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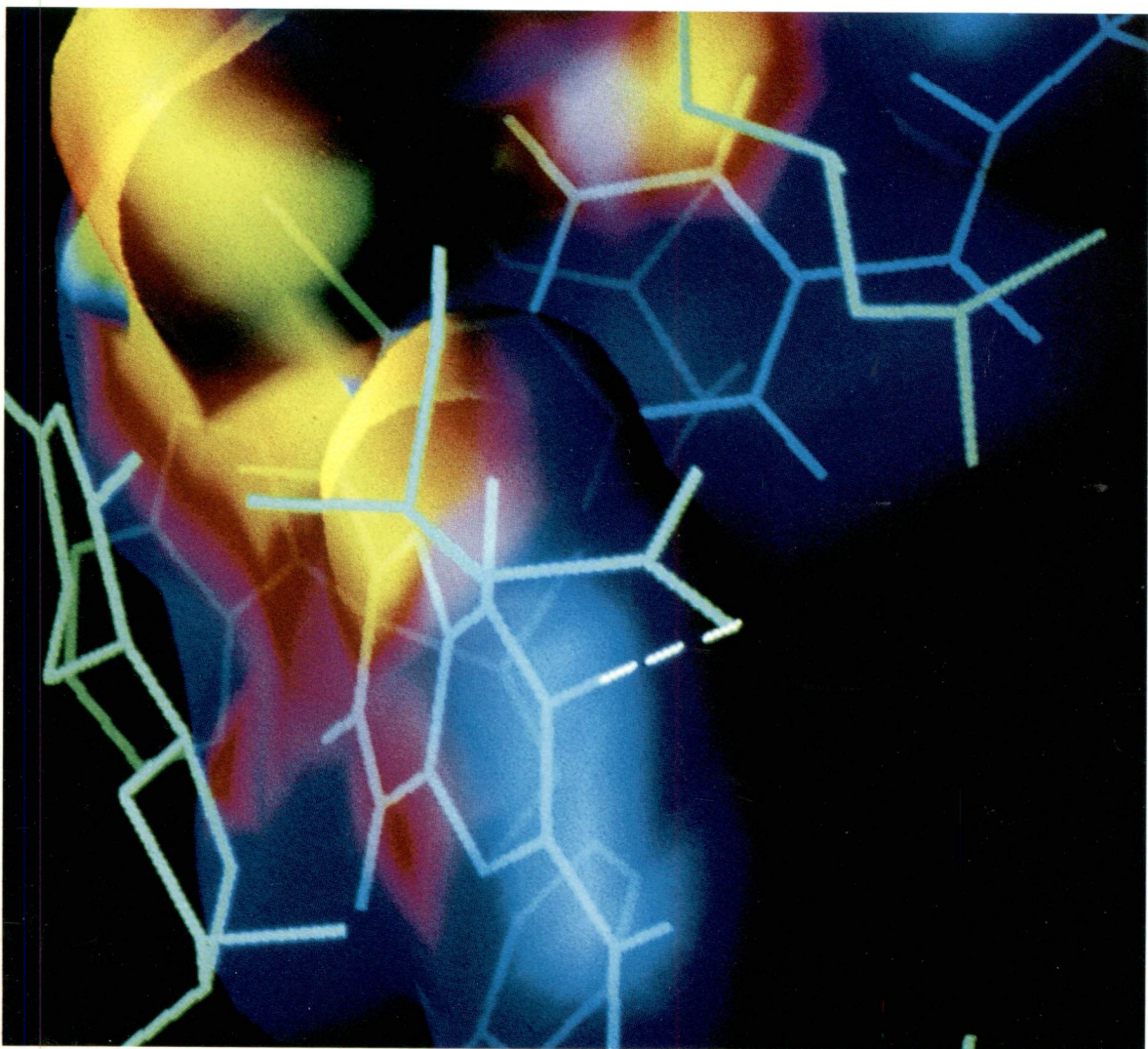
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Biotech 91: A Changing Environment

*Fifth annual survey of business and financial issues
in America's most promising industry*

G. Steven Burrill and Kenneth B. Lee, Jr. of Ernst & Young



Cover: Detail of the structure of a quinazoline-based anti-cancer lead compound as it is bound to the active site of the enzyme thymidylate synthetase (TS). Designing drugs by determining and then matching the three-dimensional structure and electric field of a functional target receptor or protein is an emerging strategy in the fight against disease. TS is a prime target for anti-cancer drugs since it provides the sole *de novo* path to the synthesis of dTMP, which is required for DNA synthesis as cells divide. The structure shown was determined by X-ray crystallography in the laboratory of Dr. Robert Stroud at the University of California—San Francisco, and colored according to the electric potential surrounding it within the target site. The computer graphics were created by Julie Newdoll using software written at the UCSF Computer Graphics Lab.

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A Changing Environment

The 1990s are roaring in with unprecedented merger and acquisition activity, increased volatility in the financial markets, and continuing regulatory confusion and delay. Pricing pressures on health-care products and special interests' opposition to biotechnology in the environment and the food chain are gathering force. The dream of creating vertically integrated new Mercks serving broad markets is giving way to a realistic appreciation of the opportunities awaiting innovative companies with strong corporate alliances in niche markets.

Nothing in this developing industry remains the same for long. What is certain is continuing uncertainty. Change is the underlying dynamic.

Biotechnology itself is bringing about monumental change. Its powerful new products for diagnosing and treating human ills, developing superior crops, making food production more efficient, and reversing the ravages of pollutants are changing the way we work, the environment in which we exist, and the quality of our lives. But just as biotechnology is transforming its environment, so, too, is the environment transforming biotechnology.

The major changes of the past year, while anticipated by some, were unforeseen by many. Naive and inflated expectations may have contributed to the element of surprise. Yet certain of the year's events were simply the first of their kind, unforeseeable by their very nature. An industry that is still inventing itself must expect the unexpected.

In most of the year's watershed events, top-tier companies have been the key players. These are the companies with products on or close to the market, the companies most embroiled in the regulatory processes, and the companies the stock analysts follow. Their experience provides both a paradigm and a cautionary tale.

The Big Deal

Hoffmann-La Roche's acquisition of a majority stake in Genentech took many by surprise, but in

retrospect, it has an inescapable logic. Genentech faced an integral dilemma of a technology company coming of age—the conflict between funding new product development versus Wall Street's demand for quarterly earnings' growth.

The company's \$400 million in sales, impressive as it was, had fallen far short of its investors' and management's expectations that Genentech would be a billion-dollar company by 1990. At the same time, Genentech's management was committed to reinvesting 40 percent of the company's revenues into product development. Under the circumstances, earnings could not be expected to rise dramatically. As a result, the company's valuation and ability to raise capital in the financial markets deteriorated.

Genentech's solution? Strike a deal with a wealthy partner on terms that would allow it to survive as an independent culture. The transaction brings the financial resources to support Genentech's R&D and the organizational resources to advance the worldwide commercialization of its products.

By the same stroke, the deal helps solve a challenge facing Hoffmann-La Roche as well as other pharmaceutical giants. These companies' massive marketing machines need a continuous flow of new, competitive products — more than they can readily generate with traditional methods of discovery within their traditional corporate cultures. Genentech's technologies provide Roche with efficient avenues to product development and synergies to complement Roche's own research. It is a classic win-win situation.

Yet, the acquisition of Genentech, the powerhouse that developed four of the first six biopharmaceutical products to be commercialized, raised the inevitable question, "If they can't make it, who can?" There is much in the experience of the industry to argue that companies will make it in a variety of different ways—some of which we probably do not now foresee. Genentech is not so much a case of a company "not making it," as it is of a company

making a choice about how it will continue to grow, accomplish its mission, create value, and satisfy its shareholders.

Consolidation is not unique to biotechnology companies. Among established pharmaceutical companies, we have recently seen the creation of SmithKline Beecham, Marion Merrell Dow, Bristol-Myers Squibb, American Home Products/A. H. Robbins, and Rhône-Poulenc/Rorer.

Companies will make it in a variety of different ways

Biotechnology companies also are acquiring or merging with other biotech companies, witness Genzyme/Integrated Genetics (discussed in our interview with CEO Henri Termeer), Xoma/Ingene, and Quidel/Monoclonal Antibodies. Even more aggressively, Chiron (in a joint venture with Ciba-Geigy) made a run at Canadian vaccine producer Connaught Laboratories—although in the end it was outbid by Institut Merieux. In our interview with Edward Penhoet, Chiron's CEO characterizes its pursuit of a more developed company as a "forward-integration strategy" in an industry where Chiron's technology had driven fundamental change. In yet another segment where Chiron is carving a franchise, Chiron and Ortho Diagnostic Systems jointly purchased Du Pont's blood-screening labs to lock up the number two position in blood screening worldwide. As other major companies consolidate or refocus their strategies, there should be more opportunities for smaller companies, like Chiron, to enlarge their market share by acquiring divested divisions.

Many companies are likely to be on one side or another of a consolidation scenario as the 1990s progress. Our survey indicates that approximately 40 percent of biotechnology companies expect to be acquired in the next five years, and

nearly half expect to acquire other companies. In an industry that is dynamically changing, many strategies for creating value continue to emerge.

The Big Products

The product gates opened a little wider this year, a significant change itself. But equally important is what companies are learning about the opportunities and obstacles that await their products as they move from the laboratories to the marketplace. In the course of three days this past summer, the Food and Drug Administration (FDA) released a string of momentous rulings that highlight both the fulfillment and the impediments companies encounter on the road to commercialization.

The FDA's approval of alpha interferon for the treatment of hepatitis C (which afflicts a half-million Americans alone) was a significant boost for its developer, Biogen, and marketing licensee, Schering-Plough. The following day, results published in *The New England Journal of Medicine* indicated that their product, known as Intron-A, is even more effective in curing hepatitis B, the ninth leading cause of death worldwide. The news precipitated a run on Biogen's stock, and simultaneously raised the "stock" of interferon and biopharmaceuticals in general. The great hope in the early days of the industry, interferon became a great disappointment to many investors when it failed to be the "magic bullet." These latest developments affirm that a powerful biologic can never be counted out.

The success of Cetus's polymerase chain-reaction technology, which enables researchers to amplify bits of genetic material into large quantities of analyzable material, was never in doubt. In 1989, *Science* magazine named it the "Molecule of the Year," and hailed it as a research, diagnostic, and forensic tool. Yet the risks and unpredictabilities in product development were underscored when Cetus's kidney cancer therapy, interleukin 2 (IL-2), failed to obtain approval from the FDA's Biological

Response Modifiers Advisory Committee. A day later, the committee postponed approval of Immunex's granulocyte macrophage colony stimulating factor (GM-CSF) for the treatment of bone marrow transplant failure. Both companies were asked to supply additional data on the subgroups of patients who will benefit from the therapies. The assumptions on which the companies had based their clinical trials proved to be less than firm. The committee did not accept assertions that new products receive preferential consideration on the basis that they are "the only treatment options available." It asked for more information than the companies had known would be needed. At the eleventh hour, the rules changed.

The regulatory influence pervades all aspects of the industry

In the days immediately following the announcements, the share prices of both companies plummeted. As we go to press, Immunex's GM-CSF is expected to bounce back quickly under expedited review, although approved applications are expected to be confined to a narrow band. However, data on the efficacy of Cetus's IL-2 in treating kidney cancer are less compelling given the drug's severe side effects. Because the uncertainties surrounding the approval of products cause such enormous swings in the fortunes of companies, the regulatory influence pervades all aspects of this industry.

Pricing and reimbursement issues further confound the situation, even after a product is commercialized. Amgen's erythropoietin, for example, is approaching a blockbusting \$200 million in sales in its first year. But its pricing, approved at the outset by the Health Care Financing Administration,

has come under scrutiny by the Department of Health and Human Services and Congress. This investigation may be an early salvo in what could become a major war for biotechnology companies as they drive to recoup their product investments and generate the profits to support continuing new development.

On the diagnostic front, the approval of an assay for the cystic fibrosis gene will enable individuals who carry the gene to determine if it has been transmitted to a fetus. While this is a boon for families who wish to make an informed choice about the continuation of a pregnancy, it raises questions of personal values and public policy. And now that the National Institutes of Health also has cleared the first two tests in humans of gene therapies (for the treatment of metastatic melanoma and adenosine deaminase deficiency), the ethical issues posed by our ability to manipulate life at the genetic level multiply.

Public concern over the uses to which we put genetic technology are not limited to human diagnostics and therapeutics. The battle over bovine somatotropin (BST) makes it clear that the genetic engineering applied to food and the farm still has far to go in winning public acceptance. A growth hormone that increases cows' milk production, BST should have been expected to draw opposition. Using as basic and emotionally laden a product as milk for biotechnology's first foray into foods helped fuel the critics' fires. Opponents of BST in Wisconsin and Minnesota raised the banner of food safety to bolster what was really more of an argument about the economic effects BST would have on small farmers.

Still, a lower-profile bioengineered substance was approved for use in food processing—recombinant rennin, an enzyme used in the production of cheese. And, as a harbinger of gains to come, BioTechnica International is field testing the first genetically engineered corn.

On yet another front, bioremediation technologies received a welcome boost when the state of Texas authorized the use of microorganisms supplied by Alpha Environmental to eat up an oil spill off the coast of Galveston. Given the growing societal focus on environmental issues and increased awareness of environmental threats, the potential contributions of environmental biotechnology may be far greater than were earlier anticipated. However, as current applications in bioremediation employ only naturally occurring organisms, the prospect of releasing genetically modified bacteria into the environment is a threshold, and potentially a minefield, that the industry still has to cross.

The Windows of Opportunity

The run on biotechnology health-care stocks following the Roche/Genentech announcement jump-started the market indexes for biotech stocks on an upward trajectory. The transaction refocused investors' minds on the values inherent in biotechnology companies—values that are being affirmed by the continuing product stories.

The top-tier companies especially benefitted from the spotlight. Financial markets generally treated these companies very well this year, providing ready financing. To a degree, the buoyancy of the leading companies gave a lift to other biotechnology stocks. As Jonathan MacQuitty (GenPharm International) observes in one of our CEO roundtables, "The share prices of biotech stocks move up and down largely together, despite the fact that the companies have very different targets."

Yet the windows of financing opportunity can shut quickly. Regulatory rejections can reverse an upward trend in biotechnology stocks, and economic developments and political hot spots can drive down stocks in general.

Not all companies were able to capitalize on the excitement over biotechnology stocks in the public markets. The windows did not open quite as

wide for many smaller public and privately held companies. Financing was not as forthcoming for companies far upstream in product development and companies addressing markets outside of outside human health care.

The stratification of the industry is growing more pronounced

After more than a decade of experience with biotechnology companies, investors have learned to apply a finer screen. Approximately 70 percent of the one billion dollars in public financings last year went to the top-tier companies. Perhaps this is as it should be, as approximately 80 percent of the PLAs and new drugs entering clinical trials were products developed by these firms. The stratification of the industry—a phenomenon to be expected in any industry's development—is growing more pronounced.

Companies that benefitted from last year's window have been able to complete a wide array of public financial offerings—among them, initial public offerings (in the first fairly-large receptive market since 1987), as well as secondary offerings, preferred and convertible stocks, unit rights offerings ("SWORDS"), and various forms of debt issues. Biotech companies are displaying pragmatism and flexibility in getting capital—using the strategy outlined in our interview with Cytogen's CEO, George Ebright, to "raise your capital when the market has an appetite to give it to you."

Genzyme proved the point in an exemplary series of financial transactions over a six-month period. The company rolled up an R&D limited partnership for its orphan drug, Ceredase (for the treatment of Gaucher's disease) which had received FDA approval as a treatment protocol. It issued another limited partnership for a new drug in development. It also issued a secondary offering for

Genzyme and an initial public offering for shares in a subsidiary. Finally, it divested a joint-venture business. In our interview with Genzyme's CEO, Henri Termeer, he explains his philosophy that, "Building companies means using the opportunities that the marketplace offers to build an internally working economy."

Strategic alliances continue to be both the industry's second major source of capital, and an important mechanism for accessing manufacturing and marketing/distribution capabilities, regulatory expertise, and complementary technologies. According to our survey, while biotech companies, on average, have three strategic alliances, the top-tier companies, on average, participate in nine—partnering with both larger, traditional companies and other biotechnology firms. These relationships are clearly an underpinning of their success. Strategic alliances are also a barrier against the wave of acquisitions that some observers predict in the wake of Roche/Genentech. They tie up the real assets of these companies—their intellectual property, and patent and marketing rights—within a web of relationships.

Strategic alliances are clearly an underpinning of success

As companies at every stratum in the industry work to expand their alliance base, competition for alliances grows more heated. But the competition in this arena cuts two ways. The large, established companies in the traditional industries also vie among themselves to lock in access to promising technology. The same dynamics that might drive them to acquire a biotech firm, more often impel them to form alliances with biotech companies around products or technologies that will help to revitalize the large companies' product lines

and enlarge their market penetration. Michael Riordan, CEO of early-stage Gilead Sciences, notes in one of our roundtables that pharmaceutical companies are cutting deals with biotech companies earlier and earlier in the product development cycle, all the way back to discovery research. Two months after we spoke with Dr. Riordan, Gilead signed its first major strategic relationship, a \$20 million alliance with Glaxo.

Like consolidation, partnering is not limited to big company/small company pairings. The week after Gilead signed with Glaxo, Du Pont reorganized its pharmaceutical operation into a new company which it will own jointly with Merck. Last year, Merck formed a development and marketing joint venture with Johnson & Johnson, which went on to acquire the over-the-counter products subsidiary of ICI America (Imperial Chemical Industries). One might well ask, "If Merck can't make it alone, can anyone?" The answer is, "No." Partnering is fast becoming an essential strategy for companies of every size to maintain and maximize the value of their market franchises.

Yet change takes its course here, too. Partnerships can unravel. Collagen and Bristol-Myers Squibb dissolved a development agreement for applications of Collagen's Transforming Growth Factor beta type 2 to immune-mediated diseases. Eli Lilly terminated its license to develop California Biotechnology's technology for nasal delivery of insulin. As corporate marriages are evaluated over time, there naturally are divorces.

The Big Issues

Biotechnology is a research- and capital-intensive industry, grounded in intellectual property, and regulated by government. It is emerging into a highly competitive domestic and international marketplace at a time when the rules in both arenas are changing. Of necessity, the industry is concerned about questions of economic and regulatory policy.

Roche's acquisition of Genentech, Chugai's of Gen-Probe, and Fujisawa's of Lymphomed raise the fear that we may be seeding an important industry in the United States only to see its long-term values reaped by foreign interests. Or, to put it another way, will biotechnology go the way of microchips?

U.S. corporations are at a significant disadvantage in pursuing acquisitions of capital-intensive companies that are building real value for the long term. Genentech, in fact, tried to identify a U.S. acquirer before taking its proposition overseas. U.S. companies unfortunately have to account for the "goodwill" (the differential between the purchase price of an acquired company and its book value) and amortize it through their earnings stream. This practice penalizes companies in the earnings-driven Wall Street environment.

European and Japanese companies do not have to account for acquisition premiums in this way. And a number of European pharmaceutical and chemical companies (including Hoffmann-La Roche) are closely-held, giving their management and directors greater latitude than their U.S. counterparts to make capital commitments that have long-term horizons. In general, foreign companies and investors take a far longer-term view of investments in new technologies than Wall Street's focus on quarterly earnings allows in the United States.

Yet it is inevitable that foreign multinationals will compete with U.S. multinationals to access developing technology on a worldwide basis. Interestingly, three-quarters of our survey respondents indicate they would be equally receptive to a foreign or domestic acquisition. Their premise is elementary: "A deal is a deal."

Are American interests at risk in foreign acquisition of U.S. biotech companies and in foreign access to U.S. technology through international strategic alliances? The answer is unclear. The concept of national industries is changing.

The leading pharmaceutical companies—Merck, Hoffmann-La Roche, SmithKline Beecham, Glaxo, Hoechst, etc.—are more international than national, with operations, markets, and investors all around the world. And as Jonathan MacQuitty, CEO of Dutch- and American-owned GenPharm International comments in one of our roundtables, "If a technology is going out of the country, it will be offset by situations where it comes back in."

Are American interests at risk in foreign acquisition of U.S. biotech companies?

It is clear that many U.S. biotech companies may have to join forces with foreign companies to access the global markets for their products, whether through combinations or alliances. Survey participants report that one-third of their alliances now are with foreign companies—motivated by their need to access capital, increase marketing reach, and enlist expertise in foreign regulatory frameworks. Foreign markets already account for 20 percent of the sales of U.S. biotech companies, a proportion which survey respondents expect will grow to 33 percent within five years.

The global playing field is ultimately the only game in town. However, the financial markets' obsession with short-term profits, the obstacles and delays in our regulatory processes, and our inability to protect intellectual property from foreign encroachment combine to tilt the field against U.S. companies. U.S. companies also are burdened with higher interest rates than their foreign competitors. And the taxation of capital gains and the loss of the R&D tax credit discourage investment with long-term horizons.

Capital gains relief has been high on the industry's public-policy agenda ever since the capital-gains differential was eliminated by the Tax Reform Act of 1986. In our interview with Senator Albert Gore, he concurs on the desirability of "a well-focused capital gains measure, which is targeted on long-term investment." It remains to be seen whether responsible arguments for policies that promote capital formation to support emerging industries will be heard in the clamor of the budget debate.

Undoubtedly the highest item on the industry's Washington agenda is relief from the regulatory obstacles that impede the efficient and orderly flow of biotechnology's products to the marketplace. First and foremost is the slow turning of the gears in the Food and Drug Administration. Sixty percent of our survey respondents would support user fees at the FDA if the proceeds would be used to expedite drug/device approvals.

Henry Miller, Director of the FDA's new Office of Biotechnology, asserts in our Washington roundtable. "Approval times [for biotech products] have averaged only about half of the mean 32 months required for non-biotech products." This is true—but the approval cycle is the last stage of a drawn-out process of testing, filing, and documentation, followed by more testing, filing, and documentation.

*Regulatory obstacles impede
the efficient and orderly flow
of products*

The Pharmaceutical Manufacturers Association found that the 23 new drugs approved by the FDA in 1989 underwent an average of six years and four months of government-monitored human testing, followed by another three years of administrative review. In addition, most drugs require one or two years of pre-clinical studies before they are tested in human beings. This adds up to 10 to 12 years for an average drug to move from the lab to the patient. This torturous road is hard on cash-poor companies with little experience in negotiating the regulatory thickets.

Delays and inconsistencies in the issuance of patents, and the unevenness of the patent playing field worldwide, add to the uncertainties that biotechnology companies face. A recent U.S. General Accounting Office study found that biotechnology applications wait three to four years for approval, versus a waiting period for all types of patents of only 18 months. New technology is exposed long before it is protected, and many companies become deeply invested in a product before intellectual property rights are made clear.

Even when patents issue, there can remain critical chinks in the patent armor. With proteins, for example, the numerous patents that can cover the various aspects of products and processes lay the groundwork for much dispute. U.S. patents do not protect companies from certain end-runs around patents by foreign companies. Also, U.S. companies are at a distinct disadvantage in competing in many foreign countries because of the "first-to-file" convention that is prevalent elsewhere.

U.S. firms are particularly stymied by the impenetrability of the Japanese framework to outsiders. To illustrate the point, in 1990, Texas Instruments was the first U.S. company to receive a patent for an integrated circuit in Japan—after waiting for 17 years. Competitiveness with Japan is likely to become an increasingly important issue, as the Japanese government has designated a drive to dominate the biotechnology industry by the year 2000 as its number one industrial priority.

But also relevant to the industry's patent problems is the way the industry itself responds to patent disarray. When patent claims come into conflict, companies often prefer to litigate rather than work out a cross-licensing agreement. However, the communal bloodletting that transpires in courtroom battles frequently does companies more harm than good. In one of our roundtables, Louis Fernandez, formerly chairman of Monsanto and a veteran of the patent wars in the chemical industry, reflects, "The patent litigation that's going on is a sign of the industry's immaturity. After you get into a couple of those fights, spend a lot of money, end up at the mercy of some judge who doesn't really understand your arguments, and lose or half-lose, you see the sense of [cross-licensing]."

Changing the ground rules by which companies have constructed strategies

Two legislative initiatives are attempting to resolve certain regulatory and patent issues that have emerged. But they also create new problems by changing the ground rules by which a number of companies have constructed long-term strategies. Legislation just passed in the House of Representatives and now pending in the Senate would limit the exclusivity provisions of the Orphan Drug Act in the future. Another bill would extend process patent protection to biotechnology products and close some of the international loopholes. With various vested interests at stake, the industry is divided on these issues. Jerry Caulder, CEO of Mycogen and Chairman of the International Biotechnology Association, suggests that the solution, as in cross-

licensing of patents, will require a give and take: "If the law is written badly, we ought to change it, as long as we do not retroactively penalize companies that have made investments based on that law as it stood. We should be able to find the compromises."

The issue of the 1990s will be reimbursement

Other uncertainties await biotechnology companies in their various markets. For companies developing health-care products, the issue of the 1990s undoubtedly will be reimbursement. The products of biotechnology are coming into use just as the health-care environment is undergoing drastic change. Government reimbursement authorities, private insurers, and corporate benefits departments all are engaged in initiatives to impose control over upwardly spiraling costs. They are becoming gatekeepers over more than pricing. Through the proliferation of managed-care programs, the payers are increasingly involved in determining treatment protocols, thus wielding an inordinate influence on whether a product, having survived the rigors of the approval process, will be able to reach its market.

In this cost-conscious environment, the pricing of all new products is being scrutinized. The challenge for biotech companies is to definitively demonstrate the value of their products beyond the routine questions of safety and efficacy. They will have to provide cost-effectiveness and cost/benefit ratios, and document their products' impact on patients' quality-of-life.

By contrast, ag-bio companies will benefit from the greater clarity being introduced into their regulatory environment by the conclusion, this past

summer, of a four-year process of defining the types of microbes, plants, and animals that must be subjected to federal review before they can be field-tested. But ag-bio products are also being subjected to another kind of review—less objective and quite virulent—which is being framed by critics who do not trust science or business to be socially and environmentally responsible. The detractors succeeded in persuading the legislatures of two states to bar the use of BST. Skilled in communicating their messages in sound bites, they attract media coverage totally disproportionate to their numbers, and their impact is being felt across the industry.

There are policy issues that are central to the industry's ability to counter its critics. Government must establish a regulatory structure that the public will trust. The poor state of science education in the United States (documented in a recent study by the National Science Foundation) must be addressed, for it threatens not only the development of a skilled and talented work force to produce further U.S. progress in biotechnology, it also results in a populace ignorant of science and vulnerable to manipulation by special interests.

For its part, the industry must be vigorous in communicating the benefits of its products. As Jerry Caulder points out, "The lower people's knowledge, the higher the anxiety curve. As people understand more, the curve comes down very rapidly."

Critics attract media coverage totally disproportionate to their numbers

Finally, companies must not lose sight of their identity within the biotechnology fold. As biotechnology companies become commercialized, it is natural for them to identify themselves with their markets—as therapeutic/pharmaceutical companies, seed companies, specialty chemical companies, and so on. This is an essential rite of passage and a keystone of competitive positioning.

Yet there are issues that are essential to the success of all biotechnology companies—the investment climate in the United States, the clarity and efficiency of the regulatory process, a legislative framework that supports innovation and healthy competition, and the education of the public on the benefits new technologies bestow. There is no one voice that speaks authoritatively for the biotechnology industry on these matters with regulators, elected officials, the media, and the public at large—and this handicaps the ability of the industry to further its agenda. While companies pursue their individual destinies, they must unite to affirm the values that they share.

The Changing Vision

Biotechnology is emerging from its infancy, a process of profound change which brings frustrations as well as new strengths and possibilities. Not all companies will grow at the same pace or follow the same course. The direction and pace of the industry's development may tack and shift. But the growth is happening, the promise is being fulfilled, and the values that companies and the industry have been building are being affirmed.

Change will always be the underlying dynamic in this industry—change generated by the technology as it progresses from milestone to milestone, and change in the business and regulatory environment. Companies are adapting creatively, flexibly, and pragmatically to the changes that surround them.

There is much to suggest that the goal that companies set early on—to build new, totally-integrated, world-class companies—has been put aside. Biotechnology companies are making it, but not according to the original script. They are making it by developing broad product lines for niche markets. They are making it by enlarging their thrust and resources through alliances with companies large and small in the U.S. and around the world.

In the data reported in this year's survey, as well as in our discussions with biotech CEOs, we are struck by the creativity with which biotech companies keep raising capital through good and bad financing markets; the resourcefulness with which they keep forming alliances for the development and commercialization their products; and the dedication with which they keep adding to the scientific base. Amid the uncertainties of a changing environment, the industry's confidence is hard won, but it is certainly well grounded.

The Survey Team

A survey of this scope requires the talents and commitment of many people. Some members of our team have been involved with this annual endeavor for much of its history. Some came on board this year. All have made contributions.

Shirley Ruskin of Ernst & Young's National Marketing Group in New York joined our team this year as writer/editor. Her skill, dedication, and "grace under pressure" helped make this book happen. Kyle Kelhofer, of Ernst & Young's San-Francisco based National Manufacturing/High Technology Industry Services, analyzed the statistics and prepared the initial draft of the survey report. Without his experience, spirit, and tenacity the project would have struggled. Daniel Short assisted in developing the statistics. Tom Gossard,

Marcia Lempert, Chris Reder, and Dan Faletti handled data entry.

Members of our San Francisco-based Manufacturing/High Technology Group helped coordinate and carry through the effort—Laura Schefflow, Allison Smith, Kathleen Reichert, Penny Klotz, John Call, Pat Warnock, John Buchanan, Shawn Tillman, Colleen Villaroel, Cindy Yates, Pat Jackson, and Jeanne Cunicelli. Colleen Kenney of our Cleveland office assisted with the research. Lisa Burns of Burns McClellan once again contributed her special insights. From Ernst & Young's National Marketing Group in New York we received the design assistance of Frank Young and the advice and support of Jim Taylor, Elisabeth Coleman, and David Coleman. Jim Velardo and Marie Pecek of our National Marketing Group in Cleveland went all out to manage an accelerated production schedule.

Thanks go also to all the people of Ernst & Young who helped us with information, insight, and reviews. This endeavor is truly a team effort.

Finally, we wish to thank the executives and friends of the biotech community who participated in the interviews and roundtables. Their clarity of insight and purpose and their passion for the biotech industry are precious certainties in this changing environment.

G. Steven Burrill
*National Director—
High Technology
Industry Services
Ernst & Young*

Kenneth B. Lee, Jr.
*National Director—
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Industry Services
Ernst & Young*

Survey Report

Summary of Findings

Growth Benchmarks

- *Over a thousand points of light* Nationwide, there are approximately 1100 companies, increasing little from last year. (see p. 88)
- *Industry sales growth continues* The public companies have \$1.74 billion in total sales, \$2.53 billion in total revenues. The industry as a whole is estimated to have approximately \$2.9 billion in total sales, \$4.7 billion in total revenues. (see p. 31)
- *Exponential projected sales growth* Sales revenues are expected to more than double over the next two years, increase more than seven times over the next five years, and in 10 years, be more than 20 times above current levels. (see p. 31)

Government Policies

- *Industry split on biotech policy* Half of all companies support the development of a national biotechnology policy. (see p. 53)
- *Assistance most needed in research* If additional federal funds were available for biotechnology, companies would allocate the largest portion (50 percent) to research—basic, applied, and academic. Increased tax incentives (14 percent), and additional funds for the FDA (12 percent) and the Patent Office (9 percent) also are favored. (see p. 49)

Regulatory Issues

- *FDA creating problems* More than half the companies believe that turmoil at the FDA has had a negative effect on the biotech industry. (see p. 59)
- *FDA user fees acceptable* Sixty percent of the industry would support FDA user fees if the additional funds were used to expedite the drug/device approval process. (see p. 52)

- *Majority favors Orphan Drug Act status quo* Only 38 percent of the companies believe that the Orphan Drug Act should be amended. (see p. 53)
- *Patent Office trying* Despite continuing patent delays and inconsistencies, over 30 percent of the industry report improvements in their dealings with the Patent Office in the past year. (see p. 62)
- *Effects of rising health-care costs* Forty-two percent of the health-care companies with products in the market believe they are negatively affected by public concern over health-care costs. (see p. 54)
- *Ag-bio desires regulatory coordination* Only half of the ag-bio companies believe that the federal agencies responsible for approving the testing and selling/distribution of ag-bio products are clearly defined. (see p. 60)

International Arena

- *U.S. has biotech edge* The overwhelming majority (88 percent) of companies believe that the United States currently has a technological edge in biotechnology. (see p. 26)
- *Research levels and personnel greatest U.S. assets* The greatest supports of the international competitiveness of the U.S. biotech industry are thought to be the depth of research and the availability of qualified personnel. (see p. 27)
- *Financial markets and regulatory obstacles impede competitiveness* Items most negatively affecting U.S. competitiveness are thought to be the short-term outlook of the financial markets and regulatory obstacles. (see p. 27)
- *International sales activity increasing* Foreign sales account for one-fifth of all sales now and are expected to increase to one-third of all sales in five years. (see p. 32)

- *Japanese market entry problematic* The failure rate of attempts to enter the Japanese market is extremely high—approximately 26 percent. (see p. 33)
- *The industry is linked globally* One-third of strategic alliances are foreign—the majority with companies in Western Europe. (see p. 42)

Consolidation

- *Recent acquisitions very positive for industry* The recent acquisitions of U.S. biotech companies by foreign buyers have increased partnering opportunities and raised investor interest. (see p. 44)
- *Being acquired is highly desired* Establishing enough value to attract an acquisition is a strategic goal of 46 percent of the companies. (see p. 25)
- *Consolidation activity expected* Within five years, nearly half of all companies expect to acquire another company and 39 percent expect to be acquired. (see p. 46)
- *Nationality of acquirer unimportant* Approximately three-quarters of all companies believe it does not matter whether an acquirer is foreign or domestic. (see p. 45)

Increasing Stratification

- *Larger companies most profitable* Sixty-five percent of the top-tier companies are currently profitable—virtually the same as last year. Overall, only 21 percent of all companies are profitable. (see p. 78)

- *Continued selectivity of public markets* Nearly two-thirds of the top-tier companies and more than 40 percent of the large companies find the public capital markets responding favorably to their needs. However, only 26 percent of the industry overall finds the markets to be receptive. (see p. 65)
- *Mid-size companies in financing crunch* Twenty-six percent of the companies were negatively affected by the unreceptive public markets during the past year. Mid-size companies were the most severely impacted (34 percent). (see p. 66)
- *Smaller companies having problems with venture capital* Twenty-seven percent of the companies were negatively affected by the drop in venture-capital financings over the past year. The small companies were hardest hit. (see p. 66)

Partnering

- *Partnering most critical business issue* Over 30 percent of all companies rate the need for strategic partners as a primary business issue. (see p. 20)
- *Partnering most common milestone* For most companies (67 percent), the most significant milestone in the past year was furthering their strategic alliances. (see p. 24)
- *Biotech companies have many links* On the average, companies are involved in three strategic alliances. However, the top tier have an average of nine. (see p. 41)

Report Design and Organization

This report, the fifth in our annual series, analyzes survey data on financial and managerial issues from 422 biotechnology companies.

The biotechnology industry encompasses a diverse group of companies, ranging widely in size and serving a number of disparate markets. The thread that binds them is their mission: to use biological processes to develop products for human health, animal health, human and animal nutrition, agricultural productivity, and improving the environment. While a number of pharmaceutical, chemical, and agricultural companies now employ biological processes, these are not their primary activities; thus, those companies have not been included in this survey.

For four years now, our annual reports have charted this industry as it expands, encounters obstacles, gains experience, and pursues new opportunities. The fifth report follows, with a special focus on the current status of key industry trends and indicators, as well as anticipated future directions. In addition, this year's survey zeroes in on the major events of the past year and gauges the industry's reactions and responses to these events. Thus, we paint a picture of the changing environment in which biotechnology companies currently operate.

The survey topics, as always, are financial and business performance; strategies and issues for growth; operations; key government interfaces, such as regulation and patents; and other matters of general interest to the industry. The report also describes activities and trends regionally in the United States, including an update of our "Landscape of an Industry—the fold-out map facing page 96 that shows the geographic distribution of U.S. biotechnology companies in 1990.

Profile of Survey Participants

Questionnaires this year were sent to 1,240 companies, of which 1,107 were ultimately designated the mid-1990 universe of biotechnology firms. (The remaining companies were deleted because they

are no longer in business, or no longer engaged primarily in biotechnology.) Differentiated questionnaires were sent to the chief executive officer and the chief financial officer of each company.

We received completed questionnaires from 422 companies—a 38 percent response, which includes substantially all of the major biotechnology companies. We are grateful to the participating firms for the high response rate, which allows the Ernst & Young survey to be that much more complete and accurate. Statistical sampling techniques, however potent, are best applied to a broad and fully representative survey population of the kind generously provided by the industry this year.

Many firms responded to both the CEO and CFO questionnaires, thus providing even more information than suggested by the number of respondent companies. Financial data received from public companies were supplemented by data from each company's annual report and SEC Form 10-K.

Company Size

As in previous editions, the size categories adopted for this survey are based on the number of a company's employees. This variable is preferred to various alternatives (e.g., assets, revenues, profits), because it provides stable comparative data for a young industry in which standard financial measures may be misleading or inapplicable. This report parallels a practice of many industry analysts by giving separate consideration to data from the approximately 30 firms which constitute the top tier of biotech companies in terms of company size by employee count (and, frequently, in terms of capitalization or earnings as well). The size categories are defined as follows:

Small companies:	1 to 50 employees
Mid-size companies:	51 to 135 employees
Large companies:	136 to 299 employees
Top-tier companies:	300 or more employees

Chart i-1

Profile of Survey Respondents by Company Size

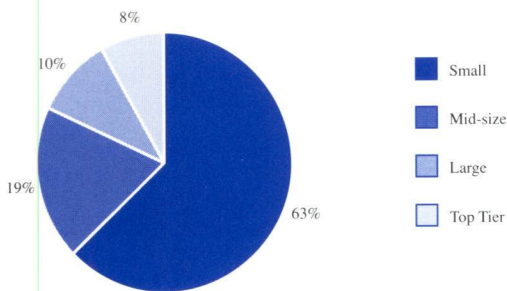
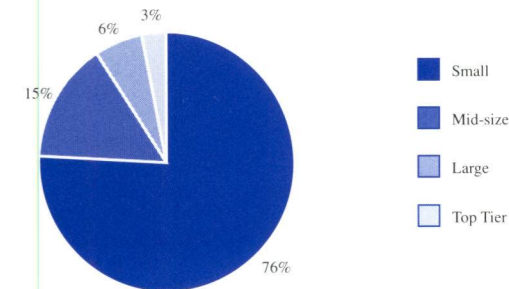


Chart i-2

Profile of Total Biotech Industry by Company Size



Compared with last year, the percentages in *Chart i-1* show a three-point increase in the number of small companies (63 vs. 60 percent), which is counterbalanced by a three-point decrease in the number of mid-size companies (19 vs. 22 percent). The large and top-tier companies again comprise 18 percent of the respondents, but the top tier now encompasses 8 percent vs. 6 percent last year.

The data in *Chart i-2* more accurately depicts the composition of the industry as a whole. The larger, public companies are often better prepared to respond to a detailed survey, thus their greater representation in the respondent group. From a statistical standpoint, the survey population reflects the industry to a highly acceptable degree of accuracy.

Market Segments

More than a dozen market segments are served by the two core biotechnologies—both of which have their source in the science of molecular biology. Even though *recombinant-DNA technology* has existed for nearly two decades, its uses continue to multiply. The basic applications are DNA manipulation, gene targeting, and gene therapy. Derivative applications include protein and enzyme engineering, carbohydrate engineering, transgenics, and the development of vaccines.

