
DataWatch

Health Care Innovation: Progress Report And Focus On Biotechnology

by J. Leighton Read and Kenneth B. Lee Jr.

Abstract: Funding for biomedical research has shifted from government to the private sector. One reason is rapid expansion in the number and strength of U.S. biotechnology companies, which collectively spend more than \$6 billion a year on biomedical research. Most of these companies are not yet profitable and therefore depend on flows of capital from private investors, Wall Street, and large pharmaceutical company collaborations. Investment in the new drugs, devices, and vaccines in this pipeline is sensitive to signals emanating from the debate on health care reform, suggesting that new federal policy will have a major impact on steering the type of innovation to emerge in the future.

Health care reform has heightened interest in measures of medical innovation and raised the stakes for those involved in the business of creating and selling new products. Here we update a number of measures of innovation published in a previous DataWatch.¹ We also provide an overview of a uniquely American industry now playing a central role in health care innovation: more than 1,200 companies primarily engaged in biotechnology research and development.

Participants in this young industry are increasingly making their voices heard in the debate over health care reform; thus, it is important for policymakers to understand the factors that are driving innovation in this arena. We contrast the biotechnology industry with the traditional pharmaceutical companies and describe the sources of financing for biotechnology companies, what they have accomplished, and their work in progress.

National Investment In Research And Development

Recent figures from the National Science Foundation estimate that U.S. research and development (R&D) expenditures by all sponsors totaled \$161 billion in 1993.² In constant dollars this is only a 1 percent increase since 1988. The federal government provides 43 percent of these funds but

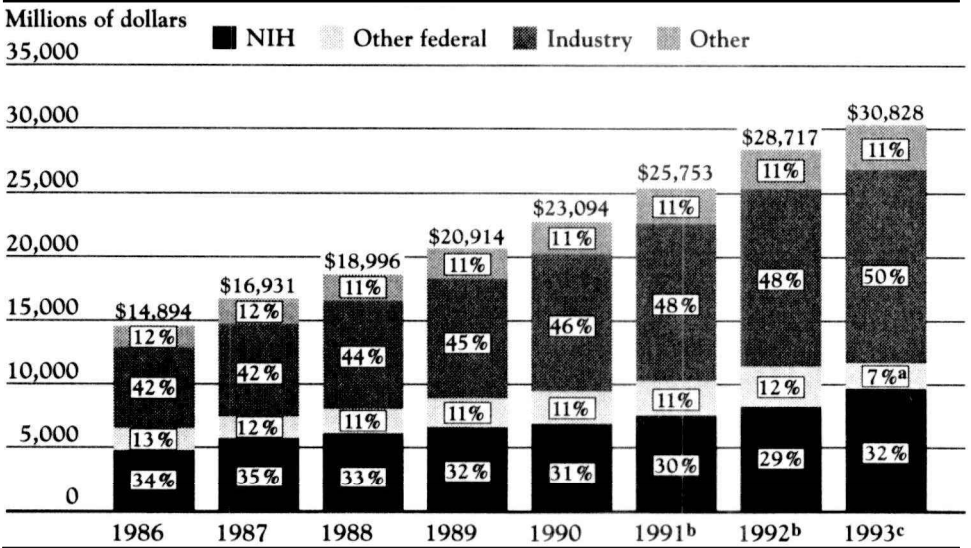
Leighton Read is chairman and chief executive officer of Aviron, a research-stage company applying genetic engineering to create new vaccines for infectious diseases, and has served as a founder, senior executive, director, or active investor in a number of biotechnology companies. Ken Lee is national director, Life Sciences Industry Services, at Ernst and Young, one of the leading international accounting and professional services firms.

performs only 11 percent of the R&D work. Industry contributes 51 percent of the money and performs 70 percent of the R&D, with universities and other not-for-profit institutions making up the difference.³

The National Institutes of Health (NIH) provides more finely grained estimates according to sources of funds and where this work is performed (Exhibit 1). Since our previous report in 1988, there has been a 50 percent increase in current-dollar health R&D spending to more than \$30 billion. This represents a constant-dollar increase of only 22 percent, however.⁴ The proportion of these expenditures borne by industry has continued to climb and is now believed to account for more than half of all health R&D in the United States. In addition to the \$9.7 billion 1993 NIH appropriation, federal agencies committing more than \$100 million per year to health-related R&D include several Public Health Service agencies (the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Agency for Health Care Policy and Research), as well as the Departments of Agriculture, Defense, Energy, and Veterans Affairs and the National Aeronautics and Space Administration.

