DBCs through equity or collaborative ventures. Equity investments in DBCs by large, established firms tend to be more passive, allowing the larger companies the opportunity to keep abreast of new developments. Collaborative ventures, on the other hand, usually

Figure 5-3.-Sources of Investment in Commercial Biotechnology



SOURCE: Adapted from James R Murray & Co Chicago, IL, 1986

involve R&D contracts or product licensing agreements, with the larger firm often handling the final development, approval, manufacturing, and marketing of the product. The DBC receives royalties from the sale of the product and usually retains patent rights.

The sources of funding for DBCs tend to depend on company maturity and size. An increasing number of firms are turning to public offerings and corporate equity investment as their source of funding as they mature, but venture capital and private equity placement are the mainstay of start-ups. Over time, the average company shows a decreased dependence on private investment, a doubling of U.S. equity holders, and a 10-fold increase in public stock offerings.

In addition, global markets have emerged, facilitating multi-source funding for the more secure firms. The bigger companies, such as Genentech and Cetus, are able to go overseas and access the Eurobond markets. In addition, the Japanese markets have opened.

Methods of financing differ from field to field. OTA found that DBCs focusing on therapeutics are more likely to be publicly held than any other type of firm (57 percent). Plant agriculture firms are less often publicly held (20.8 percent), and specialty chemical firms are least likely to have gone public (17.6 percent). In 1987, six agricultural biotechnology firms issued an initial public offering, indicating a shift toward public capital in the future as they require additional financing to bring their products to the market.

Levels of Financing

Ninety-four DBCs responded in full to OTA requests for financial information. To date, levels of financing are five times higher in public companies than in private companies. As would be expected, financing is much higher in large companies (average 267 employees), exceeding that in small companies (average 11 employees) by nearly 20-fold.

Of those companies reporting on levels of financing, 73 percent appeared at $1 million to $50 million. Responses ranged from $10,000 to $320 million. The median response was $8 million. Values are depicted in table 5-2. Companies involved in human therapeutics report more than twice the average level of financing of all companies. Companies developing biotechnology reagents reported the least amount of financing (about one-third the average).

Sources of Investment

According to one analyst, total private investment in U.S.-based biotechnology through the end of 1985 was over $4 billion (27). These figures break down to 65 percent equity purchase ($2.581 billion), 15 percent contract research and joint venture ($578 million), 14 percent research and development limited partnerships (RDLPs) ($558 million), 6 percent grants to universities ($260 million), and 1 percent product license agreements ($4 million).

Table 5-2.—Levels of Financing of Dedicated Biotechnology Companies

Level of financing ($ millions)	Percent of companies
0 to 0.1	5.3
0.1 to 0.5	6.4
0.5 to 1	7.4
1 to 5	25.5
5 to 10	13,8
10 to 50	34.0
50 to 100	5.3
100 plus	2.1

The range is $10,000 to $320,000,000.
The median value is $8,000,000.

SOURCE: Office of Technology Assessment, 1988.

The dominant investment area is health care applications: cancer therapeutics at 43 percent ($1.7 billion), other therapeutics at 19 percent ($773 million), and diagnostics at 13 percent ($519 million), totaling 75 percent of all investment. Agricultural applications, plant and animal, have received only 16 percent of the total investment, with crop or plant improvement receiving 12 percent, or $479 million, and agrichemicals receiving 4 percent, or $154 million (27).

Analysts are more likely to agree on levels of investment than they are sales. One estimates that $3.01 billion has been raised by dedicated biotechnology companies from 1980 to mid 1987. Included in this estimate is capital raised through major R&D partnerships and corporate equity investments, plus convertible debt (2). The breakdown per year is shown in table 5-3.

Venture Capital

Practically all DBCs in existence have been the recipients of some level of venture capital, either from institutional or corporate venture capitalists. Approximately $775 million of venture capital was invested in biotechnology between 1976 and 1986, but half of that investment occurred in 1981 and 1982. Since 1982, an average of ten new companies per year have been financed by venture capital (9). Venture funding is not as sensational as it was 5 years ago, but venture funds remained available until the stock market crash of October 1987 (2)10). Until October 1987, OTA found no evidence that venture capital funds for biotechnology had diminished. There is some evidence, however, that venture capitalists are more sophisticated, and therefore more conservative, in their investment choices (36).

Table 5-3.-Funds Raised by Dedicated Biotechnology Companies, 1980-87

Year	Capital raised (millions)
1980	$ 43
1981	140
1982	210
1983	542
1984	165
1985	249
1986	960
1987 (through July)	704
Total	$3,013

SOURCE: M. Kathy Behrens, personal communication, 1987.