The use of *monoclonal antibodies* (made available through the development of hybridoma technology) has existed for more than ten years. Their use in *in vitro* diagnostics was the first commercial application emanating from the new wave of biotechnology. They are now close to the market for use as *in vivo* imaging agents and targeted therapeutics.

Other applications that make use of these base technologies include rational drug design and biosensors.

The survey respondents have been classified on the basis of the *primary* market which they serve or intend to serve (*Chart i-3*). The market definitions used in this report are as follows:

- Human Diagnostics.
- Human Therapeutics (includes transgenic processes designed for human therapeutic purposes).
- Ag-bio (plant genetics, microbial crop protectants, and food processing).
- Suppliers to the industry (instrumentation, lab supplies, reagents, etc.).
- Other (animal health care, bioremediation, contract R&D, energy, etc.).

Chart i-3
Profile of Survey Respondents by Market Segment

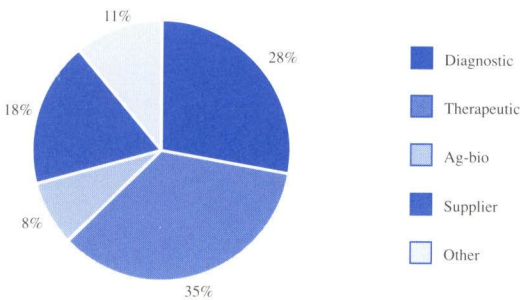
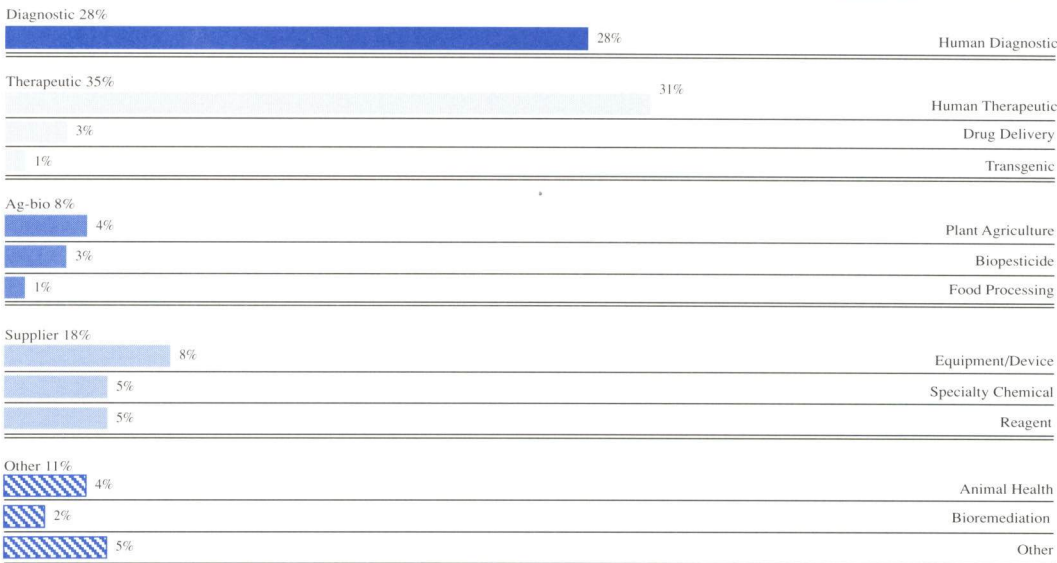


Chart i-4
Expanded Profile of Survey Respondents by Market Segment



Although animal health-care companies have many similarities to companies addressing human health care, this year's survey departs from the practice of previous years of combining them to provide a more accurate picture of the more-advanced human health-care segment. Readers will find an expanded profile of the survey population by market segment in *Chart i-4*.

Short definitions of the primary market segments may be helpful. The goal of biotech companies focused on *Human Diagnostics* is to develop clinically important tests which are highly accurate and suited to the site where they will be used, whether it is a sophisticated urban reference laboratory or a rural clinic. Generally, these are subject to approval by the U.S. Food and Drug Administration.

Human Therapeutics are pharmaceutical products subject to extensive testing and clinical trials in regulatory environments administered by the FDA, and, if applicable, certain foreign regulatory agencies. The biotechnology industry is currently addressing therapeutic challenges ranging from cardiovascular disease, cancer, and AIDS, to chronic inflammatory diseases and wound healing.

Ag-bio companies focus on plant genetics and the development of microbial pesticides and herbicides in order to improve yields of major crops, develop new strains, and prevent spoilage. Also included in this category are companies applying innovative technology (diagnostic kits, enzymes, etc.) in the processing of agriculturally-based food products.

Suppliers have carved out a distinct niche in the overall market for lab instrumentation and supplies for life-science research by developing instruments and chemistries specifically suited to biotechnology.

Animal health care, transgenic animals (for research or biologic-products production purposes), and technologies that improve the nutritional characteristics of animal foods and that make the production of these foods more efficient are included within the designation *Other*. Bioremediation products are included within this designation as well. These market segments are developing vigorously and in time may command separate groupings. Their potential is enormous.

Over the years, there has been a steady increase in the percentage of companies involved in human health care. In *Biotech 88: Into the Marketplace*, human diagnostic and therapeutic companies each represented 23 percent of survey population. Their increase to respectively 28 and 35 percent in 1991 has come mainly at the expense of ag-bio (from 20 percent in *Biotech 88* to 8 percent today) and supply companies (from 25 percent in *Biotech 88* to 18 percent).

The increased concentration in human health care is attributable to its vast market potential. This enormous business opportunity has attracted greater funding than in other segments. Notwithstanding the large number of therapeutic companies, we have only begun to scratch the surface of biotechnology's potential to address the problems of human health care.

Chart i-5

Profile of Survey Respondents by Company Status

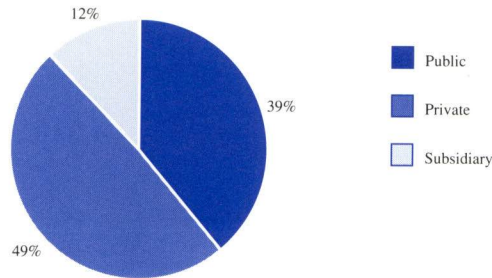
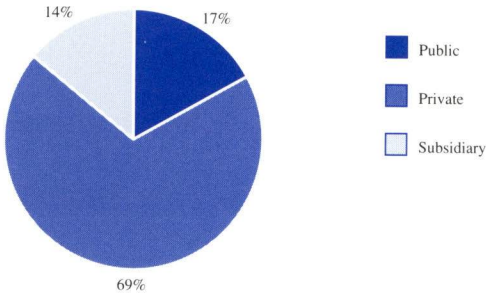


Chart i-6

Profile of Total Biotech Industry by Company Status



Funding Status

The distribution of public, private, and subsidiary companies in *Chart i-5* reflects this year’s survey population. *Chart i-6* depicts the proportions of public, private, and subsidiary companies within the industry as whole. Public companies are more willing and able to share data, and routinely prepare financial and operating information to comply with SEC regulations. Thus they are more heavily represented in the survey population than in the industry at large. Again, these differences in representation do not adversely affect the survey results from a statistical standpoint.

The survey distinguishes subsidiaries from public and private companies. The importance of certain subsidiaries—some acquired by larger firms, others spun off from larger firms attempting to create relatively autonomous biotech units—argues for the distinction.

1. Key Business and Competitive Issues

Unfolding events and the industry's own development keep the biotechnology environment in a state of continuing change. Major events and developments of the past year have added new complexities to the ongoing concerns of biotechnology CEOs:

- *The volatility of the public financial markets.* Biotech stocks surged following a series of significant acquisitions early in the year. Later, when long-awaited products from Cetus and Immunex ran into unexpected regulatory delays in their home stretch, biotech stocks declined. As we go to press, events in the Middle East are creating new financing anxieties across the board for U.S. industries.
- *Regulatory uncertainty.* The Cetus and Immunex experiences underscored the uncertainties surrounding when, and how well, companies' investments in product development will pay off. For Immunex, postponement of FDA approval may prove no more than a temporary disappointment. For Cetus, it ushered in a change in top management and a period of reassessment, both internally and in the investment community, about the company's future prospects. How Cetus—one of the most prominent of the first-generation of biotech companies—could come to such a pass, is a question that must preoccupy all biotech CEOs.
- *The rigors of competing in the marketplace.* As biotech companies become more commercialized and market-focused, they are increasingly competing with established, traditional companies. Meanwhile new biotechnology competitors are being nurtured overseas—most notably in Japan, the United Kingdom, France, Switzerland, and West Germany—by more favorable economic and industrial policies than biotechnology, or any technology, enjoys in the United States. They are not real competitors for the more-developed U.S. industry yet—but they have U.S. companies looking over their shoulders.

- *Increased competition for strategic alliances.* Strategic alliances are emerging more strongly with each passing year as a vehicle for companies both to meet many of their financing needs and to access the sales and marketing capabilities they require to launch and sustain their products in the global marketplace. Numerous new alliances were formed this year (see Appendix B), and many existing alliances deepened. As more companies emphasize alliances, the competition to secure them heats up.
- *The growing stratification of the industry.* Readers will see a pronounced stratification of the industry borne out in the differing ways that companies of varying size respond to our survey. Financial markets—when they are strong on biotechnology and even when they are not—are more accessible to top-tier companies than to less-developed enterprises. These companies are scoring the greatest successes in securing corporate partners. Many of these companies are profitable or soon will be, and are seeing their concerns shift from issues of financial survival (of which they are largely now assured) to issues of competitiveness.

The macro issues translate into the micro questions of specific company strategies that CEOs grapple with every day. Events and issues do not affect all companies in the same way, and companies at different levels of the industry do not respond to developments in the same way. But the same events and developments have an impact on all biotechnology companies.

Key Findings

Critical Concerns

- The primary business issues facing biotech companies today are the need for strategic partners (31 percent), the cost of capital (22 percent), and competitive pressures (30 percent). The focus on partnering and competition is markedly up from last year; the concern about capital somewhat down.
- The small and mid-size companies still place greatest weight on issues related to financing—the need for strategic partners and the cost of capital.
- The large and top-tier companies—which have more consistent access to capital—voice the greatest concern about issues affecting their success in the marketplace—competition, the regulatory environment, and the uncertainties surrounding product reimbursement.
- For most companies (67 percent), the most significant milestone in the past year was a furthering of their strategic alliances.
- Companies anticipate that competition will be, by far, their most critical concern five years hence (50 percent versus 30 percent today). Product issues in general (regulation, reimbursement, etc.) will loom more important than financing concerns.

Strategic Goals

- The most common strategic goal (61 percent) is to develop products which will be marketed by corporate partners—reiterating the emphasis throughout these findings on corporate links.

- Establishing enough value to attract an acquisition is a strategic goal of 46 percent of the companies. This sentiment, strongest among the small and mid-size companies, reflects a marked turn from the thinking of a decade ago, when companies aimed to build independent, fully integrated enterprises.

International Competitiveness

- The overwhelming majority (88 percent) of companies believe that the United States currently has a technological edge in biotechnology.
- The greatest supports of the international competitiveness of the U.S. biotech industry are thought to be the depth of research and the availability of qualified personnel.
- Items most negatively affecting U.S. competitiveness are thought to be the short-term outlook of the financial markets and regulatory obstacles.

Critical Concerns

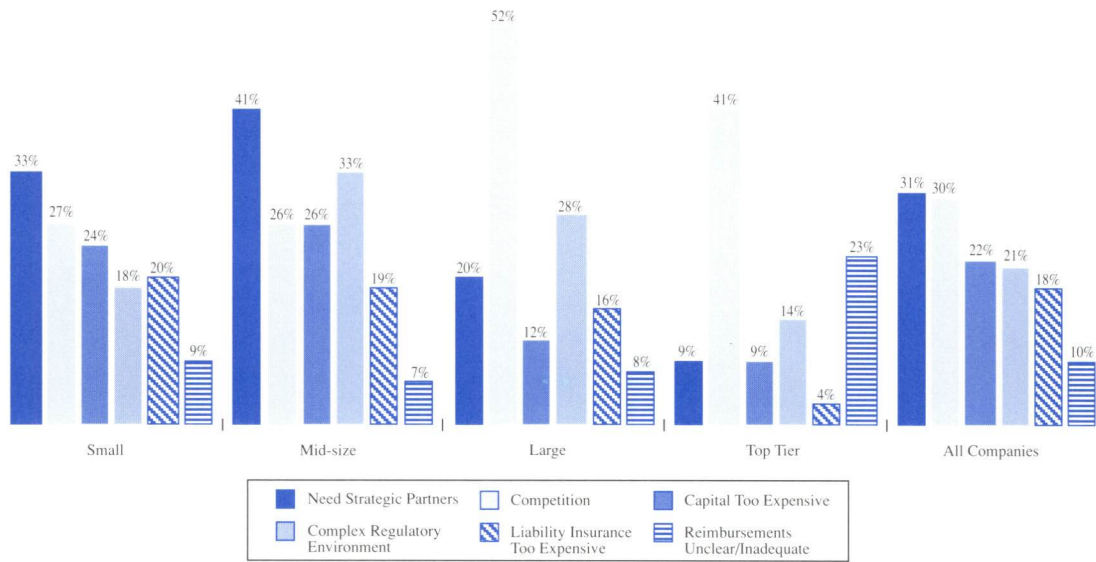
Companies were asked to rate the significance of key business problems for biotech companies (itemized in *Charts I-1 and I-2*). While a number of problems are consistently rated as significant, there are clear differences among the problems most affecting companies of different sizes and in different markets.

Overall, the companies view financing (expressed both in the need for strategic partners and concern over the cost of capital) and competition as their primary challenges. When this year's responses are compared to last year's, some notable developments emerge. Although the high cost of capital is still a concern, it is relatively less pressing. The top-tier and large companies appear little troubled over accessing capital. This reflects their

Chart 1-1

Key Problems Currently Facing Company by Company Size

percentage rating most important



improved funding opportunities (the “rich get richer” syndrome that has characterized 1990’s resurgence of investment in biotech companies) and the commencement of meaningful revenue streams from product sales. These factors are widening the gulf between the have and have-not companies and increasing the stratification of the industry.

There is an increased emphasis over last year on strategic partnering. While historically regarded as a source of R&D funding, these relationships with other, usually larger, companies are increasingly valued for the sales, marketing, and regulatory capabilities they bring, and the cultural fit that enables partners to leverage each other’s capabilities for their mutual benefit.

Last year, 10 percent of CEOs identified competition as their overriding issue. This year, 30 percent place it among their top two concerns. Biotechnology companies compete for technology, product sales, financing, partners, and people.

Success in the product marketplace is not driven by technology alone. There are many biotechnology companies with good science, and many of them will compete head to head. They will also compete with traditional companies. Product positioning, success in obtaining regulatory approvals, the effectiveness of their sales and customer support organizations, and product pricing all will help determine the market winners, runners-up, and also-rans.

Success in competing for financing and alliances places a premium on the ability of companies to:

- Focus on a technology in which they have a realistic chance to be a leader.
- Target a market in which their technology can make a meaningful difference to the end user.
- Define an initial line of products that can be realized in a reasonable time frame (if they do not already have products).

By Company Size

As depicted in *Chart 1-1*, the small and mid-size companies rate a range of problems as nearly equal to them in significance. While the need for strategic partnering is the greatest concern in general, there is considerable variation in priorities among the various company-size classifications.

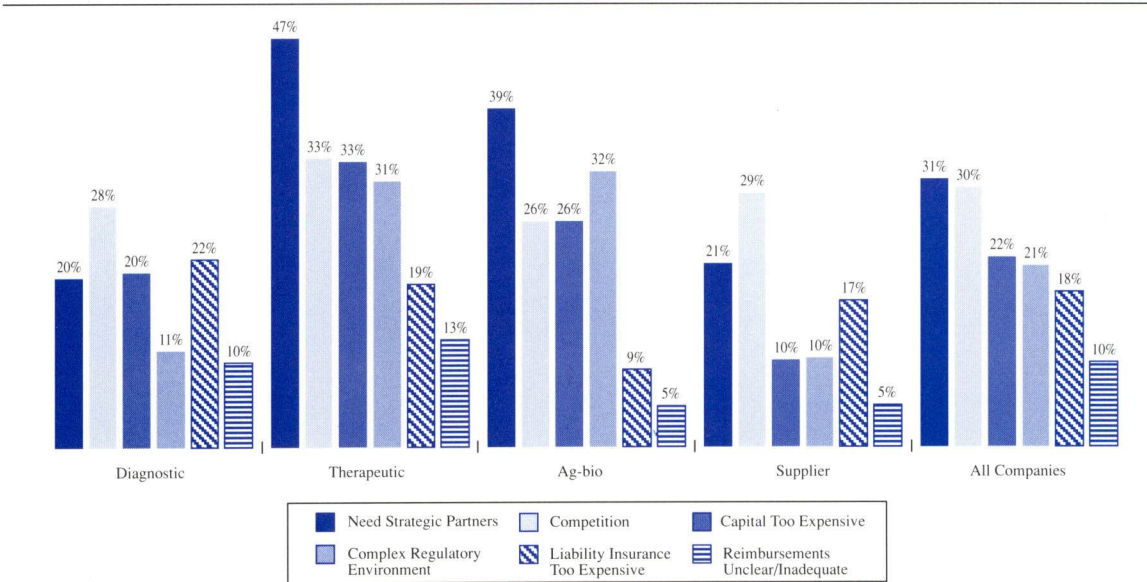
Small biotech companies are focused on research. Their number one need is for capital to compensate their personnel and obtain equipment and materials. As they progress from research to product development, they begin to interact with the regulatory structure. Additional financing becomes necessary to add in-house regulatory personnel, conduct tests and trials, and keep the company alive until regulatory approval is received.

Although the bulk of our responses come from small companies, the top-tier firms (and, to a lesser extent, the large companies) will be the primary source of biotechnology product activity and sales revenues during the next few years. Some of these companies have products in the market or on the verge of regulatory approval. Their attention centers on their ability to commercialize and compete. Questions surrounding product reimbursement jump to second in importance for the top tier. This stratum includes the leading therapeutics companies, whose flexibility in product pricing is critically affected by the reimbursement decisions made by the Health Care Financing Administration, corporate benefits departments, and private health care insurers. (*See the Ernst & Young Roundtable for a discussion of the impact of reimbursement.*)

Chart 1-2

Key Problems Currently Facing Company by Market Segment

percentage rating most important



By Market Segment

The CEOs of therapeutic and ag-bio companies identified more issues as being problems than did their counterparts in the supplier and diagnostic segments (*Chart 1-2*).

The importance of strategic relationships to the therapeutic and ag-bio sectors reflects the pre-commercialization status of the bulk of these companies. They look to partners for capital to fund them through commercial entry and to provide sales and marketing resources.

For ag-bio companies, the complex regulatory environment ranks relatively higher among their concerns than for any other segment. This finding is striking in relation to the high level of criticism of the regulatory structure generally voiced by health-care companies (*See Chapter 4: Government Involvement*). A key difference is that, while health-care companies may not be satisfied with the quality of their dealings with the FDA, it is clear that the FDA is the agency in charge of their products. For a number of ag-bio products, the situation is less clear.

Food products fall under both USDA and FDA authority; herbicides and pesticides under both USDA and EPA. Having to apply for approval to two agencies, rather than one, doubles the potential cost, time, and complexity of the approval process. However, ag-bio companies give high marks to the USDA's efforts to minimize the burdensomeness of the regulatory process and coordinate with other agencies. Their main complaint is not at the federal level.

The wild card that is causing the most concern in the ag-bio sector is the emerging regulatory activities of the states. This past summer, North Carolina became the first state to implement regulations over field tests of genetically engineered organisms. If other states follow suit, this will produce a patchwork of criteria for companies to contend with, some of which may be far removed from issues of safety and efficacy, as the controversy over bovine somatotropin in a number of states has

demonstrated. The proliferation of regulations also multiplies the opportunities for special interest groups to create pressure points.

For the therapeutic companies, regulatory concerns are driven by the sheer time it takes to obtain product approval from the FDA. In recent years, the FDA has been addressing more and more challenges—speeding approvals of treatments for life-threatening diseases, monitoring generic drugs, and evaluating a gathering flow of revolutionary new therapies developed principally by biotech companies. Yet the agency's staff is actually reduced from its complement in the mid-1980s, and its budget from year to year barely keeps pace with inflation. Biotech products generally are approved in about the half the time of traditional therapeutics—in an average of 16 months versus 32—once the agency takes action on a New Drug Application (NDA). However, the preceding drug-trial process can take as long as ten years. While large, well-capitalized pharmaceutical companies can absorb these lags and costs, small biotech firms struggle to hang on.

At the same time, the hurdles for new biologic therapies are high. If confirmation were needed, it came in the FDA's requests this past summer for additional data on Cetus's long-developing IL-2 drug and Immunex's GM-CSF—despite the fact that Cetus's Proleukin is already approved and in use in Europe.

Diagnostic companies report themselves the most sanguine. They point to no overriding problems but, rather, issues of reasonable concern. Diagnostic products generally do not face as complex an approval process as therapeutic products. However, they typically have shorter life cycles. As a result, diagnostic companies are most concerned about their ability to compete in the marketplace in order to recoup their product investment and earn profits to fund new development.

Company Milestones of Past Year

The industry’s milestones still consist primarily of financing-related events, rather than product successes (*Chart 1-3*). Less than one-quarter of companies experienced a major product approval.

Success in linking with corporate partners is the key event in the current lives of most companies. This dovetails with the finding reported in *Chart 1-1* that the need for strategic alliances is CEOs’ most pressing current concern. Given the generally unfavorable financial markets for much of the past year, the emphasis makes consummate sense—only a few companies were able to finance successfully without the use of alliances.

Key Problems During Next Five Years

Chart 1-4 highlights the evolving priorities of the industry. As commercialization continues over the next five years, CEOs anticipate that competition will soar. Likewise, issues associated with entering and selling in the marketplace will attract increasing attention—regulatory approvals, liability exposure, reimbursement policies, customer access, distribution channels, competitive behavior. Concern over the twin supports of capital resources and strategic partners is expected to be a constant.

The ability to attract and retain key people will be an issue of growing importance. As companies mature, they need to increase their ranks of scientifically qualified workers at all levels in the

Chart 1-3

Company Milestones of Past Year by Company Size

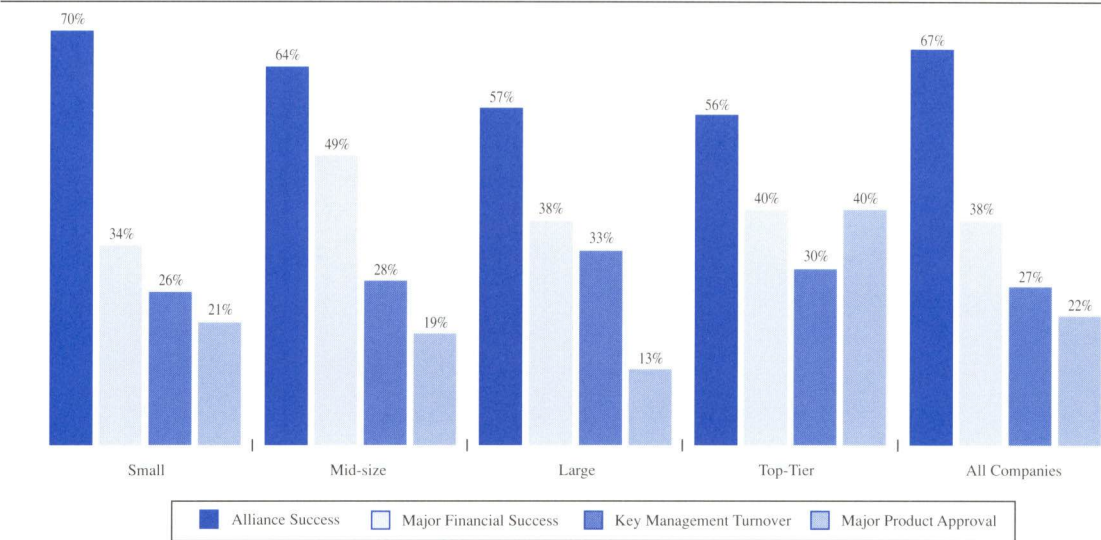
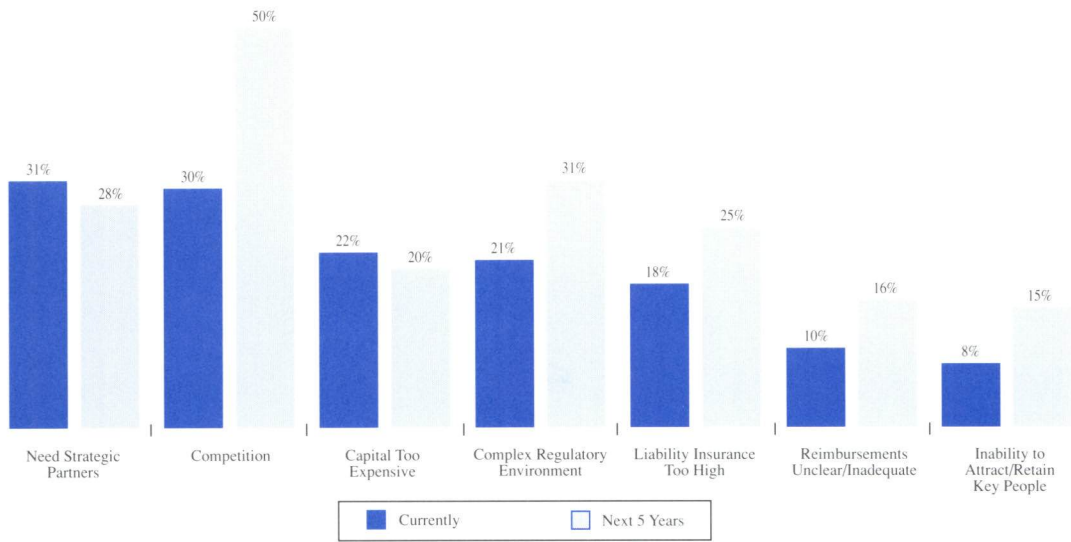


Chart 1-4

Key Problems Currently and During Next 5 Years—All Companies

percentage rating most important



organization—in the lab, manufacturing, marketing, and management. The “baby bust” demographic phenomenon as well as the poor quality of U.S. science education (and education in general in the United States) are particularly of concern. Fewer young people will be entering the manufacturing work force, and many will be weak in the scientific and general literacies required in this exacting industry.

Strategic Goals

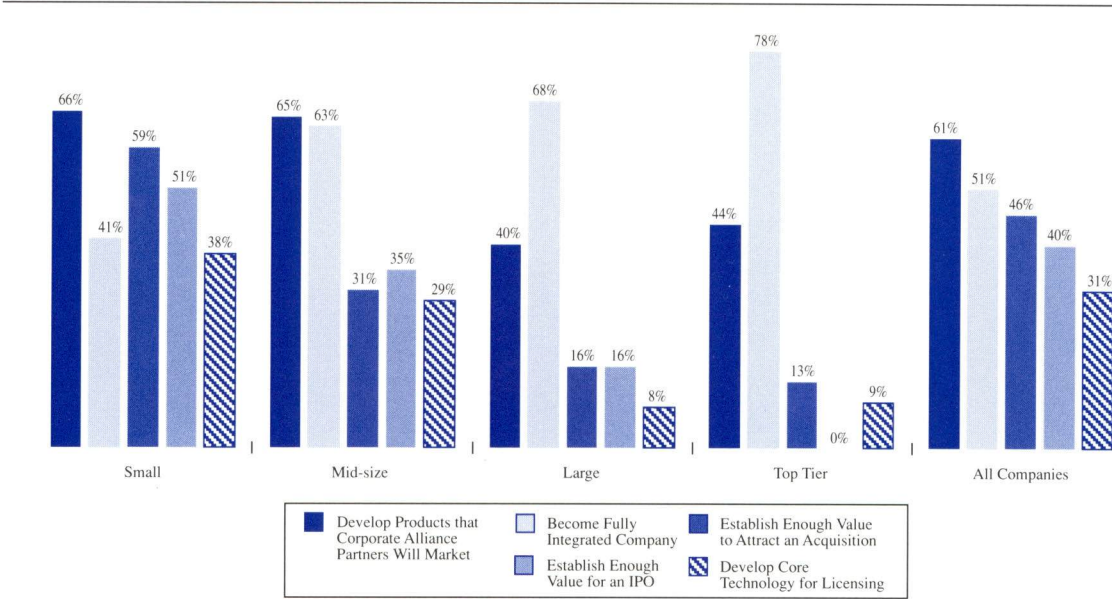
While there is no common strategic goal for the industry as a whole, there are goals that are largely shared by companies comparable in size (*Chart 1-5*). The strategic goals of the large and top-tier companies contrast sharply with those of the small and mid-size companies—highlighting, again, the bifurcation taking place.

Indeed, one can follow the trend lines as companies grow. Establishing value for an initial public offering (IPO) disappears as a goal as com-

panies grow in scale. The same applies to the goal of attracting an acquisition—it is highest among the smallest companies and lowest in the top tier. Becoming a fully integrated company glows more brightly as companies grow closer to being able to achieve it. A fair percentage of small and mid-size companies also hold this aspiration. Considering the resources consumed in obtaining regulatory approvals, and the costs of manufacturing scale-up and competing in the marketplace, this goal may seem over-optimistic. Yet it may be achievable for companies that are targeting important niches rather than a broad market. The industry will not grow many, if any, new Mercks. But many biotechnology companies are developing a fully integrated capability to serve discrete markets through their own R&D, through acquisitions of products and companies, and alliances with other product-based companies. These goals are realistic. They require focus and dedication, not just on a technology or product, but also on the size,

Chart 1-5

Strategic Company Goals by Company Size



behavior, and needs of a marketplace (*See the interviews with Edward Penhoet and Henri Termeer*).

The most common strategic goal is to develop products to be marketed by corporate partners. This is the most realistic goal for companies entering broad markets traditionally dominated by pharmaceutical, device, and chemical companies. It builds on what biotech companies do best—develop innovative products and technology. It leaves manufacturing and marketing/distribution to the established companies that have the resources and experience. Even companies that aim to become fully integrated still see the need for product partnerships. In fact, even the giants do. The Mercks and IBMs also align with other companies to access synergistic products and marketing/distribution channels. (*Strategic alliances are discussed further in Chapter 3: Corporate Development Strategies.*)

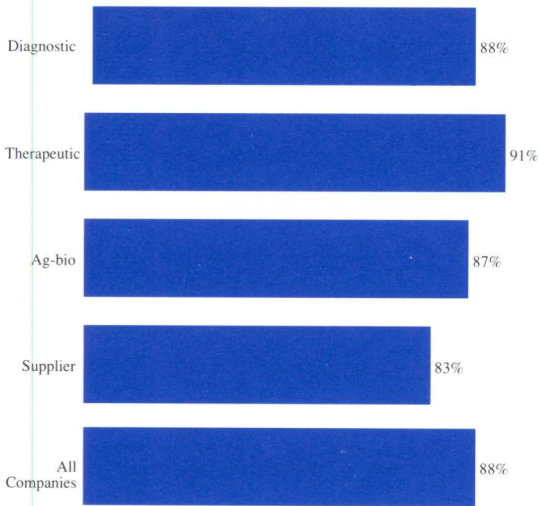
International Competitiveness

The markets for innovative diagnostic, therapeutic, agricultural, environmental, and specialty-chemical products exist around the world. And companies around the world are competing for their market shares.

U.S. companies affirm that the U.S. biotechnology industry—the first out of the gate—still commands an overwhelming technological competitive edge over foreign competitors (*Chart 1-6*). This finding contrasts well with the state of another key technology grown in the United States, electronics. In the Ernst & Young survey, *Electronics 90: The New Competitive Priorities*, U.S. electronics CEOs cited competitive strengths in software, computers, CAD/CAM, and networking, but identify deficiencies in semiconductors, surface-mount technology, and optoelectronics. Seventy percent of the CEOs believe the technological edge

Chart 1-6

Percentage Believing U.S. Has a Technological Competitive Edge in Biotechnology by Market Segment



of U.S. electronics companies is slipping away. Only 13 percent believe it is improving. Biotechnology CEOs clearly regard their industry in better shape.

However, many observers of the international scene are concerned that the U.S. technological lead in this industry could erode in the face of competition from Europe and Japan, where government policies are more supportive of technology industries and investors take a longer-term view of the potential for building value. In addition, strategic alliances between foreign companies and U.S. biotechnology firms are giving potential overseas competitors broad access to U.S. technology, which they may adapt and further develop on their own. A 1990 U.S. Government Accounting Office report notes particular concern vis-à-vis Japan. Japan has been “by far the most active foreign player in the U.S. biotechnology industry” during the 1980s according to the report, and U.S. companies have enormous difficulty protecting their intellectual property rights under the Japanese first-to-file patent framework.

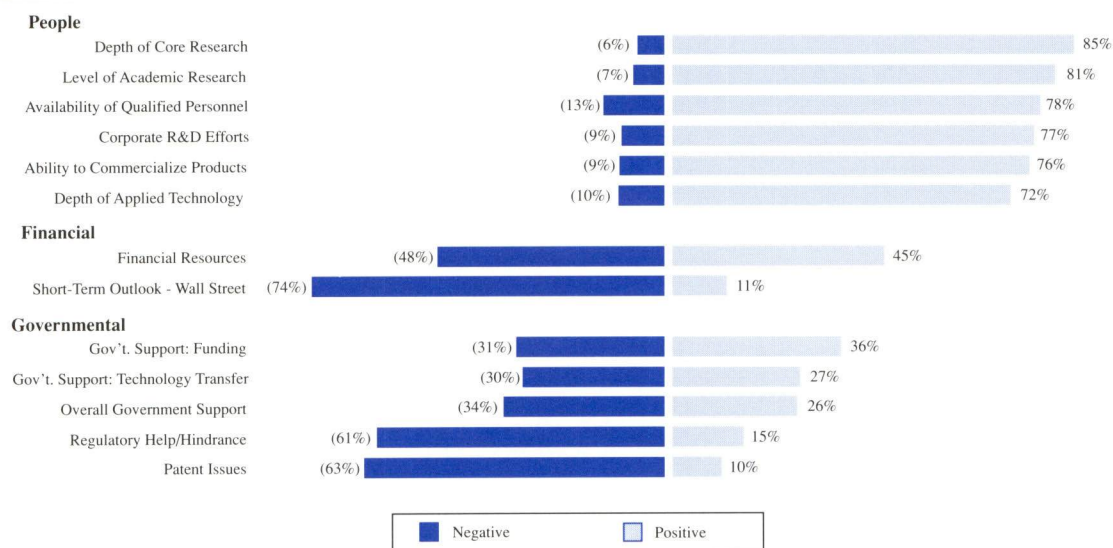
Factors Affecting U.S. Competitiveness Internationally

CEOs identified three groups of related factors as favoring U.S. companies in competing internationally (Chart 1-7). Having the greatest positive impact are the “people” factors—the scientific and technological talent the industry draws on. All aspects of U.S. research and technological capability are considered positive. Core and academic research are regarded as outstanding. For the health-care segment of the industry, this is, to a great extent, an outgrowth of the birthright bestowed by NIH funding of basic research. The ability to commercialize products is also considered to be a key strength, and a tribute to the U.S. entrepreneurial spirit.

Regarding the “financing” factors, the ratings are mixed to poor. Financial uncertainties plague emerging industries in the United States—from continuing changes in tax laws, to the speculative mentality that drives large segments of the investment community.

There is little disagreement that the public markets’ focus on short-term profits is the most negative influence on the international competitiveness of U.S. companies. When there are few incentives for long-term investment, capital-intensive companies that are building long-term value are at a disadvantage. Yet 45 percent of the companies identify existing financing sources as an asset. This highlights the disparities in the ease with which companies are able to achieve their financing objectives.

The government is not perceived as a positive support by the industry’s CEOs. The grades on government funding, technology transfer, and tax and trade policies that promote the development of biotech companies are, at best, mixed. In regulatory and patent activities, government receives an unequivocal F. The lag in issuing patents, inconsistencies in patent approvals, and lengthy regulatory processes are perceived to be burdens that handicap companies’ ability to devote resources to international competitiveness.

Factors Affecting U.S. Competitiveness Internationally—All Companies

There are also hindrances presented by foreign regulatory and patent structures. The jury is still out on the changes that the integration of the European market will bring. However, the message from Japan is clear. Intellectual property is not given meaningful protection when a narrow refinement to a patented product can qualify for a new patent. And the Japanese regulatory and patent structures present many barriers to companies not rooted in the Japanese business community. (*The difficulties of competing in Japan are discussed further in Chapter 2.*)

It is encouraging, however, that U.S. companies have the field advantage in the “people” factors of research and commercial ability. These are strengths that are not quickly created. But improving regulatory structures and instituting policies that encourage long-term investment merely take acts of political will. More beneficial regulatory and financing environments for U.S. companies are obtainable with the right commitment of care and resources. (*For discussions of how public policy can make the international playing field more even, see the Washington Roundtable; the roundtable, “One Industry or Many?”; and the interviews with Senator Albert Gore and Jerry Caulder.*)

2. Product Development and Sales

In the end, biotechnology is about products. 1990 brought some distinct progress:

- Genentech's tissue plasminogen activator (t-PA), historically the industry's flagship product, achieved sales of \$196 million.
- Amgen's erythropoietin (EPO)—perhaps the industry's new flagship product—chalked up nearly \$200 million in first-year revenues.
- Biogen/Schering Plough's alpha-interferon was approved for treatment of hepatitis C and showed even greater promise in clinical tests for treating hepatitis B.
- Human growth hormone—developed by Genentech and already a \$123 million product—was shown to reverse effects of aging in elderly men.
- Chiron's hepatitis C blood test was approved.
- A test for the cystic fibrosis gene was introduced.
- Recombinant rennin was approved for use in cheese production.
- Microbes were used to eat up oil spills.
- And bovine somatotropin (BST) was *not* banned in Vermont.

As with the fortunes of BST (which was, however, barred in Wisconsin and Minnesota), there were other product events of the “glass is half empty” or “harsh light of day” kind. Calgene endured a massive assault from environmental activists for its progress in developing an herbicide-resistant cotton plant; although they are a minority, biotechnology's critics are strident and determined. The very success of EPO has attracted Congressional scrutiny of Amgen's pricing, raising questions about the industry's ability to set value-prices for its products. And the battle for dominance in the clot-dissolving market among Genentech's t-PA, Hoechst's streptokinase, and

SmithKline Beecham's Eminase illustrates how healthy competition can turn into a slugfest.

Products are moving into the marketplace, with all the new challenges the passage entails. But along with the challenge comes, finally, the reward. The confidence of scientists, investors, and entrepreneurs is being fulfilled. The revenues are growing. While some of the early expectations of the pace of revenue growth have turned out to be premature, long-term values are building and significant returns are clearly in sight.

Biotechnology has grown up as an international industry with its products finding markets around the world. But global opportunities also bring new challenges from overseas competitors and foreign governments nurturing their national biotech industries. As U.S. companies launch their products into foreign markets, their regulatory, pricing, and competitive concerns multiply.

Key Findings

Sales Growth

- Industry revenues from product sales have increased to \$2.9 billion in 1989.
- Sales revenues are expected to more than double over the next two years, and increase by a factor of more than seven over the next five years. In 10 years, sales are expected to be more than 20 times above current levels. Small companies expect the most rapid sales growth—to eight times their current levels in two years.
- Even so, expectations of future sales growth have decreased significantly since last year.
- Small companies expect the most rapid sales growth—to eight times their current levels in two years.
- Therapeutic companies project sales to increase by a multiple of 17 over the next five years.