The distribution of effort among entities that perform federally sponsored health research has changed little from the mid-1980s, with roughly half of

Exhibit 1
National Support For Health Research And Development (R&D) By Source,
Millions Of Dollars, 1986-1993



Source: NJH Data Book, 1993 (Washington: DHHS, 1993).

^a Decrease in 1993 reflects the transfer of research efforts from the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) to the National Institutes of Health (NIH) in 1993.

^b Estimated.

^c Projected.

the funds going to universities and the remainder divided between federal institutions and other entities. The universities' share of NIH dollars is slightly higher, about 60 percent. The number of persons in NIH-sponsored research training programs has been fairly level over the past decade, averaging between 12,000 and 13,000.⁵

Since 1988 the large pharmaceutical companies have spent more on R&D than the annual NIH appropriation. The Pharmaceutical Manufacturers Association (PMA)—now the Pharmaceutical Research and Manufacturers of America (PhRMA)—reported that its members, “the research-based pharmaceutical industry,” spent \$12.6 billion on R&D in 1993, up 13.5 percent from the previous year.⁶ PhRMA expects this year's figure to be \$13.8 billion, up only 9 percent—the first year of less than double-digit growth since 1977.⁷ (About 82 percent of this total is spent in the United States.)

Despite the growth in R&D spending, the number of new drugs approved by the FDA each year has remained in a range of twenty to thirty for the past decade. The time required for FDA review has dropped 10-15 percent since the mid-1980s to an average of 26.5 months in 1993.⁸ Of the twenty-five approvals last year, three were biotechnology products and one was a vaccine. These biologics enjoyed a shorter average review time of 19.8 months. The Prescription Drug User Fee Act of 1992 was intended to further accelerate approvals, by allowing the FDA to collect fees from applicants to support a 600-person increase in its professional staff.

The U.S. Biotechnology Industry

Since the founding of pioneering companies, such as Genentech in 1976, Biogen in 1978, and Centocor in 1979, a new U.S. industry has defined itself in terms of its R&D focus, the technology employed, and an extraordinary system of funding projects still years away from commercialization.

The accounting firm of Ernst and Young has tracked financial performance of biotechnology companies for several years and has compiled a series of reports on the industry.⁹ These provide an overview for comparison with the large pharmaceutical companies. For the purposes of this analysis, a “universe” of biotechnology companies includes 1,272 companies, of which 235 are publicly held. These companies have a mean age of thirteen years and an average of seventy-six employees. There was a bulge in the pattern of company formation in the mid-1980s, but growth continues with more than 100 companies organized in the past two years.

Exhibit 2 presents aggregate financial data to contrast the fifteen largest pharmaceutical companies with the biotechnology universe for which Ernst and Young has assembled data. Global sales by United States-based

Exhibit 2

Aggregate Financial Data On Large Biotechnology And Pharmaceutical Companies. Based On 1992 Annual Reports