OTA found that the percentage of DBCs relying primarily on venture capital for financing (over half of their source of funds) dropped from 25 percent in their first year of operation to 15 percent now. As companies grow, they maintain their emphasis on venture capital, but increase their use of private equity holdings, debentures, and bank borrowings (39). Cumulatively, venture and other fund managers have provided 12 percent or $500 million of total financing. Venture funds, by the nature of their providers, tend to be short term, and they have served early-stage financing needs of many companies. As the companies continue to mature, venture capitalists may be less willing to finance forward integration.

Research and Development Limited Partnerships (RDLPs)

An important funding mechanism for the biotechnology industries has been research and development limited partnerships (RDLPs). Almost 25 percent of the dollars collectively invested in biotechnology have come from RDLPs (22). RDLPs have been described by a Commerce Department official as being a management concept and an off-balance-sheet funding source (24). They allow individuals or companies to invest in a firm's R&D and write off the investment as an expense. Investors become limited partners and are entitled to royalty payments from future sales. The royalties are then taxed as capital gains. RDLPs provide start-up companies with a source of funding and transfer much of the risk of research and development of a new product to the limited partners who have acquired shares in the ventures. They are often seen as an alternative financing mechanism to venture capital companies, and provide a vital source of capital for start-up companies.

There are obvious advantages to both the sponsoring company and its limited partners. RDLPs allow a company to avoid early negative cash flow and permit the sponsor to use its capital for other purposes. This is true as long as it can generate enough cash to make royalty payments to the limited partners. Before the Tax Reform Act of

1986 (TRA) (Public Law 99-514), RDLPs were costly for the Federal Government. As an RDLP project became more financially successful, it represented forgone taxes to the government, because some of the royalty payments could be treated as long-term capital gains that were taxed at a lower rate than ordinary income. If the company produced a patentable product, all of the royalty payments to the limited partners could be treated as capital gains. In addition, RDLP limited partners could use the losses incurred to offset their personal income, allowing RDLP investors to reduce their total income and ultimately their bottom-line tax (22). Now losses can't be used to offset income from dividends and interest, rather they can only be used to offset passive gains from other partnership investments. With the passage of TRA, capital gains rates were phased out, which may have reduced the desirability of RDLPs because gains will now be taxed as ordinary income.

Attendees at a 1987 Industrial Biotechnology Association conference agreed that despite TRA–which does not allow deductions to be used to offset salary income—RDLPs remain as an important option in the funding of biotechnology R&D (14). Financial analysts agree that investors will need near-term cash flow to help offset the loss of several tax advantages. In addition, biotechnology companies will have to make important decisions when determining the size and the content of the RDLP.

Industry representatives told OTA that although the potential size in dollar amounts of RDLPs are quite large, they are not widely available. Larger companies closer to production and marketing of products tend to use them more than smaller companies. Recently, companies such as Cetus, Genentech, and California Biotechnology have begun to buy back the partnerships, taking a one-time charge against earnings (and a subsequent loss) to finance the buyouts (5). Repurchasing allows the DBC to purchase product rights licensed to the limited partners.

One of the more innovative approaches was recently offered by Cetus. Cetus wanted to form a European subsidiary for conducting clinical trials with Cetus' investigational drugs and use the trials with results of these studies for product registration. Funding for this subsidiary, EuroCetus, would be supplemented by a $100 million RDLP. The RDLP was available to the public in $10,000 units with a minimum cutoff of $50 million. The offering was terminated after $62 million was raised due to deteriorating market conditions. Some analysts think this failure reflects a greater skepticism of investors about the ability of DBCs to develop manufacturing and marketing capabilities competitive with those of experienced and powerful incumbents in downstream sectors (34).

It is not yet clear how well RDLPs will continue to serve the R&D financing needs of the industry. A study by Arthur Young found that RDLPs are significant sources of funds for DBCs working in diagnostics and agricultural biotechnology (39). Others have argued that the market for RDLPs has all but dried up (15). OTA found that only three DBCs relied on RDLPs for more than half their funding. It is likely that RDLPs will continue to be a substantial financial tool for a select few firms.

Public Stock Offerings

Increasingly, DBCs have gone public to raise additional funds. OTA identified 82 publicly held DBCs. Of the 60 firms typically followed by Wall Street, only 27 have been able to raise $4 million or more at one time between 1981 and 1986 (7).