International Markets

- Foreign sales already account for one-fifth of all sales. This percentage is expected to increase to one-third of all sales in five years.
- Both actual foreign sales and projections of future foreign sales have increased over last year's levels.
- The majority of companies currently have foreign sales. Sales activity is greatest in Western Europe and Canada.
- While a significant number of companies have sales in Japan, the failure rate of attempts to enter the Japanese market is extremely high — approximately 26 percent. Therapeutic companies have experienced an especially high 67 percent failure rate.

- Competition and regulatory impediments are obstacles to entering both the U.S. and overseas markets. Additionally, restrictive health-care reimbursement is a hinderance in Europe, and cultural and trade barriers are problems in Japan.

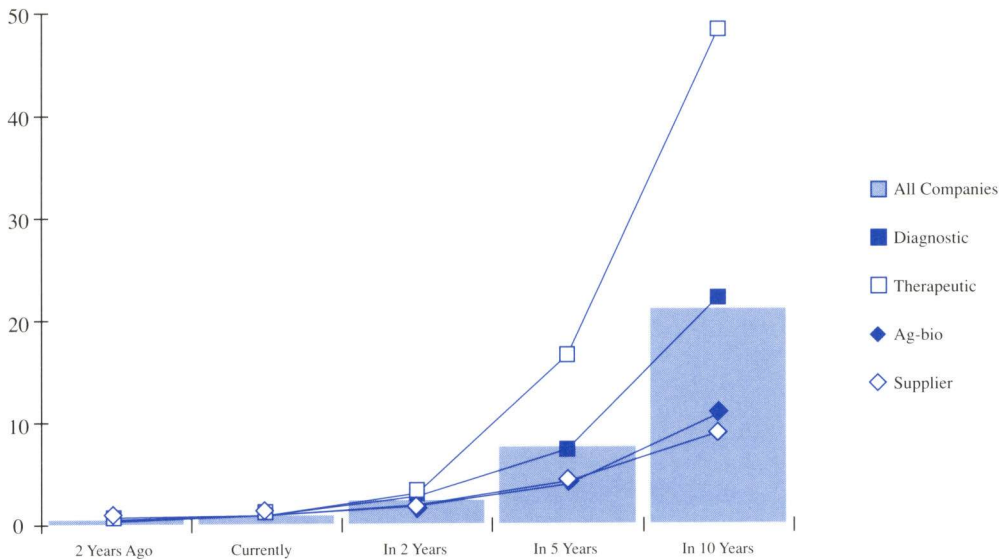
Product Pricing

- The factors that companies consider most important in pricing their products are the pricing and effectiveness of competitive products/protocols.
- Current health-care reimbursement practices are seen as being somewhat more damaging than beneficial for product sales. While 36 percent of the diagnostic and therapeutic companies with current sales perceive a negative effect, only 21 percent believe there is a positive effect. However, the largest group (43 percent) reports no effect either way.

Chart 2-1

Projected Sales Growth by Market Segment

multiple of current sales



Sales Growth

The 1990s will be a decade of dramatic sales growth in all segments of the industry (*Chart 2-1*). Product sales in the past year were approximately \$2.9 billion. But past growth provides little clue to the scale of growth to come. Sales overall are expected to more than double over the next two years, and increase more than 20 times over the next ten years.

The therapeutic segment anticipates the most extraordinary growth—to more than 50 times the level of current sales by the end of the decade. While the projection is astonishing, it is quite logical. These companies are relatively young and most of them, currently, have minimal sales.

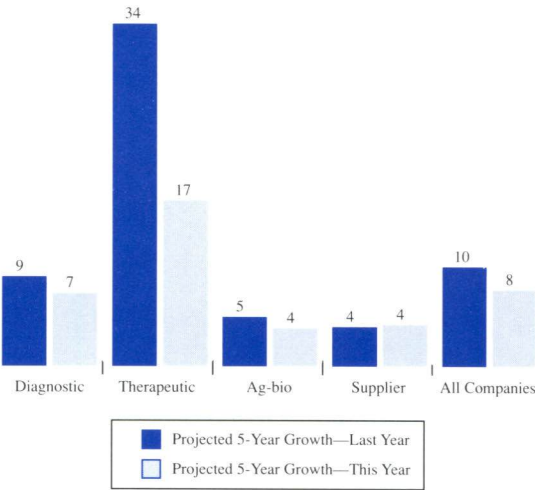
While the sales growth projections of diagnostic companies mirror the industry averages, suppliers and ag-bio companies lag. Suppliers were the earliest segment of the industry to commercialize—manufacturing raw materials and equipment for the other industry segments. These companies form the most mature segment of the industry. Ag-bio companies by and large are building their sales and distribution networks with traditional products—seeds, foods, and specialty chemicals. They are using yesterday’s products to learn the skills and processes they will need tomorrow. Their recombinant products are still being tested and evaluated by regulatory authorities. These companies are just at the brink of their real commercial lives.

Small companies—with a small to negligible base of current sales—expect the greatest growth. However the larger companies also expect significant growth as their blockbuster products enter the markets.

Chart 2-2

Change in Projected 5-Year Sales Growth by Market Segment

projected multiple of current sales

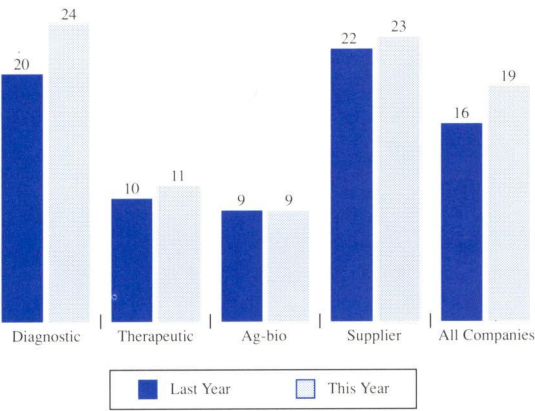


In comparison with last year’s five-year sales-growth projections (*Chart 2-2*), this year’s projections sharply drop off. The drop was most significant among the therapeutic companies, whose prediction of a multiple of 34 in growth over a five-year period has been halved. These drops in all sectors (except suppliers, which envisions steady growth) evidences an increased appreciation of the impediments to commercialization. Financing for many companies is difficult and time-consuming. No company, no matter how flush, ever can take it for granted. Partnering, although generally successful, is also not a sure thing—there can be delays, failed commitments, and, occasionally, “divorces.” Possibly the most constricting factor of all—regulatory approval—is mired in time-devouring, frustrating bureaucratic processes. Finally, the products themselves sometimes disappoint. The net effect is that biotechnology companies have toned down their sales expectations to levels—yet still lofty.

Chart 2-3

Change in Foreign Sales Percentage of Total Sales by Market Segment

percentage of total sales



International Markets

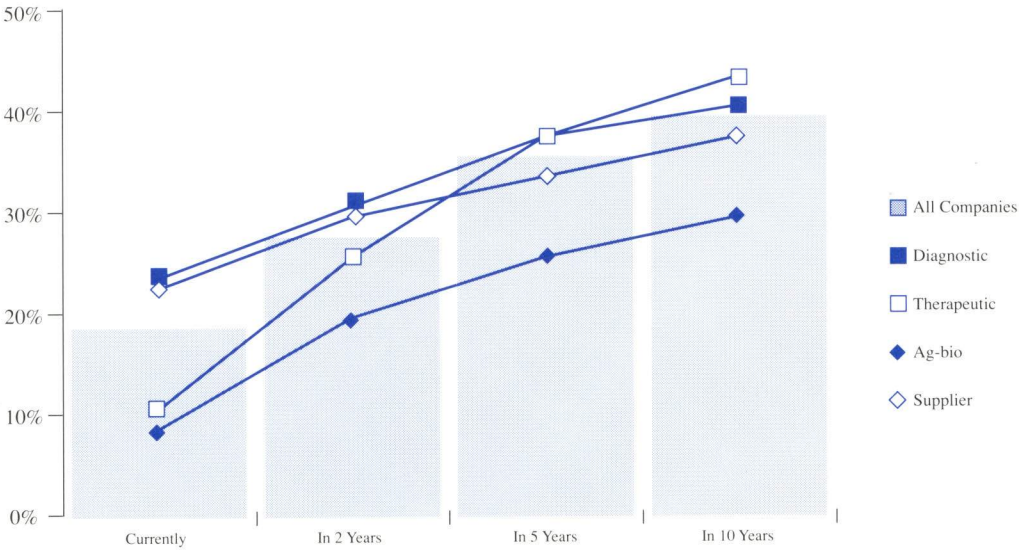
Biotechnology companies are deeply involved in foreign markets. The international portion of industry sales has increased slightly since last year (Chart 2-3) and is projected to increase further during the coming years (Chart 2-4). As a percentage of total sales, foreign sales increased from 16 percent to 19 percent during the past year. This number is expected to grow to 29 percent in the next two years, and 36 percent over the next five.

Diagnostic and supplier companies are currently the most foreign-sales integrated, with almost one-quarter of their sales outside the United States. However, the suppliers do not expect this component of their sales to grow tremendously. This may reflect growing competition from “home-grown” supplier segments in key international markets, especially Japan.

Chart 2-4

Projected Foreign Sales by Market Segment

percentage of total sales

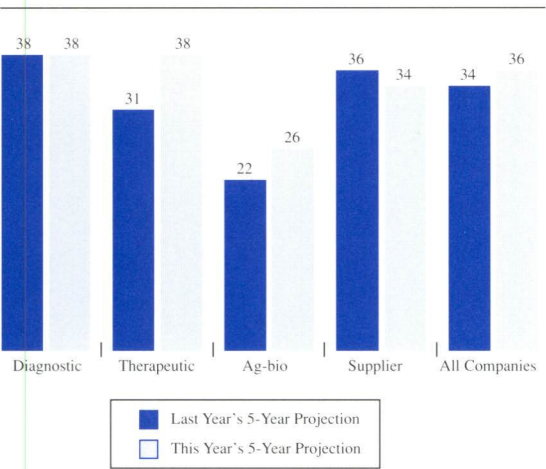


The therapeutic companies expect substantial increases in the level of their foreign sales. Many are awaiting foreign regulatory approvals for products they currently are selling domestically. Other companies may obtain product approvals in Europe even before obtaining them in the United States, as Cetus did for IL-2 and Biogen for gamma interferon.

Overall, this year's expectations for growth in foreign sales over a five-year period slightly exceeds last year's (Chart 2-5). This is noteworthy in light of the drop-off in the five-year projection of sales growth overall (Chart 2-2).

Chart 2-5

**Change in Projected Foreign Sales
Percentage of Total Sales by Market Segment**
percentage of projected total sales



Geographic Markets

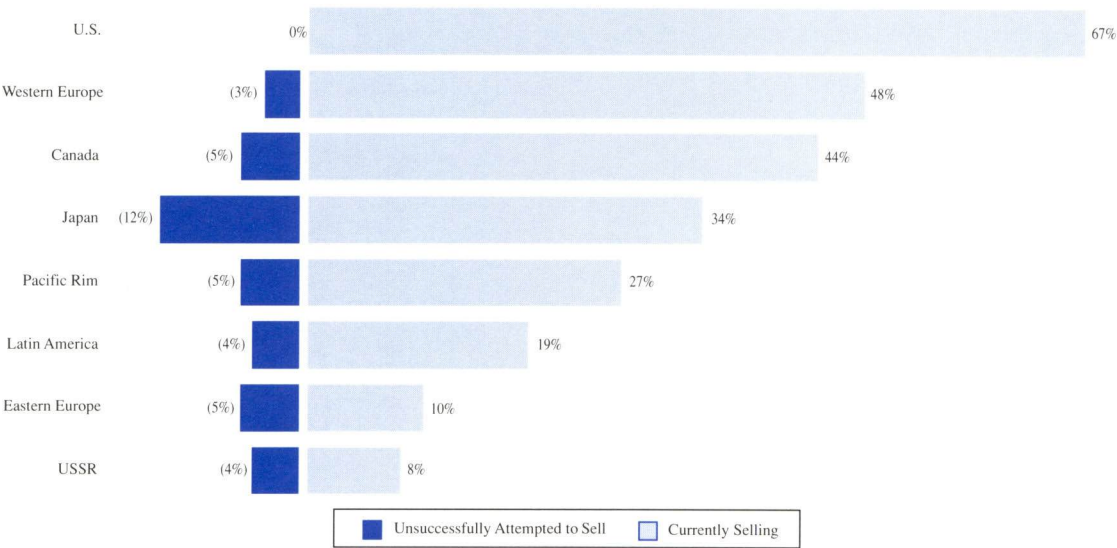
Looking to the various geographic regions (Chart 2-6), nearly two thirds of the companies with sales in the United States are also selling in both Western Europe and Canada. The low failure rate in these markets (i.e., the number of companies unsuccessful in entering these markets divided by the total number of companies attempting to sell) indicates these regions are fairly easy to access.

While roughly half of all firms selling in the United States are also selling in Japan, the failure rate there is high, approximately 26 percent. Therapeutic companies experience the highest percentage of failed attempts (67 percent). While Japan has the highest per capita pharmaceutical consumption in the world, the pharmaceutical market is intensively competitive. There are complex cultural as well as trade barriers to operating in Japan—for example, the practice of allowing Japanese doctors to capture a fee for prescribing specific products has tremendous impact on “buyer” behavior.

Japanese trade and cultural barriers are identified as obstacles by a significant percentage of all companies (Chart 2-7). The regulatory climate is equally daunting. Clearly, Japan is the most difficult of the three major markets for U.S. companies to enter. It does not present a level playing field.

Chart 2-6

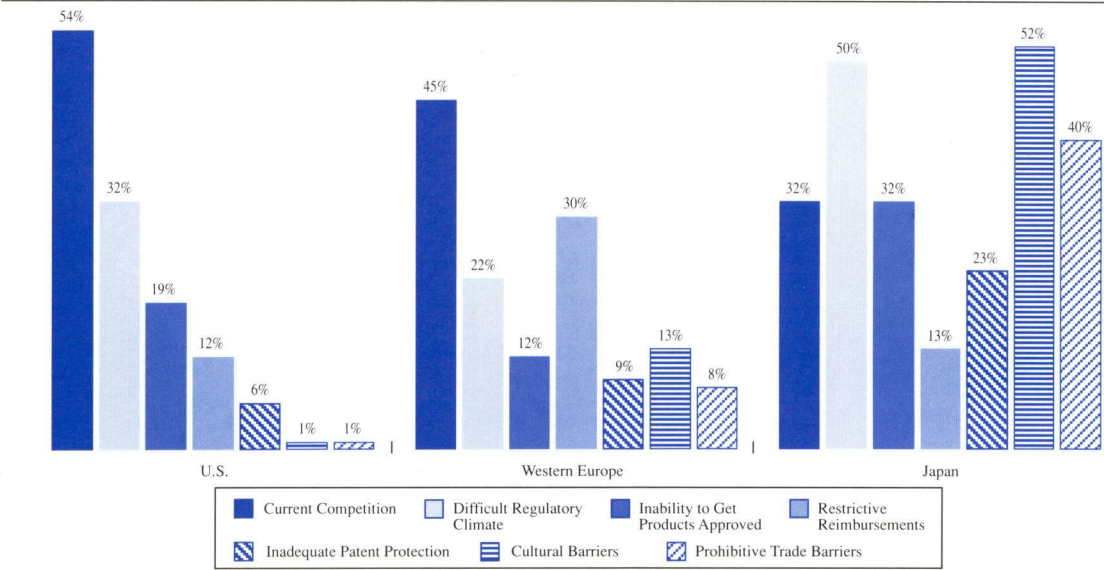
International Sales Activity of U.S. Biotech Companies



Note: Many companies have made no sales attempts in the above areas.

Chart 2-7

Major Obstacles to Entry in Geographic Markets—All Companies



The primary obstacle in entering the domestic market is the level of competition in the United States. Many respondents also cited problems with regulatory processes. (*Regulatory issues are examined at length in Chapter 4: Government Involvement.*)

In Western Europe, competition appears to be somewhat less strenuous for U.S. companies. The advanced development of U.S. biotechnology provides a competitive edge. However, in Europe’s socialized health-care environment, government-reimbursement programs are a dominant factor to contend with, especially with the significant cost-containment efforts that are currently underway. Further, the hostile stance and political clout of Europe’s environmentally-focused Green parties, while particularly challenging to ag-bio companies, creates tough going for genetically engineered products in general.

Product Pricing

The issue of product pricing, complex in itself, is compounded for companies involved in health care by the growing influence of reimbursement authorities in determining the pricing the market will bear (*See the Ernst & Young roundtable, “Biotech and the Health Care Agenda”*). Pricing must adequately cover a product’s development costs, generate capital for future product development, and create profits to compensate shareholders for their invested capital and risk.

Chart 2-8 details the various factors that go into pricing in the individual market segments. As can be seen, there are wide discrepancies.

Chart 2-8

Factors in Product Pricing by Market Segment

percentage rating most important

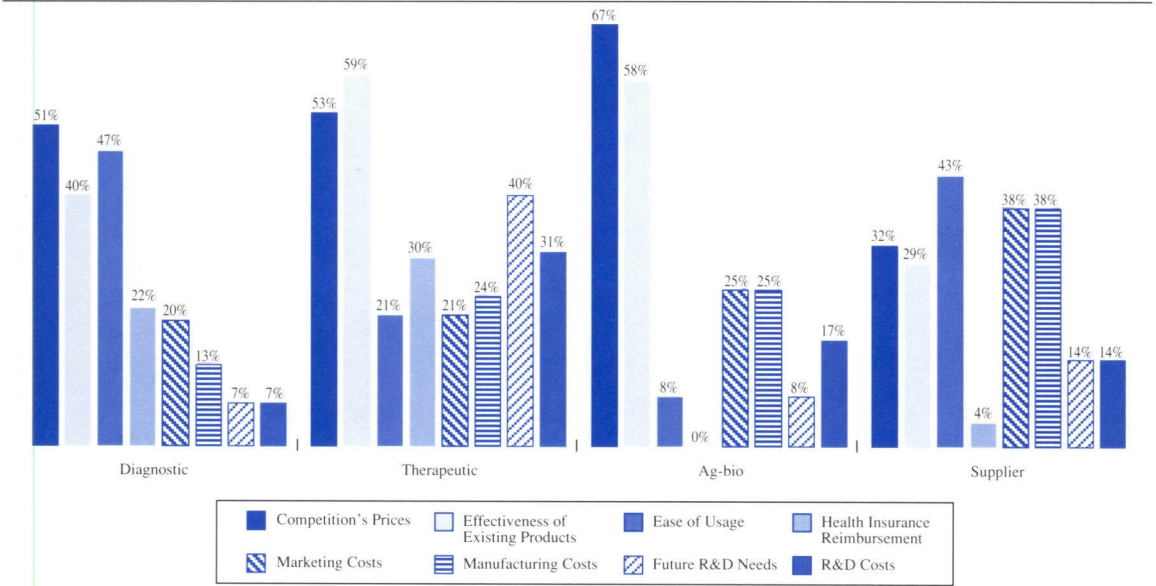
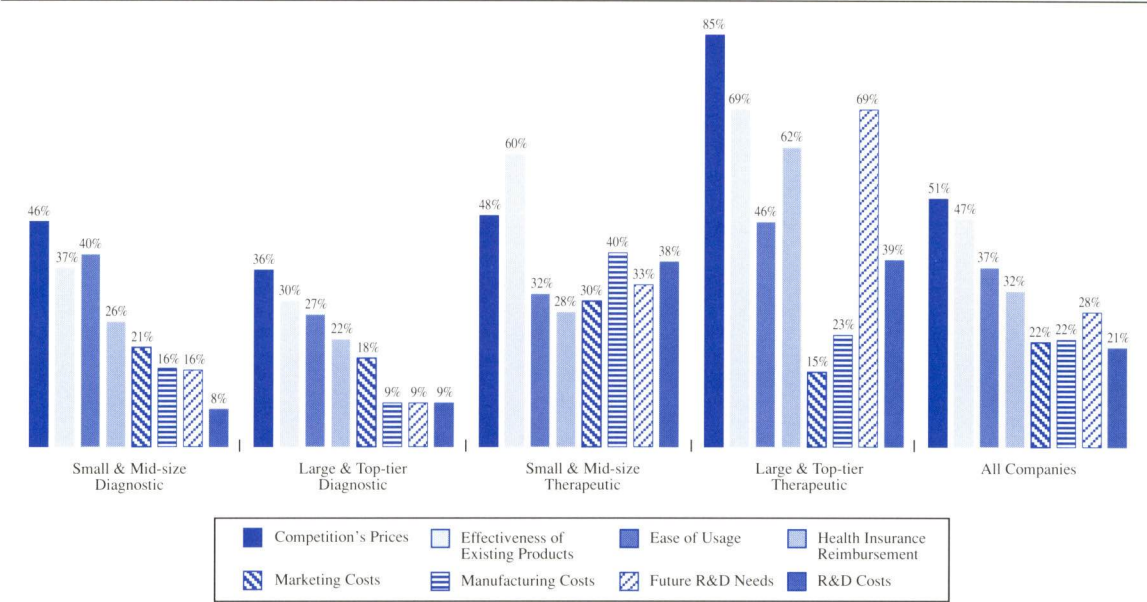


Chart 2-9

Factors in Product Pricing for Health-Care Companies by Market Segment

percentage rating most important



Each of the first four factors shown are market-driven, that is, they refer to conditions in the current product market: competitive prices, comparative product effectiveness, ease of usage, and reimbursement. The second group of factors are driven by the costs of marketing, manufacturing, and developing the products. Future R&D needs are also included among the cost factors because companies' long-range success depends upon developing a continuing flow of products. (See the interview with Frederick Frank for a discussion of the importance of this factor in the Roche/Genentech transaction.)

The diagnostic, therapeutic, and ag-bio companies are all intensely market-driven in pricing. Reliance on market factors typically results in substantial profits in up markets and thin coverage of expenses when markets are down. These effects are most noticeable in cyclical agricultural markets.

Therapeutic companies have the most intensive R&D needs of almost any industry. It is not surprising that they place a high premium on product and future R&D costs. Suppliers, whose product line parallels traditional products more than the other industry segments, give greater heed to the traditional cost factors than do other biotech companies.

Chart 2-9 provides further detail on the pricing considerations for health-care products. While diagnostic companies of all sizes tend to use fairly uniform pricing strategies, the large and top-

tier therapeutic companies place much greater emphasis than their smaller brethren on reimbursement issues.

Reimbursement is understandably important to these companies. They have major products on the market—many of which are expensive on a unit basis compared to products traditionally available. These companies have had the greatest exposure to reimbursement authorities and private insurers.

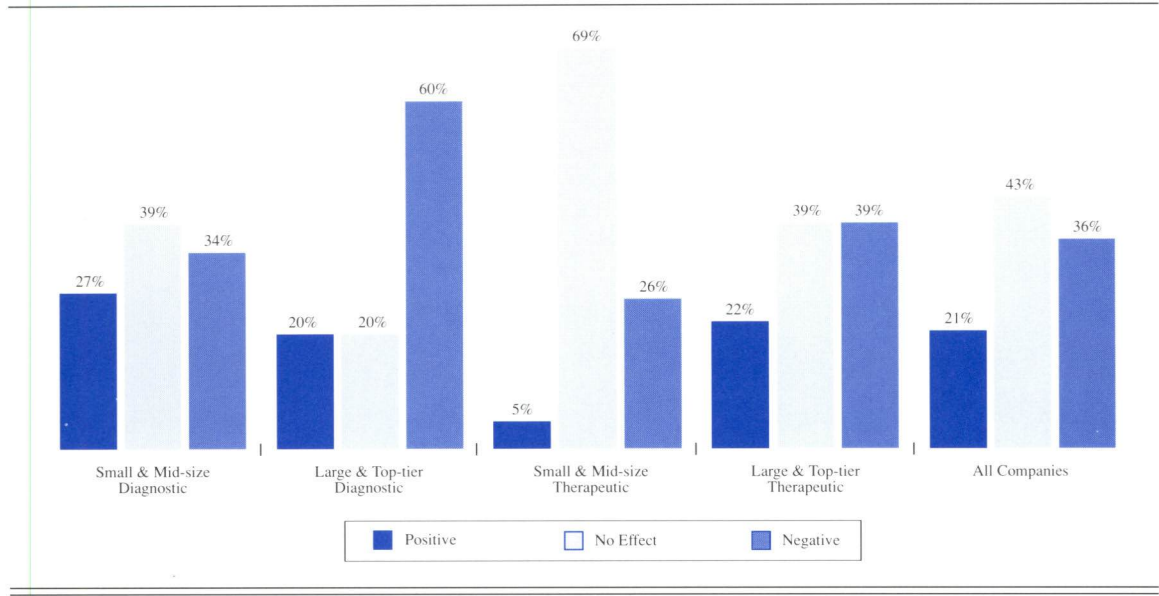
There is a deep and growing concern in the United States over the rapid growth of the costs of health care. Currently representing 11.4 percent of the GNP, health-care costs are projected to account for 15 percent by the late 1990s. Even though drugs represent only six percent of total health care expenditures, they are coming under intense pricing pressures from public and private insurers/payers of health care products and services.

Therapeutic companies, unlike most other companies, do not sell directly to the consumers of their products. Patients have little to do with demand and pricing questions. Traditionally, physicians determined the drugs their patients use. Today, even physicians' responsibility is waning. The payers—the Health Care Financing Administration (HCFA), the insurance industry, the full range of managed-care plans, and corporate America's benefits departments—are increasingly calling the tune. They are the new gatekeepers between therapeutic companies and the consumers of their products. Not only are they determining how much of a product's cost they will reimburse; they also are designating which products will be reimbursed for a particular application, and which will not. They are venturing into setting treatment protocols.

Initiatives have been launched in Washington in the spring and summer of 1990 to develop formularies of allowable drugs for Medicaid reim-

Chart 2-10

Effect of Health Insurance Reimbursements on Product Sales—All Health-Care Companies



bursement, one in a proposal floated by the director of the Office of Management and Budget (OMB), Richard Darman, and the other in a bill introduced by Sen. David Pryor. The common criterion in the two proposals is cost. These initiatives are designed to pressure companies to negotiate discounts.

Safety and efficacy alone no longer suffice to ensure reimbursement for new therapeutic products. But cost need not, and certainly should not, become the driving force. Gatekeepers also are looking at the quality-of-life outcomes in treatments for chronic diseases for which cures are not yet available. They are attending to products' cost-effectiveness compared to competing treatment modalities. These criteria often play to biotechnology's strengths.

Chart 2-10 provides additional detail regarding the effects of health-care reimbursement. Interestingly, scrutiny of pricing by reimbursement authorities is not perceived to have a decidedly limiting effect on product sales. While 36 percent of the companies perceive a negative effect, 21 percent see a positive impact, and 43 percent see little effect or none. The larger diagnostic companies, the companies with the most commercial product experience, are the most negatively affected. This suggests greater difficulties ahead for other companies.

While the gatekeepers are in a position to deny companies adequate reimbursement in order to keep overall health care costs down, they are also in a position to recognize the real cost-benefits of innovative products over traditional treatments. It is up to the companies to make a strong case for the value of their products and the cost/benefit tradeoffs.

3. Corporate Development Strategies

Strategic alliances are proving to be an integral part of the development of biotechnology companies—alliances with other biotech companies and with larger, established corporations. There is no major biotech company that does not have significant alliances in place. There is no start-up that can ignore the importance of forming these vital links. At some point, almost all of our interviews and roundtables with industry CEOs came around to the benefits they derive from these relationships.

A spate of acquisitions this year ranging from the large (Roche/Genentech) to the significantly smaller (Quidel/Monoclonal Antibodies) are making the consolidation option more prominent. There is an interesting opposing dynamic between strategic alliances and combinations. Companies that are well-partnered are generally less open to consolidation overtures. Not only are their needs to access greater resources being met by the relationships they have in place; those relationships also are a barrier to consolidation because they commit many of their assets to third parties.

Alliances and consolidations are not confined to biotech companies. Established companies also are forming links (Merck/Du Pont, Rhône-Poulenc/Chugai) and consolidating (SmithKline Beecham, Marion Merrell Dow). Companies in every sphere understand that, in a global marketplace, companies need to link their strengths to the strengths of other companies to position themselves to compete.

During the 1990s, alliances and combinations involving biotechnology companies will increasingly be international. This will change the structure of the industry and perhaps shift the center of gravity from the United States to a more global plane.

Key Findings

Strategic Alliances

- Biotechnology companies, on average, are involved in three strategic alliances. However, the top tier have an average of nine. These numbers are expected to increase to five and 11, respectively, over the next year.
- One-third of existing alliances are foreign—the majority with companies in Western Europe.
- Companies seek alliances primarily to increase their marketing capabilities and penetration, and to satisfy current and future capital needs.
- Japanese partners are valued for their ability to deal with the Japanese regulatory environment, in addition to their access to Japanese customers and their deep capital resources.
- Capital needs are a driving factor in therapeutic and ag-bio companies' alliances with other U.S. companies. Diagnostic and supplier companies emphasize the potentially expanded marketing opportunities.

Consolidation

- The industry is very positive about the effects of the recent acquisitions of U.S. biotech companies by foreign buyers—citing, especially, an increase in partnering opportunities and raised investor interest.
- Approximately three-quarters of all companies believe it does not matter whether an acquirer is foreign or domestic.
- Within the next five years, nearly half of all companies expect to acquire another company, 39 percent expect to be acquired, and 32 percent expect to merge with a firm of comparable size.

Strategic Alliances

Strategic alliances used to be regarded primarily, if not exclusively, as a means to obtain bridge financing until a company could bring a proprietary product to market. Now they are valued equally for the additional reach and resources they bring—in regulatory affairs, marketing, sales, and customer support. Historically, the industry-standard configuration has been a partnership between a biotech company and a large, established pharmaceutical/chemical/agricultural corporation. Now we are increasingly seeing strategic relationships develop within the biotech industry between biotechnology companies.

Each partner has an asset (a product, technology, or research capability) or a resource (capital, manufacturing capability, and/or a marketing/distribution channel) that the other can leverage. When well-chosen and successfully managed, these relationships create a whole that enhances the value of the parts.

A strategic alliance is not a truncated acquisition. Partners are strategically important to each other. Certain of their product interests are aligned—but they otherwise are independent.

Nor are these relationships unidimensional technology transfer or product license agreements. They may also include R&D funding and collaboration, and manufacturing and marketing endeavors. They may involve equity positions.

It is important for partners to enter the transaction with an awareness of the elements it takes to make a corporate alliance work. These include:

- A common objective that benefits both companies.
- Cultures that are sufficiently flexible to encompass the differences that exist between them.
- Clear delineation of the expected contributions of both parties and of the decision-making process.
- Contingency plans for exiting the arrangement if indicated by the course of events.
- Commitment to making the alliance work.

Chiron's CEO, Edward Penhoet, who characterizes his company as "probably the company that has been most committed to corporate partnering as a fundamental commercial strategy," stresses two key practical considerations in our interview with him: "First, we get as close to equal participation in the relationship as we can, so that both parties have real standing. Second, we work at developing a positive understanding in both companies about the relationship. Partnerships are hardest to implement at the middle-management level; that's where parochial interests can sandbag your shared interests."

Number of Strategic Alliances

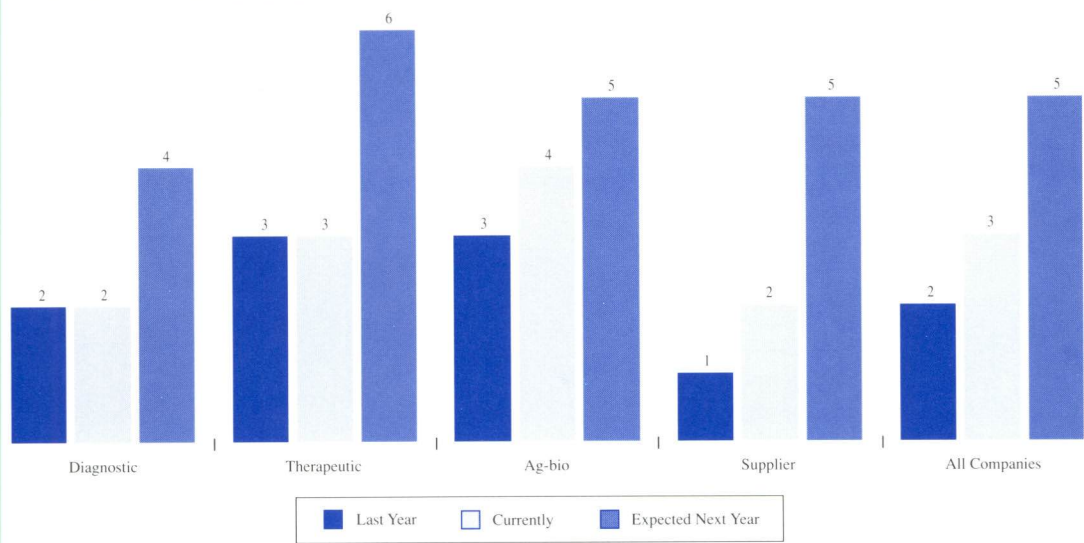
The industry expects a growing emphasis on alliances. The average number of alliances for companies of all sizes increased from two to three during the past year. During the coming year, this number is expected to reach five. The expansion of alliances cuts across all market segments (*Chart 3-1*).

Even suppliers, who have exhibited the least amount of alliance activity in the past, expect to ratchet up to the industry average (a phenomenon which parallels developments for suppliers in other U.S. industries, including autos and electronics). The information reported in *Chart 3-6* later in this chapter suggests that the increase in partnering activity may reflect suppliers' need to access new products, stay tapped into the technology development processes of the companies they supply, and increase their market penetration through synergistic distribution channels as their markets mature.

Therapeutic companies also predict a surge of alliance activity. The difficulties that many of these companies face in obtaining adequate financing for product development is surely a factor. Therapeutic companies are also developing a

Chart 3-1

Past, Present, and Future Number of Strategic Alliances by Market Segment



deeper understanding of the many hurdles that they face—financial, regulatory, distribution, and sales/marketing—in bringing products through approval and realizing their potential in the marketplace. Alliances are becoming the primary strategy for dealing with these challenges.

Table 3-1

Past, Present, and Future Number of Strategic Alliances by Company Size

Company Size	Last Year	Currently	Next Year
Small	1	2	4
Mid-size	2	2	4
Large	3	4	5
Top Tier	8	9	11
All Companies	2	3	5

The small and mid-size companies expect to double their number of alliances (from two to four) while the large and top-tier companies expect to add steadily to their large alliance base (Table 3-1). Clearly, an extensive network of working strategic relationships has become an underpinning of growth in this industry.

However, companies’ projections of additional alliances may be flawed. Several companies can be angling for the same corporate partner. Further, alliances, like marriages, can be dissolved if unworkable differences emerge. For example:

- Partners’ needs that were once in sync may diverge.
- The development of a technology may take a different direction or cost a great deal more than the partners anticipated.
- Development may take too long, and/or competing technologies may come onto the scene—both of which can alter the competitive dynamics.
- Capital markets change, altering the financing needs and opportunities of both companies.

Chart 3-2

Reasons for Geographic Strategic Alliances—Companies with Strategic Alliances in Each Region

percentage rating most important

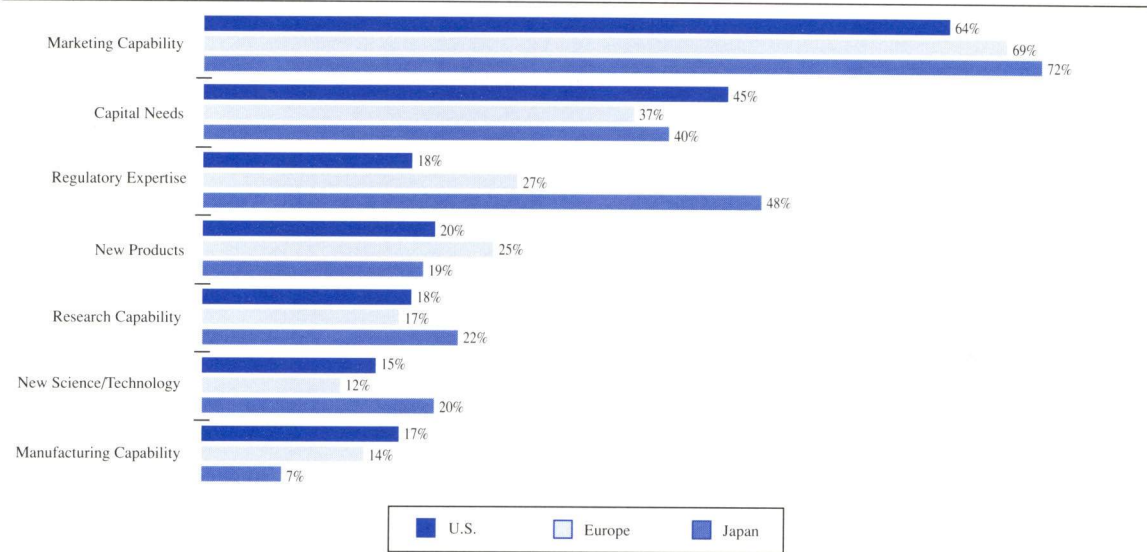


Table 3-2

Geographic Distribution of Current Strategic Alliances by Company Size

Company Size	U.S.	Europe	Japan
Small	1	1	0
Mid-size	1	1	0
Large	2	1	1
Top Tier	4	4	1
All Companies	2	1	0

Table 3-3

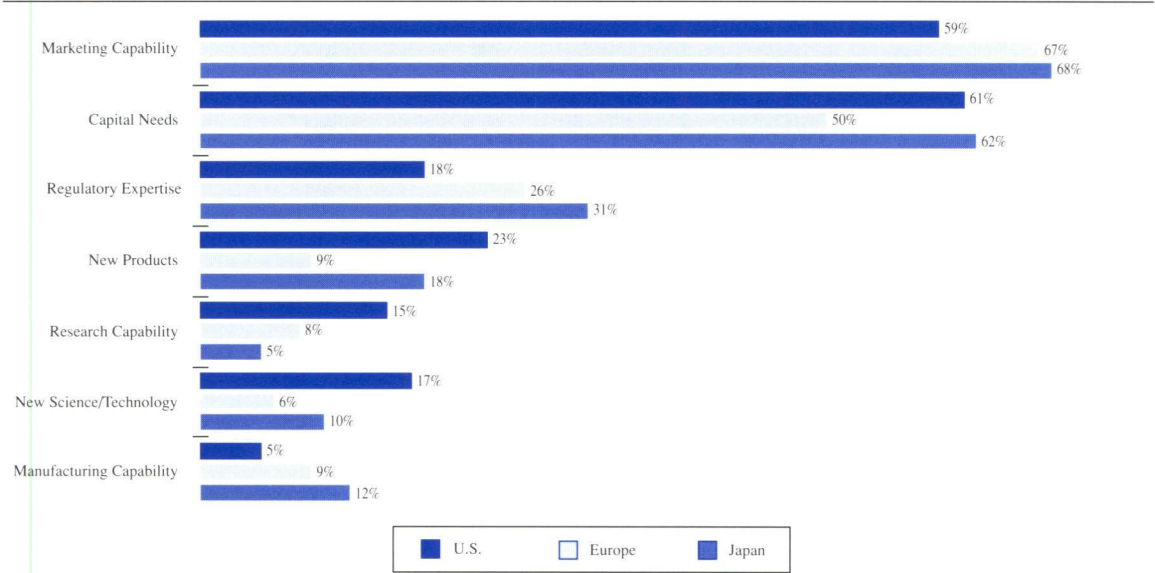
Geographic Distribution of Current Strategic Alliances by Market Segment

Company Size	U.S.	Europe	Japan
Diagnostic	1	1	0
Therapeutic	2	2	0
Ag-bio	2	1	1
Supplier	1	1	0

Nearly half of the survey respondents' alliances are with foreign partners. This proportion holds fairly constant among all company sizes and in all market segments (Tables 3-2 and 3-3). Overwhelmingly, these trans-national relationships are formed with companies based in Western Europe. However, ag-bio and supplier companies have formed equal links with companies headquartered in Japan. Biotech companies clearly understand that their markets already are global, and that their capital sourcing is increasingly so. (Appendix B summarizes the major alliances established during the past year.)