	Sales ^a	Sales per employee ^b	R&D ^a	R&D per employee ^b	R&D as percent of sales	Net income ^a	Employees	Market capital ^a
Biotech industry ^c	\$ 7,000	\$ 72	\$ 5,700	\$ 59	81%	(\$3,600)	97,000	\$ 45,000
Individual firms								
Amgen	1,051	447	182	77	17	358	2,350	4,960
Chiron	112	60	143	77	128	(103)	1,870	2,040
Genzyme	180	121	91	61	51	(31)	1,490	930
Biogen	122	349	60	171	49	38	350	1,030
Genentech	391	168	279	120	71	21	2,335	4,970
Pharmaceutical industry ^d	\$114,000	\$184	\$11,722	\$ 19	10%	\$16,000	618,000	\$261,000
Individual firms								
Johnson & Johnson	13,753	163	1,127	13	8	1,030	84,400	27,200
Bristol-Myers Squibb	11,156	212	1,083	21	10	1,962	52,600	29,910
Merck	9,663	252	1,112	29	11	2,447	36,200	40,630
Schering-Plough	4,056	192	522	25	13	720	21,100	13,920
Syntex	2,085	178	374	32	18	472	11,700	4,030

Source: Ernst and Young, Biotech 94 (San Francisco: Ernst and Young, 1993).

^a Millions of dollars.

^b Thousands of dollars.

^c Aggregate of publicly traded companies.

^d Aggregate of top fifteen companies.

biotech companies totaled \$7 billion in 1992, compared with \$114 billion for the large pharmaceutical companies, yet R&D expenditures were almost half of those of the big companies. This works out to \$59,000 of R&D per employee in biotech companies, compared with \$19,000 in large pharmaceutical companies. R&D expenses as a percentage of sales average more than 80 percent in the biotechnology industry, in contrast to PhRMA's estimate of just over 18 percent for 1994. A similar contrast is seen between large and small medical device companies: According to the Health Care Technology Institute, companies with less than \$5 million in sales spent 77.5 percent of sales on R&D, while for those with more than \$100 million in sales, the figure was 4.5 percent.¹⁰ Spending by these small companies is not compatible with profitability in an industrial steady-state. It indicates that the current period is one of evolution in the organization and financing of biomedical research.

Although large pharmaceutical companies have been consistently profitable, individual companies experience major variations in their rate of sales and profit growth, according to the life cycle of major products. In contrast, all but a few biotechnology companies are incurring net losses, year after

year, and are funding operations either through the sale of stock or via technology deals with the major pharmaceutical companies. According to investment analysts who follow the industry closely, approximately half of biotechnology companies have less than two years of cash reserve, even though many of these companies need to increase spending to move their products into clinical development.¹¹

Exhibit 3 illustrates the range of products still in development at the largest biotechnology companies. Another survey of seventy-nine companies tabulated 745 publicly disclosed products, of which 250 are in human clinical trials for more than 365 medical indications.¹² Exhibit 4 shows the biotechnology products either approved in the United States or with applications pending at the FDA.

It is important to note that not all of the U.S. biotechnology R&D effort

Exhibit 3
Number Of Products In Development By Top Public Biotechnology Companies, 1993

Indication	Phase I	Phase II	Phase III	NDA/PLA ^a	Approved
AIDS ^b	6	13	2	0	1
Allergy	1	1	0	0	0
Autoimmune	2	2	0	0	1
Blood disorders	2	0	0	1	5
Bone disorders	3	1	0	0	0
Cancer					
Unspecified types	20	33	14	0	3
Generalized therapies	3	12	5	5	4
Cardiovascular disease					
Disorders	4	6	3	2	2
Drug classes	0	2	1	3	1
Diabetes	1	6	0	0	0
Genetic inherited deficiencies	0	1	0	3	1
Hormone deficiencies	0	1	0	0	1
Infectious diseases	5	19	9	2	1
Inflammatory disorders	3	12	0	0	5
Kidney disease	1	1	2	0	0
Multiple sclerosis	2	2	2	0	1
Neurological disorders	10	3	4	0	0
Ophthalmic	1	2	0	0	1
Respiratory disorders	4	4	0	0	0
Skin disorders	4	5	0	0	0
Wound healing	2	12	3	0	0
Total	74	138	45	16	27

Source: Data from Smith Barney Shearson in Ernst and Young, *Biotech 94* (San Francisco: Ernst and Young, 1993).

^a NDA is new drug application; PLA is product license application (for biologics).