Currently, equity financing in the public markets accounts for 36 percent of total financing. Genentech made a historic public offering in 1980, when its stock underwent the most rapid price increase in Wall Street's history, rising from $35 to $89 per share in the first 20 minutes of trading. Later that year, Cetus raised $110 million in an initial public offering. The bull market in biotechnology had begun and would peak in 1983 (25). More than $500 million was raised for biotechnology ventures between 1979 and 1983 through public venture capital. This was followed by a period of disillusionment as investors saw the reality of the lag time between investment and payoff. In 1986, the public financing market again opened its arms to biotechnology; companies raised $800 million in 1986 through public equity markets. In the first half of 1987, $357 million had been raised through public financing, with a

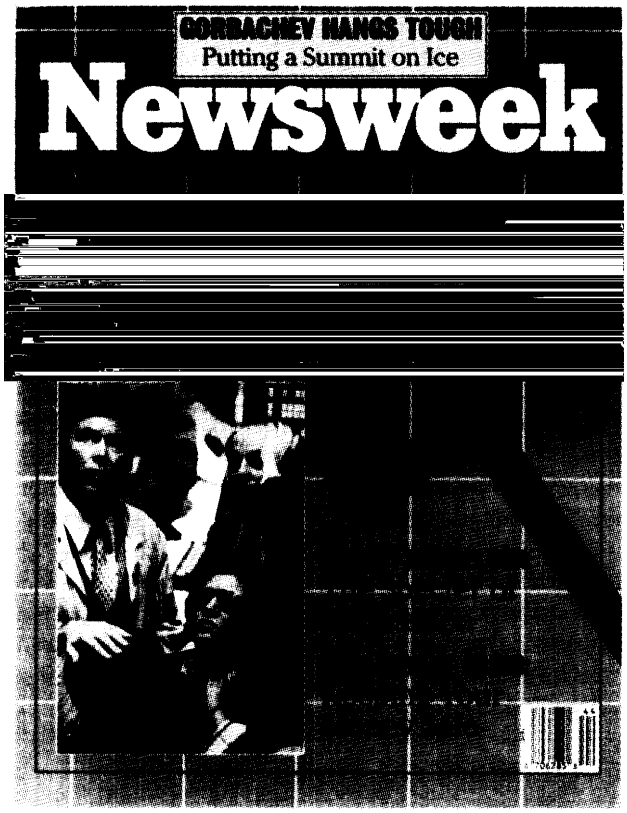


Photo credit: Newsweek, Nov. 2, 1937

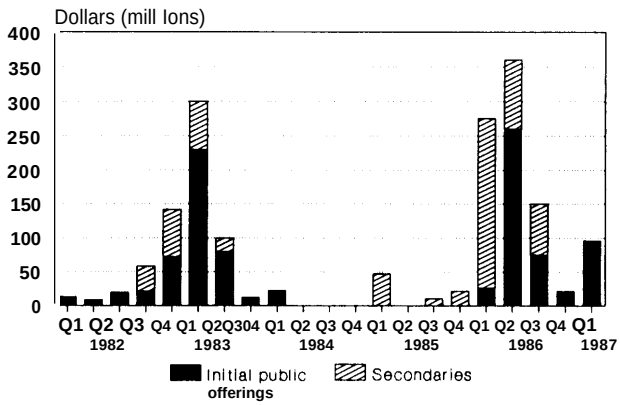
Media coverage of the 1987 stock market crash.

nearly equal amount still registered with the Securities and Exchange Commission (17). Biotechnology continues to boast the highest price to earnings ratio of any industry (21).

Companies focusing on human therapeutics tend to have the most public stock offerings, whereas companies involved in diagnostics, reagents, animal agriculture, and specialty chemicals have not gone public at the same rate. In 1987, however, five of the eight biotechnology companies making initial public offerings emphasized agriculture (17).

The market valuation for biotechnology prior to October 19, 1987 was $9 billion to $10 billion, excluding any participation by companies with diverse businesses, such as large drug or chemical companies. Three to four billion of the total market valuation went to Genentech alone. A new wave of second and third offerings swept Wall Street in 1986 and early 1987 as some of the more mature firms financed production scale-ups and

Figure 5-4.-Capital Raised in Public Offerings for Biotechnology



SOURCE: Adapted from Russell Ray; Alex, Brown & Sons, 1987.

clinical trials. Fifteen companies returned to the public market in 1986, raising another $390 million (15) (see figure 5-4).

In 1986, stocks appreciated in value 60 percent on average and in 1987, stock climbed another 50 percent in price (25). Approval of new products as well as the presence of takeover bidders, helped precipitate these gains. However, analysts estimate that the stock market crash of October 1987 devalued biotechnology companies by 40 to 60 percent on average, reducing total industry market capitalism to about $4.5 billion. Less flexible venture capital markets are likely to hurt biotechnology companies because of their capital intensive, cash consuming nature.