Chart 3-3

Reasons for Geographic Strategic Alliances—by Companies Expecting Their First Alliance in Each Region During the Next Year
percentage rating most important



Reasons for Alliances

Companies form alliances primarily to build and increase their market penetration and fulfill their financing needs. While these motivating factors are generally consistent with last year’s findings, this year’s findings surface some interesting nuances.

Chart 3-2 summarizes companies’ objectives in the alliances they currently have with U.S., European, and Japanese partners. Chart 3-3 depicts the objectives of companies that do not have an alliance in a given region, but expect to establish one or more in the coming year. While marketing and capital needs remain the prime motivation in both categories, the companies that currently have alliances place a higher emphasis on secondary needs. Most notable are the greater weight the experienced companies place on the contributions of Japanese partners in the regulatory area, of European companies in product development, and of U.S. companies in manufacturing. This pattern suggests that companies derive broader benefits from strategic alliances than they anticipate at the outset, and that

companies’ alliances grow more complex as companies mature.

Chart 3-4 further details the reasons for partnering with other U.S. companies by industry segment. Here, differences clearly come to the fore.

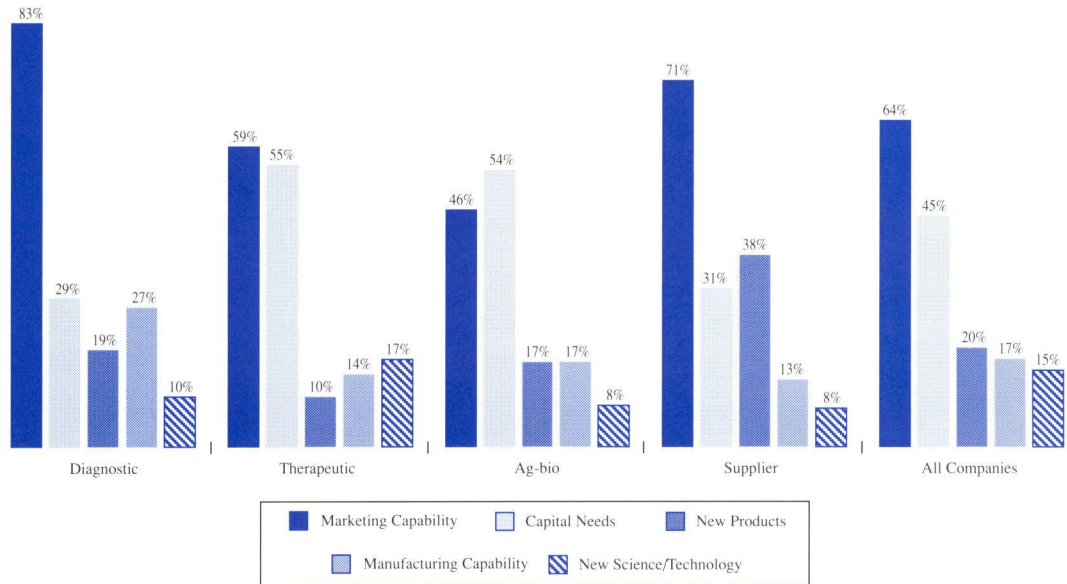
The diagnostic and supplier companies are far and away the most interested in marketing assistance, with minor interest in any other benefits. This complements the finding, reported in Chapter 1, that these companies face the fewest critical problems and hence have the least need to use alliances as broad problem-solving tools.

While the therapeutic and ag-bio companies also rate marketing support important (although not as high as the diagnostic and supplier companies), their needs for immediate and future capital loom large. Again, this is consistent with a finding in Chapter 1 that the most pressing problem of these industry segments is the need for capital. It would be expected that as more of these companies move closer to commercialization, their appreciation of the other benefits of alliances will deepen.

Chart 3-4

Reasons for Partnering with U.S. Companies—Companies with Alliances in the U.S.

percentage rating most important



Consolidation

“Friendly” consolidations have been the norm in the biotech industry thus far, reflecting the fact that these companies have few hard assets. The real assets of a biotech company are the people who walk into the lab every morning, and have the option to walk out, for good, if the firm takes a turn they don’t like. These human assets must be won over, not taken over. Another potential barrier to unwanted consolidation is the target company’s strategic alliances, which may assign its jewels—its products and technology—to other companies’ jewelry boxes. An acquirer would have to absorb, unwind, or renegotiate the existing relationships.

As the top-tier companies build their market shares, obtain broad patent rights, and bring more products through the regulatory process, they may amass the hard assets that attract “hostile”

takeovers. However, the price for a hostile acquisition can be prohibitively high. In the CEO roundtable, “Life After Roche/Genentech,” Biogen’s James Vincent argues that most large pharmaceutical companies have internal reasons for balking at high-ticket transactions.

Effects of Recent Consolidations

As summarized in Appendix C, there were over 30 acquisitions involving biotech companies during the past year. Among them were significant domestic acquisitions (American Cyanimid/Praxis Biologics and Genzyme/Integrated Genetics). But what generated the most interest was a decidedly international tilt (Roche/Genentech, Chugai/Gen-Probe, and Fujisawa/Lyphomed).

There has been much discussion in the industry, the press, and government about the pros and cons of foreign involvement in this important U.S. technology. As shown in *Chart 3-5*, biotechnology CEOs overwhelmingly perceive the foreign acquisitions as having positive effects on their companies, on a number of strategic fronts. These transactions clearly have been a factor in the run-up in the stock prices of the top-tier firms. As James Vincent commented in the aforementioned round-table, “The Genentech deal pushed up our stock prices about 15 percent.”

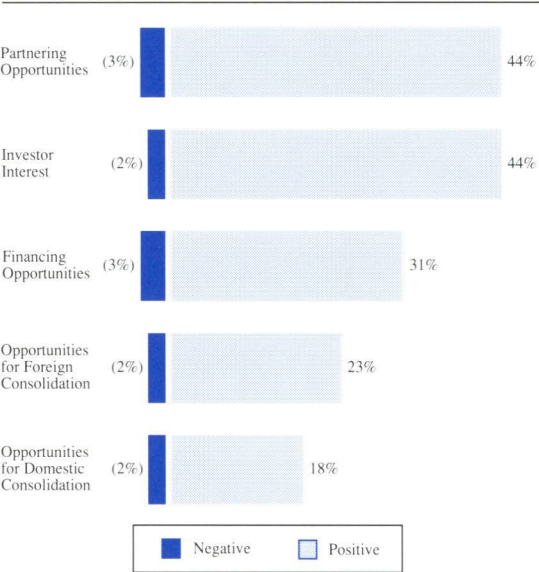
The companies acquired this year were far from bargains if measured by the premiums paid above their market values: Roche acquired 60 percent of Genentech at a 40 percent premium over its market valuation. Gen-Probe went to Chugai at a 92 percent premium, and Praxis Biologics to American Cyanimid at a 175 percent premium.

These purchase prices affirmed the worth of the technology. They sent a message to investors that many companies will return value, either by growing into profitable businesses (operating value) or by being acquired (exit value). This affirmation is making it easier for companies to raise capital and transact alliances. It is supporting a wave of secondary offerings and increasing the opportunities for companies to be acquired, which is a strategic goal for many (*see Chapter 1*).

Are companies concerned whether the suitor that approaches them is domestic or foreign? For three-quarters of the companies, it is a non-issue (*Table 3-4*). This finding is consistent across all market segments and company-size categories.

Chart 3-5

Effects of Recent Foreign Acquisitions—All Companies



Many companies view being acquired as the answer to the unending struggle for financial and other resources. They are more concerned about the terms of the deal they can transact (purchase price, capital infusion, degree of independence, etc.) than the nationality of the company across the table. As one respondent summed it up, “A deal is a deal.” Further, biotech companies are already allied with foreign partners. In this global industry, international transactions are a norm.

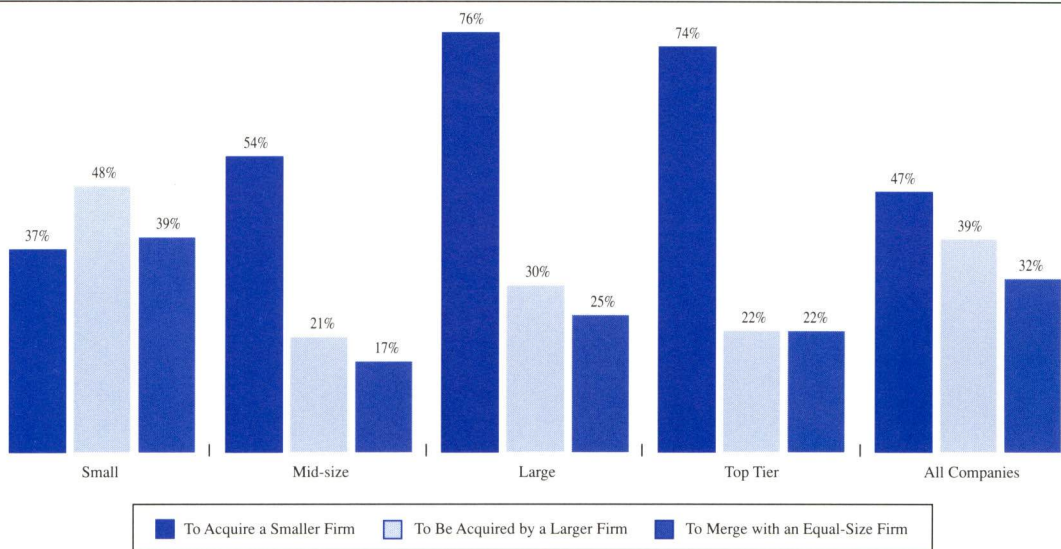
Table 3-4

Percentage Concerned Whether Acquirer is Foreign or Domestic

Company Size	% Concerned	Market Segment	% Concerned
Small	27%	Diagnostic	20%
Mid-size	16%	Therapeutic	22%
Large	17%	Ag-bio	29%
Top Tier	36%	Supplier	35%
All Companies	25%		

Chart 3-6

Plans for Consolidation Within the Next 5 Years by Company Size



Expected Consolidations

As *Chart 3-6* details, companies expect a great deal of consolidation activity. Consistent with previous years, the smaller companies see themselves the most likely to be acquired, while the larger companies are the most likely to acquire other companies during the next five years. Companies of all sizes are giving consideration to combinations with companies of equal size.

The high number of large and top-tier companies expecting to be acquirers indicates that much of the expected consolidation will take place within the industry. Taking a leaf from the book of the major pharmaceutical companies, the larger biotech companies, too, are looking for acquisitions as a means to broaden and diversify their product lines and keep their R&D pipelines full.

4. Government Involvement

The biotechnology industry has a uniquely intimate relationship with the U.S. government:

- Funding from the National Institutes of Health (NIH) and the Department of Agriculture (USDA) supports much of the industry's basic research.
- Regulatory agencies determine when the industry's products are proven sufficiently safe and effective to be made available to users.
- Government-issued patents protect companies' intellectual property.
- Medicare/Medicaid reimbursements, which serve as a bellwether for many private health-care reimbursement programs, influence what companies will be paid for their products.

Government activities that affect industries in general also have a profound influence:

- Tax and fiscal policies can stimulate or stifle investment.
- Product liability responsibility is set by government regulation or law.
- Legislation can promote the interests of some industry constituencies over others.
- Overall trade and industrial policies invite or discourage competition in domestic and foreign markets.

Government has the potential to affect the industry for good or for ill in numerous ways. On balance, the industry is not giving our government good marks.

Government activities affecting biotech companies cannot by any leap of the imagination be construed as a deliberate industrial policy. The effects of various government actions on the industry are often unforeseen or unintended, but many of their consequences have been detrimental.

Government did not target the industry to lose advantages when it eliminated the capital gains differential and R&D tax credits. Yet this loss intensifies the industry's most critical problem, the difficulty of obtaining financing.

Government did not intend to construct a three-to-four-year time frame for the issuance of biotechnology patents and a decade-long process to obtain a product approval from the Food and Drug Administration (FDA). But these critical delays in protecting intellectual property and approving products for commercialization are not being attended to.

The Health Care Financing Administration (HCFA) is increasing the pressure on all providers of health-care products and services to drive costs down, not biotech companies alone. But capital-intensive companies that are just beginning to turn a profit have no fat in their product pricing to trim.

Last fall's proposed "Guidelines for Policies on Conflict of Interest" would have hindered the transfer of NIH-funded research to the private sector. The proposal, fortunately, was withdrawn. Had any such rule been in effect in the early 1980s, it would have crippled the industry's development.

Through acts of omission and commission that have a net unfriendly impact, the U.S. government may be letting this country's competitive lead in biotechnology erode. While Washington turns a deaf ear to the industry's cries of pain, governments in Europe, Japan, and the Pacific Rim are implementing regulatory, tax, and industrial policies to support the development of their national biotech industries.

There is much rhetoric in Washington about whether we should have a national biotech policy. We do, by default, have one. But is it the policy we want?

Government Policies—Key Findings

Overall Federal Activity

- More than a third of the companies rate federal government activity in the past year as having a negative effect on the industry. Only 24 percent believe the effects have been positive.
- Fifty percent of the top-tier companies give federal government activities a negative rating. By market segment, health-care companies are the most critical of the government's role.
- If additional federal funds were available to support biotechnology, companies would allocate the largest portion (50 percent) to research—basic, applied, and academic. Increased tax incentives (14 percent), and additional funds for the FDA (12 percent) and the Patent Office (9 percent) also are favored.

Specific Federal Priorities & Issues

- Sixty percent of the industry would support FDA user fees if the additional funds were used to expedite the drug/device approval process. This sentiment is strongest among the larger companies.
- Slightly more than half of all companies support user fees at the Patent and Trademark Office (PTO).
- Thirty-eight percent of the companies believe that the Orphan Drug Act should be amended.
- Half of all companies believe that the federal government needs to develop a national biotechnology policy. However, this belief is less prevalent among the large (42 percent) and top-tier (32 percent) companies.
- Forty-two percent of the health-care companies with products in the market believe that public concern over health-care costs negatively affects their companies.

- While nearly half of these companies see the public's concern affirming the need for innovative products, an almost equal percentage are concerned about the downward pressure on pricing.
- Over the next five years, more than 55 percent of the industry expects to benefit from the scientific knowledge and greater awareness of biotechnology that will flow from the Human Genome Project.
- Nearly 55 percent of suppliers expect to benefit directly by selling equipment, materials, and services to the Human Genome Project.
- The recent controversies over the use of synthetic chemicals and biotechnology in the food chain do not seem to have either a markedly positive or negative effect on ag-bio companies.

Overall Federal Activity

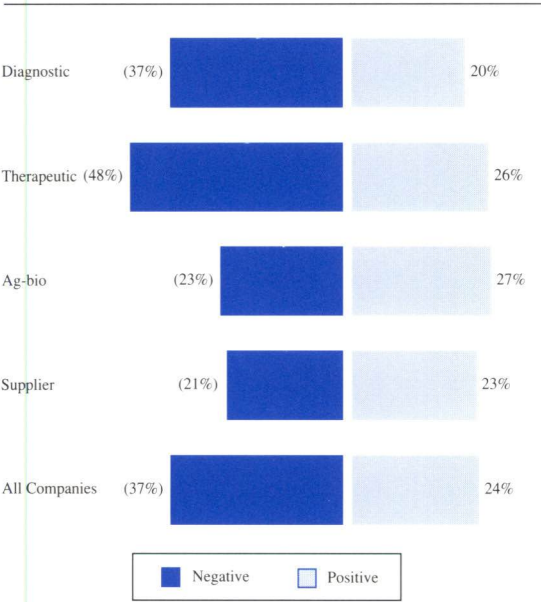
Federal government activities related to biotechnology during the past year included:

- Consideration of user fees at the FDA and PTO.
- Proposed changes in the Orphan Drug Act. (*The bill sponsored by Rep. Henry Waxman was passed in the House in August; as we go to press, the companion bill in the Senate sponsored by Sen. Howard Metzenbaum is still pending.*)
- Proposed legislation to protect intellectual property internationally (the Boucher Bill).
- The proposed (later withdrawn) NIH "Guidelines for Policies on Conflict of Interest."
- Changes/improvements in Patent Office handling of biotechnology applications.
- HCFA reimbursement decisions.
- Continuing rhetoric about capital-gains tax relief.

We asked industry CEOs whether the aggregate effect on the industry of current government activity is positive, negative, or neutral. As shown in *Chart 4-1*, there is no consensus. Thirty-seven percent deem the effects negative, 24 percent perceive a positive impact, and the greatest percentage (43 percent) either are undecided or see the industry unaffected. By market segment, however, the therapeutic companies are more decided. Approximately half are critical. Half of the top-tier companies also express a negative view. These are telling results, because these two groups include the companies that have the greatest involvement with government processes related to patents, product approval, orphan-drug status, and product reimbursement.

Chart 4-1

Overall View of General Government Activity in Biotechnology by Market Segment



Allocation of Additional Federal Funding

If the federal government were to budget additional funds to support biotechnology, how would the industry allocate the monies? The industry-wide response is shown in *Chart 4-2*.

Additional research is overwhelmingly identified as the number one need. If it were up to the industry, half of any additional funds would go to a combination of basic, applied, and academic research activities. This finding is a ringing affirmation of the criticality of government-sponsored research, which stems primarily from the NIH. Implicit in this finding is the importance of the industry being able to continue to access this research through appropriate transfer to the private sector. The industry also may be voicing a need for increased federal support to maintain the U.S. lead in biotechnology in light of growing government support for life-sciences research in the European Community and Japan.

The industry would allocate one-quarter of additional funds to improve the regulatory processes in the FDA, PTO, USDA, and EPA (Environmental Protection Administration). This is a surprisingly low allocation. These agencies often attribute their inability to be more efficient and responsive to the lack of sufficient funding. One would think the industry might have been more liberal in committing funds. Perhaps too few companies are sufficiently mature to feel the regulatory pinch. Some CEOs may believe that the problems at these agencies are more fundamental than the lack of sufficient funds. And some may question whether additional funds would actually be used to accelerate the regulatory processes or only help to enlarge the bureaucracy.

The regulators seem unsure of whether their role is to get reasonably safe products onto the market or keep reasonably unsafe products off. The lack of clarity about their mission affects everything they do. There are no incentives for regulatory personnel to expedite new product introductions, and no penalties for miring product evaluations in delay.

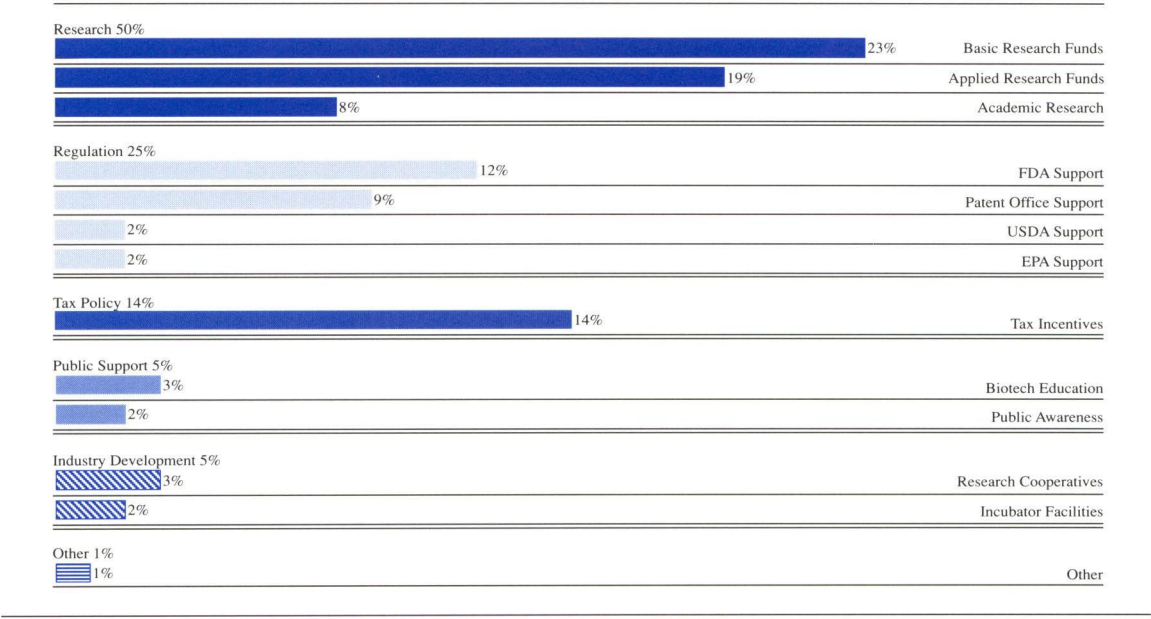
Tax incentives for investment in biotechnology draws considerable support (14 percent). This is arguably a research-related need, as the most likely incentive would be some form of an R&D tax credit. Indirect support through tax incentives, as opposed to direct government support (i.e., grants) would leave it to companies to determine how to use the funds made available, without requiring a bureaucratic stamp of approval. *(In the roundtable, “One Industry or Many?,” GenPharm International CEO, Jonathan MacQuitty, argues for the reinstate-*

ment of these incentives in order to bring back the R&D limited partnership, an important source of industry capital in the past.)

Funding for biotech education and greater public awareness both were rated very low. This is a fascinating finding in relation to the views expressed by Washington hands in our interviews and roundtables. Citing this year’s National Science Foundation report on the poor quality of U.S. science education and science literacy, Sen. Albert Gore argues the importance of funding science education to assure that we develop the talent and skilled resources that the biotech industry will need. In our Washington roundtable, Rachel Levinson (White House Office of Science and Technology) distills the sentiment of the group when she says, “Educating the public is crucial. If you don’t have public acceptance, our discussions about tax incentives, regulatory procedures, or other policy questions become academic.”

Chart 4-2

Allocation of Additional Federal Funding for the Biotech Industry—All Companies



The issue of public acceptance is having the most direct impact in the ag-bio and animal health segments—in relation to the environmental release of genetically modified organisms, the development of herbicide-resistant crops, the introduction of genetically engineered enzymes and organisms into the food chain, and the use of animals (transgenic and unmodified) in research. While this last item also affects health-care companies, in general, these companies have had little difficulty with public acceptance until now. They have developed credit with the public because their products save lives (e.g., t-PA), prevent the spread of disease (hepatitis C test), and are safer than synthetic or animal-derived therapies that they replace (rDNA human growth hormone). However, as these companies delve into gene therapy, they may elicit more strident comment than they have experienced thus far.

Also ranking low is funding for any government-sponsored infrastructure to support the industry’s development, such as research cooperatives and incubator facilities. In theory, research cooperatives could save companies the cost of engaging in redundant R&D activities to develop basic generic processes. Incubator facilities could support research activities for early-stage companies with limited resources to invest in their own plant. However, most of our respondents prefer to maintain the independence of their efforts and be in a position to reap the rewards of proprietary discoveries. It is worth noting that most of our respondents have facilities and current if not long-range funding to support their R&D. Thus, our findings overall represent the views of the “haves.”

While the views compiled in Chart 4-2 are fairly consistent across the various company-size and market segments, there are several notable exceptions. These are outlined in *Tables 4-1 and 4-2*.

Table 4-1
Notable Discrepancies in the Allocation of Additional Federal Funding by Company Size

	<i>Small</i>	<i>Mid-size</i>	<i>Large</i>	<i>Top Tier</i>
Applied Research	23%	16%	10%	7%
Academic Research	7%	9%	14%	12%
Tax Incentives	17%	16%	10%	7%
FDA Support	9%	14%	13%	19%
EPA Support	2%	2%	2%	1%
USDA Support	2%	2%	4%	2%
Patent Office	8%	9%	8%	12%
Public Awareness	2%	2%	3%	3%
Incubator Facilities	3%	1%	1%	1%

The smaller companies voice far greater desire for applied research funding than the larger companies. Smaller companies need applied technology to develop their research discoveries into commercializable products. The larger companies already have developed their technologies, and have the experience and financial resources to readily develop the additional technology applications they may need.

Table 4-2

Notable Discrepancies in the Allocation of Additional Federal Funding by Market Segment

	<i>Diagnostic</i>	<i>Therapeutic</i>	<i>Ag-bio</i>	<i>Supplier</i>
Basic Research	16%	26%	30%	25%
Applied Research	26%	13%	18%	20%
Academic Research	5%	7%	7%	16%
Tax Incentives	17%	16%	10%	7%
FDA Support	9%	19%	8%	3%
EPA Support	1%	1%	5%	2%
USDA Support	2%	1%	5%	2%
Patent Office	7%	12%	8%	5%
Public Awareness	2%	1%	6%	2%
Incubator Facilities	3%	1%	1%	3%

The small and mid-size companies are more in favor of tax incentives than the larger companies. R&D tax credits would help these companies attract venture funding and other pools of much needed capital. Such credits were available when many of today’s larger companies were growing and provided considerable support to their development.

The larger companies—essentially health-care companies with many products moving through the regulatory channels—would direct the largest share of additional resources to FDA and Patent Office support.

Table 4-2 shows a striking discrepancy between the views of therapeutic and diagnostic companies on additional assistance for the FDA. Clearly, the regulatory process for diagnostics/ devices is not as problematic as for therapeutic products.

Specific Federal Priorities & Issues

The issues on the Washington agenda receiving the most attention right now are the possible institution of FDA and Patent Office user fees, amendment of the Orphan Drug Act (*just passed in the House and now pending in the Senate*), and the role government should play in fostering the biotechnology industry. The survey responses to these issues are shown in *Chart 4-3*. Unless noted otherwise below, these findings are consistent across company-size categories.

A solid majority (60 percent) of the health-care and supplier companies would support FDA user fees if the additional funds were used primarily to expedite the drug/device approval process. Slightly more than half of all companies (52 percent) would support user fees at the PTO. This finding reflects some improvements in the efficiency of the Patent Office since it received additional funding this year and implemented a program to improve its biotechnology resources. FDA problems, on the contrary, generally are perceived to have worsened since the departure of Commissioner Frank Young last fall.

Only 38 percent of all companies believe that the controversial Orphan Drug Act needs to be amended, but 45 percent of therapeutic companies do. These are the companies whose products are affected by the legislation. The finding suggests that they are close to evenly divided.

The industry is split on whether the federal government needs to develop a national biotechnology policy—i.e., specific legislation to promote biotechnology. The larger companies are more disinclined—only 32 percent of the top tier and 42 percent of the large companies expressed support. One respondent’s view, “More government involvement means more interference,” probably encompasses the sentiment of many others.

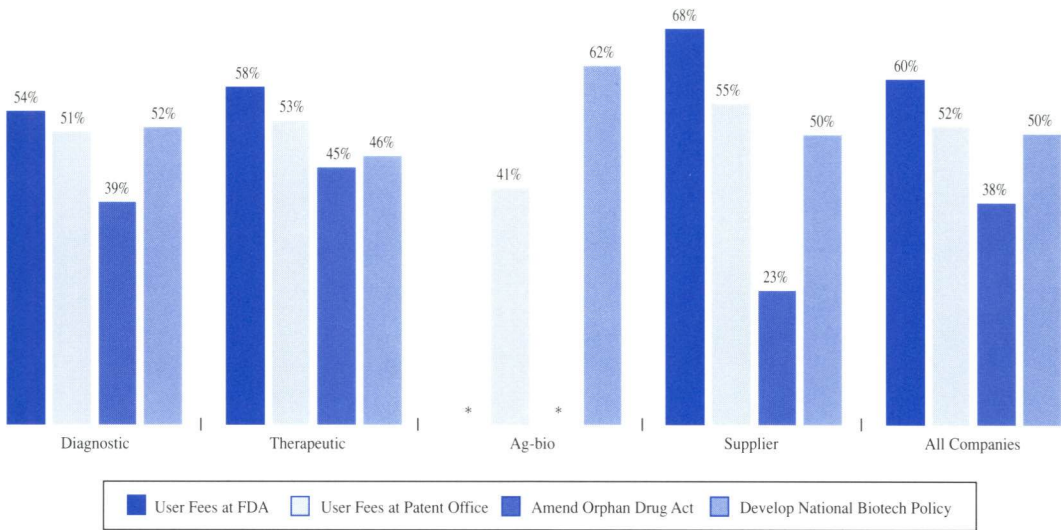
These views are understable if the question is taken to mean, “Do we need a biotechnology bill?” However, if the question is interpreted as, “Do we need to revise existing policies that negatively impact biotechnology, such as capital gains

taxation, FDA/PTO delays, etc.?,” the survey respondents have indicated in numerous ways that the answer is “Yes.”

As we stated earlier, we have a national biotechnology policy in this country by default. It is constructed of the numerous laws and policies that affect biotechnology companies. It is not a policy that helps companies to grow and develop in the United States. Nor does it enable U.S. companies to compete on an equal footing with foreign companies that are nurtured by national industrial policies and benefit from more supportive tax and trade policies. For example, the Japanese government has initiated a program to mobilize its universities, industries, and government to achieve dominance in biotechnology by the year 2000. In the United States, these three pegs of the industry are often in conflict. By default, we may let our competitive advantage in biotechnology slip away.

Chart 4-3

Desired Federal Activities by Market Segment



* Ag-bio companies were not surveyed on these issues.

Health-Care Expenditures

The U.S. health-care bill, now 11.4 percent of the GNP, is projected to reach 15 percent before the decade is out. Public concern over this massive expenditure is both spurring efforts to control health-care costs and creating widespread skepticism about the validity of many charges for health-care services and products. *(There is an extensive discussion of the implications of the health-care cost crisis for the biotech industry in the Ernst & Young Roundtable.)*

We asked the survey respondents how the intensifying scrutiny of health care costs is impacting on their companies at this time. *Chart 4-4* portrays the responses of the diagnostic and therapeutic companies that have product sales. Overall, only 15 percent feel that their companies benefit

from the public concern, while 42 percent discern negative effects. However, the majority of the large and top-tier diagnostic and therapeutic companies fear, or already are experiencing, negative effects. With products on or close to the market, these are the companies most exposed.

Chart 4-5 details some of the specific effects on these companies. The only notably positive effect is a premium on novel products that deliver better outcomes and/or lower costs than current protocols. This effect is important, because it is at the very basis of the mission of the biotech industry. As Gabriel Schmergel (Genetics Institute) puts it in a CEO roundtable, “We are not working on beta blocker number 28. We are working on some of the most critical unsolved health-care problems, such as cancer, Alzheimer’s disease, arthritis, and AIDS.”

Chart 4-4

Effect of Public Concern Over Health-Care Expenditures—Health-Care Companies with Sales

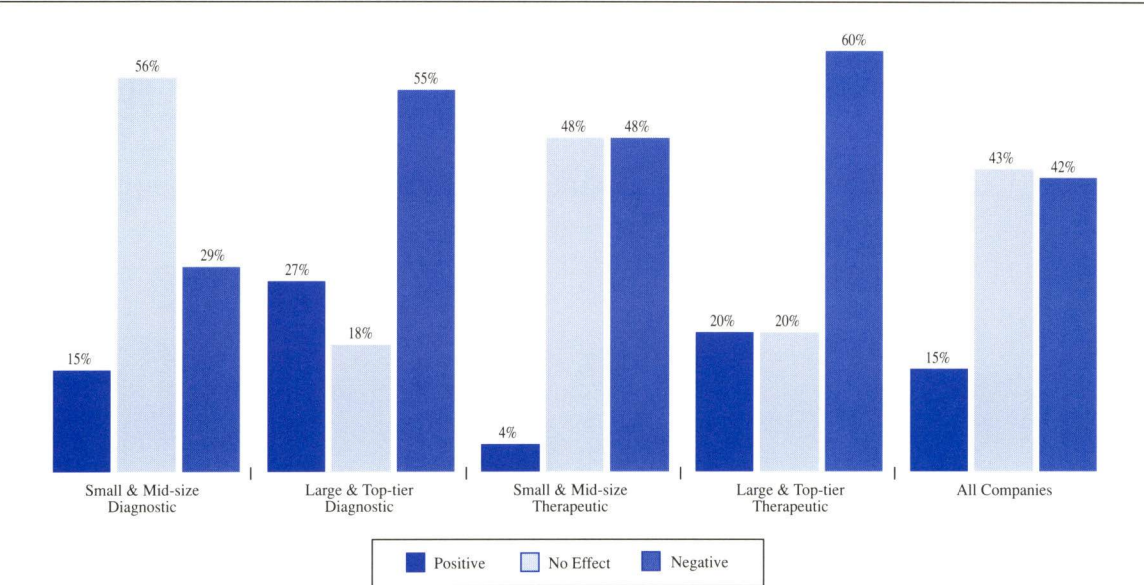
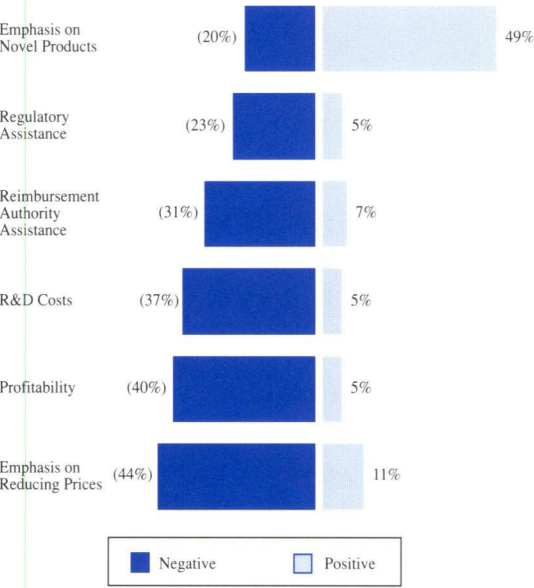


Chart 4-5

Specific Effects of Public Concern Over Health-Care Expenditures—Health-Care Companies with Sales



The greatest concerns revolve around the related issues of the influence of the reimbursement authorities, a downward pressure on pricing, and the effects on profits and R&D expenditures. The mission of the insurance companies, managed-health care programs, and HCFA is to provide their clients adequate levels of care at the lowest possible costs. The ability of these authorities to deny or constrict reimbursement can be devastating to companies that have invested as much as \$200 million to develop a new therapeutic product. Companies need to recoup their investment plus be compensated for the value they have created when their products come into use.

The only way for companies to effectively counter the pressure on pricing from reimbursement authorities is to demonstrate the value of their products—in terms of improvements in patient survival and quality of life, shorter hospital stays (or none), less invasive treatments, lower relative costs for specific outcomes, more productive use of

health-care personnel, and combinations of benefits like these. As Dr.Carolyn Davis, formerly the administrator of HCFA states in the Ernst & Young roundtable, “HCFA always looks at the question of benefit.”

Less than optimum pricing has a ripple effect on companies’ profitability and their future creation of value. The equation is quite simple—if a company cannot expect that it will be adequately reimbursed for an innovative treatment, then the company cannot afford to develop it. Referring to the public pressure on Burroughs-Wellcome this past year to bring down its pricing for the AIDS therapy, AZT, James Vincent (Biogen) points out in one of our roundtables, “If you had a drug candidate that had the potential to be a significant therapeutic step beyond AZT, and . . . the cost associated with it would be above \$10,000 a year, you [might] never get the reimbursement for that drug that you need to survive.” Increasingly, companies will have to develop cost/benefit data in tandem with a new product to make sure that a solid case for the product exists.

For every company that generates seemingly large profits from a blockbuster product, there are others that have invested huge sums of money on similar products that have failed. Companies have to be able to anticipate adequate returns to compensate their people and investors for the risk they take as well as the value they create. Otherwise the industry’s own cost-benefit equation will create an environment unfavorable for the development of innovative health care products.

Human Genome Project

The 15-year, \$3 billion program is now in its second year. This vast undertaking to map all of the human genes (and the genomes of several research animals) is expected to accelerate identification of the genes that cause or contribute to diseases and disorders. It will produce enormous gains in applied technologies, such as gene sequencing. It should spawn multitudes of new diagnostic and therapeutic products.

Over 55 percent of the companies we surveyed expect to receive some direct or indirect benefit from this work during the next five years. As a group, suppliers regard themselves the most likely to benefit (71 percent), followed by therapeutic (56 percent) and diagnostic (41 percent) companies. (The project has little application for ag-bio companies.) By size, top-tier (85 percent) and large (68 percent) companies are most likely to reap the early rewards. However, for now, the benefits for biotechnology companies are more indirect than direct, more long-term than immediate.

In the initial years, the largest impact on the industry as a whole will be in terms of increased public awareness, new discoveries and applications, and accelerated development of the biotechnology work force (Chart 4-6). Only in the supplier segment, which is furnishing the project's materials and instrumentation, do a significant number of companies (54 percent) expect to receive direct benefits from the start.

Ag-bio Issues

Ag-bio companies feel the heat of public debate at the point where chemical and biological sciences meet the food supply. In the past 12 to 18 months use of a bioengineered growth hormone (BST) in milk, Calgene's progress in developing a genetically engineered herbicide-resistant plant, and the application of the chemical preservative, Alar, on apples each have started conflagrations.

Transgenic plants were used on the farms of the United States long before the secrets of the plant genome began to be unravelled—and to no recorded harm. Chemical herbicides, pesticides, and preservatives also have been extensively used. The record here is more equivocal. Many of these substances have been shown to have deleterious effects to humans (although, in many cases, not in the small quantities ingested) and to the environment. People are concerned, and rightfully, about the documented and potential long-term effects of biological and chemical substances.

Chart 4-6

Expected Benefits of Human Genome Project in the Next 5 Years by Market Segment

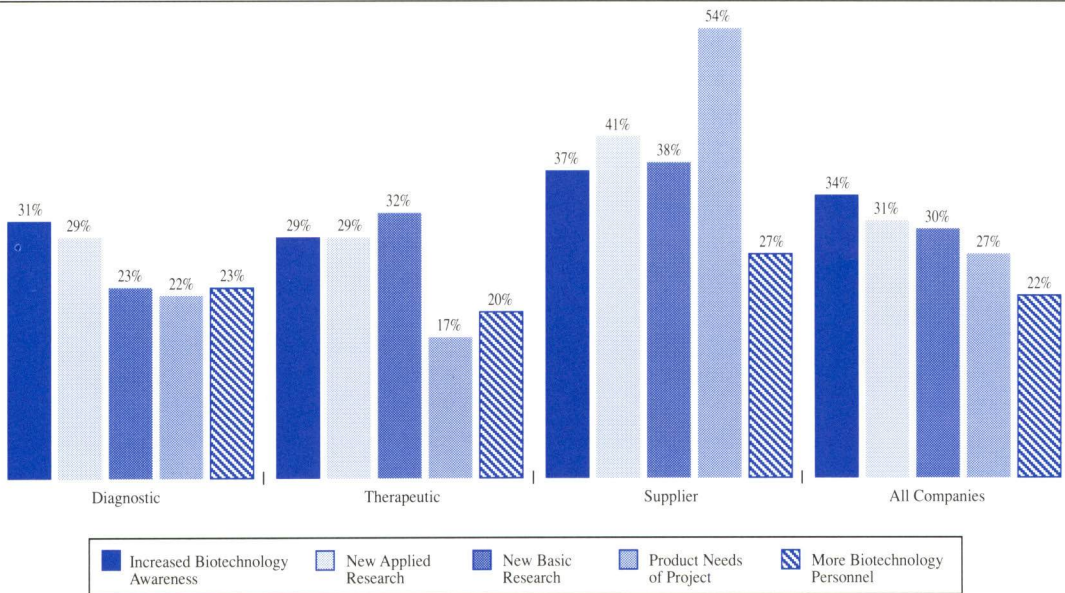


Table 4-3

Effects of Public Concern About Synthetic Chemical Agricultural Products on the Development of Biotechnology Products—Ag-bio Companies

Positive Effect	32%
No Effect/Mixed	52%
Negative Effect	16%

Yet, the road to progress in agriculture and nutrition must intersect the road of scientific innovation at many points if we are to produce more and better food for the people of the world, and foster agricultural productivity with more humanly and environmentally benign technologies that are. Agricultural biotechnology represents a responsible and promising avenue toward these goals. *(The interview with Jerry Caulder, the CEO roundtable, “One Industry or Many?,” and the Washington roundtable examine aspects of the ag-bio safety debate.)*

Table 4-4

Effects of the Recent Use of Biotechnology in Foods/Food Processing on Individual Companies—Ag-bio Companies

Positive Effect	39%
No Effect/Mixed	48%
Negative Effect	13%

Our survey polled ag-bio companies on the effects that public concern is having on their product development. Most of them see little effect from the outcry about the use of synthetic chemicals (Table 4-3). This finding may result partially from the fact that few ag-bio products have been, or are close to being, commercialized. The reception that many of these alternative products will find is still unknown. It is also possible that the interest groups pursuing this issue receive more coverage by the news media than their real influence merits.