^b Acquired immunodeficiency syndrome.

Exhibit 4
Biotechnology Products Approved Or Pending At The FDA, 1993

Product	Indication	Company	Marketing partner	Year entered market
Erythropoietin	Anemia associated with renal failure, AIDS, cancer	Amgen	Johnson & Johnson	1989
G-CSF	Adjunct to chemotherapy	Amgen		1991
Alpha interferon	Cancer, genital warts, hepatitis	Biogen, Genentech	Schering-Plough, Merck, Roche	1986
Hepatitis B vaccine	Prevention	Biogen, Chiron	Merck, SmithKline Beecham	1986
Hepatitis B antigens	Diagnosis	Biogen	Abbott, Ortho Diagnostics	1987
IL-2	Renal cell cancer	Chiron		1992
Beta interferon	Multiple sclerosis	Chiron	Berlex	1993
Indium, 111 labeled antibody	Cancer imaging	Cytogen	Knoll	1992
PEG-adenosine deaminase	Immune deficiency	Enzon		1990
Human insulin	Type 1 diabetes	Genentech	Eli Lilly	1982
Human growth hormone	Deficiency	Genentech		1985
t-PA	Myocardial infarction, pulmonary embolism	Genentech		1990
Gamma interferon	Chronic granulomatous disease	Genentech		1990
Factor VIII	Hemophilia	Genentech, Genetics Institute	Bayer AC, Baxter	1993
DNAse	Cystic fibrosis	Genentech		1993
Aglycerase	Gaucher disease	Genzyme		1991
Hyaluronic acid	Ophthalmic surgery	Genzyme		1991
GM-CSF	Bone marrow transplant	Immunex		1991
CMV immune globulin	Prevention in organ transplants	MedImmune		1990
Antibody-ricin conjugate	Organ transplants	Xoma	Johnson & Johnson	Pending
NR1-LU-10 antibody	Lung cancer imaging	NeoRx		Pending

Exhibit 4**Biotechnology Products Approved Or Pending At The FDA, 1993 (cont.)**

Product	Indication	Company	Marketing partner	Year entered market
PEG-L asparaginase	Leukemia	Enzon		Pending
Monoclonal antibody	Colorectal cancer imaging	Immunomedics	Adria	Pending
TRAx CD4 test kit	HIV testing	T Cell Sciences		Pending
RSV immune globulin	Prevention in children	MedImmune	American Cyanamid	Pending
RGD peptide	Diabetic foot ulcers	Telios		Pending
Polyclonal antibodies	Idiopathic thrombocytopenic purpura (ITP)	Univax Biologics		Pending
IIb/IIIa monoclonal antibody	Angioplasty	Centocor	Eli Lilly	Pending

Sources: M. Ho and B.K. Liu, *Biotechnology Industry Quarterly* (14 February 1994); and Smith Barney Shearson, *Biotechnology Industry Product chart* (12 January 1994).

is taking place in young biotechnology companies. In a recent study of eight large pharmaceutical companies, it was determined that a third of their in-house research projects were based on modem molecular biology.¹³

Financing Biotechnology

Exhibit 5 shows selected financial highlights of biotechnology companies in different market segments. The money to start and sustain biotechnology research typically comes from different sources, depending on its stage of development. So-called seed financing is almost always provided by venture capitalists. Typically, the investment decision is made by the general partner of a limited partnership that represents the investment interests of several life insurance companies, pension funds, and university endowments. These venture capitalists are usually quite experienced in evaluating specific technologies and markets and often become involved in the management of new companies by serving on the board of directors. Seed financing ranges in size from a few hundred thousand to one or two million dollars.