Despite the ability of biotechnology firms to raise capital, industry losses totaled $70 million in 1985 and approached $450 million in 1986. Even Genentech at $60 per share reported earnings of only $0.18 per share in 1986. Unlike other industrial sectors, biotechnology is dominated by a few firms: those able to withstand the consolidation that occurred between 1983 and 1986. Genentech has dominated in terms of industry revenues (30 percent), market capitalization (50 percent), and property, plant, and equipment invested in by the independent firms (30 percent) (25). In 1987, when Genentech initially failed to receive FDA approval for tissue-plasminogen activator (tPA), more than 14 million shares changed hands in a single day, with its stock plunging $11.50 a share to $36.75.

The financial activity surrounding biotechnology depends heavily on the successes and failures of the frontrunners.

The status of a company's product in the regulatory process at FDA will continue to affect stock activity as concerned investors take profits. When approval is granted expeditiously, the biotechnology group gains. If approval is delayed, stock prices slide. Meaningful operating profits will eventually be reliable indicators of a company's potential profitability, but for most, it is still an illusory concept.

Some analysts contend that Wall Street has created a false high through hype and overpromotion of "star" companies or products. In August 1986, Endotronics, a Minnesota-based biotechnology company, closed at its all-time high of $35.50 a share—130 times the company projected earnings. Eight months later it traded at 75 cents. In April 1987, it filed for bankruptcy. Critics and company stockholders contend that the company was fueled more by its promotion that its potential (31).

In addition, most public stock offerings have been by pharmaceutically based DBCs. Analysts are predicting more initial public offerings in the agricultural field (19). **Given the uncertain regulatory climate prevalent in crop and related microbial biotechnology, regulatory delays could have a significant effect on stock prices.**

Finally, the bull market that has existed since 1982 has served all biotechnology well. In a bear market, all but the top ten firms may have to face serious constrictions on the availability of capital through the public markets. As Richard Bock writes (4):

> With the first products just coming on the market, it's obvious that biotech shares are not selling due to earnings, sales, or the payout of dividends. . . . Financial fundamentals eventually will be important in weighing the worth of biotech companies, but they are not at this juncture. Analysis based on financial results alone could lower biotech stock prices and kill the goose that cloned the golden egg right in the middle of Wall Street.

Debt Financing

As companies mature, debt financing has become an available means of financing without giving up equity. A survey of firms conducted by Arthur Young found that 13 percent of the larger companies made use of bank borrowings as compared to 3 percent of the small firms (39). Genentech, Cetus, and Bio-Technology General have turned to convertible debt financing in the past year. DBCs may also raise capital on interest from short-term loans and industrial revenue bonds.

Debt financing is a sign of maturity for some firms. Because the company is obliged to service the debt almost immediately, it must be in the position of having products nearly ready for marketing. It is not a desirable method of financing for companies still requiring high cash flows for R&D.

COLLABORATIVE VENTURES IN BIOTECHNOLOGY

Despite the predominance of a few companies, more than 400 dedicated U.S. biotechnology companies remain in business operating at annual losses. Alliances between DBCs and between DBCs and large diversified corporations have become an important source of funds as alternative sources become more conservative. Wall Street relies on corporate alliances as one indication of the value of the firm (36).

Large, diversified corporations increasingly access the potential benefits of these technologies through their own in-house capabilities, or through strategic alliances and acquisitions of DBCs. In addition, large corporations are better able to withstand the prolonged approval and marketing processes inevitable in the final stages of product development, making alliances with DBCs to acquire technology.

These collaborative ventures, or strategic alliances, are associations between separate business entities that fall short of a formal merger, but that unite certain agreed upon resources of each entity for a limited purpose. They are an important means for technology transfer: few biotechnology companies can conduct all aspects of R&D from bench to market. Collaborative ventures may

involve acquisition, equity purchase, licensing agreements, marketing agreements, research contracts, or joint ventures.

Collaborative ventures have been essential in the development of industrial biotechnology for two reasons:

- They allow small biotechnology-intensive firms to overcome resource limitations which may prevent them from developing or marketing a product themselves. Smaller firms seem to be seeking near-term cash flow to bankroll their projected growth and gain access to the marketing capabilities of large corporations.
- They allow established companies less costly methods to develop expertise in areas in which they lack in-house capability. Benefits for the large firms in such arrangements are primarily access to cutting edge research and highly trained scientists.

Collaborative ventures can create a protective environment for the external commercialization of a DBC's research. The DBC can avoid the problem of having to expose its innovation to a wide range of prospective licensees and can mitigate the appropriability problem by having the licensee pay for some portion of the R&D costs up front. Through equity investments and joint ventures, the DBC can prevent the established firm from opportunistically appropriating rents on the technology through contractual safeguards. Manufacturing and marketing agreements allow the DBC to disclose far fewer scientific or technical details.