Similarly, most of the ag-bio companies are not experiencing a fall-out from public scrutiny of biological products in the food supply (Table 4-4). Surprisingly, 39 percent believe these developments have a positive effect. Perhaps they feel that the battle lines are being drawn, the issues are being aired, and the resolution will come.

Regulatory Issues

Regulation is the crucial interface between government and biotechnology companies. The regulators hit companies where they live—their ability to bring their products to the marketplace in a reasonable time and in an orderly manner.

Delays and confusion in the regulatory agencies have become legend in the industry. Some of this is due to a lack of sufficient resources to handle the amount and complexity of product applications that biotechnology has spawned. Some is due to internal turmoil, such as the FDA’s generic drug scandal, and the failure to expeditiously replace Commissioner Frank Young. Some is due to a lack of clarity regarding the regulatory responsibility for classes of products, most notably in the agricultural-biotechnology sector. Some, simply, reflects the nature of government bureaucracy.

At the most basic level, what the industry needs from the federal government is a working regulatory structure that—as Jerry Caulder (Mycogen/IBA) phrases it in our interview with him—“gives us reasonable assurance that the science can progress, while giving the public reasonable assurance that the products are safe and effective.” The lack of such a structure fans companies’ uncertainties, adds burdensome costs, gives the states a rationale for adding their own layers of safeguards and impediments, and places U.S. companies at a competitive disadvantage vis-à-vis foreign companies that are not equally beset.

Key Finding

FDA Problems

- More than half the companies believe that turmoil at the FDA has had a negative effect on the biotech industry. However, only 15 percent report a direct negative impact on their company.
- Top-tier companies (67 percent) are more directly affected by FDA problems than smaller companies. Therapeutic companies (25 percent) are more affected than other market segments.
- Companies experience the negative effects of the FDA delays most keenly in the areas of sales/distribution (47 percent), financing ability (45 percent), competitive position (36 percent), and product development (34 percent).
- The lack of incentives within the FDA for product approvals are regarded the most troublesome aspects of companies' interactions with the agency. Also cited are time-consuming and frequently changing filing processes, and examiners' unfamiliarity with biotechnology.
- Because of the vagaries in regulatory behavior, companies consistently underestimate the amount of time and money they need for the various stages of regulatory approval.

Ag-bio Issues

- Only half of the ag-bio companies believe that the federal agencies responsible for approving the testing and selling/distribution of ag-bio products are clearly defined.
- However, only a minority of ag-bio companies are experiencing federal regulatory delays—16 percent in relation to the testing of their products, 16 percent in relation to selling/distribution.
- Regulatory delays at the state level affect even a smaller percentage—11 percent in product testing and 5 percent in selling/distribution.

FDA Problems

Companies developing products for human health care as well as many ag-bio and supplier companies are regulated by the FDA. There are roles and responsibilities that have to be well-played on both sides of the interaction in order to make it work. Companies have to communicate effectively and meet regulatory requirements on time and in toto. Regulators must communicate requirements clearly and comprehensively, respond to product filings and applications in a timely and responsible manner, and maintain a reasonably stable framework.

Historically, the FDA has a good record of achievement. Approval by the FDA is often sufficient to have products approved in many other countries. However, the agency's ability to respond to the novel products of biotechnology and guide these rapidly-developing companies through the regulatory thickets falls far short of what is needed.

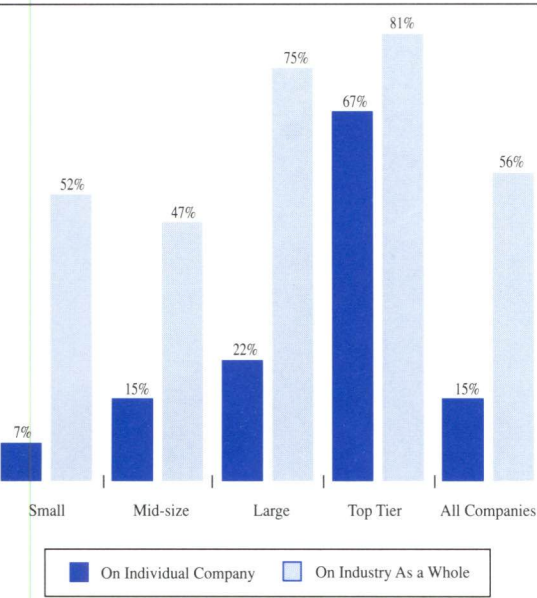
The small companies that are developing cutting-edge products have shallow pockets and limited regulatory expertise. The efficiency and clarity with which the FDA manages the trials and approval process is crucial to the fate of these companies. They cannot readily adapt nor recover when:

- FDA requirements are not clear, or are not clearly communicated.
- Filings that consume a huge amount of time and financial resources do not receive reasonably prompt attention.
- They get contradictory responses from different levels within the agency.
- There is confusion regarding the priority within the FDA of facilitating the flow of safe, effective products to the market.

Chart 4-7

Negative Effects of Turmoil at FDA by Company Size

percentage citing negative effect



More than half of the survey participants that are subject to regulation by the FDA—primarily diagnostic and therapeutic companies—believe that the turmoil has negatively affected the industry (Chart 4-7). Table 4-5, which delineates these views by market segment, shows that 25 percent of the therapeutic companies experience a direct negative impact. These companies, of course, are the most intensively under the FDA’s gaze and are dependent on its most intricate processes for product approval. Likewise, by size, the top-tier companies which are the furthest along in product development are the most vulnerable (64 percent) to FDA disarray.

Table 4-5

Negative Effects of Turmoil at FDA by Market Segment

	Diagnostic	Therapeutic	Ag-bio	Supplier
On Individual Company	9%	25%	7%	16%
On Industry as a Whole	46%	65%	50%	56%

Chart 4-8 depicts more specifically the effects of the delays. Most common, and to be expected, is the impairment of companies’ sales/distribution function when products are bottled-up in the pipeline. The second most cited effect, impairment of financing ability, is of special note. This finding argues that not only does the current FDA environment fail to help companies; it also causes fundamental harm. Uncertainty is the enemy of financing.

Chart 4-8

Specific Effects of FDA Delays—All Companies

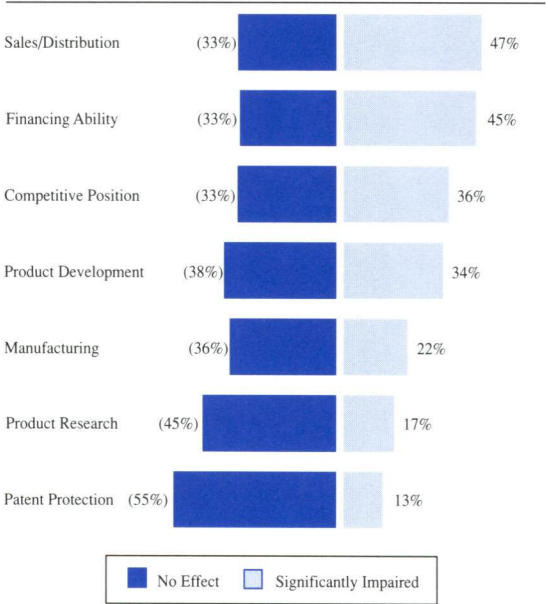
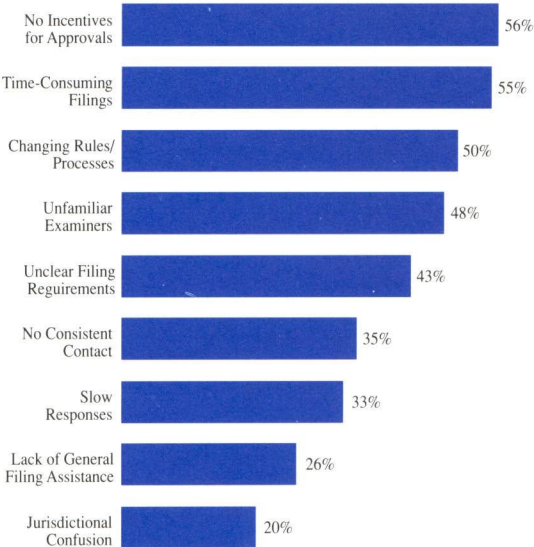


Chart 4-9

Most Troublesome Aspects of FDA Delays—All Companies



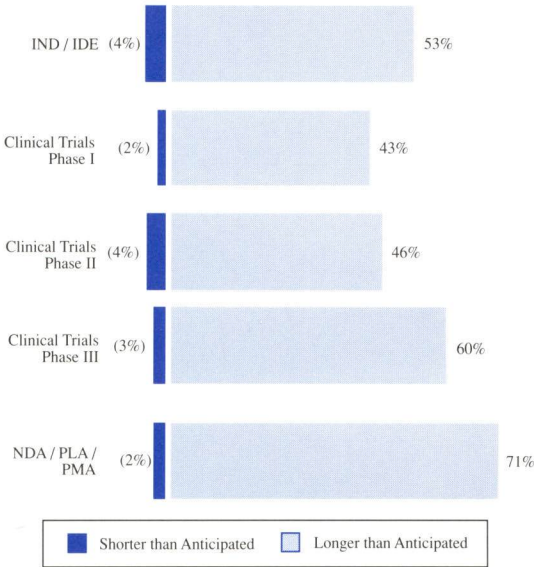
The particular factors that most frustrate and impede companies in dealing with the FDA are shown in *Chart 4-9*. At the root of many of the problems is the motivational issue that received the greatest comment—the fact that examiners receive no incentives for approving products and no penalties for delay.

Almost as galling is the time-consuming nature of the filings. This may reflect the findings shown in *Chart 4-10*. However long companies estimate the process will take at any stage of product development, it takes significantly longer and therefore costs significantly more.

There are two ways of looking at this finding. One is that the regulatory process continually throws unanticipated obstacles in companies' path. The other is that companies are naive in their

Chart 4-10

Actual vs. Estimated Time of Product Development Stages—All Companies



expectations. Whatever the interplay between companies' high hopes and the harsh realities, it is clear that the FDA interface has an inescapable impact on the ability of companies to achieve their commercial and financial objectives.

Ag-bio Issues

Agricultural-biotechnology companies fall under the auspices of at least three federal regulatory agencies—the FDA, USDA, and EPA. The agency/agencies involved for a given product depends on the technology used to develop the product and the product's intended use.

Further, starting with North Carolina and Minnesota this year, individual states are enacting their own regulations regarding products released into the environment or entering the food chain. Potentially every state and locality could legislate intervention in the development and commercialization of new products—a truly alarming prospect.

Table 4-6

Percentage Believing Division of Responsibility is Clearly Defined among Federal Agencies—Ag-bio Companies

For Testing of Products	47%
For Selling/Distribution of Products	47%

The federal government is preparing legislation to more clearly and efficiently coordinate the activities of the agencies regulating ag-bio products. This will be welcome. As the results in *Table 4-6* show, the majority of companies do not find the regulatory lines of responsibility to be clear. Companies now have to devote valuable time and resources simply to determine the relevant regulatory process. They often file with multiple agencies (consuming more time and resources) to ensure they cover all bases. As shown in *Table 4-7*, however, ag-bio companies are not bedeviled by regulatory delays nearly to the degree that health-care companies are.

Table 4-7

Percentage That Experienced Regulatory Delays with Products—Ag-bio Companies

	<i>Federal Level</i>	<i>State Level</i>	<i>Local Level</i>
Testing of Products	16%	11%	0%
Selling/Distribution of Products	16%	5%	0%

Patent Issues

Like the FDA, the Patent and Trademark Office had been criticized for delays and a failure to address fully the complexities of biotechnology processes and products. From May, 1988 to December, 1989 the backlog of biotechnology patent applications grew from 5,977 to 8,424 (*PTO statistics, courtesy of Wegner & Bretschneider, Washington, D.C.*). A General Accounting Office study reports that the waiting period for biotechnology patents averages three-to-four years versus 18 months for other types of patents.

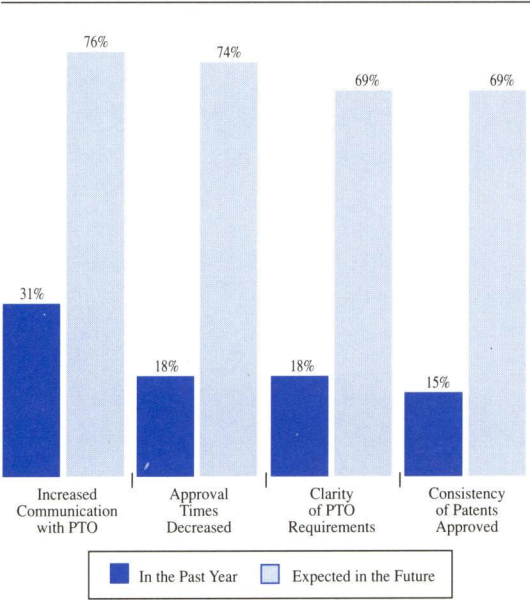
In the past year, the federal government has begun to address the problem by instituting a special status for biotechnology examiners. The initiative includes a salary differential to enable the PTO to compete more equitably with industry attracting and retaining qualified people, and authorization to hire additional examiners to address the biotech boom. The PTO is also sending biotechnology examiners to a Biotechnology Institute created for this purpose by the Industrial Biotechnology Association (IBA).

The industry's problems with patents go beyond the issuance process. The United States awards patents on the basis of "first to invent." This criterion is more ambiguous and thus more liable to legal dispute than the "first to file" system employed in many other countries. The first-to-file approach not only complicates the process of protecting intellectual property rights in the United States, but also complicates the process for both U.S. and foreign companies in cross-border filings.

Further, holders of patents on products do not necessarily hold rights to the processes that produce those products—a loophole (or an opportunity, depending on how you look at it) that competitors can exploit. The much-debated Biotechnology Patent Protection Bill (the Boucher bill) attempts to close the loop with regard to foreign products. And in a landmark case, a U.S. District Court ordered Amgen and Genetics Institute to cross-license each others EPO technologies and end their litigation of product versus process rights. Indeed, most of the CEOs with whom we discussed patents in our interviews and roundtables came up strongly on the side of cross-licensing. As Edward Penhoet (Chiron) remarked, "We're going to have to be sensible about paying each other. One way or another, everybody's going to be playing in somebody else's sandbox, patent-wise."

Chart 4-11

Percentage Benefiting/Expecting to Benefit from Recent Patent Office Changes—All Companies



Key Findings

- The PTO’s improvement program is chalking up gains. Over 30 percent of the industry report that communication with the Patent Office has improved in the past year; more than 75 percent expect continuing PTO improvement over the next five years.
- Patent delays, however worrisome, do not have as negative an impact as FDA delays do on product development.
- The most negative effect of patent delays are the risks in exposing technology without patent protection (43 percent). The delays also undermine companies’ competitive positions (35 percent) and ability to finance (29 percent).

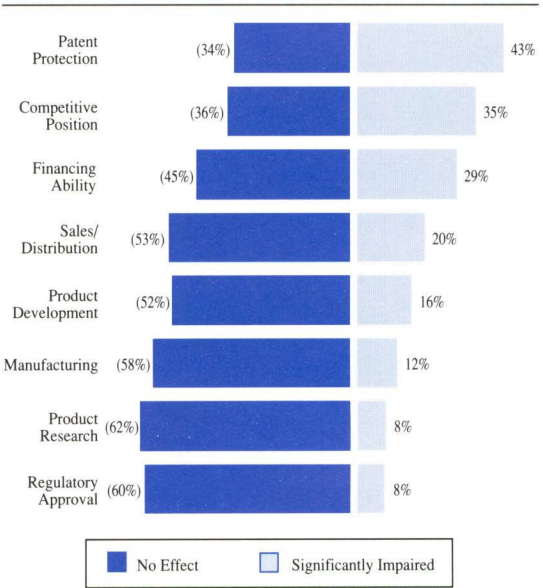
Approximately 40 percent of companies believe they have benefited from the PTO’s efforts

of this past year to improve the processing of biotechnology patents (*Chart 4-11*). Nearly 80 percent expect continuing gains in the years ahead. More and better communications between the PTO and companies is the most significant benefit thus far. Interestingly, the larger companies, which are the most embroiled in current patent disputes, are the most inclined to note improvements in communications with the PTO (45 percent).

Although the PTO is making headway, it still has far to go to issue biotechnology patents in a reasonable time frame. However, in comparing the effects of patent delays (*Chart 4-12*) with the effects of FDA delays (*Chart 4-8*), it is clear that the fall-out from the FDA turmoil is far more damaging. This is because patent approvals do not pay off until approval to sell a product also is granted. In the interim, any patent protection that has been obtained just ticks away. In an ideal world, patents and regulatory approvals would issue at the same time.

Chart 4-12

Specific Effects of Patent Office Delays—All Companies



5. Financial Picture

The biotechnology industry is driven by science. Biotechnology businesses are driven by their financial strategies. At each stage of a company's development, the financing demands and opportunities shape the priorities.

Early-stage companies are financed by venture and private capital that is investing in the long-term development of a breakthrough technology. Some of these companies receive additional funds from contracted research and government grants. The focus of these companies is discovery and initial development.

As companies give form to their underlying science and formulate product ideas and market direction, they burn their start-up capital on R&D and building their business infrastructure. Their additional capital needs drive them to seek corporate alliances. Further rounds of venture financing are usually dependent on companies' success in developing their technology and attracting other investors, both private and corporate.

Companies often are required to make trade-offs between the product, technology, market, and geographic rights that they can afford to relinquish to a corporate partner, and the rights they must keep proprietary in order to accomplish their essential goals. How they are able to balance this equation is a function of the state of their survival index (the number of months that their cash resources will sustain them) and the financing opportunities available to them.

As companies continue to develop, they approach the public equity markets to increase their financial muscle. These markets dictate their new agenda—steady progress toward the commercialization of their products and the certainty of earnings. Quarterly progress becomes more important and more measurable. Milestones and financial returns are carefully projected and monitored. Minor variations often result in major reactions. Companies put additional energy behind bringing products to the market and enlarging their

resources from existing corporate partners and new alliances. They have to begin to demonstrate, as George Ebright (Cytogen) says in our interview with him, that they can “take a product through clinical trials, bring it to the FDA in a scientifically sound and well-presented filing, get an approval, and become a commercial company.” When companies progress steadily toward this goal, their ability to finance is sustained. When companies get thrown off that track, financing dries up.

Companies are competing for financing in an environment that grows more competitive and volatile with every year. As the large and top-tier companies deliver their products, they attract more and more of the available investment capital and corporate interest. The less well-capitalized companies are left a smaller portion of the pie.

This year, the vagaries of the financing markets were intensified by FDA postponement of product approvals and the invasion of Kuwait. Company events, industry events, events in the overall financing and investment climate, and political and international events—these all affect the capital markets. Thus, they all affect the financing of biotech companies and dictate their strategies.

Editor's Note: Any survey of the financing opportunities of an industry so buffeted by change as biotechnology can only be a snapshot in time. This is particularly so in the volatile financing climate that developed in 1990. Companies responded to our questionnaire during the months of May and June, a period in which the public markets were growing increasingly favorable, before the FDA and Middle East shocks.

Financing Strategy—Key Findings

Public Markets and Venture Capital

- Nearly two-thirds of the top-tier companies and more than 40 percent of the large companies find the public capital markets responding favorably to their needs. However, when the small and mid-size companies are factored in, only 26 percent of the industry overall finds the markets to be receptive.
- Improvement is anticipated. Nearly half of the companies expect the public markets to be receptive within the next year, and three-fourths within the next two years.
- Twenty-six percent of the companies were negatively affected by the unreceptive public markets during the past year. Mid-size companies were the most severely impacted (34 percent).
- A comparable 27 percent of the companies were negatively affected by the drop in venture-capital financings over the past year. As would be expected, the small companies were hardest hit (38 percent).
- Companies' primary response to the unreceptive public markets and the constrained venture-capital markets was an increased emphasis on strategic alliances.

Projected Financing Needs

- Future financing needs are only half the amount projected by companies last year. On average, companies expect they will need approximately \$3 million during the next year in new financing, \$17 million during the next five, and \$32 million over the next ten years.
- Therapeutic companies forecast the largest financing need—averaging \$61 million over the next ten years. This figure factors in the many small companies in this segment. The financing needs of the top-tier companies are significantly larger.
- Public equity (39 percent) and strategic alliances (34 percent) are expected to provide the bulk of the industry's capital during the next five years. The percentage of total capital that companies expect to obtain from strategic alliances is twice the proportion projected in last year's survey.

Public Markets and Venture Capital

The increased stratification of the biotechnology industry is nowhere more clearly demonstrated than in the ability of companies of varying size to finance. Investment banker Frederick Frank (Lehman Brothers) comments on the phenomenon in our interview, "There probably are four levels in this industry. The third- and fourth-level companies are still in serious difficulty, but the second level, at least, is part of the wave [of financing opportunity at the top] that's forming now." (*A list of the year's financings is provided in Appendix A.*)

Chart 5-1

Time Until Public Capital Markets Become More Favorable by Company Size

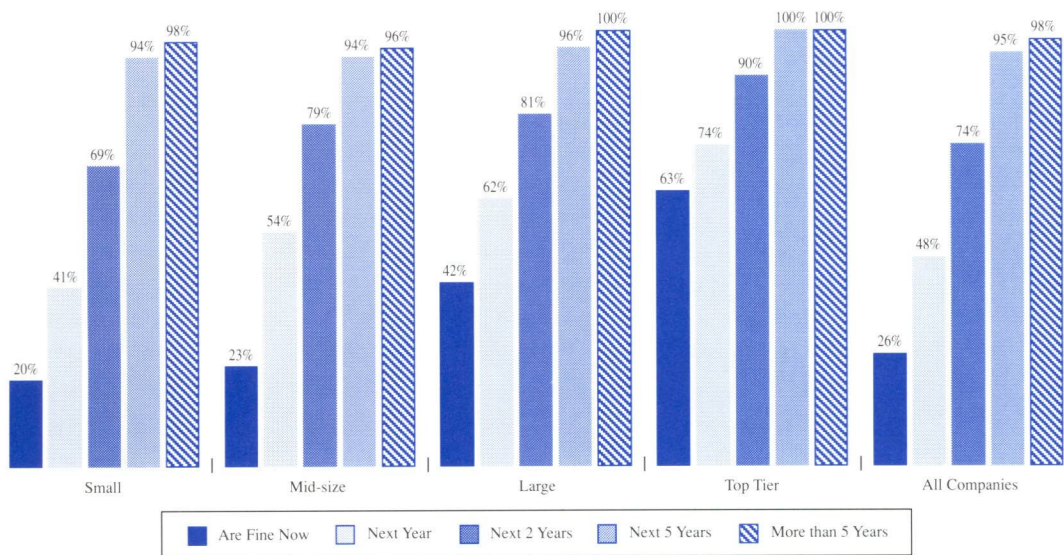


Chart 5-1 profiles how CEOs see the markets responding to their companies now, and how they expect the market reception to improve in the coming years. While nearly two-thirds of the top tier report the markets are responding very well, only 26 percent of the industry overall is able to get the public financing it needs.

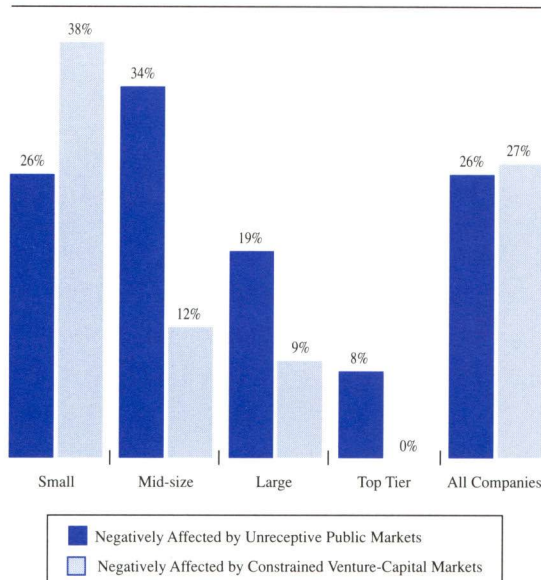
The large and top-tier companies have many advantages in the eyes of investors. They have a history. They have products on the market or near the end of the approval cycle, with more products in earlier stages of development. They have managerial experience and depth, and alliances with valuable partners. These attributes reduce some of the uncertainties inherent in investing in biotechnology.

The renewed investor interest in the top tier has spilled over to the the large companies, as financiers search deeper within the biotech industry for value. Over 40 percent of the large companies found the public markets favorable this year. However, mid-size and smaller companies generally were not able to get the public markets' attention.

Yet the overall confidence of biotech companies persists. Within the next two years, the greatest share of companies at every stratum of the industry expect the public markets to be responsive to their financing needs.

Chart 5-2

Percentage Affected by Unreceptive Financing Markets by Company Size



Impact of Unreceptive Financial Markets

While only 26 percent of companies find the public markets currently satisfying their financing requirements, no more than that percentage regard themselves adversely affected by the lack of current public financing opportunities. Twenty-seven percent of the industry is adversely affected by the constrained venture-capital markets (*Chart 5-2*).

The golden age of biotechnology funding ended with the stock market crash of October, 1987. Since then, not only the public markets, but also the venture capitalists have been less and less forthcoming. Actual funds raised by venture capitalists to invest in all industries are down from 1987's peak of more than \$4 billion to 1989's approximately \$2 billion—more than a 40 percent decline.

Venture capitalists compete for capital against other market opportunities for investors. During the latter years of the 1980s, the return on

investment of these funds steadily declined. Biotechnology turned out to be much more of a long-term play than was anticipated by venture capitalists who had cut their teeth on faster-developing electronics companies. Therapeutic companies in particular, with their long road to regulatory approval, consign early-stage investors to an extended period of uncertainty.

Venture capitalists are attracting less investment, therefore they have less to invest, and therefore they are being more discriminating in their investments. This is leaving its mark on 38 percent of the small companies. These companies may find themselves having to pay a higher price in terms of dilution of equity for the funds they receive and/or are cutting back on R&D. They are also scrambling for strategic alliances in a buyers' rather than a sellers' market.

One-fourth of the small companies also report themselves adversely affected by the unreceptive public markets. As most of these companies do not access public financing directly, this response most likely reflects the secondary effects of the less-receptive public markets on venture capital and other private financing sources. One must remember that the public equity markets also provide liquidity for the earlier-stage investors, refueling the venture capitalists' appetite and capability to reinvest in emerging companies.

Especially vulnerable in the harsher financing climate are the mid-size companies needing a third or even fourth round of venture funding (mezzanine capital). The magnitude of the continuing financing needs of these companies places many of them outside of the range of many venture funds. However, they are not sufficiently developed commercially to attract public financing. This puts them in a crunch.

Chart 5-3

Percentage Affected by Unreceptive Financing Markets by Market Segment

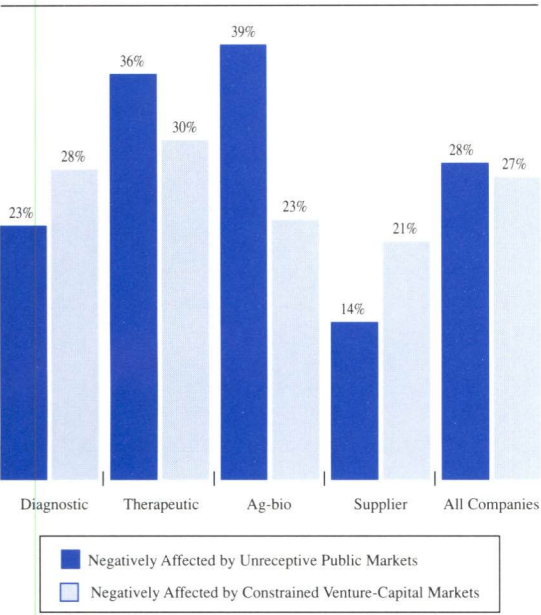


Chart 5-3 shows the impact of the unreceptive financing markets by industry segment. The supplier segment is the least troubled in meeting its financing needs. This is the most commercially mature segment of the industry, and is largely profitable. Suppliers’ product-development cycles are typically short, and their products generally are not regulated. These companies present the fewest uncertainties to prospective investors—and their financing needs are the lowest among biotech companies.

Ag-bio and therapeutics companies are the most hampered by the public markets’ limited interest. These companies have the longest product-development cycles and experience the full force of regulatory scrutiny. Investment in these companies is high in uncertainty.

Specific Effects of Unreceptive Markets

Charts 5-4 and 5-5 detail companies’ responses to the difficulties they are encountering in the financing markets. Pursuing alternative financing through strategic alliances is the primary response reported—clearly demonstrating the way that financing strategy dictates business strategy in this industry.

Corporate partners are less vulnerable to the uncertainties that deter investors. Being in allied industries, they have a firmer grasp of the commercial potential of biotech’s technologies and products. They know how they can realize this potential through their own distribution and marketing capability. Finally, the capital they provide generally is earmarked for a specific technology or product. In other words, corporate partners provide capital for biotech companies to accomplish what the corporate partners want.

Chart 5-4

Specific Effects of Constrained Venture-Capital Markets—All Companies

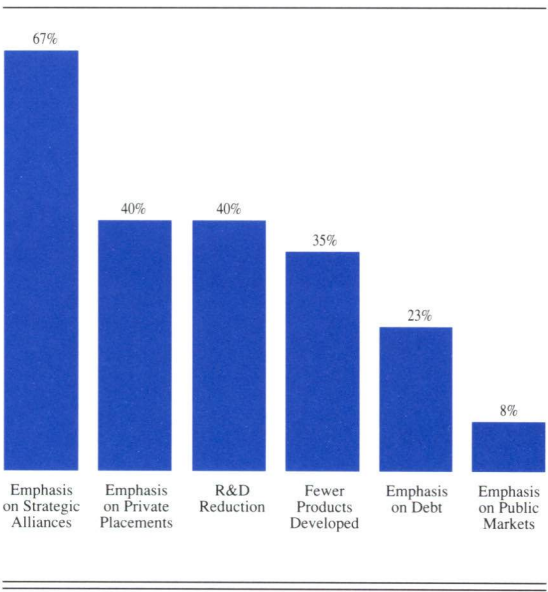
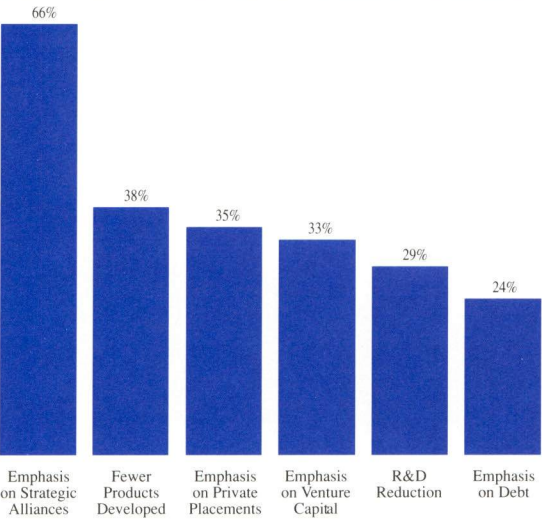


Chart 5-5

*Specific Effects of Unreceptive Public Markets
—All Companies*



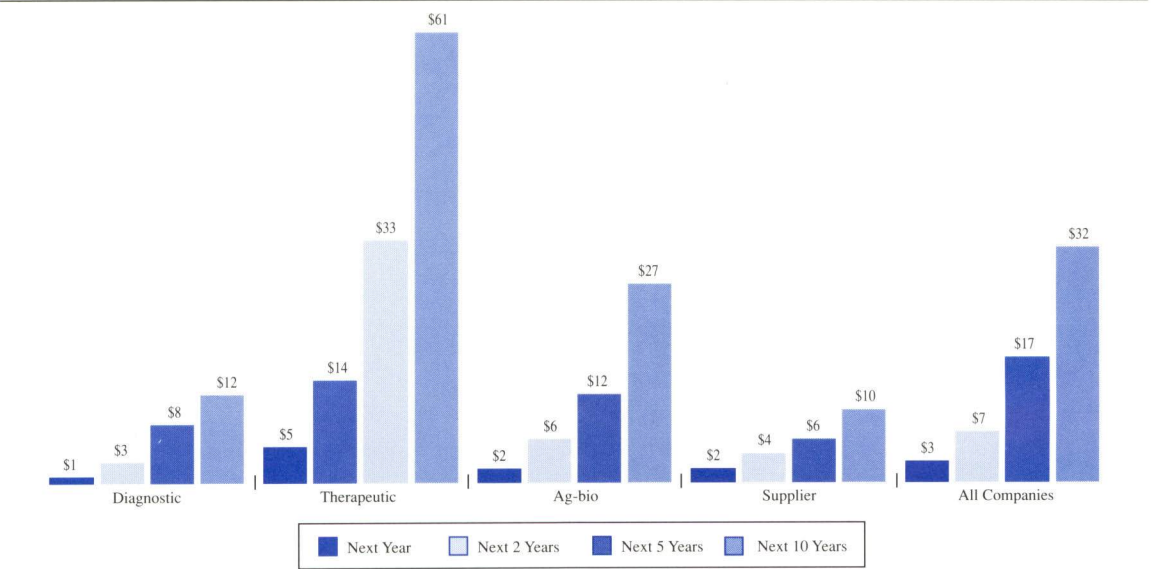
Another strategy that some of the more mature biotech companies employ to obtain project funding for a specific technology is to spin it off into a new company through a unit “rights” offering in the public markets. Known as SWORDs (stock warrant off-balance sheet R&D financing), these transactions allow investors to purchase units consisting of shares in the new company as well as warrants for the sponsoring company’s stock. The SWORD strategy has given birth to Tocor by Centocor, BioElectric Systems by ALZA, and Receptech by Immunex, among others, and brought an aggregate \$106 million of new capital to these companies. (As we went to press, Genzyme announced a public rights offering for a new company, Neozyme.)

In addition to the offensive strategies of pursuing alternate forms of funding, companies also are employing the defensive strategies of reducing their R&D and product development expenditures while they wait for the markets to turn around.

Chart 5-6

Projected Financing Needs by Market Segment

in millions of dollars



Projected Financing Needs

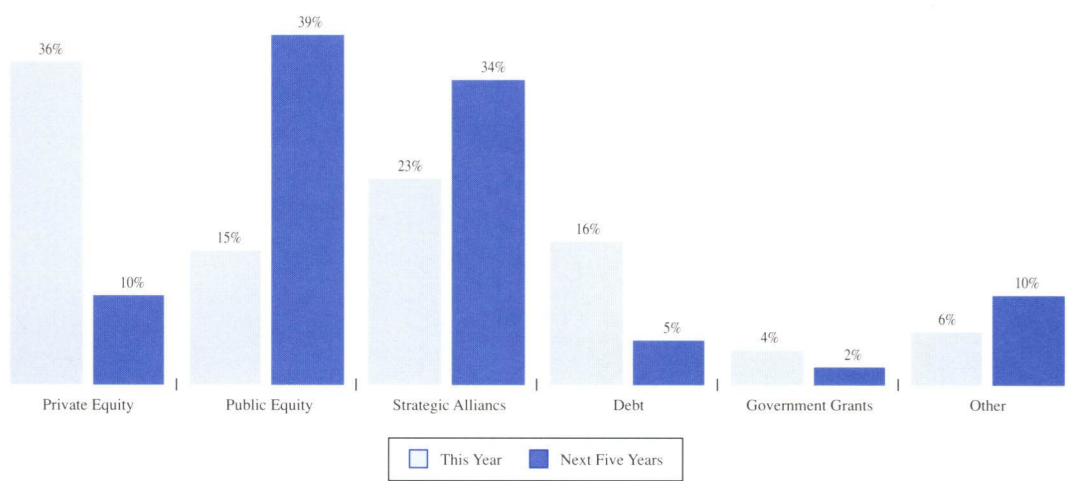
The average biotechnology company projects a need for \$3 million in financing during 1991, and \$32 million in total over the next ten years (*Chart 5-6*). These numbers are surprisingly low—in the neighborhood of half the amounts projected last year (\$7 million for the next year and \$55 over the ten-year span). Some companies are expecting more and more of their funds to come from product commercialization—but these are the more developed few. Some companies are narrowing their product focus so they will need to consume less funds. Most companies are probably being more realistic about their financing needs. But one must keep in mind that the preponderance of small companies in the industry skews the projections to the low side. And not to be forgotten, as reported in

Chapter 2, companies typically underestimate what it will cost to bring a product through approval.

While the therapeutic companies project far and away the greatest financing needs, the \$61 million they require over the ten-year period pales in comparison to the \$200 million it costs, on average, to bring a drug through a 10- to 12-year development and approval process and into the marketplace. Ag-bio companies, too, have a longer and more costly development cycle than diagnostic and supply companies—although not nearly as capital-consuming as the therapeutic segment. Further, many ag-bio companies are generating revenues by distributing traditional agricultural products while they develop recombinant crops and biopesticides. Thus their financing needs fall into the middle of the range. Supplier and diagnostic companies have minimal financing needs because they are more commercially developed.

Chart 5-7

Distribution of Financing Sources—All Companies



By size, the top-tier companies anticipate the greatest capital needs, averaging \$83 million over ten years; the small companies anticipate the least, averaging \$24 million over the same period.

Distribution of Financing Sources

Chart 5-7 displays where the industry is getting its financing now, and the financing sources it expects to depend on in the future.

Private equity, which consists primarily of venture capital, is an early-stage, limited financing source. As the industry and companies develop, its influence becomes less pervasive.

Public equity, barely increasing its contribution during the current year, is expected to become the primary source of capital in the future. Optimism about the equity markets, however, must always be seen in the context of the markets' volatility. Equity financing is the appropriate goal. When it is available, it is the least expensive form of financing. Because the windows of equity-financing opportunity open and shut without warning, Roger Salquist (Calgene) advises in one of our roundtables that a biotech CEO, "should always have a draft prospectus in his top drawer."

The reliance on strategic alliances for financing in the future—a significant shift from financing strategies of the past—demonstrates again how partnerships are the strategy of choice for filling biotech companies' financing voids.

(Partnerships should not be seen as unidimensional financial relationships. Companies pursue them for a multiplicity of competitive ends. These are examined in Chapter 3.)