As a fledgling company proves itself by assembling its technical and management team and achieves milestones in the research lab, it can raise additional capital. The next investment round may be from \$2 million to \$10 million, enough to last for one to two years as the company continues

Exhibit 5
Selected Financial Highlights, By Biotechnology Market Segment, Average Dollars
(Thousands)

Market	Diagnostic		Therapeutic		Supplier		All companies ^a	
	Current year	Percent change from prior year	Current year	Percent change from prior year	Current year	Percent change from prior year	Current year	Percent change from prior year
Productsales	\$11,157	11%	\$19,197	48%	\$38,629	12%	\$18,824	35%
Contract/ collaborative research	1,241	29	4,586	52	1,979	37	3,552	48
Total revenues	14,068	18	28,654	47	42,572	16	26,099	38
cost of product sales	5,312	22	6,805	44	19,024	19	7,786	32
Research and development	3,518	5	16,806	26	4,806	0	12,448	24
Selling, general, and administrative	6,406	30	10,568	27	16,959	15	9,997	28
Total costs and expenses	15,417	19	34,689	29	41,539	15	30,676	27
Net income (loss)	(1,722)	16	(7,912)	(3)	(351)	(16)	(6,063)	0
Cash and cash equivalents	3,377	(9)	10,193	(28)	3,358	(3)	8,003	(24)
Short-term investments	4,743	54	27,816	36	4,009	95	20,164	36
Total assets	24,473	20	75,388	23	40,449	11	60,012	23
Total stockholder's equity	19,039	34	57,491	29	23,406	27	44,863	30

Source: Ernst and Young, Biotech 94 (San Francisco: Ernst and Young, 1993).

Note: Financial averages from 235 publicly held biotechnology companies in the following market segments: therapeutics, 41 percent; diagnostics, 27 percent; supplier, 15 percent; chemical, environmental, and services, 8 percent; and agricultural, 8 percent.

^a Totals include agricultural and chemical, environmental, and services categories, which are not shown.

to expand its R&D effort. If the company is thought to be making good progress, investors will be willing to pay a higher price per share at each successive round. The ownership interest of early investors is diluted by the sale of new stock, but the value of their original holdings increases as long as the share price keeps going up. Recombinant Capital, a consulting firm that tracks investments in biotechnology, calculates that \$723 million was raised by private companies in 1993; this amount is similar to that of the previous two years.¹⁴

One milestone that can be of critical importance in attracting funds is the consummation of a research collaboration with a major pharmaceutical company. Not only is this a source of additional cash, but investors attach

importance to these deals as validation that the biotechnology company is on the right track and has technology of value.

Biotech/pharmaceutical company deals come in many varieties, but it is common to see large companies pay the full cost of research on specific biotechnology projects for which they will receive marketing rights. In addition to payment for work done, the smaller company earns cash payments as the product moves through preclinical and human trials, as well as royalties if there are eventual sales. As much as biotech investors like to see this corporate endorsement, they are also wary of companies that give away too much in the way of marketing rights. This is because the greatest slice of pharmaceutical profit margins historically is earned by the entity that controls manufacturing and marketing. Hoping to get the best of both worlds, biotechnology companies try to retain the right to make and sell the results of their innovative work for certain medical indications or in specified geographic territories or medical practice settings (hospital versus doctor's office). Ernst and Young estimates that payments from large pharmaceutical companies to U.S. biotechnology companies have recently been exceeding \$2 billion per year, if both contract R&D and equity investments are considered.

Individual venture capital partnerships rarely contribute more than \$5 million to a single company. At some point, typically after one to three private investment rounds, most biotechnology companies must access the public securities market. The Initial Public Offering (IPO) is a highly regulated process, after which a company assumes many new obligations to report financial and business results to its new shareholders and the public. Biotechnology IPOs typically have yielded \$10 million to \$25 million in capital, although a handful have been in the \$100 million range. The IPO also represents a watershed for early investors, who will achieve some degree of "liquidity"—a mechanism for selling some or all of the shares acquired in the private rounds.

Once company's shares are publicly traded, the company can raise additional money in follow-on offerings if there is investor appetite for its shares. For biotechnology, this is a highly seasonal phenomenon, with periods of intense investment interspersed with months in which there is very little financing activity. The biotechnology financing "window" appears to be influenced by the overall economic environment as well as by industry-specific events.