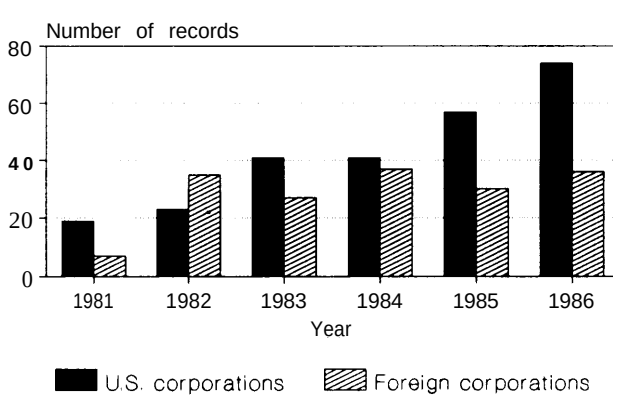
To stay independent, most DBCs are strengthening their alliances with major corporations. Few DBCs have succeeded in becoming full-fledged, fully integrated pharmaceutical or chemical houses, though many aim to do so. Corporate investments in public companies provided the bulk of new capital for biotechnology (approximately $128 million) in the first nine months of 1985 (7). Cumulatively, corporations have provided $2.2 billion or 56 percent of funds for biotechnology through 1985 (27). All indications seem to be that the percentage will increase.

An important difference exists between the collaborative activities of biotechnology firms and the semiconductor firms that emerged in the early stages of that industry. The semiconductor firms of the 1950s did not resort to licensing and joint ventures to commercialize their technology as have biotechnology firms (34). This may be due to the fact that the semiconductor industry was selling largely to the Department of Defense, a market that had much lower marketing and product introduction costs than the markets for new biotechnology products (26).

An OTA review of 552 industrial collaborations between 1981 and 1986 found a steady rise in the number of collaborative ventures. Collecting complete information on the number and nature of collaborations in commercial biotechnology is complicated by the proprietary nature of such information. Companies that are publicly held usually document their collaborative agreements with other industrial firms in their mandatory 10K filings. However, most of the new biotechnology ventures are privately held firms that are under no such requirements. Figure 5-5 illustrates collaborative ventures between U.S. biotechnology companies and between U.S. and foreign companies between 1981 and 1986.

Collaborations are not always between large corporations and small companies, although that is the norm. There are about 800 firms active in bio-

Figure 5-5.-Collaborative Ventures of U.S. Biotechnology Companies, 1981-86



SOURCE: Office of Technology Assessment, 1988.

technology worldwide, with between 1,000 and 1,500 joint venture agreements among them, although it is not known how many of these are strictly research collaborations. An estimated three-quarters of the agreements are between large and small firms and less than one-quarter of the agreements are international collaborations (32),

Research to date suggests that big firms are mostly gaining licenses to market products through these agreements, but not licenses to the technology to manufacture products. Contrary to the belief of many analysts who think that the trend toward such joint venture agreements is on the wane, the number of these agreements is increasing, or at least remaining level (34).

In addition, although there is an increase in the number of collaborative ventures per year, no one type of action (e.g., equity purchase, licensing agreement) has increased. This is true for both U.S./U.S. agreements and U.S./foreign agreements. Table 5-4 displays the number of each type of agreement between US. firms and between U.S. and foreign firms between **1981** and 1986. Most records of agreements specify the type of action; where this was not the case, unspecified collaborative ventures were categorized as joint ventures.

Two companies serve as examples of the level of activity generated by strategic alliances--Amgen (pharmaceuticals) and Calgene (agriculture). Amgen's March 1986 secondary offering prospectus listed eight prominent corporate partners: Johnson & Johnson, Kirin Brewery, Abbott Laboratories, SmithKline Beckman, Eastman Kodak, Arbor Acres Farm, Upjohn, and Texaco. Calgene has teamed up with Procter& Gamble, Rhone-Poulenc, Agrochimie, Kemira Oy, Roussel-Uclaf, Ciba-Geigy, Campbell Soup, and Philip Morris (20). One interesting aspect of these alliances is that in both cases, the DBC has managed to negotiate separate agreements with proven competitors.

On the corporate side, many companies have used major licensing strategies to move into biotechnology. Kodak signed nine deals in 1984 with biotechnology start-ups, Kodak has signed research contracts with DBCs to work in areas as diverse as cancer drugs and genetically engineered indigo dye for blue jean manufacturers. Johnson & Johnson owns equity stakes in 11 biotechnology companies. American Cyanamid signed more than 15 licensing agreements with DBCs over the past five years (12).