Debt apparently is being used as a stop-gap this year because of the fickleness of the public markets. Many companies have grown to the point of having leverageable assets—buildings, equipment, inventory, and receivables. This reflects their commercial success. Companies, however, seem to anticipate that their continuing commercial development and growing market valuations will enable

them to rely less on debt in the future. Thus, during the past year, Amgen and Xoma took advantage of the favorable equity markets to call in their convertible debentures, thereby converting the debt to equity and eliminating future debt service. Convertible issues are favored by many companies for this flexibility, while investors find them attractive because they provide a good yield, "pay while you wait," and still retain the upside potential.

Chart 5-8

Change in Projected Financing Sources—All Companies

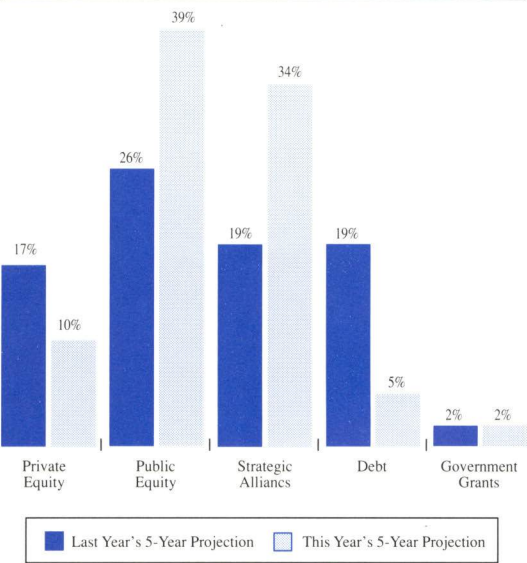


Chart 5-8 compares the projections of the five-year going-forward financing sources reported in last year's survey to those reported this year. Back then—in the spring of 1989—the biotech financing window was essentially closed, as it had been since 1987. Public equity was especially difficult to come by. Companies were holding onto their venture-capital sources, and making use of many forms of debt (standard public debt, convertible debt, debt with warrants, bank debt, credit lines, etc.). In extreme situations, they sold subsidiaries and product lines to keep the core of their com-

panies alive. The window of financing opportunity did not start to reopen until the late summer, after last year's survey process had been completed. Thus companies last year were more pessimistic about public equity than they are this year, and were only beginning to shift their sights to the many advantages of funding through strategic alliances.

Burn Rates and Survival Indices

The burn rate is an indicator of the amount of cash per month a company is consuming. The survival index calculates how many months companies can sustain themselves at the rate they are consuming their available capital.

Burn rates and survival indices are complementary; the magnitude of the burn rate drives the survival outlook. Together, these measures help biotech executives gauge spending and estimate the timing of any re-financings that may be needed. The measures are also used by venture capitalists and analysts to assess capital management in the early years when revenues are insufficient to cover costs.

Key Findings

- Nearly two-thirds of the industry increased their R&D burn rate during the past year.
- While the survival index for the industry overall remained essentially unchanged from last year, nearly half the companies increased their survival indices. The top-tier companies posted a considerable gain in projected longevity (from 74 to 100 months), while the mid-size companies reported a significant decline (from 40 to 29 months).
- Companies' primary response to a decrease in their survival index is to increase their emphasis on financing (82 percent) and partnering (71 percent).

- Factors that supported an increase in companies' survival indices this year were product revenues (61 percent—most prevalent among diagnostic/supplier companies), alliance funds (40 percent), and equity financings (39 percent—most prevalent among therapeutic/ag-bio companies).

Burn Rates: Definition

The burn rate in its simplest form was developed by venture capitalists to answer the question: At its present rate of expenditure, how much cash per month is a company consuming? As in previous years, this survey broadens the venture capitalists' burn rate into four related measures, each of which has its uses.

R&D Burn Rate. The rate of R&D spending per month.

Technology Burn Rate. The sum of R&D spending per month plus the average monthly expenditure on (and depreciation of) property, plant, and equipment. This calculation reflects more comprehensively the monthly cost of developing technology.

Overall Burn Rate. The sum of total costs and expenditures per month plus the average monthly expenditure on (and depreciation of) property, plant, and equipment. This calculation reflects the overall rate at which a company spends its resources.

Net Burn Rate. A measure calculated by subtracting average monthly revenues from the overall burn rate, yielding insight into net consumption of financial resources on a monthly basis.

Typically, burn rates are not judged against industry benchmarks reflecting widely accepted performance norms. Managers, investors, and analysts who make use of them tend to set their own norms on a rule-of-thumb basis that satisfies their own criteria. While each of these rates provides valuable information, the steepness of the increase from the R&D burn rate to the overall

Table 5-1

Burn Rates and Survival Index by Company Size

in thousands of dollars

Company Size	R&D Burn Rate	Technology Burn Rate	Overall Burn Rate	Net Burn Rate	Cash Reserves	Current Survival Index	Percent with Increase in Survival Index
Small	\$ 131	\$ 124	\$ 289	\$169	\$ 2,678	16	43%
Mid-size	308	348	866	277	8,040	29	46%
Large	707	687	1,712	409	22,019	54	42%
Top-tier	2,335	3,201	7,370	543	54,195	100	56%
All Companies	489	577	1,368	267	12,155	46	45%

burn rate indicates the extent of non-R&D expenses. More important from the standpoint of company stability, the extent to which revenues cover expenditures is measured by the difference between the overall burn rate and the net burn rate.

Survival Index: Definition

The survival index uses net burn rate data to measure the adequacy of existing cash reserves (booked cash and cash equivalents) to meet the drain on resources. The survival index is a relative measure, owing to the fact that it cannot take into account “off-book” financial resources such as the future financial commitments of contract/collaborative research partners or changes in spending,

new income sources, or other revenues and expenses (both anticipated and unanticipated) that are not reflected in the financial statements. Given this limitation, the survival index can yield a bleaker picture than may actually prevail, but it remains a useful analytic tool.

Burn Rates

The average burn rates for the industry, profiled by company size and market segment, are shown in *Tables 5-1 and 5-2*. While the distinctions between the various size and market classifications are meaningful, there are relatively few changes from similar distinctions in prior years. Basic patterns continue.

Table 5-2

Burn Rates and Survival Index by Market Segment

in thousands of dollars

Market Segment	R&D Burn Rate	Technology Burn Rate	Overall Burn Rate	Net Burn Rate	Cash Reserves	Current Survival Index	Percent with Increase in Survival Index
Diagnostic	\$283	\$389	\$1,143	\$193	\$ 8,758	45	50%
Therapeutic	831	969	1,746	461	18,584	40	49%
Ag-bio	394	456	996	338	14,271	42	50%
Supplier	278	322	1,927	(115)	7,589	∞	29%
All Companies	489	577	1,368	267	12,155	46	45%

∞ Companies have a positive cash flow

Although the top-tier companies still have the highest R&D burn rates, these companies are able to recover much of their R&D and technology expenses through revenues and financing. On average, their net burn rate for top-tier companies has dropped considerably since last year (from \$992,000 to \$543,000), reflecting that these companies, as a group, are growing closer to profitability.

The therapeutic companies are still far and away the R&D burn-rate leaders. However, it is instructive to compare their net burn rate with that of the ag-bio segment. Ag-bio companies' R&D burn rate is less than half that of therapeutic companies—but unlike the therapeutic companies, they do not yet recover substantial shares of these expenditures by way of revenues. As for suppliers, for the second year in a row these companies, on average, are profitable, with revenues exceeding total expenses.

Changes in Burn Rates

Charts 5-9 and 5-10 depict the percentage of companies with increasing burn rates relative to last year. A comparison of the top-tier and small companies illustrates the greater ability of the larger companies to finance their R&D. The discrepancies exemplify the industry's increased stratification. Approximately 80 percent of the top-tier companies increased their R&D burn rate, while only 53 percent increased in their net burn rate. Among the small companies, a comparable 54 percent increased their net burn rate, but only 57 percent increased their R&D rate of investment. The larger companies, more sure of their financing, have been able to expand their R&D efforts. Smaller companies, facing greater uncertainties, have been forced to keep a tighter rein on spending.

Chart 5-9

Changes in Burn Rates by Company Size

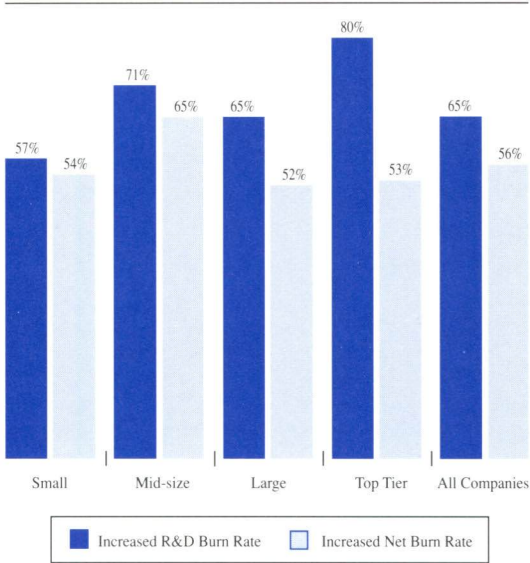
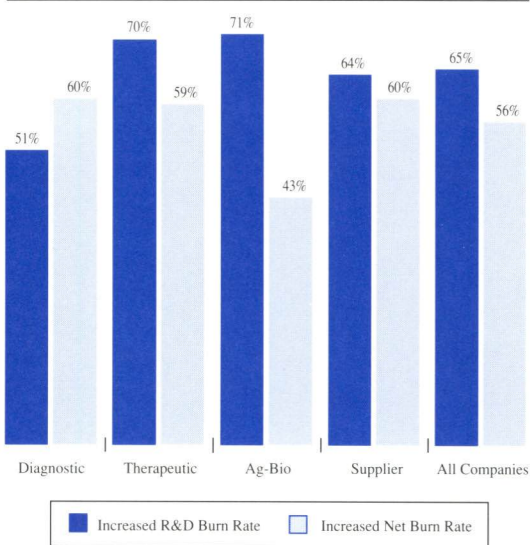


Chart 5-10

Changes in Burn Rates by Market Segment



By market, therapeutic and ag-bio companies reported nearly equal increases in their R&D burn rates over the previous year. However, many of the ag-bio companies were more successful in matching their R&D expenditure increases with revenues growth (or perhaps, capping the increases of other expenses), as only 43 percent reported an increase in their net burn rate versus 59 percent for the therapeutic companies. A reverse trend appears among the diagnostic companies. While only half of these companies increased their R&D burn rate, 60 percent saw their net burn rate increase.

Survival Indices

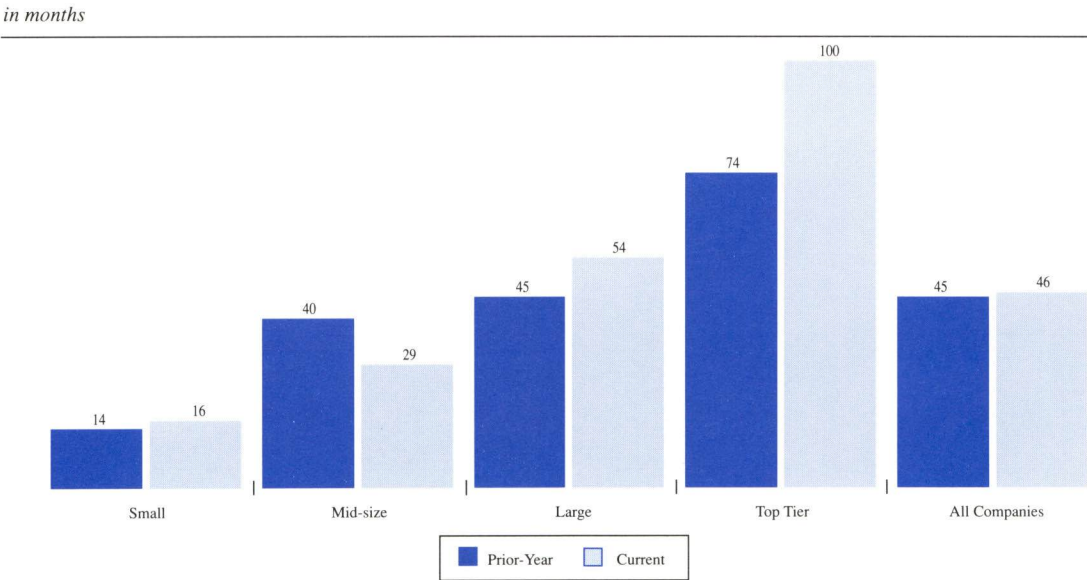
Referring back to *Tables 5-1 and 5-2*, the right-hand columns show the current survival indices and the percentage of companies that increased their survival index since last year. Overall, approximately

half of the companies (45 percent) posted an increase, with the top-tier companies (56 percent) leading the field.

Surprisingly, only 29 percent of the suppliers have increased their survival index, or level of positive cash flow (profits). The competitive nature of this more mature segment is driving down survival indices (in profitable companies, these are a facet of profit margins). In some areas, the growth of supply is outstripping the growth of demand, as growth in other industry segments is not proceeding as quickly as the industry earlier anticipated.

As shown in *Chart 5-II*, survival indices vary considerably among the different size companies. The top-tier companies are breaking away from the pack more clearly than ever. More commercially viable, more financially stable, they more consistently are able to obtain financing. In the coming years, their sales revenues will increasingly

Chart 5-11
Current and Prior-Year Survival Indices by Company Size



cover their expenses. The survival of these companies is growing more certain. The large companies also enjoyed a gain in their survival rates.

The mid-size companies show a serious drop in their average survival index—from 40 months to twenty-nine. As nearly half of the mid-size companies increased their survival index since last year (Table 5-1), this argues that a considerable number have suffered a major drop. As noted earlier, many of these companies are in the most difficult phase of their development. Beyond the venture-capital stage, they are angling for alliances with corporate partners and hoping to ready themselves to issue an initial public-equity offering when the window of opportunity opens. By tightening expenses, developing alliances and other sources of revenues, and bringing products closer to realization, many of these companies can weather the crisis and attract investors' confidence. Some of them, too, may be part of the wave of consolidation that the industry anticipates.

Chart 5-12

Current and Prior-Year Survival Indices by Market Segment in months

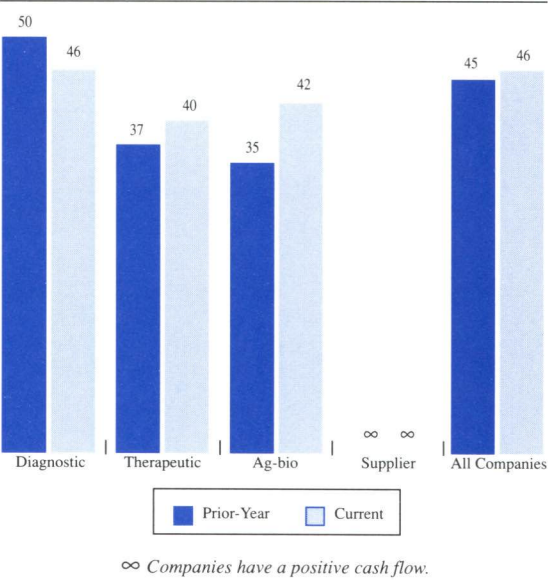


Chart 5-13

Means by Which Companies Increased Their Survival Index by Market Segment

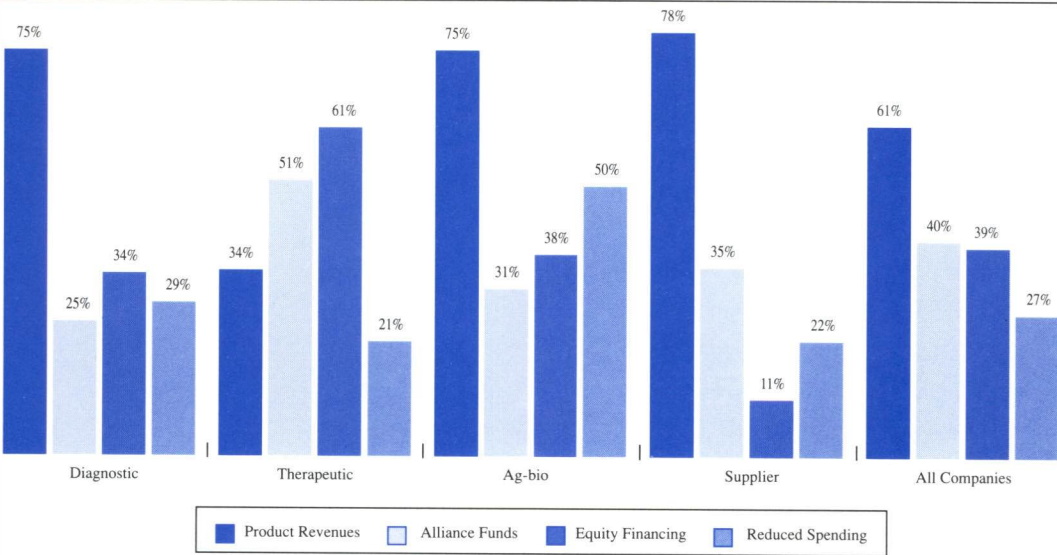
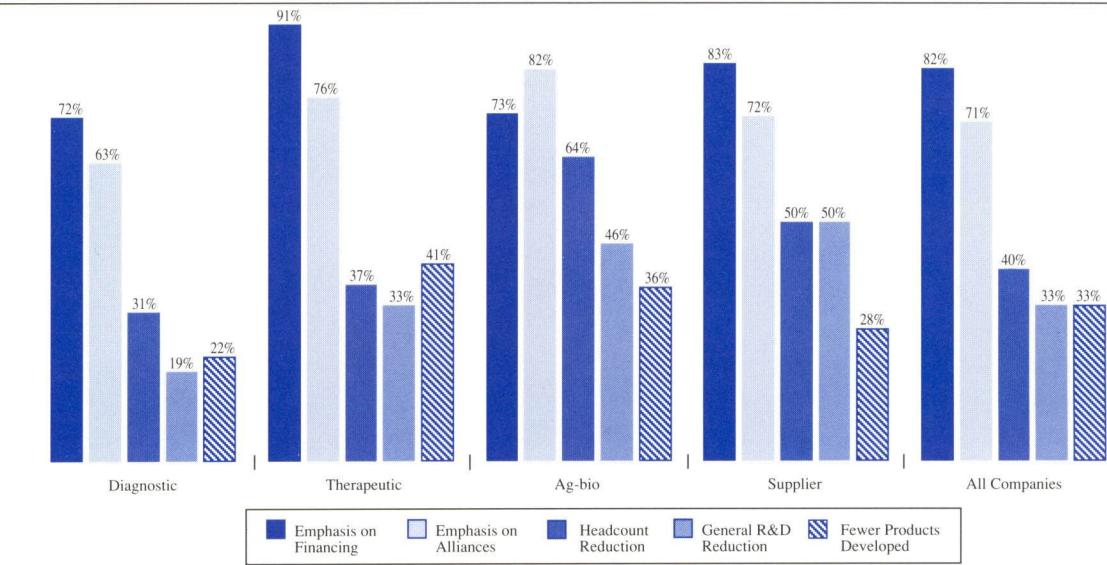


Chart 5-14

Effects of Decrease in Survival Index—By Market Segment



Suppliers stand out from the pack in the market segment analysis because they are profitable; therefore, their aggregate survival index is no longer quantifiable (*Chart 5-12*). Otherwise, the changes by segment from last year are small, with ag-bio companies showing the largest increase in their survival horizon. In general, no market segment is especially plagued by low survival indices. Clearly, future outlook is more a function of a company's size than its market.

Factors Affecting Companies' Survival Indices

The various means by which companies have been able to increase their survival index during the past year are profiled in *Chart 5-13*. Nearly two-thirds of the companies chalked up gains due to product revenues. This factor was most significant for companies with the most developed products and markets—diagnostic and supplier companies—as well as ag-bio companies that are supporting them-

selves through their R&D years by distributing traditional agricultural products.

Equity financing, the third most important factor overall (39 percent), was the most common factor for therapeutic companies. Again, their long product-development and approval cycles call the tune. These companies also place the greatest reliance on alliance funds.

Finally, when revenues and financings fail to cover the costs of activities, reducing spending is always a viable solution, as evidenced by the 27 percent that cite this strategy as a means for increasing their survival index.

By the same token, companies that are experiencing a decrease in their survival outlook (*Chart 5-14*) turn to the defensive strategies of decreasing costs (headcount, R&D, and product development) only as a last resort.

Financial Statements—Key Findings

Income Statements

- While the industry’s overall sales increased by 13 percent during the past year, the sales of the top-tier companies increased by approximately 18 percent.
- Ag-bio companies achieved the largest sales increase—approximately 60 percent.
- Although 73 percent of all companies increased their total revenues, only 44 percent improved their bottom line.
- Sixty-five percent of the top-tier companies are currently profitable—virtually the same as last year. For the industry as a whole, only 21 percent of all companies are profitable.
- Relatively few of the therapeutic (10 percent) and ag-bio companies (14 percent) have attained profitability.

Balance Sheets

- On the average, companies increased their assets by 9 percent during the past year.
- Eighty-five percent of the top-tier increased their total assets versus 58 percent of companies overall.
- Over three-quarters of the diagnostic companies increased their overall assets during the past year.

Income Statements

Tables 5-3 and 5-4 highlight the benchmark changes in companies’ performance from last year. Overall, the level of sales and revenues for survey respondents increased approximately 13 percent. While product costs increased by a similar margin, R&D expenses increased by a moderately higher 18 percent. This finding correlates with the increased level of R&D burn rates versus net burn rates reported earlier.

Table 5-3

Highlights of Income Statement Increases from Previous Fiscal Year—by Company Size

	<i>Small</i>	<i>Mid-size</i>	<i>Large</i>	<i>Top Tier</i>	<i>All Companies</i>
Product Sales	3%	19%	11%	19%	13%
C/C Research	34%	4%	19%	17%	13%
Total Revenues	11%	16%	11%	18%	12%
Cost of Product Sales	3%	12%	8%	17%	10%
R&D Expense	36%	24%	11%	22%	18%
Total Expenses	19%	20%	14%	22%	16%

Table 5-4

Highlights of Income Statement Increases from Previous Fiscal Year—by Market Segment

	<i>Diagnostic</i>	<i>Therapeutic</i>	<i>Ag-bio</i>	<i>Supplier</i>
Product Sales	15%	16%	62%	13%
C/C Research	22%	7%	23%	14%
Total Revenues	16%	11%	39%	12%
Cost of Product Sales	14%	13%	64%	8%
R&D Expense	16%	16%	20%	22%
Total Expenses	15%	18%	26%	13%

Chart 5-15

Comparison of Percentage with Increase in Revenues and Bottom Line—by Company Size

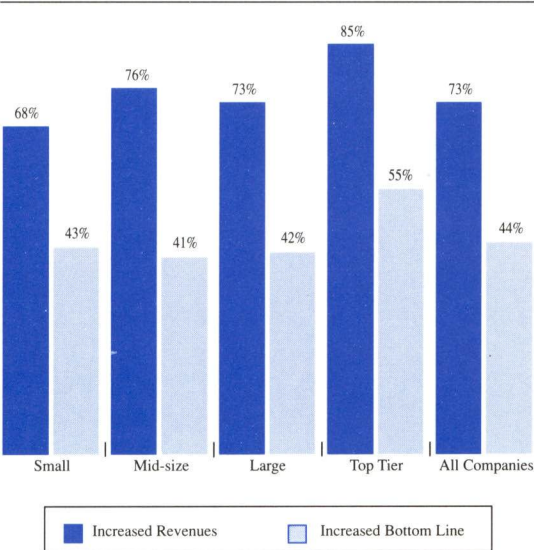
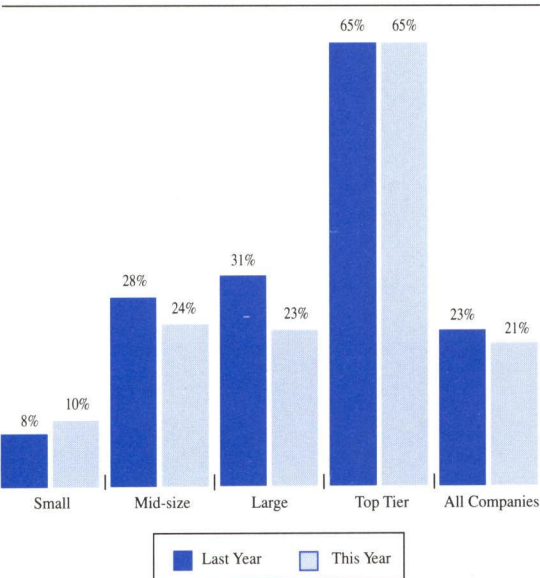


Chart 5-16

Comparison of Percentage Profitable, This Year and Last Year—by Company Size



As expected, the top-tier increased their overall revenues the most—by approximately 18 percent. However, surprisingly, the mid-size companies increased their total revenues by 16 percent.

By market, the ag-bio achieved an astonishing level of sales growth, over 60 percent. While product costs increased at the same level, the sales growth emphasizes that this small sector is burgeoning and merits increasing attention.

The actual percentage of companies (by size and market) that have increased their revenues and bottom line (profits or losses) is presented in Chart 5-15 and Table 5-5.

Table 5-5

Comparison of Percentage with Increases in Revenues and Bottom Line by Market Segment

Market Segment	Increased Revenues	Increased Bottom Line
Diagnostic	78%	52%
Therapeutic	63%	34%
Ag-bio	71%	43%
Supplier	77%	54%

Three-quarters of the companies increased their total revenues. However, one-quarter did not. This argues that a weeding-out process is taking place. Survival strategy for many of the companies in difficulty would dictate cutting back or closing off peripheral products and their related revenue sources in order to push for progress in the products with the greatest potential.

By size, while the top-tier companies continue to outperform the field, the revenues and bottom-line growth of the other company-size classifications were largely comparable.

By market, the differences are more marked. Nearly 40 percent of the therapeutic companies suffered a cut-back of some sort in their revenue stream. They also struggled with their bottom lines, with only 34 percent showing any improvement. Finally, only 10 percent of the therapeutic were profitable this year (*Chart 5-16*). As would be expected, the supplier segment, followed by the diagnostic companies, include the highest percentages of profitable firms.

The stratification of the industry is reiterated in the comparison by company size (*Chart 5-17*). Nearly two-thirds of the top-tier companies are profitable versus less than a third of the rest. The percentage of large and mid-size companies that are profitable decreased during the past year—perhaps a sign of the harder times faced by the companies caught in the middle.

Chart 5-17

Comparison of Percentage Profitable, This Year and Last Year—by Market Segment

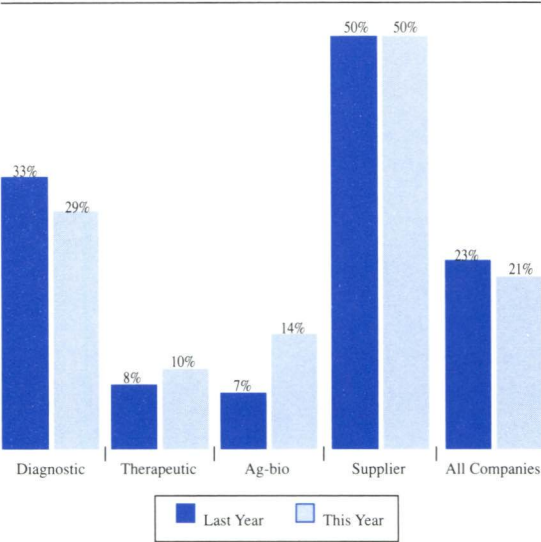


Chart 5-18

Comparison of Employee Benchmarks—by Company Size (dollars in thousands)

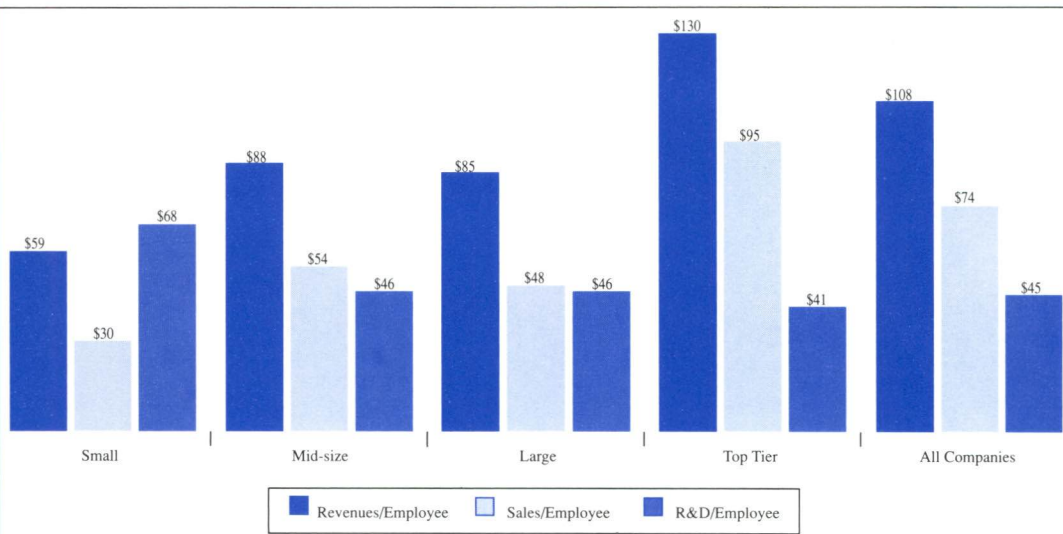
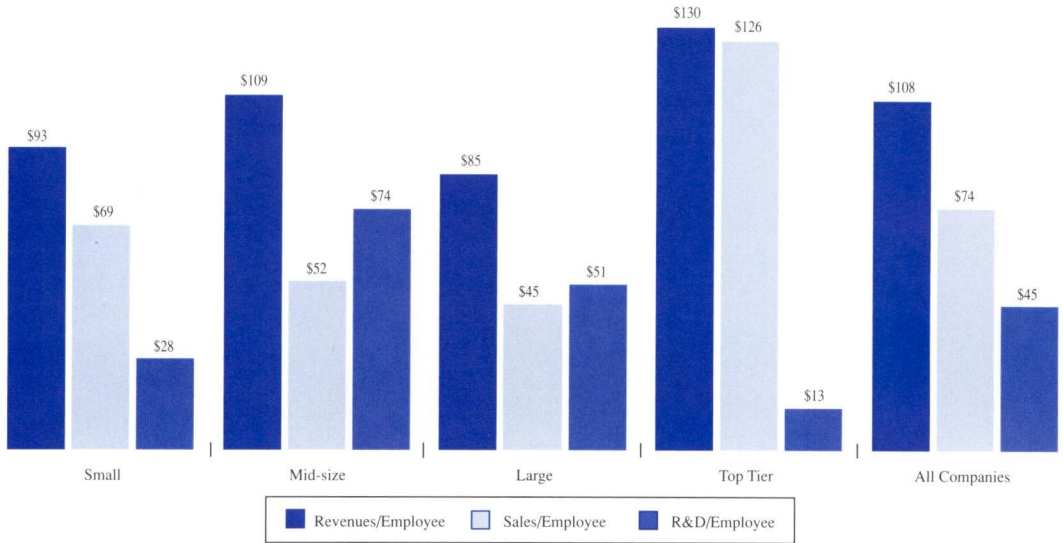


Chart 5-19

Comparison of Employee Benchmarks—by Market Segment (dollars in thousands)



With only one-fifth of all companies profitable, the percentage has decreased slightly from the previous year. Companies generally seem to be ignoring the bottom lines of their financial statements to concentrate on other areas of development.

Charts 5-18 and 5-19 detail additional important comparisons—the ratios of revenues, sales, and R&D per employee, by both size and market. The top-tier companies with more products

on the market and greater overall revenues have the highest average ratios of revenues and sales per employee. The small companies, which are primarily focused on research, show the highest levels of R&D expenditures per employee—approximately \$68,000. It is noteworthy that the sustaining level of R&D per employee remains at over \$40,000 in every size classification.

By contrast, in the market analysis, supplier and diagnostic companies weigh in well below this R&D level, and therapeutic and ag-bio companies well above. Suppliers, the most commercially-developed segment, show the highest sales and revenues per employee.

The composite income statements for the industry as a whole, detailed by size and market, is displayed in *Tables 5-6 and 5-7*. The basic patterns documented in our previous surveys persist:

- Companies show increasing losses as they grow until they become commercialized.

- Companies rely on contract/collaboration revenues and royalties for one-quarter of their revenues until they approach the top tier, where they begin to realize product revenues.
- Therapeutic and ag-bio companies, the least commercialized segments, are the most dependent on contract/collaboration revenues and royalties.

Table 5-6

Composite Statement of Operations by Company Size

	Company Size									
<i>in thousands of dollars</i>	<i>Small</i>		<i>Mid-size</i>		<i>Large</i>		<i>Top Tier</i>		<i>All Companies</i>	
Revenues:										
Product sales	\$ 687	51%	\$ 4,300	62%	\$ 8,920	57%	\$65,820	73%	\$ 9,455	68%
Contract/collaborative research	331	25%	1,427	21%	4,397	28%	16,181	18%	2,798	20%
Royalties and license fees	45	3%	300	4%	133	1%	1,287	1%	252	2%
Interest income	191	14%	651	9%	1,929	12%	4,100	5%	948	7%
Other revenues	88	7%	298	4%	264	2%	2,299	3%	395	3%
Total Revenues	1,342	100%	6,976	100%	15,643	100%	89,687	100%	13,848	100%
Costs and Expenses:										
Cost of product sales	396	30%	2,611	38%	5,077	32%	24,817	28%	4,123	30%
General and administrative	1,097	82%	2,308	33%	4,946	32%	27,325	30%	4,635	33%
Marketing and selling	81	6%	304	4%	617	4%	1,025	1%	309	2%
Research and development	1,550	115%	3,691	53%	8,489	54%	28,024	31%	5,772	42%
Interest	57	4%	286	4%	594	4%	1,418	2%	330	2%
Purchase of R&D Partnership	0	0%	0	0%	279	2%	245	0%	63	1%
Other expenses	215	16%	513	7%	792	5%	2,795	3%	637	5%
Total Costs and Expenses	3,396	253%	9,713	139%	20,794	133%	85,649	95%	15,869	115%
Income (loss) before taxes	(2,054)	(153%)	(2,737)	(39%)	(5,151)	(33%)	4,038	5%	(2,021)	(15%)
Income tax credit (expense)	(6)	0%	(167)	(2%)	(86)	(1%)	(3,196)	(4%)	(388)	(3%)
Extraordinary credit (expense)	31	2%	0	0%	1	0%	(34)	0%	12	0%
Other	39	3%	(43)	(1%)	(177)	(1%)	(85)	0%	(24)	0%
Net Income (loss)	(\$1,990)	(148%)	(\$2,947)	(42%)	(\$5,413)	(35%)	\$ 723	1%	(\$2,421)	(17%)

Table 5-7

Composite Statement of Operations by Market Segment

in thousands of dollars	Market Segment				
	Diagnostic		Therapeutic		
Revenues:					
Product sales	\$ 8,003	74%	\$ 6,750	48%	
Contract/collaborative research	1,875	17%	4,704	33%	
Royalties and license fees	106	1%	497	4%	
Interest income	578	6%	1,438	10%	
Other revenues	239	2%	658	5%	
Total Revenues	10,801	100%	14,047	100%	
Costs and Expenses:					
Cost of product sales	3,705	34%	2,009	14%	
General and administrative	3,533	33%	4,947	35%	
Marketing and selling	532	5%	88	1%	
Research and development	3,286	30%	9,462	67%	
Interest	270	3%	393	3%	
Purchase of R&D Partnership	0	0%	150	1%	
Other expenses	532	5%	897	7%	
Total Costs and Expenses	11,858	110%	17,946	128%	
Income (loss) before taxes	(1,057)	(10%)	(3,899)	(28%)	
Income tax credit (expense)	(399)	(3%)	(259)	(2%)	
Extraordinary credit (expense)	(2)	0%	37	0%	
Other	41	0%	(88)	0%	
Net Income (loss)	(\$1,417)	(13%)	(\$4,209)	(30%)	

Market Segment									
Ag-bio		Supplier		Other		All Companies			
\$ 4,136	52%	\$33,073	97%	\$ 2,995	72%	9,455	68%		
2,559	33%	291	1%	808	19%	2,798	20%		
15	0%	38	0%	72	2%	252	2%		
1,008	13%	646	2%	242	6%	948	7%		
171	2%	122	0%	21	1%	395	3%		
7,889	100%	34,170	100%	4,138	100%	13,848	100%		
2,985	38%	16,161	47%	1,720	42%	4,123	30%		
2,403	30%	10,279	30%	1,822	44%	4,635	33%		
543	7%	548	2%	184	4%	309	2%		
4,725	60%	3,332	10%	1,430	35%	5,772	42%		
390	5%	412	1%	96	2%	330	2%		
0	0%	0	0%	0	0%	63	0%		
153	2%	164	0%	84	2%	637	6%		
11,199	142%	30,896	90%	5,336	129%	15,869	115%		
(3,310)	(42%)	3,274	9%	(1,198)	(29%)	(2,021)	(14%)		
(2)	0%	(1,465)	(4%)	8	0%	(388)	3%		
0	0%	(40)	0%	6	0%	12	0%		
(9)	0%	14	0%	0	0%	(24)	0%		
(\$3,321)	(42%)	\$ 1,783	5%	(\$1,184)	(29%)	(\$2,421)	(17%)		

Balance Sheets

A comparison of the changes in the balance sheet benchmarks for companies overall in the past year is presented in *Table 5-8*. While assets grew nearly 10 percent, total liabilities increased by a larger 13 percent as companies continued to exhaust resources faster than they could be replenished. This is also apparent in the lagging increase of overall stockholders equity.

Table 5-8

Highlights of Balance Sheet Increases from Previous Fiscal Year

	Percentage Change
Cash & Short-Term Investments	2%
Current Assets	5%
Total Assets	9%
Current Liabilities	5%
Total Liabilities	13%
Total Stockholders' Equity	7%

The actual percentages of companies that experienced an increase in their total assets is depicted in *Table 5-9*. As expected, the top-tier companies did the best overall by size, and the diagnostic firms did the best by market segment. It is surprising, however, that the percentage of suppliers enlarging their total assets did not far outstrip the percentages of therapeutic and ag-bio companies. This may be a reflection of the increased competition within this segment documented in Chapter 1.

Table 5-9

Percentage with an Increase in Total Assets

Company Size	Percentage with Asset Increase	Market Segment	Percentage with Asset Increase
Small	52%	Diagnostic	76%
Mid-Size	61%	Therapeutic	51%
Large	54%	Ag-bio	50%
Top Tier	85%	Supplier	54%
All Companies	58%		

The composite balance sheets are presented in *Tables 5-10 and 5-11*. The magnitude of the differences among the total assets of companies of different sizes is striking—each step up in company size classification shows two to three times the total assets of the step below. This industry's stages of development are clearly marked.

It is worth noting the larger companies' decreasing levels of cash reserves as a percentage of total assets. Companies are clearly sinking substantial levels of cash into product infrastructure to make commercialization feasible.

By market, the larger average asset bases of the therapeutic and supplier companies is worth noting. For the suppliers, this underscores the maturity of this segment. For the therapeutic companies, the large base of assets attests to the magnitude of financial resources needed to develop therapeutic products. The diagnostic companies which experience relatively few obstacles to market entry demonstrate that smaller companies can be fully commercialized. Finally, the small asset base of the ag-bio companies illustrates the overall youth of this segment.