It is widely believed in the industry that health care reform has slowed investment in biotechnology, because of the uncertainty that President Clinton's early proposals cast over the entire health care economy. More specifically, discussion of formal or informal price controls in the form of a breakthrough drug committee has been blamed for the loss in investor

confidence because this form of oversight would reduce the financial upside for the most innovative (and risky) forms of R&D.

There has been a decline in money obtained from public markets, but publicly traded biotech companies have been resourceful in tapping a novel financing mechanism: going back to private investors who were willing to buy stock with restricted resale privileges at a 10-20 percent discount to the public common stock price. According to Alex. Brown and Sons, a Baltimore firm, the prices of many biotechnology stocks fell 30-40 percent in 1993, before recovering somewhat in the fourth quarter.¹⁵ Some of this was undoubtedly due to disappointing news about some key biotechnology products in development, but large pharmaceutical stock prices also lost 10-20 percent of their value in 1993, suggesting that the market capitalization of the entire industry was negatively affected by the climate of health care reform.

Industry spokespersons argue that lower stock prices mean that the cost of capital is higher and that biotechnology companies therefore will scale back their growth, reducing R&D investment in important areas such as acquired immunodeficiency syndrome (AIDS) and cancer. These linkages between cost of capital and research effort are difficult to prove, but the logic is quite plausible given the industry's need for \$25 billion in public risk capital over the next ten years.¹⁶ This period of health reform comes at a critical time in the evolution of the biotechnology industry. As the industry matures toward a stage of greater self-sufficiency (funding R&D through sales), there will be an inevitable period of consolidation, with mergers, acquisitions, and even business failures.

From discussions with many industry leaders, we find that they clearly understand that high prices and generous reimbursement should not reward innovation for the sake of novelty alone. Their concern is that current reform proposals do not allow for clear economic signals that reward innovators on the basis of the value they bring, measured in terms of improved health outcomes and averted health care expenditures. Policy must be carefully considered so that the health care system does not give mediocre returns for high-risk projects that are successful in producing high-value products.

NOTES

1. J.L. Read and P.M. Campbell, "Health Care Innovation: A Progress Report," *Health Affairs* (Summer 1988): 174-185.
2. National Science Board, *Science and Engineering Indicators*, 1993 (Washington: U.S. Government Printing Office, 1993), 1.
3. National Science Foundation, *Science and Technology Pocket Data Book* (Washington: NSF, 1992).
4. National Institutes of Health, *NIH Data Book*, 1993 (Washington: U.S. Department of Health and Human Services, Public Health Service, 1993); and Patricia E. McKinley, Office of Strategic Planning and Evaluation, National Institutes of Health, personal communication, 25 February 1994.
5. *Ibid.*
6. Pharmaceutical Manufacturers Association, *Facts at a Glance* (Washington: PMA, 1993).
7. PMA press release, 13 January 1994.
8. PMA press briefing on new drug approvals in 1993, January 1994.
9. Ernst and Young, *Biotech 94: Long-Term Value, Short-Term Hurdles*, Ernst and Young's Eighth Annual Report on the Biotechnology Industry (San Francisco: Ernst and Young, 1993).
10. Health Care Technology Institute, *Variation in Research and Development Spending within the Medical Technology Industry* (Washington: HCTI, June 1993).
11. M. Ho and B.K. Liu, *Biotechnology Industry Quarterly* (14 February 1994).
12. Smith Barney Shearson, *Biotechnology industry Product Chart* (12 January 1994).
13. The Boston Consulting Group, *The Changing Environment for U.S. Pharmaceuticals* (Boston: The Boston Consulting Group, April 1993).
14. Mark Edwards, managing director, Recombinant Capital, San Francisco, California, personal communication, 12 January 1994.
15. Jim Scopa and Jim Shapiro, Alex. Brown and Sons, personal communication, 1 February 1994.
16. Jeffrey Casdin, Oppenheimer and Company, as quoted in *FDC Reports*, "The Pink Sheet," 9 August 1993.