Most U.S./U.S. collaborative ventures on record are in the area of human therapeutics (29 percent) or clinical diagnostics (25 percent). Most DBCs are working in those areas and the costs of forward integration are high, making joint agreements desirable. Collaborative ventures in therapeutics are largely responsible for overall increases in collaborative actions over the years. It is clearly the area of the most intense business activity.

In one study (34), R&D contracts and R&D marketing agreements accounted for all the collaborative ventures in plant biotechnology. The lack of straight marketing, supply, or technology transfer agreements in the study sample suggests that DBCs in plant biotechnology are not carrying out R&D on their own. Of the 48 plant agriculture product developments listed by Paine Webber, biotechnology companies were acting without a commercial partner in only 8 cases (30). Some assert

Table 5-4.—Collaborations Between U.S. Firms and Between U.S. and Foreign Firms, 1981-86

	U.S./U.S. (U.S./Foreign)						
Type	1981	1982	1983	1984	1985	1986	Total
Joint venture[a]	5 (3)	6 (22)	27 (8)	14 (17)	29 (11)	23 (16)	104 (77)
Equity purchase	8 (1)	7 (6)	3 (1)	8 (2)	9 (2)	13 (4)	48 (16)
Licensing agreement	4 (1)	4 (2)	4 (5)	6 (5)	8 (5)	4 (1)	30 (19)
Marketing agreement	4 (1)	O (6)	2 (4)	5 (4)	8 (5)	13(7)	32(27)
Research contract	1 (2)	6 (3)	7 (1)	6 (3)	6 (5)	15 (4)	41 (18)
Totals	22 (8)	23 (39)	43 (19)	39 (31)	60 (28)	68 (32)	255 (157)

[a]Unspecified collaborations were categorized as joint ventures.

SOURCE:Office of Technology Assessment, 1988.

that biotechnology in plant agriculture is not as commercially advanced as in other sectors, and that in order to fund long-term R&D, agriculture biotechnology companies have had to turn to corporate sponsors. In addition, small companies may rely on large companies for their marketing network in order to reach more farmers (13).

U.S./Foreign Collaborative Ventures

As DBCs near development and production, collaborations with foreign firms provide them access to international markets. While this strengthens the financial position of the DBC, there is some concern that the enhancement of biotechnology in foreign firms reduces the future rent-earning potential of U.S. biotechnology (37). One protection against such a loss is rigorous protection and enforcement of intellectual property and patent rights in the United States.

As shown in figure 5-5, while the number of collaborative ventures between biotechnology firms has steadily increased, the bulk of the activity has been between U.S. companies rather than with foreign firms. U.S. biotechnology companies have only two-thirds as many joint actions with foreign corporations as with U.S. corporations. U.S. private investors accounted for 90 percent (or $3.7 billion) of all international biotechnology investment dollars as of 1985 (27). OTA did not collect data on collaborative ventures between foreign firms. However, many collaborations do not involve U.S. firms and biotechnology-based industries are developing in Western Europe, Japan, and South America.

OTA found that 41 percent of U.S./foreign collaborative ventures occurred in human therapeutics, 13 percent in diagnostics, and 9 percent in plant or animal agriculture.

Japanese corporations lead all other countries in the number of collaborations arranged with U.S. biotechnology companies (see table 5-5), but do not lead in amount of private dollars invested. Figure 5-6 displays the cumulative investments of private investors by the United States, and six specific Western European countries. Swiss, Swedish, and West German corporations have been active collaborators with U.S. firms. In fact, collaborations between U.S. and Japanese firms have dropped and leveled off in the past 3 years, whereas collaborations with companies from an increasing number of European countries has increased, suggesting "internationalization" of commerce in biotechnology.

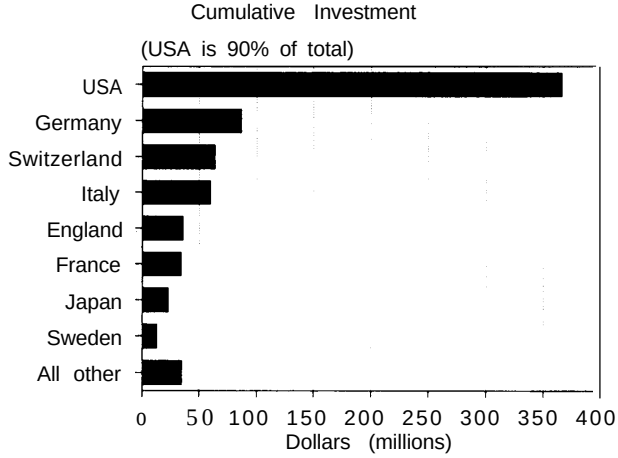
Table 5=5.—Collaborative Ventures Between U.S. Dedicated Biotechnology Companies and Foreign Corporations, 1981-86