Table 5-10

Composite Balance Sheets by Company Size

	Company Size									
<i>in thousands of dollars</i>	<i>Small</i>		<i>Mid-size</i>		<i>Large</i>		<i>Top Tier</i>		<i>All Companies</i>	
Assets										
Current Assets:										
Cash and short-term investments	\$2,559	58%	\$ 7,223	47%	\$20,071	48%	\$ 51,478	33%	\$11,175	40%
Accounts receivable, net	212	5%	952	6%	2,974	7%	17,164	11%	2,524	9%
Inventory	193	4%	898	6%	2,561	6%	14,673	9%	2,189	8%
Other current assets	153	4%	433	3%	1,040	3%	3,886	3%	730	3%
Total Current Assets	3,117	71%	9,506	62%	26,646	64%	87,201	56%	16,618	60%
Net property, plant and equipment	728	17%	3,282	22%	10,126	24%	49,631	32%	7,701	28%
Patents, net of amortization	68	2%	237	2%	385	1%	678	0%	218	1%
Goodwill, other tangibles	256	6%	733	5%	751	2%	2,316	1%	660	2%
Investment in partnerships, and other entities	10	0%	44	0%	399	1%	1,993	1%	276	1%
Long-term cash and marketable securities	31	1%	817	5%	1,947	5%	2,716	2%	772	3%
Other long-term assets	187	4%	675	4%	1,137	3%	10,017	6%	1,456	5%
Total Assets	\$4,397	100%	\$15,294	100%	\$41,391	100%	\$154,552	100%	\$27,701	100%
Liabilities and Stockholders' Equity										
Current Liabilities:										
Accounts payable	\$ 270	6%	\$ 883	5%	\$ 1,511	3%	\$ 5,254	3%	\$ 1,111	4%
Accrued liabilities	166	4%	420	3%	1,096	2%	7,825	5%	1,147	4%
Short-term debt	148	3%	318	2%	328	1%	1,384	1%	344	1%
Current portion of deferred revenue	35	1%	310	2%	339	1%	514	0%	197	1%
Current portion of long-term debt	73	2%	291	2%	310	1%	1,339	1%	293	1%
Other current liabilities	23	0%	290	2%	663	2%	3,112	2%	497	2%
Total Current Liabilities	715	16%	2,512	16%	4,247	10%	19,428	13%	3,589	13%
Long-term debt	425	10%	2,777	18%	8,637	21%	27,521	18%	4,937	18%
Deferred revenue	24	1%	48	0%	155	0%	123	0%	58	0%
Other non-current liabilities	57	1%	753	5%	183	1%	3,492	2%	611	2%
Total Liabilities	1,221	28%	6,090	40%	13,222	32%	50,564	33%	9,195	33%
Stockholders' Equity:										
Preferred stock	998	23%	2,486	16%	1,426	3%	57	0%	1,351	5%
Common stock	369	8%	2,862	19%	2,363	6%	7,759	5%	2,062	7%
Other paid-in capital	9,389	214%	14,966	98%	51,409	124%	95,201	61%	25,416	92%
Other	(117)	(3%)	(108)	(1%)	(280)	(1%)	(199)	0%	(145)	(1%)
Retained earnings (losses)	(7,463)	(170%)	(11,002)	(72%)	(26,749)	(64%)	1,170	1%	(10,178)	(37%)
Total Stockholders' Equity	3,176	72%	9,204	60%	28,169	68%	103,988	67%	18,506	67%
Total Liabilities and Stockholders' Equity	\$4,397	100%	\$15,294	100%	\$41,391	100%	\$154,552	100%	\$27,701	100%

Table 5-11

Composite Balance Sheets by Market Segment

	Market Segment			
<i>in thousands of dollars</i>	<i>Diagnostic</i>		<i>Therapeutic</i>	
Assets				
Current Assets:				
Cash and short-term investments	\$ 7,777	39%	\$16,857	44%
Accounts receivable, net	2,093	11%	2,498	7%
Inventory	1,691	9%	1,615	4%
Other current assets	858	4%	708	2%
Total Current Assets	12,419	63%	21,678	57%
Net property, plant and equipment	4,575	23%	11,977	31%
Patents, net of amortization	167	1%	325	1%
Goodwill, other tangibles	583	3%	581	2%
Investment in partnerships, and other entities	315	2%	404	1%
Long-term cash and marketable securities	670	3%	705	2%
Other long-term assets	1,052	5%	2,340	6%
Total Assets	\$19,781	100%	\$38,010	100%
Liabilities and Stockholders' Equity				
Current Liabilities:				
Accounts payable	\$ 997	5%	\$ 1,021	3%
Accrued liabilities	886	4%	1,540	4%
Short-term debt	360	2%	258	1%
Current portion of deferred revenue	152	1%	125	0%
Current portion of long-term debt	188	1%	161	0%
Other current liabilities	380	2%	358	1%
Total Current Liabilities	2,963	15%	3,463	9%
Long-term debt	2,900	15%	8,372	22%
Deferred revenue	110	0%	47	0%
Other non-current liabilities	797	4%	650	2%
Total Liabilities	6,770	34%	12,532	33%
Stockholders' Equity:				
Preferred stock	699	4%	2,344	6%
Common stock	2,538	13%	1,207	3%
Other paid-in capital	16,609	84%	39,057	103%
Other	32	0%	(309)	(1%)
Retained earnings (losses)	(6,867)	(35%)	(16,821)	(44%)
Total Stockholders' Equity	13,011	66%	25,478	67%
Total Liabilities and Stockholders' Equity	\$19,781	100%	\$38,010	100%

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Market Segment			
Ag-bio	Supplier	Other	All Companies

\$12,628	54%	\$ 6,142	19%	\$ 2,103	32%	\$11,175	40%
876	4%	6,499	20%	751	11%	2,524	9%
1,308	6%	7,218	22%	1,285	19%	2,189	8%
366	2%	1,190	3%	300	5%	730	3%
15,178	66%	21,049	64%	4,439	67%	16,618	60%
3,868	17%	7,870	24%	1,665	25%	7,701	28%
362	2%	42	0%	27	0%	218	1%
1,316	6%	1,266	4%	113	2%	660	2%
202	1%	0	0%	0	0%	276	1%
1,643	7%	1,447	5%	1	0%	772	3%
259	1%	1,043	3%	338	5%	1,456	5%
\$22,828	100%	\$32,717	100%	\$ 6,583	100%	\$27,701	100%

\$ 768	3%	\$ 2,669	8%	\$ 414	7%	\$ 1,111	4%
476	2%	1,623	5%	215	3%	1,147	4%
190	1%	245	1%	81	1%	344	1%
934	4%	196	1%	98	2%	197	1%
24	0%	1,713	5%	283	4%	293	1%
418	2%	1,624	5%	64	1%	497	2%
2,810	12%	8,070	25%	1,155	18%	3,589	13%
3,614	16%	2,641	8%	527	8%	4,937	18%
5	0%	31	0%	13	0%	58	0%
63	0%	767	2%	117	2%	611	2%
6,492	28%	11,509	35%	1,812	28%	9,195	33%
729	3%	784	2%	25	0%	1,351	5%
90	0%	5,816	18%	1,683	25%	2,062	7%
32,098	141%	8,568	26%	7,239	110%	25,416	92%
(100)	0%	(86)	0%	(23)	0%	(145)	(1%)
(16,481)	(72%)	6,126	19%	(4,155)	(63%)	(10,178)	(37%)
16,336	72%	21,208	65%	4,769	72%	18,506	67%
\$22,828	100%	\$32,717	100%	\$ 6,581	100%	\$27,701	100%

6. The Landscape of an Industry

The landscape of the industry, shown in the fold-out map following page 89, delineates where biotechnology is happening in the United States this year. The changes from year to year are subtle overall, but significant for local pockets of activity.

The number of companies is approximately the same as last year. While the San Francisco Bay Area continues to dominate the industry geographically, biotechnology is a national industry with a number of significant hubs.

Key Findings

- There are approximately 1100 biotechnology companies in the United States, little changed from last year.
- The San Francisco Bay Area dominates the industry—accounting for over 50 percent of the industry’s revenues and 20 percent of its employees.
- Three East Coast areas of major activity—the New York Tri-State Area, Boston, and Washington D.C.—also account for a significant amount of the industry’s companies, employees, and revenues.
- Other West Coast areas of major activity include San Diego, Los Angeles/Orange County, and Seattle.
- Other regions with significant activity include Research Triangle Park (North Carolina), Houston, Atlanta, Minneapolis, Madison, Denver, and Philadelphia.

Chart 6-1

Regional Distribution of Biotech Industry by Number of Companies

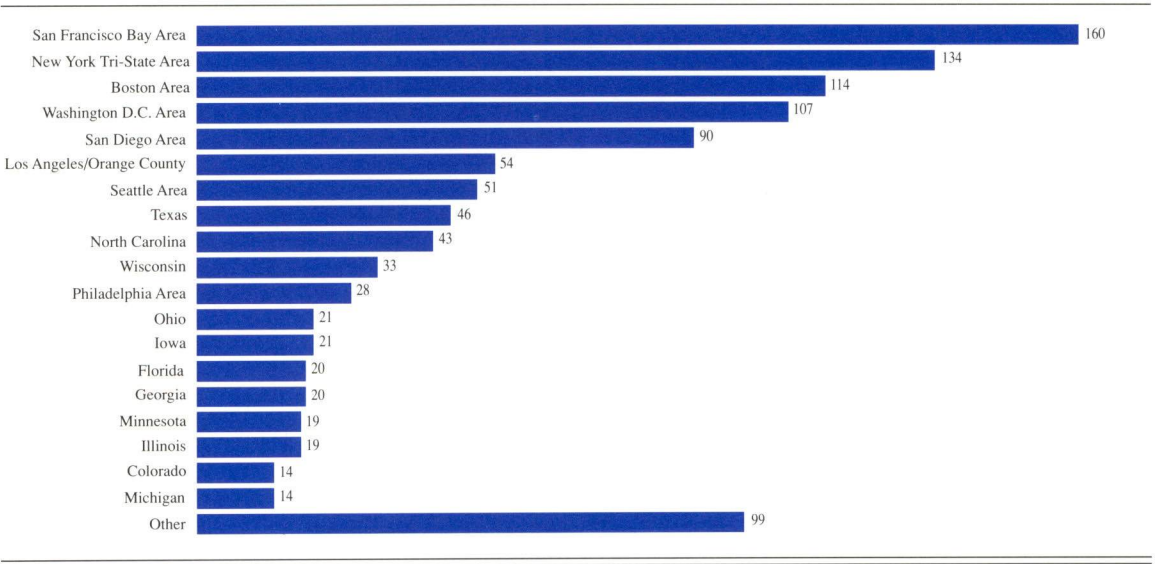


Chart 6-2

Regional Distribution of Biotech Industry by Number of Employees

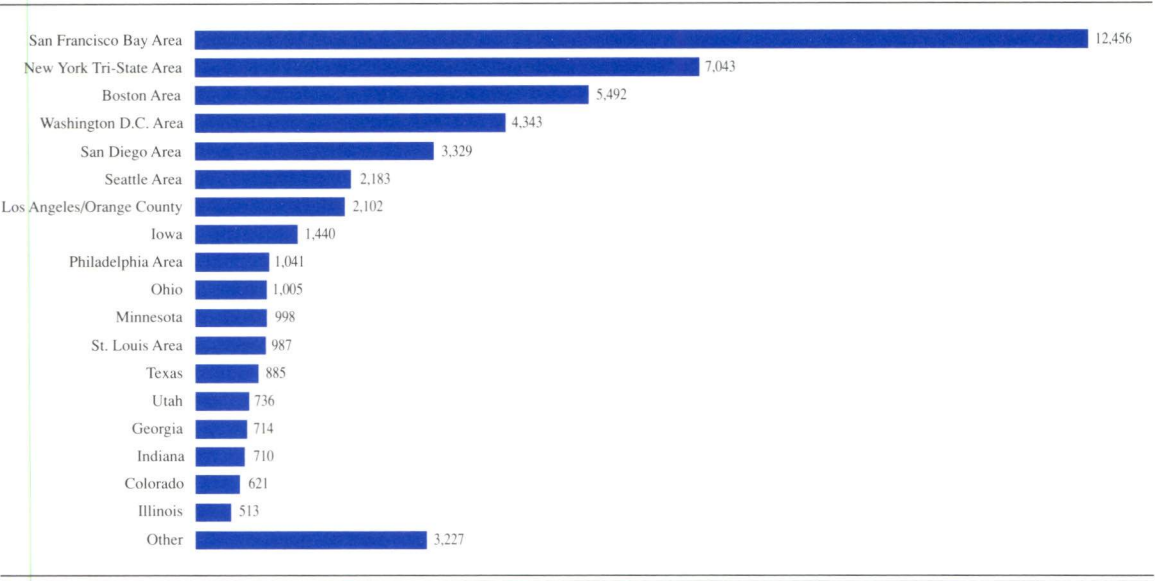
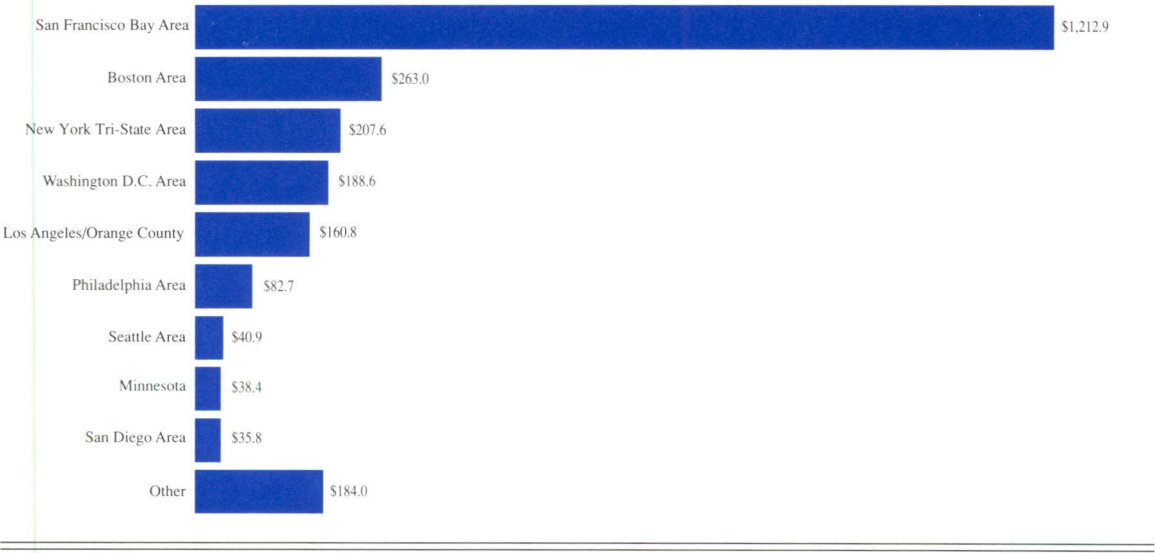


Chart 6-3

Regional Distribution of Biotech Industry by Total Revenues—Public Companies

in millions of dollars



Charts 6-1, 6-2, and 6-3, and the fold-out map provide an overview of the activity of the biotechnology industry nationwide.

The number of companies within the industry as a whole has remained relative constant since last year. The level of start-up activity (including 24 new companies to date in 1990) apparently is at an equilibrium with the number of companies exiting the industry via acquisition, change in business focus, or going out of business. An anticipated “shake-out” is transpiring, but new growth continues to replace the old.

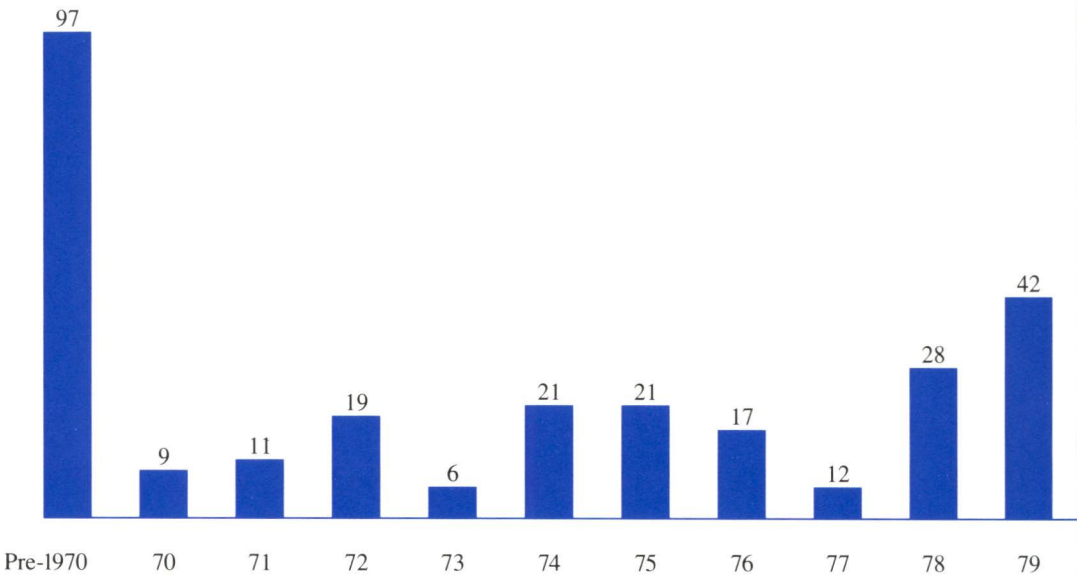
Biotechnology companies flourish in areas where certain conditions exist, including:

- Local centers of medical, agricultural, and environmental sciences activity.
- A local venture capital community and the attention of the national venture capital funds.
- Communities and cultures that encourage entrepreneurial activity.
- Positive quality-of-life and cost-of-living factors.

The Biotech Timeline

Year of Company Founding—All Companies

number of companies



SCIENCE

1953

Watson & Crick—
Double Helix

71

Restriction (cutting)
Enzymes
Discovered

72

Initial Work with
Embryo Transfer

73

Cohen & Boyer
Perfect Genetic
Engineering
Techniques to Cut
and Paste DNA
(using restriction
enzymes and
ligases) and
Reproduce the new
DNA in Bacteria

75

First Monoclonal
Antibodies
Produced

Asilomar
Conference
(Moratorium on
genetic engineering
research)

76

DNA Sequencing
Discovered

First working
Synthetic Gene

77

First Expression of
Human Gene in
Bacteria

Methods for
Reading DNA
Sequence Using
Electrophoresis
Discovered

78

High Level
Structure of Virus
First Identified

Recombinant
Human Insulin
First Produced

79

Human Growth
Hormone First
Synthesized

1970

First Synthesis
of a Gene
(non-functional)

BUSINESS

71

Cetus Founded

75

AgriGenetics
Founded

76

Genentech Founded

77

Genex Founded

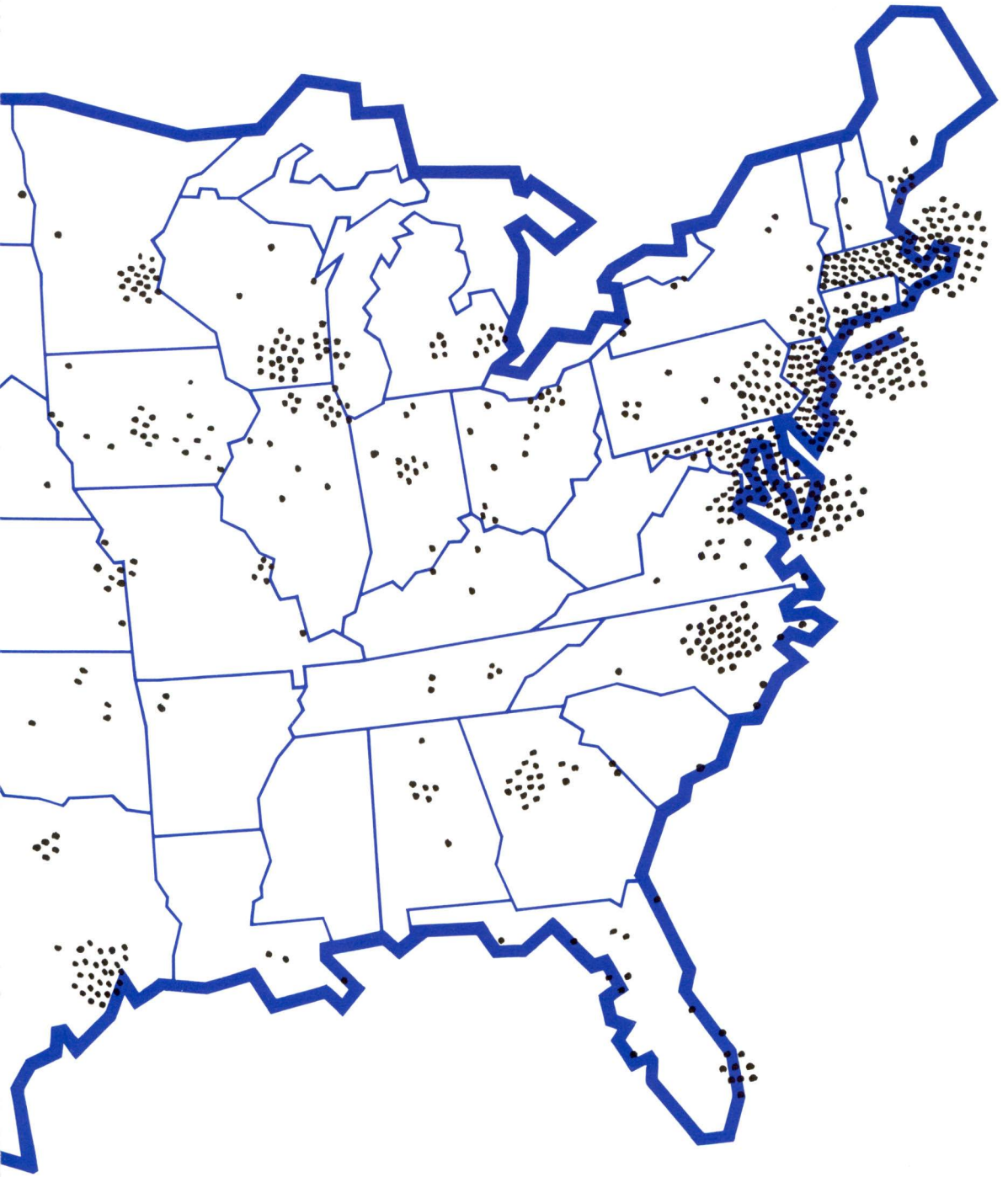
78

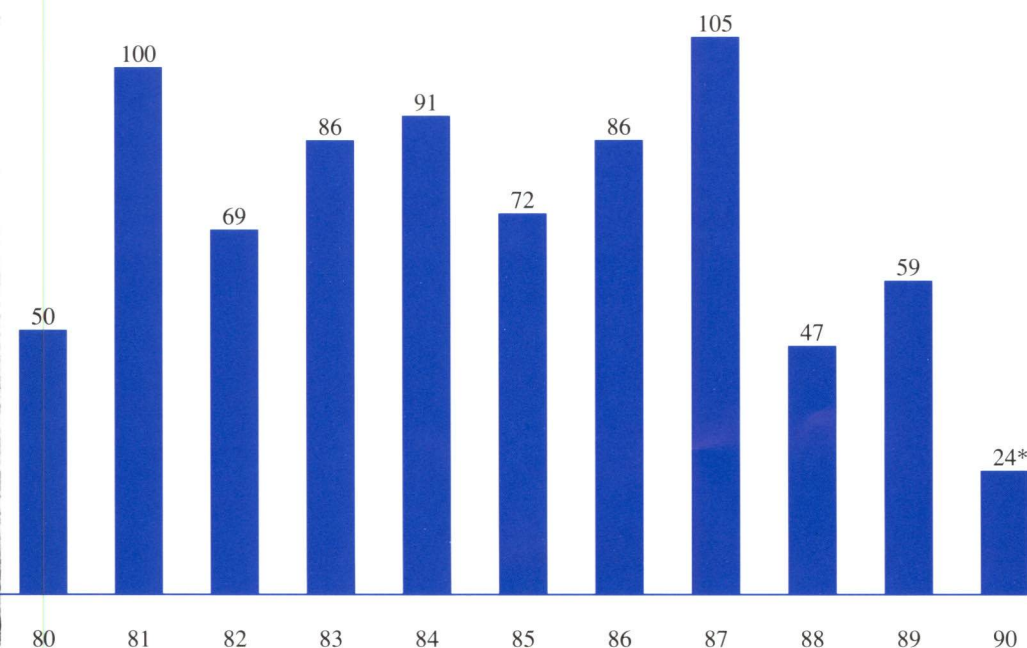
Biogen and
Hybritech Founded

79

Centocor Founded

Landscape of an Industry

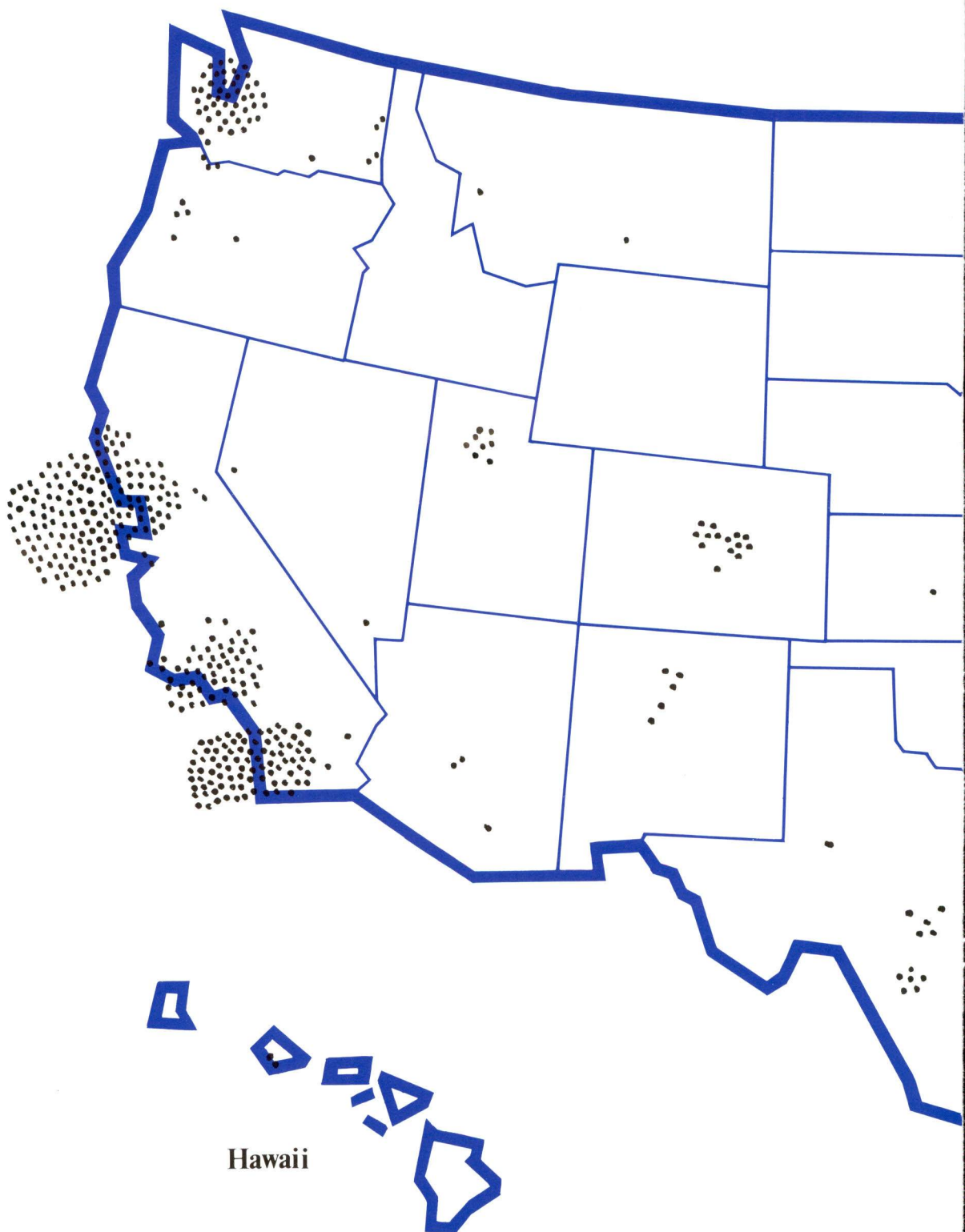




*As of 7/15/90

80 Supreme Court Concludes Lifeforms are Patentable—Chakrabarty Patent	81 Gene Synthesizing Machines Developed	84 Technique for DNA Fingerprinting Discovered First Genetically Engineered Vaccine	86 First Field Trials of Genetically Engineered Plant—Tobacco	88 First U.S. Patent for a Vertebrate—a Transgenic Mouse	90 First Human Gene Therapy First Tests/Applications of Microbials to Combat Oil Spills
	82 Rat Gene Transferred into Mice First Synthesized Vaccine	83 First Artificial Chromosome First Field Test with Altered Bacteria is Delayed First Markings for Inherited Diseases Found in Genes	85 Genetic Markings Found for Kidney Disease and Cystic Fibrosis	87 First Field Trials of a Genetically Altered Bacterium	89 First Field Trial of a Recombinant Viral Crop Protectant Cystic Fibrosis Gene Discovered NIH Conflict of Interest Guidelines Proposed (later dropped)
80 Genentech IPO Amgen, Calgene and Genetic Systems Founded	82 FDA Approves First rDNA Product for use—Human Insulin (Humulin) Centocor and Genex IPO's	85 FDA Approves Human Growth Hormone—Second Genetically Engineered Drug Bristol Acquires Genetic Systems, Lubrizol Acquires Agrigenetics	87 Stock Market Crash t-PA Approved	89 FDA Approves EPO IL-2 Approved in Parts of Europe	90 Roche Acquires Genentech FDA Defines Genetic Engineering First Genetically Engineered Food Product—Rennin
81 First Monoclonal Antibody Diagnostic Kit Approved Cetus, Genetic Systems and Hybritech IPOs Applied Biosystems, Chiron, Genetics Institute and Xoma Founded	83 First Sales of rDNA Product—Humulin Amgen, Applied Biosystems, Biogen and Chiron IPO's	86 FDA Approves First Genetically Engineered Vaccine (Hepatitis B) Eli Lilly Acquires Hybritech Calgene, Genetics Institute and Xoma IPO's	88 FDA Enacts Accelerated Regulatory Process for Products Combating Terminal Diseases		

Biotech 91: The Land



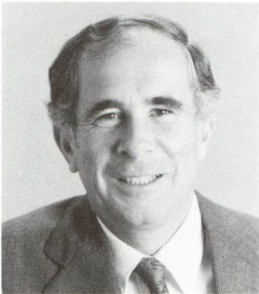
*Roundtables and
Interviews*

Life After Roche/Genentech

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“I would not be doing my job if
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I didn’t try to understand why they
.....
made such a decision.”
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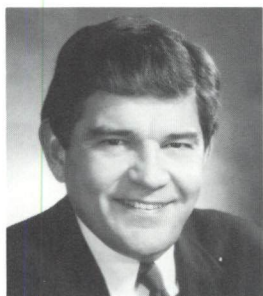
Three CEOs gathered in Boston with G. Steven Burrill, National Director of Ernst & Young’s High Technology Industry Services, to take stock of the realities their companies face in the current period. One has been at the helm of a top-tier biotechnology firm virtually since its launch. Another is a former pharmaceutical executive who turned a troubled company into another industry leader. The third is a founder of a privately held, early-stage company on the cutting edge of a promising new technology.

Casting its shadow over many of the topics addressed in the wide-ranging discussion—financing, product development, corporate alliances, the future of biotech companies—was Roche Holding’s watershed acquisition of a majority position in Genentech. The events of the year in the industry, as well as in their individual companies, have altered and broadened the issues that these CEOs are contending with. What has not changed is the essential leadership process: charting direction and making decisions on a playing field whose ultimate topography is still far from clear.



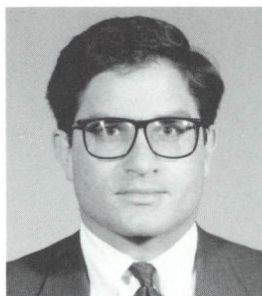
Gabriel Schmergel
President and Chief
Executive Officer
Genetics Institute, Inc.

Gabriel Schmergel was a veteran manager of Baxter Travenol Labs’ international operations when the scientist founders of Genetics Institute (GI) recruited him as President and CEO, shortly after the company’s inception in 1981. The Cambridge, MA, company’s key products and corporate relationships include EPO (Chugai-Upjohn, Boehringer Mannheim), Factor VIII (Baxter Healthcare), and GM-CSF (Sandoz, Schering-Plough). GI is collaborating with Yamanouchi on bone growth factors and with Hoffmann-La Roche in research related to HIV-RT. It operates a joint-venture manufacturing facility in Providence, RI, with Burroughs Wellcome. GI’s GM-CSF, in Phase I/II clinicals in 1990, is slated to become the company’s first self-funded proprietary product.



James L. Vincent
*Chairman and Chief
 Executive Officer*
 Biogen, Inc.

James L. Vincent, earlier President of Allied Health and Scientific Products and COO of Abbott Laboratories, joined Biogen as Chairman and CEO in 1985. At the time, the Cambridge company, founded in 1978, was floundering. Mr. Vincent engineered a remarkable turnaround, and in 1989 led the company to its first year of profitability. Biogen's products-and-relationships portfolio include hepatitis B antigens (Abbott Laboratories, Ortho Diagnostic Systems), hepatitis B vaccine (Merck), alpha interferon (Schering-Plough), gamma interferon (Rentschler, Shionogi). Products in research or development include CD4 for AIDS therapy (with funding from New York Life Insurance Company); thrombin inhibitors and a platelet receptor antagonist for the treatment of cardiovascular disease; and vascular cell-adhesion molecule inhibitors as treatment for inflammation and autoimmune diseases.



Michael Riordan, M.D.
*President and Chief
 Executive Officer*
 Gilead Sciences, Inc.

Michael Riordan brought a broad background to the creation of Gilead Sciences. He holds an M.D. degree from Johns Hopkins, a Harvard M.B.A., a B.S. in chemical engineering, and a B.A. in biology. He co-founded the Foster City, CA, company in 1987, while working as a venture capitalist at Menlo Ventures. Earlier, he was an international lending officer at the Industrial Bank of Japan in Tokyo, a consultant with McKinsey & Co. and Arthur D. Little, and a Luce Fellow in East Asia. Gilead Sciences is developing a new class of pharmaceuticals which employ antisense technology and other methods to inhibit disease processes at the DNA and RNA level. Its primary disease targets are severe viral infections and oncogene-derived cancers for which no adequate therapies exist. The company's investors include Menlo Ventures; J. H. Whitney & Co.; Venrock Associates; Merrill, Pickard, Anderson & Eyre; Concord Partners; William Blair Venture Partners; John Hancock Venture Capital; the Vista Group; and Abingworth Management Limited. Two months after this roundtable, Gilead signed \$20 million strategic alliance with Glaxo.

Managing the Uncertainties

Mr. Burrill: One of the biggest problems you face as CEOs is uncertainty about the regulatory process, patents, litigation, environmental issues, and capital markets. Are the uncertainties higher for a company like Gilead Sciences starting out today, than they were for Biogen and Genetics Institute in their early stages?

Mr. Schmergel: As we go along, certain things get resolved. For example, with patents, court decisions have been reached and precedents established. At the same time, new uncertainties are being created. The Orphan Drug Act may change, and regulatory positions on biopharmaceuticals are still evolving.

In the beginning we were uncertain whether the technology would work. That uncertainty disappeared when Genentech received final approval from the FDA for human growth hormone.

Regarding the uncertainty over financing—we now know that if your products are credible, the money will come to you. If not, the money will not come to you; but then it probably shouldn't.

Mr. Vincent: Then each of us gets down to the uncertainties of building a business: Will you have \$200 million in sales in 1994? Will you have a product on the market in 18 months? Will you own or share the market? On that level, the uncertainty always is high.

Some major pharmaceutical companies are like elephants pirouetting on a single toe

Dr. Riordan: One certainty that the Roche/Genentech deal underscores is that some major pharmaceutical companies are like elephants pirouetting on a single toe—massive entities which are dependent upon a single product, or a small group of products. Since traditional drug discovery is serendipitous, many pharmaceutical companies are recognizing biotechnology as a means to put down one or two more toes to keep the elephant more stable.

Cost reimbursement is a growing uncertainty that will have great bearing on our profitability. An additional unpredictability is that product life cycles are shortening. Ten years ago you could expect a product to be good for ten to twenty years; not anymore. Now you must expect competing products to erode your market share. There also is a set of different uncertainties in patent law.

There is less certainty now about financing than when Genetics Institute and Biogen were at Gilead's stage. R&D limited partnerships essentially don't exist now. The pirouetting elephants will probably be the major source of financing, and that's a more restricted portfolio.

Mr. Burrill: Can we look at the question of uncertainty in light of the Roche/Genentech deal? What might have been the uncertainties that brought a Genentech—or could bring a Biogen or GI—to make that kind of move?

Mr. Schmergel: I look at Genentech and see two good products, a sales force of 300, and sales of \$400 million. They are the industry leader. They set many patterns for the industry over the past fourteen years. I would not be doing my job if I didn't try to understand why they made such a decision.

It is known that Genentech was wrestling, as we are, with the biology/organic chemistry interface, and that they created some organic chemistry

groups. It also is known that they had difficulty raising adequate funding for these groups. From receptors or various enzymes to a small molecule is a big and expensive step. If you don't take it, someone else will pick up your receptor and develop the small molecule. Then, depending on your patent rights, you'll get perhaps a five percent royalty.

*For less than \$100 million a year,
you cannot be a player in
organic chemistry*

Biotechnology companies the size of a GI and a Genentech have to address this. I have to assume that Genentech identified, as we have, that for less than \$100 million a year—and these are running costs, not capital costs—you cannot begin to be a player in organic chemistry. And that amount just puts you in the game in a very small way. Currently, we have decided not to add the organic chemistry and related disciplines in-house. Rather, we are doing three projects in a joint venture with Syntex, and one in collaboration with Roche.

The Reimbursement Question

Mr. Burrill: Michael touched on what could be the mega-uncertainty of the 1990s for both biotech and pharmaceutical companies—reimbursement. How does this uncertainty affect your decisions today?

Mr. Vincent: I expect that government decision-making about reimbursement will extend to 75 percent or more of expenditures for drugs in the United States. Control of pricing is going to be a major, major issue. And if you look at models in

other countries—Canada or Italy—there is no question that if you tinker with pricing, you change the whole research investment equation.

Mr. Schmergel: Perhaps we biotechnology-based firms are more insulated from the problem than the big pharmaceutical companies. We are not working on beta blocker number 28. We are working on some of the most critical unsolved health-care problems, such as cancer, Alzheimer's disease, arthritis, and AIDS. We are not doing defensive research to maintain existing market positions in areas which are overcrowded or, in some cases, becoming commodities. Most of our products create their own markets. There are no pricing precedents. Solid reimbursement rates should be achievable.

Mr. Vincent: What scares me is that we make a six- to ten-year front-end investment before the people in HCFA make their decision about reimbursement which, in effect, sets a product's price. When you're in that deep, you have no option but to market. You will sell at any price above your variable cost. But you won't make the next investment that might result in a similar experience.

*Tinker with pricing, and you
change the whole research
investment equation*

One of the reasons why the greatest productivity in development of new drugs has come from the United States, is that we've had the least invasive regulation of pricing. As regulation intrudes further, there will be a corrosive impact on capital sourcing and the rate of innovation. Gabe, you probably know this: How far below what Amgen was going to charge did they set the reimbursement for EPO?