	Year						
Country	1981	1982	1983	1984	1985	1986	Total
Belgium	0	0	0	0	0	2	2
Canada	0	0	0	1	0	0	1
China	0	0	1	0	0	1	2
Denmark	0	1	1	0	0	2	4
France	1	1	0	1	1	2	6
Italy	0	1	0	2	3	1	7
Japan	6	22	12	15	8	8	71
Malaysia	0	1	0	0	0	0	1
Netherlands	0	0	1	1	0	3	5
Sweden	0	2	0	3	5	4	14
Switzerland	1	3	2	9	5	9	29
United Kingdom	0	1	0	2	4	2	9
West Germany	0	3	0	3	6	2	14
Totals	8	35	17	37	32	36	165

SOURCE: Office of Technology Assessment, 1968,

U.S. firms have collaborated with Japanese firms more than any other foreign firms (8). Of the 71 U.S./Japanese collaborations identified between 1981 and 1986, 39 large Japanese corporations, and 43 American firms were involved. The collaborations are overwhelmingly in the application of biotechnology to areas of human health care.

Figure 5-6.-Country of Private Investor



SOURCE: Adapted from James R. Murray & Co., Chicago, IL, 1986.

The Vice President for investment banking at Nomura Securities International claims that while most of Japan's biotechnological activity takes place within its established industry, the Japanese pharmaceutical industry has been the last industrial entity to get involved **(16).** This could explain Japan's heavy involvement with U.S. biotechnology companies. These collaborations provide a number of business opportunities for American firms, including research funding, sponsorship of Japanese clinical trials, and marketing and distribution of products within Japan. Of the collaborations analyzed, Japanese companies are less likely to engage in equity arrangements than U.S. companies collaborating together. In addition, Japanese firms are more likely to arrange a licensing agreement with a U.S. firm and are twice as likely to form a marketing agreement than would be found in U.S./U.S. collaborations. These agreements tend to be smaller dollar-wise, explaining the discrepancy between number of agreements and dollars invested (28). A listing of U.S./Japanese collaborative agreements between **1981** and 1986 appears in table 5-6,

Table 5-6.–U.S./Japanese Joint Actions in Biotechnology, 1981.86

U.S. company	Japanese company	Action	Product
1981			
Biogen	Green Cross	J	**vaccine**
Collaborative Research	Green Cross	E	**urokinase**
Enzo	Kinto	J	**enzymes**
Genentech	Toray Industries	M,R	**interferon**
Hybritech	Mitsubishi	L	**anti-lGE kit**
1982			
Bioassay Systems	Toray Industries	**M**	bioassay
Biogen	Fujisawa	**J**	tPA
Biogen	Meiji Seika	**J**	antibiotic
Biogen	Shionogi	**J**	HSA
Biogen	Teijin	J,M	Factor Vlll
Biogen	Yamanouchi	J	anti-inflammatory
Biotech Research Lab	Fujizoki	E,J	MAB
Collaborative Research	Green Cross	M	B-interferon
Enzo	Meiji Seika	L,M	HCG Test
Genentech	Mitsubishi Chemical	J	tPA
Genentech	Takeda	?	B-interferon
Genex	Green Cross	J	HSA
Genex	Mitsui Toatsu	J	urokinase
Genex	Yamanouchi	J	tPA
Hana Biologics	Fujizoki	E,J	diagnostics
Hybritech	Green Cross	J	immunoglobulins
Hybritech	Teijin	J	MABs
Interferon Sciences	Green Cross	J	interferon
Interferon Sciences	Green Cross	M	G-interferon
Monotech Labs	Eken	R	diagnostics
Technic lone	Fujizoki	L	diagnostics
1983			
Biogen	Shionogi	**L**	**IL-2**
Biogen	Suntory	**J**	**TNF**
Centocor	Toray Industries	J,L	**diagnostics**
Collaborative Research	Green Cross	L	**interferon**
Genentech	Daiichi Seiyaku	L	**G-interferon**
Genentech	Mitsubishi	J	**tPA**
Genex	Yoshitomi	J	**IL-2**
Innovax Labs	Snow Brand Milk	L	**?**
Integrated Genetics	Toyobo	J,M	**tPA**
Repligen	C. Itoh	E,M	**proteins**
University Genetics	Nissho Iwai	M	**?**
Xenogen	Mitsui Toatsu	J	**feed additives**

(continued on next page)

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Table 5-6.—U.S./Japanese Joint Actions in Biotechnology, 1981=86—Continued

U.S. company	Japanese company	Action	Product
1984			
Amgen	Kirin Brewery	J	erythropoietin
Atlantic Antibodies	Oriental Yeast	M	antisera
Battelle Development	Mitsubishi	J	?
Endotronics	Mitsui	M	instrumentation
Genentech	Fujisawa	L,M	lymphotoxin
Genetics institute	Chugai	J,M	erythropoietin
Integrated Genetics	Fujirebio	J	DNA probe
Human Antibody Tech	Kyowa Hakko	J	diagnostics
Hybritech	Toyo Soda	J,M	diagnostics
Lymphomed	Fujisawa	M	anti-pneumonia
Molecular Biosystems	Funakoshi	M	microsphere
NPI	Sumitomo	J	foods
Plant Genetics	Kirin Brewery	J,E	seed
Queue Systems	Shin Meiwa Industry	M,L	Bt products
Ventrex	Funakoshi	M	MAB
1985			
Applied Biosystems	Japan Scientific	J	reagents
Biogen	Sumitomo	J	colony stimulating factor
Calgene	Kuraray	J	agrichemicals
Collagen	Lederle Japan	L	implants
Genentech	Mitsubishi	L	vaccines
Molecular Genetics	Shionogi	M	veterinary
Unigene Labs	Toyo Soda	L	immunization
1986			
Bioreactor Technologies	C.Itoh	M	bioreactors
Cyanotech	Daikyo Oil Co.	E	?
Diagnostic Products	Dainippon Ink & Chemical	M	immune-diagnostics
Endotronics	Nippon Chem. Indus.	J	hGH
Genzyme	Nagase & Co.	J	amylase
Ingene	Mitsubishi	J	sweeteners
Liposome Technology	Takeda	R	?
Zymogenetics	Teijin Ltd.	J	blood factors

KEY: E = equity purchase, J = joint venture, L = licensing agreement, M = marketing agreement, R = research contract

SOURCE: Office of Technology Assessment, 1988.

SUMMARY AND CONCLUSIONS

U.S. commercial biotechnology remains healthy and competitive. OTA identified 403 U.S. companies dedicated to biotechnology (DBCs) and 70 large, established U.S. corporations with significant investments in biotechnology. Combined, U.S. industry devoted about $1.5 to $2.0 billion to biotechnology R&D in 1987.

The shakeout predicted to occur among dedicated biotechnology companies has not occurred, although the frontrunners have become stronger. Financing is concentrated heavily in a few firms. Methods of financing for DBCs continue to evolve and are heavily dependent on the conditions of financial markets. Despite industry losses and until the stock market decline of October 1987, commercial biotechnology has been able to raise capital. Financial activity depends heavily on the successes and failures of the frontrunners. Meaningful operating profits are not yet reliable indicators of a company's potential profitability. Thus far, many companies have been able to attract financing based on potential alone, but it appears that safe and reliable products and wise marketing strategies will eventually be the safety net for survival. Increasingly, large established companies are playing a critical role in innovative research as well as in the final stages of commercialization of biotechnology products and processes; they are more able to bear the development, regulatory, and marketing costs of commercialization. A few

DBCs have successfully used the benefits of RDLPs to raise capital.

Human health care, primarily therapeutics and diagnostics, continues to be the focus of most biotechnology R&D investments, both by DBCs and major corporations. The sectoral breakdown of the industry has remained fairly constant since OTA last reported on commercial biotechnology in 1984, with chemicals and agriculture ranking second and third as the fields of application of industrial biotechnology. There is evidence, however, that agriculture, plant biotechnology in particular, is a growing field and has begun to attract the attention of the public financial markets. A strong support industry of companies producing reagents, equipment, and customized processes in such areas as cell culture continues to grow and has been successful in generating revenues. Revenues based on products directly derived from biotechnology R&D remain scarce. No reliable data are available on total industry sales of biotechnology products.

Strategic alliances between large corporations and DBCs are on the rise and have become an indicator to Wall Street of the value of a firm. Although 95 percent of the large corporations investing in biotechnology have in-house capabilities, 83 percent also rely on outside sources of innovation either DBCs **or universities There appears to be a mutual benefit to these collaborations, and there is no indication that a takeover of biotechnology's potential by corporate interests is imminent.**

While collaborations between U.S. firms are on the rise, collaborations between U.S. firms and foreign firms seems to be declining. There were twice as many collaborations between U.S. companies as between U.S. and foreign companies in 1986. Of those foreign firms collaborating with U.S. companies, the breakdown is more diverse, with Japan playing less of a role and other countries becoming more active.

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