Mr. Schmergel: I don't know. But I know that the price in Japan is roughly double that in the U.S., and the price in Europe is at least 30 percent higher. And these are with government control.

Dr. Riordan: The industry's response, as Gabe suggested, must be that our therapies are cost-effective solutions to problems that, right now, cost enormous sums of money. Drugs represent only about six percent of national health-care expenditures. There is an opportunity to position that six percent as leverage to reduce costs in the other 94 percent.

Mr. Vincent: Look at what Burroughs Wellcome is experiencing with AZT because the cost of a year's therapy initially approached ten thousand dollars—the public outcry and the threats from Congress! Wall Street analysts who have some knowledge of the situation assert that, even at the eight- to ten-thousand dollar level, AZT was priced well below typical drug margins because of the cost of the ingredients. AZT is having a very beneficial impact, and we're not talking about any "me-too" stuff here.

Like a number of other companies, we're developing an AIDS drug. The approach we've taken, CD4, is a protein that could be a very expensive end product. You'd better believe that all of this static about AZT influences our investment decisions.

If you had a drug candidate that had the potential to be a significant therapeutic step beyond AZT, and you were persuaded that the cost associated with it would be above ten thousand dollars a year, you could make a very solid case that you will never get the reimbursement for that drug that you need to survive. If you're not Merck—if you're Gl or Biogen—let me assure you, this impacts your product development strategy.

Mr. Burrill: Michael, is reimbursement playing a major role in the decisions you are making about the direction of Gilead Sciences?

Dr. Riordan: We don't yet have enough information with regard to the cost of finished goods. However, we are working very consciously to drive down the dose required for effective therapy in animals and humans. First, this will reduce the likelihood of side effects and, also, it will cost less to administer a compound that has a higher potency.

What affects our strategic placement and product focus more directly now are the length and costs of the clinical and regulatory development. We are deliberately focusing on diseases that are more likely to get accelerated review, shorter clinical trials, and more discrete early-stage end points in clinical trials.

Roche/Genentech: Implications and Effects

Mr. Burrill: Has Roche/Genentech affected your operating strategy? Or does life go on, basically, as it did before the transaction?

Dr. Riordan: I think it has focused the attention of large pharmaceutical companies even more on the ability of young companies to build a technology base of value. That is positive from our standpoint.

Pharmaceutical companies are reaching back to discovery research to cut deals

Over the last five to eight years, the pharmaceutical companies looking at outside product and technology opportunities have gone further and further back in the research cycle. It used to be that licensing was done at Phase II or Phase I, or at the

stage of advanced animal data. Now pharmaceutical companies are reaching back to discovery research to cut deals. Pharmaceutical companies used to take a five-year horizon for getting the product out of the licensing activity or collaboration. Now they wisely are doing deals with an intended ten-year stretch.

We all agree that Genentech has been a huge success

Mr. Burrill: Has Roche/Genentech been positive for the biotech industry?

Dr. Riordan: I think so. People within the industry know that Genentech did not sell out because there was no option, or because they were a failure. Genentech was an operating pharmaceutical company, a huge success. It would be unfortunate and incorrect for the relatively naive industry observer or investor to think that Genentech couldn't make it on its own, and that this signals peril for biotech companies.

Mr. Schmergel: Don't worry about the naive investor. Ten years ago, there may have been many people who bought Genentech stock with no idea of what they were doing. The investors today, the institutions as well as the individuals, are increasingly more sophisticated.

Mr. Burrill: Gabe, did Roche/Genentech affect your strategy? Is your life different today?

Mr. Schmergel: If we are honest, we have to recognize the attraction to the Genentech people of reducing the day-to-day earnings pressure that we all are under from the financial community. In the industry, we all agree that Genentech has

been a huge success. But measured against the unreal expectations of a large part of the financial community, Genentech is not viewed as a major success. That is sad and unfair.

One of the conclusions we have drawn is that, by 1995, two to four of the companies that are viewed as top tier today will have undertaken a deal like that, whether it's a 60-40 split like Roche/Genentech, or 40-60, or 50-50. Or a hundred percent.

Mr. Vincent: One effect the Genentech deal had on all of us was to push up our stock prices about 15 percent.

Mr. Burrill: You moved from the operating theory to the exit theory of value.

Mr. Vincent: Yes. My guess is that if you are one of the top ten today, or even second tier, and you are pursuing an exit strategy, the likelihood that you could pull it off within the next eighteen months has gone up.

Mr. Burrill: In the months since the deal was announced, are more large companies looking at you?

Mr. Schmergel: Over the years, we have had some exploratory acquisition approaches, which we evaluated and elected not to pursue. Historically, GI has been approached primarily for joint ventures, in which our contribution is product development, not cash. The frequency of approaches for joint ventures has increased in the last six months.

Mr. Vincent: You get lots of calls from investment bankers who want to be the Fred Frank on the next deal. (*Frederick Frank, the investment banker for the Roche/Genentech transaction, is interviewed starting on page 105.*)

Mr. Burrill: There is a belief that biotechnology companies are insulated from hostile acquisition because of the nature of the assets. Do you believe that?

Dr. Riordan: All these companies recognize that one of the major things they're buying, whether through partnership, joint venture, or acquisition, is the talent base. If that evaporates you're left with just the bag.

Mr. Burrill: Takeover firms argue that if you're friends when the deal is done, it's not hostile, notwithstanding how the acquisition started.

Mr. Vincent: In small- to medium-size high-technology companies, it takes the proactive involvement of senior management to sell it to the organization. If you don't have that support, by definition, it's hostile.

Mr. Burrill: Do you agree with Gabe's projection that, five years out, there will be two to four more acquisitions, or substantial partial acquisitions, among the top ten?

Mr. Vincent: I don't think the market is there today for four acquisitions, but it will be over that period of time. However, for companies that are doing well, with good products in their pipeline, I would say the odds are low that they will sell.

Creating value that will outdo the acquisition premium

There is a case to be made about creating value that will outdo the acquisition premium. For example, if Genentech had been absolutely persuaded that they had at least one drug in their pipeline, let's say within two years of approval,

which would generate a half-billion to a billion-dollar market several years after introduction, would they have sold, and sold for the premium they got?

Mr. Schmergel: I think they would not have sold. If a company thinks it has the next EPO, it will not sell. Of course, if you had the next EPO, even three years away, you would tell the investment community. We all have to undress periodically and talk about what's in the pipeline. If you have the next EPO in Phase II clinicals, it's published. Then your stock price should be very high. If we go back to Genentech selling at \$60, to pay a premium over that, you are getting into megabucks. With the \$5 billion market value they had a couple of years ago, they were much more shielded.

Mr. Vincent: When we were selling our Swiss facilities, there were not very many pharmaceutical companies with a billion dollars or more of sales that I didn't talk to. One of the things that became clear to me (which I should have realized up front, because I came from that world) is that most large pharmaceutical companies do their strategic planning incrementally, rather than zero-based.

The acquisition cost of our Geneva organization was in the \$25 million to \$50 million range. That should not be a big transaction for large drug companies. We found at least a half-dozen companies with which, strategically, we connected. Yet, in most cases, negotiations broke down when they looked at our burn rate of \$15 million to \$18 million a year.

A drug company may have a total research budget of \$250 million, which they increase by maybe ten percent each year. If your discretionary money is \$25 million, an acquisition like this will eat up all of your growth in research. That kind of thinking makes a half-billion dollar transaction appear much larger in financial terms.

I think the Roche move is more of a single event rather than the start of a pattern. Like most

of the Europeans, Roche doesn't have goodwill accounting. (*American companies must expense goodwill, i.e., excess costs, in purchase transactions; European and Japanese companies do not.*) More important, Roche is very closely held. I would expect that their thinking about dilution is much different than in your typical public company that is scrutinized quarter to quarter because of a much larger shareholder base.

Today's Financing Strategies

Mr. Burrill: How do your financing options look today versus a year ago? Are you spending money differently?

Dr. Riordan: Compared to a year ago, our financing strategy has not changed. Over the next few years, our strategy will revolve around the versatility of our technology. Our financing strategy is to engage in substantial corporate partnerships. There's been an increased interest on the part of pharmaceutical companies since last year. I can't say that it can be ascribed to the Genentech deal. Many of these companies are very diligent about seeking out sources of new technology and products.

Mr. Burrill: Jim, are you doing different things this year?

Mr. Vincent: Yes, but it has nothing to do with exogenous factors. The restructuring of our commercial strategy is winding down, and a number of our first-phase drugs are building up substantial revenue streams from royalties. Our balance sheet has changed substantially over the past 18 months, and we have more options in pursuing licensing, partnerships, and so forth.

Deals will be more strategically than economically driven

Four or five years ago, 90 percent of what we were working on in the research pipeline had already been licensed. Today, that's flipped. We own worldwide rights to 90 percent of our R&D today. We'll do more licensing, we'll do more deals, but they will be more strategically than economically driven.

I would disagree that the appetite of the large pharmaceutical companies has increased. If they are looking into a substantial investment that's going to hit their P&L before the drug is on the market and generating revenue, and if it's not the replacement for aspirin—i.e., a slam dunk—I don't see a lot of change in their risk-taking appetite.

Mr. Schmergel: We have been very traditional and conservative in our financing. It's been a combination of partnering and straight equity for a long, long time—no loans. We recently issued some convertible preferred stock, but that's still equity.

However, we have more recently evaluated the SWORD type of financing, such as Centocor's Tocar transaction. In addition to generating cash, SWORD transactions result in a positive P&L impact. (*In a SWORD transaction, a technology is spun off to the public as the core of an independent company. Investors are allowed to purchase units consisting of shares in the new company as well as warrants for the sponsoring company's stock. SWORD is an acronym for stock warrant off-balance sheet R&D financing.*)

We are now at the end of our investment period, where operating losses are accepted by the financial community. Once we get to the breakeven point and then to profits, we will start to be measured as an operating company, and will have to show consistent earnings increases. So the short-term Wall Street mentality increasingly will impact our strategy. We really won't have a choice.

Mr. Burrill: A SWORD transaction can turn out to be a relatively expensive financing when you buy it back. You really are buying some financial statement engineering.

*I don't want to have to cut off
the next EPO*

Mr. Schmergel: Why are we even thinking about it? Because we now have a strategy of keeping U.S. product rights for ourselves. As more and more products get to the clinical stage, the dollar requirements to fund them explode. The way the orphan drug law operates now (and GI, as everyone knows, is supporting changes in the law), you have to rush to get to the FDA first. We are lucky enough to have a surplus of good projects in our pipeline. I don't want to have to cut off what potentially could be the next EPO. Our strategy is to move aggressively, and that impacts our financing strategies. It also makes us very open to joint ventures and other collaborations outside the U.S.

If You Had It to Do Over ...

Mr. Burrill: Let me ask you now to look back, rather than forward. What mistakes have you made, or what would you have done differently?

Mr. Schmergel: We certainly made one big mistake. We were studying whether to buy Biogen in 1985, when the stock price was four dollars—before Jim got there. We decided not to. We completely underestimated the royalty flow on interferon and hepatitis B. At the very least, I should have bought some stock personally.

Mr. Vincent: Lest you lose sleep over that, you never could have seen the hepatitis development as an outsider. In order for the hepatitis thing to work, not only did we have to get the patent to issue, but then we had to unwind commercial arrangements that weren't producing. What is producing the revenue now is 25 new contracts. As for alpha interferon, everybody was down on it through 1987—so you were in a large club which, in 1985, included me.

Mr. Burrill: Coming into Biogen in 1985, how did you assess things?

Mr. Vincent: Prior to signing up, I spent most of my time focusing on whether the science and the people were good. Once I was convinced of that, I was operating on a great deal of faith that we would find a way to turn that into a viable commercial situation. I think that's the case looking at most businesses as an outsider. Sometimes you can see a golden nugget, say, a product you could sell for 50 percent more. Usually it's more subtle than that—you have to deal in fundamentals.

Mr. Schmergel: With hindsight, I would have focused the company a lot faster than we did. We eventually dropped out of diagnostics and specialty chemicals, sold our agricultural division, and discontinued several human therapeutic projects.

*Companies our size cannot be
involved in too many areas*

Ninety-nine percent of what we do now is in areas where we have a leadership position or realistically can expect to attain one. Companies of our size cannot be involved in too many areas. There are internal pressures to do more, because everyone

has creative ideas. You have to be very tough-minded in focusing.

I also would have hired some of our top downstream people faster than I did—the top QA/QC, and manufacturing people we now have on board. I did not anticipate the speed of the evolution of the company from a research boutique to a vertically integrated pharmaceutical company. However, good downstream people are expensive. You're no longer hiring post-docs or assistant professors; you have to hire them from the pharmaceutical industry. These people are making \$150,000 or more.

I also would have insisted on complete manufacturing rights on all licensing deals, and have moved faster to retain clinical development control. That's how you build your regulatory infrastructure, your contacts with the FDA.

Mr. Vincent: One mistake stands out in my mind as a cautionary lesson. In the early part of 1986, it was obvious that we had to raise money. We had a \$30 million negative burn rate. And I wanted to move out the founding venture capital and large pharmaceutical shareholders—I didn't want competitors on our board.

We had the bankers lined up, and were going to attempt the largest equity offering that had ever been tried in biotech, way north of \$100 million. Late in the process, some information related to certain patents getting issued came in from the legal side of the shop. The information was purely anecdotal and speculative; in the end nothing came of it. But once we were aware of it, we had an obligation to disclose.

The mistake was letting it into the system in the first place. It fractured the package and delayed our program by about a year. Then we almost didn't get the offering done because the market fell apart between July and September of 1986—we came within three hours of not being able to do it. Had that happened, we would have gone broke. It was

one of those “for want of a nail, you almost bring down the house” situations.

Dr. Riordan: Our business is too young for me to fully assess our mistakes. One of which I'm aware is that our emphasis on keeping lean has led us to delay, more than we should have, bringing on managers for various groups in the company, be it patents and licensing or a certain part of R&D. The delay has taken its toll on the senior management of the company and meant that we haven't had the leadership that we needed at some levels. We're working now to fix that; we've brought on two new people in the last three months to take leadership positions.

Mr. Vincent: To expand on Gabe's point about focus, back when the first generation of firms started, there was 50 years of work in characterizing proteins hanging there like cherries on a tree. Interferon, EPO, t-PA, growth hormone—these existed in concept long before anyone had enough with which to file the patents. The first firms rushed to pick those cherries; that's one of the reasons there was so much overlap in products and projects in the first six or eight years.

Those cherries are largely gone. Now there's an enormous premium on fundamental strategy and why you can or cannot be better at what you do than someone else who is spending a lot of money.

Mr. Burrill: Earlier, it seemed everybody believed that patents were the answer to the issue of competing solutions to the same problems. Has that been true? And what are you doing to cope with the difficulty of getting a patent to issue?

Mr. Vincent: I agree with Michael's earlier point that the cycle times for new products are going to be shorter. Therefore, patents will be less important than they were in the classical drug model ten or fifteen years ago. But the ability to protect intellec-

tual property will still be important because of the enormous front-end investment.

Mr. Burrill: But your intellectual property, Jim, walks in and out of the door every day. What do you do to retain intellectual property other than just try to keep good people and get good patent lawyers?

Mr. Vincent: You protect as much as you can with patents. For the rest of it, you defend yourself mainly by running the horse race the fastest. Because of the academic grounding of this industry, you're more transparent in your know-how than in many other high-tech industries. You wind up publishing more than they do in electronics, for example, and so the horse race element becomes extremely important.

You defend yourself by running the horse race the fastest

Mr. Schmergel: With proteins, the situation often is complicated by the potential for a whole cascade of patents. You have the fundamental product patent on the purified protein, which in some cases has already issued. If it is strong, it covers a class of proteins. Then there are the various cloning patents, the DNA sequences, transformed hosts and protein manufacturing processes, the use patents, and formulation patents. If one organization ends up owning the whole cascade for a protein, it will, of course, dominate.

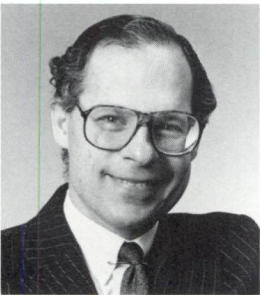
Many of the early projects were horse races, as Jim described them. Some companies got patents on certain aspects, and some on others. This has created a lot of confusion. In cases like recom-

binant Factor VIII, it has been resolved through cross-licensing. For EPO, it's being resolved through litigation, because the parties could not see eye to eye. Judicial decisions are being made, precedents are being set. Our company has been both on the winning and on the losing side in these disputes. But we welcome the process of clarification.

The other major problem is that the Patent Office does not have enough examiners. Even though they have increased their numbers tremendously, they are losing them because their people are hot commodities, and the government can only pay them so much. We all support increasing the resources of the Patent Office in the biotech area and raising the salary ceiling for the biotechnology examiners. It is important for us that they keep the good people, because the lead time to get out a patent is too long.

Dr. Riordan: Proteins often aren't fully elucidated until long after patents are filed and various studies have been done. The discrete chemical entities we make at Gilead are chemically complicated, but we know whether hydrogen is next to a carbon or a nitrogen. In that sense, they are more akin to conventional pharmaceutical chemical entities than are the products of the biotechnology. Others may take some of the directions we do, but some of our directions are completely novel. We think that we'll be able to flesh out certain patent positions with less dispute.

We invest heavily in patents. I spend two hours a day, at least, on patent matters. We have two people working on patents full-time. We use outside counsel for the present, but will be moving to have in-house counsel soon. We think we have some large patent opportunities that will cover classes of chemical entities, so we are strongly emphasizing patents.



Frederick Frank
Senior Managing Director
Lehman Brothers

.....
"I think we'll see more consolidation
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among the larger companies and
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more formations like
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Roche/Genentech."
.....

Frederick Frank is the investment banker who spliced together the genes of Genentech and Hoffmann-La Roche to craft the transaction of the 1990s, to date. Is the deal a model of more deals to come? And how do the benefits play out for the management of the two companies and Genentech's shareholders? G. Steven Burrill, National Director of Ernst & Young's High Technology Industry Services, met with Mr. Frank in his office in New York's American Express Tower to discuss these questions and the financing climate in general for biotechnology companies.

A member of Lehman Brothers' Executive Committee, Mr. Frank joined the firm in 1969. Earlier, he was Co-Director of Research, Vice President, and Director of Smith, Barney & Co. He is Chairman of the National Genetics Foundation and a member of the Salk Institute National Council. He is also a Director of Applied Bioscience International, Molecular Design Ltd., R.P. Scherer, Physicians Computer Network, and Automatic Call Processing.

Biotech is Back

Mr. Burrill: Let's start with your perspective on financing for biotech companies today.

Mr. Frank: 1990 will be a very attractive year for biotechnology companies to raise fresh equity. In 1989, starting with the Biogen convertible exchangeable preferred, most of what was raised was engineered equity. In 1990, we're going back to conventional equity financing, not only because of the more favorable overall financing climate, but also because we are in a period in which the rich biotech companies are helping to bring the poor along. The better known, larger biotechnology companies are now commercial enterprises. As we see a broadening sweep of new commercial products, it reaffirms the productivity of this tool box called biotechnology.

Mr. Burrill: So the high end does some quality financing and pulls along the mid-size and smaller companies...

Mr. Frank: ...who will do either equity or more of the engineered financing. There is a broadened horizon for many companies to finance. I've tried to convey to the ones I work with what I call the eleventh commandment of this industry—which is, to get the single most feared word of the English financial language, "dilution," out of their vocabulary.

Look at the technology companies that started up two or three decades ago, like Raychem, for example. Although they created substantial net worths for themselves, the founders eventually had very small ownerships in those companies. Their pride in making the business work kept them from obsessing over the dilution of their shares. If you raise X dollars of capital, and appropriately deploy it and get a return on it, your stake is not diluted; it is accreted.

The commercial stage of this industry is much more capital intensive than the research stage. Research isn't capital intensive; development is. The issue isn't dilution; it's aggregate resources.

Mr. Burrill: So biotech is back, and partly, you say, because the products are beginning to deliver on the promises. What are the other reasons?

Mr. Frank: The Roche/Genentech-type transaction is an important piece of it. We're having the next wave of mergers and acquisitions, and this influences the financeability of these companies. You have Gen-Probe being acquired by Chugai, Triton Biosciences being sold by Shell, and Genzyme and Amoco selling their joint-partnership venture, Gene-Trak. This activity reaffirms the value of what these companies are capable of creating.

We're having the next wave of mergers and acquisitions

Mr. Burrill: Most of the transactions today have foreign buyers. That's partly a function of there being less pressure on earnings for the big foreign companies relative to their American competitors, which enables them to be deeper-pocketed buyers. The "Greens" (*the political parties in Europe focused on environmental issues*) are definitely a factor behind the Europeans deploying more of their capital in a non-European and, certainly, non-German environment. Are there other factors?

Mr. Frank: Accounting for goodwill is a substantial drag on the financial statements of U.S. companies. And let's not forget the lure of the brain trust we have here in biotechnology. Other countries have not developed their skill set anywhere near the same degree. Also, the major pharmaceutical com-

panies in the U.S. are confident that they can access products through corporate alliances, marketing rights, or other agreements.

Mr. Burrill: The industry seems to be consolidating along two lines: increased strategic alignment domestically, and increased foreign acquisition. Looking forward, do you see the consolidation continuing, and which of the two forms do you think will predominate?

Mr. Frank: If I'm correct in my assessment, the increase we're seeing in the ability of biotechnology companies to access public capital will slow down the consolidation phase in the middle tier. These companies would rather be independent and do their own thing. However, I think we'll see more consolidation among the larger companies, and more formations like Roche/Genentech.

Let's Talk About *That Deal*

Mr. Burrill: The spectrum of reactions to Roche/Genentech have ranged from "the spiritual leader is gone," to "it's the ultimate validation of the worth of these companies." What can you tell us about what caused that transaction to happen and the tricky issues that had to be resolved to make the marriage work for both sides?

Mr. Frank: The background illustrates the point you made earlier about the short-term horizons we have in this country. Genentech's board and management were facing a difficult dilemma. They had two proprietary drugs that were extraordinarily successful, but relatively mature in terms of growth rate. They had two other licensed products on the market which had sales in excess of \$100 million, from which they were receiving royalties. They had a research effort with tremendous potential, but it would not be realized commercially for another four to ten years.

The short-term horizons we have in this country

They were faced with having to increase research and development expenditures at a faster rate than their sales line would grow. The consequences of that are obvious. Earnings would grow slowly or go down. Neither of those outcomes is attractive when the stock price already has gone down from \$65 to \$19. The alternative of slowing down research and development to maintain growth would jeopardize the spirit and integrity of the culture. So, what was the solution?

Because maintaining the integrity of that culture was considered crucial, a normal merger was ruled out. I went off to locate a match that would maintain Genentech's independence while enabling it to gain access to additional financing and an international infrastructure. People often overlook the fact that Genentech did not have an international infrastructure and clearly needed it to optimize the return on its investments. Developing that infrastructure—just like R&D—presents a cash problem, a time problem, and a P&L problem.

One of the things that was so interesting about Roche was that it was important to them that Genentech's culture be preserved. There are only some 28 pharmaceutical products in the world with sales of \$100 million. Yet this company, which only yesterday was a California start-up, has four of them! They did not want to Roche-ize Genentech; they're proud of their culture, but they recognize it's different.

As we got into the negotiations, obviously valuation became a question. We showed Roche that Genentech was not one company, but really two. One was a fully integrated pharmaceutical company with sales of \$400 million. If that company were using the normal ratio for research and development expenditures—call it 15 percent (which is actually higher than the industry

standard)—it would be spending \$60 million. At that ratio, this fully integrated pharmaceutical company would be earning \$100 million after taxes. If you take a 17.5 multiple (which was the prevailing standard for a quality pharmaceutical company at that date), that gives you a \$1.7 billion value in the marketplace for Genentech at that time.

But Genentech overall was spending \$160 million. That leaves us with this R&D company which is spending \$100 million. The market was telling us that a \$100 million research company was worth zero. But clearly it was worth more than zero, and that's what the valuation was all about in the context of a superior research and development organization.

It was the critical question for Roche. To help, Genentech hired a firm to do an independent study of the commercial promise of its \$100 million research entity. In the end, Hoffmann-La Roche put \$500 million into the research company—placing its imprimatur on the fact that intellectual property rights are worth a lot of money if their commercial promise can be demonstrated.

They did not want to Roche-ize Genentech

As you know, on the day the deal was announced, February 2, biotechnology stocks all did very well. I told the Genentech people they should send a bill to the other companies.

Mr. Burrill: The price of Genentech's stock in these last months does not seem to reflect an optimistic view of the upside of this deal for investors.

Mr. Frank: A lot of the people in the Street, as well as some in the industry, are saying that the stock price now has a ceiling and no floor. That's unattractive, if you see it that way. But, in my view,

it's quite the contrary. I think the stock price may prove to have a floor and no ceiling.

Roche needed a way to protect its cash investment of over \$2 billion in this company if things don't go well. So, it has the option to buy the rest of Genentech. But if you read the language carefully, you'll see that if things go well, there's no reason necessarily for them to do that. Let me explain.

I think the stock price may prove to have a floor and no ceiling

Roche has the right to go from 60 to 75 percent ownership by buying stock in the open market, which I think they probably will. Roche sells at 12 times earnings. Genentech on its own (if it accomplished its objectives) would probably sell at least at 20 times earnings. Isn't owning 75 percent of something at 20 times earnings better than owning 100 percent of something at 12 times earnings? I think Roche will exercise the option, if things don't go well, to really get control and make sure the company proceeds in a manner with which they are comfortable and confident. To me, that means you have a floor, and not a ceiling.

Here's another thing that I find fascinating. The stock's current price is \$26. (*Our meeting with Mr. Frank took place on May 30.*) Although the shareholders' meeting to approve the transaction doesn't take place until June 8, the market is saying that, since Roche's acquisition of 60 percent, Genentech is worth less than it was before.

What do I mean by that? Shareholders will get \$18 a share plus another half-share back. If you take the \$18 from the \$26, you've got \$8 left. Multiply it by two, because it represents the price of half a share, and you have \$16. So the stock is selling basically at \$16, whereas it was selling at nearly \$22 just before we announced the deal. Why is

Genentech worth less now than it was before it got \$500 million in extra cash? An important factor is that there's no natural buyer for the stock right out of the box; that means the arbitrage community is sitting this one out.

The focus on this so-called ceiling is so interesting. Let's assume it's correct and my theory is wrong. Genentech will probably remain "independent" until 1995, when Roche will exercise the option of \$60 a share. Well, I don't have too many stocks in my portfolio that are going to go from \$16 to \$60.

The sooner Roche exercises the option, the higher the rate of return. If they exercise their option at \$38 in December 1990, the annual rate of return would be 50 percent. That's not shabby. If you bought Genentech on its IPO and held it until the day we made the announcement, you would have had a 15 percent annual rate of return. If Roche exercises its option sometime in the next five years, the worst rate of return you can get from the \$21 $\frac{3}{4}$ price when the deal was announced, is 22 percent. How many portfolio managers have a 22 percent compound annual rate of return? Not many. The concept of this ceiling blows me away.

Mr. Burrill: You mentioned you shopped the deal among other major companies before Roche emerged as the one that executed the transaction. Why did the others back off?

Mr. Frank: I don't know the answer in all cases. Let me say that Roche was the preferred choice from day one, before we talked to anybody. I'd had a lot of experience with them. Knowing the way they think, it was my judgment that they really would understand what could be accomplished.

With American companies, clearly goodwill was a major problem. Equal to that in importance, the idea of having only partial ownership and having Genentech remain public was anathema to them. Valuation also was an issue.

Needless to say, in a transaction this size, you only talk to a limited number of companies. Their market value has to be very large. And, again, you're talking a lot of "dilution" for an American company—that fearsome word again! Yet if you look at the Merrell Dow/Marion situation, even though Dow experienced 60 cents per share dilution in that deal, the reaction was positive. The stock went from \$85 to \$105, which more than paid for the entire transaction. In the Bristol-Myers/Squibb transaction, there was a tremendous amount of dilution—18 percent in the first year. Yet Bristol-Myers stock now sells at a new high. Obviously, you had reassessment of the multiple as a consequence of the breadth of the organization. I think that's a very strong message.

Mr. Burrill: So you measure dilution post-transaction, after the market adjusts for it.

Mr. Frank: You want to look at dilution not just in terms of earnings per share, but in terms of the net benefit to the stockholders. The Squibb stockholders got the transfer premium and then the additional premium when the stock went up. The Bristol-Myers shareholders benefited from having a better company, with a higher multiple that has offset the dilution of the acquisition. This is a terrific transaction that should help change the concept of dilution and provide a broader perspective. This is especially true if the acquiring company has no need to access the capital markets to finance its growth.

The Shape of Financing to Come

Mr. Burrill: Do you think we will see more of the Roche/Genentech-type structure?

Mr. Frank: Not frequently, but I expect we'll see it again. Or we'll see something closer to the Rhône-Poulenc/Rhorer deal, which was modeled after Marion Merrell Dow. (*Dow Corporation*

acquired a portion of Marion Merrell's stock for cash and exchanged the remainder for contingent value rights. These CVRs guaranteed that, at a set future time, Marion Merrell's shareholders would receive for those shares the equivalent value of the price they received for stock they had tendered, should the market price of their remaining shares have fallen below that level.) There are some accounting controversies in the Marion deal as to how to treat the CVRs. If the treatment changes, it could change that structure as well. But I think those structures, or mutations of them, will be more prevalent than more conventional acquisition arrangements.

How to do a "non-venture capital" venture-capital deal

Mr. Burrill: Let's talk about another type of creative financing which you put together for Thermo Cardiosystems—that is, spinning off an R&D project as a publicly traded company. What is attractive to you about that mechanism?

Mr. Frank: Thermo Cardiosystems was an artificial heart research and development program—high risk, with a long-time horizon—within a company called Thermedics. It was their idea to take the project public. As far as I was concerned, we were asking the public to put up venture capital. But the public is not in a position to be venture capitalists, so the question became how to do a "non-venture capital" venture-capital deal.

The significant entities that had an interest in Thermo Cardiosystems provided the solution. One, obviously, was Thermedics, the parent company which was doing the research. But Thermedics itself was a publicly held subsidiary of the New York Stock Exchange Company, Thermo

Electron, which owned 65 percent of it. So they, too, had a vested interest.

We offered the public stock at \$8.50 a share, which they could put back to the grandparent, Thermo Electron—at windows that opened up after three years, four years, and five years—if the shareholders were not satisfied with the investment. The offering was 1.9 million shares. The stock today is at \$12 and a fraction; it's split twice, three for two. The investors are giving up the interest they could earn in a money market fund but, in exchange, they get the upside potential if this thing works, and can get their original investment back if it doesn't.

That's the cheapest form of financing I could possibly conjure up

It's a contingent liability to Thermo Electron, but they're a *Fortune 500* company—they can afford it. Let's assume at the end of four years, everybody puts their shares back. Thermo Electron will have had a four-year interest-free loan from the public. That's the cheapest form of financing I could possibly conjure up. Everybody wins in this.

Mr. Burrill: The Thermo Electron financing is reasonably well known, yet it doesn't seem to have caught on. Why?

Mr. Frank: Well, with Thermo Electron, the grandparent was a natural guarantor. Usually you don't have that linkage. For example, if XYZ Biotechnology Company wants to raise \$20 million with a new class of stock, why would a large pharmaceutical company that doesn't own equity want to guarantee it? My concept is that the guarantor company would get five percent—a million dollars worth—of the stock as the commitment fee. It also

would get some marketing rights or something in that vein to make it a natural alliance. So far, I haven't been successful in selling it further. But I think it would be the next mutation off of an ALZA/BES or a Centocor/Tocor kind of a deal (*This type of transaction, known as a SWORD, is described on page 101*), and it's much cheaper, because those others have so many warrants related to them. It may not happen this year—whenever you can do conventional equity financing, it slows down innovative financing, and rightly so.

Mr. Burrill: How do you think the biotech industry will look five years from now?

Mr. Frank: This concept of a biotechnology industry will begin to fade. The major pharmaceutical companies will have significant and more visible biotechnology efforts within their normal research setting. We'll be looking at these companies as pharmaceutical companies, diagnostic products companies, ag-chem companies, and so on. We probably will have fewer start-ups, and the start-up period will be much more difficult.

Mr. Burrill: At the moment, our venture capital friends and others are financing 50 or more new companies a year. What's going to cause this decline that you foresee?

Mr. Frank: The scientific challenges ahead are more complex and long-term. Financing them will be incredibly difficult. We haven't seen much of it until now, but in the next few years I think we're going to see the actual closing down of a lot of biotechnology companies that will neither merge nor get funded. There are a lot of companies out there whose life substance is down to six to 12 months. (*See page 74 for information on the industry's survival index.*)

Mr. Burrill: Rather than seeing companies close down, might we not experience a wave of inexpensive acquisitions?

There probably are four levels in this industry

Mr. Frank: I hope you're right, but I don't think it's going to happen. I was out talking to a number of companies about potentially acquiring one of these companies. Two credible buyers commented that they would wait for the company to go bankrupt and then buy it "really cheap."

Mr. Burrill: The market is pretty hot now. How do you see the financeability of this industry for the rest of the year, and what would you project for the next two or three years?

Mr. Frank: These brief bursts of opportunity alternating with closedowns of the system that we've been seeing are going to be replaced by more of a wave form. If the CSFs and other products coming to approval really do well, those

companies will be driving down the broad freeway of financing, not a narrow side road. The marginal companies are going to have to finance at lower prices than when they went public, and they're learning that.

There probably are four levels in this industry. The third- and fourth-level companies are still in serious difficulty, but the second level, at least, is part of the wave that's forming now. I'm pretty optimistic in general about this industry's ability to finance. I think the Genentech deal and the mergers which have taken place really affirm the values that are embedded in these companies.

Mr. Burrill: You received a lot of publicity in the media reporting the Roche transaction. How do you react to that?

Mr. Frank: Nervously. I've tried to avoid the press assiduously over the years. Both Genentech and Roche were very gracious and wanted me to share in the press interviews because, frankly, it's a very complicated transaction that needs explanation. Fortunately, it turned out to be very nice press for me and Lehman Brothers.

Pragmatism and the Business Opportunity



Henri A. Termeer
*Chairman, President, and
Chief Executive Officer*
Genzyme Corporation

.....
"I was convinced that we should
.....
use the moment of excitement
.....
about Genzyme."
.....

Our editors visited Henri Termeer in Genzyme's original headquarters in an Art Deco building in Boston's Chinatown, shortly before the office's move to a new facility in Cambridge. On a table opposite Mr. Termeer's desk was a collection of clocks—apt accoutrement for a man with a strong sense of timing.

Genzyme's 1989 acquisition of Integrated Genetics and 1990 buyback of its Ceredase R&D limited partnership on the eve of the FDA's approval of this treatment for Gaucher's disease, are among a series of transactions that have garnered the company significant investor attention.

The cost of the Integrated Genetics transaction was a major contributor to Genzyme's operating loss in 1989—its first since the company went public in 1986. Since the company's beginnings in 1981, Genzyme's manufacturing facilities in England and the United States have provided a revenue stream for its diagnostic reagents, research biologicals, fine chemicals, and bulk pharmaceuticals. The manufacturing, distribution, and sales infrastructure it has built are now also the platform for its therapeutic products business.

Mr. Termeer joined Genzyme as its President in 1983, was named Chief Executive Officer

in 1985, and elected Chairman in 1988. Earlier, he spent ten years in management positions with Baxter Travenol.

Coordinating Financial Strategies

E&Y: During the past nine months, Genzyme has undertaken a string of interesting financial transactions. How many have there been since your acquisition of Integrated Genetics? Were they all planned?

Mr. Termeer: There have been six—let me briefly outline them. In August, 1989, we merged Integrated Genetics with Genzyme. That took 3.1 million Genzyme shares, which were valued at the time at \$31.5 million. Integrated Genetics brought \$18.5 million cash into the company.

In November, we closed an R&D limited partnership to develop and commercialize hyaluronic acid-based (HA) products to lower the incidence and severity of surgical adhesions. That raised \$36.5 million, and cost us 1.9 million stock warrants.

About a month later, we closed a secondary offering which was so successful that we increased its size by thirty percent to 2.9 million shares. That raised about \$40 million.

In February, 1990, we completed the buyback of an R&D partnership which we had formed in 1987 for the development of our first therapeutic product, Ceredase, for the treatment of Gaucher's disease. That was a \$20.4 million transaction. Our investors received a 34 percent internal rate of return, with which they were very happy.

Finally, in May, we issued a public offering for IG Laboratories, our genetic disease testing subsidiary, selling about 40 percent of it. It is raising about \$14 million for the company. We also have agreed with our partner Amoco to divest our joint venture, Gene-Trak Systems, a gene-probe diagnostic business. This will produce another cash infusion when it is successfully sold.

Genzyme Financing Activities

August 1989 – June 1990

		Transaction Value	Shares Issued (in millions)	Cash Raised
8/89	Integrated Genetics Acquisition	\$31.5	3.1	\$ 18.5
11/89	Surgical Aids LP	36.8	1.9	36.8
			(Warrants)	
12/89	Public Equity Offering	39.1	2.9	39.1
2/90	Ceredase LP Roll-Up	20.4	1.4	—
5/90	IG Labs IPO	38.6	—	14.1
	Gene-Trak Divestiture	N/A	—	N/A
				<u>\$108.5</u>

So, from August to May (not counting Gene-Trak Systems) we raised approximately \$110 million. In the same period, we went from a market valuation of \$85 million prior to the merger with IG, to a valuation today of about \$300 million. While there was some dilution, we received a lot of support from analysts and investors because of the visible progress we were showing.

E&Y: Why these particular transactions? And why in this compressed time frame?

Mr. Termeer: It is all very consistent with our basic philosophy. Some people in this industry become very taken with the grandeur of the science. We have always viewed biotechnology as a powerful tool to build an important business and make valuable medical contributions. Succeeding in science is critically important, but building companies also means using the opportunities that the marketplace offers to build an internally working economy.

The financial transactions during this time actually were very dependent on each other. We had a major responsibility for absorbing Integrated Genetics, which had been losing \$1 million a month. We had to put financing into place straightaway.

The HA limited partnership was critical. Our products were approaching clinical trials. We did not want to establish a corporate partner. The limited partnership will allow us to make HA gradually independent, just as we were able to do with Ceredase.

Following the Integrated Genetics merger, I saw our stock go up about 30 percent. By mid-September, it seemed to me we could do a secondary offering to capitalize the larger company properly and build the plant that we need to carry out the HA program. I was convinced that we should use the moment of excitement about Genzyme.

We had to do the offering before Christmas so as not to be dependent on the next year's developments. But, for the SEC filing, we had to wait until we closed the HA partnership, which couldn't be done until November. That left us an extraordinarily short window.

Rolling up Ceredase in February seemed obvious. The partnership ran out in October. We had FDA approval of the treatment protocol. Every month that we delayed the buyback would have cost us in the neighborhood of \$700,000.

E&Y: You surprised the market by going public with IG Laboratories less than a year after the merger.

Mr. Termeer: When we announced our intent to acquire Integrated Genetics in April 1989, the genetic-disease piece was costing \$200,000 a month to maintain, and showed very little sales. We tried to raise some venture capital to fund the operations and allow us to collapse our ownership in that subsidiary to the value of the assets, but that didn't fly.

A very good case of how biotechnology can build a business

We completed the acquisition in August. In September, the cystic fibrosis gene was published. A few weeks later, we introduced a test for cystic fibrosis carriers through the genetic-testing subsidiary. We also test for Down's syndrome, Huntington's Disease, Factor VIII deficiency, and other genetic disorders. *The Wall Street Journal*, *The New York Times*, and *The Boston Globe* were starting to write about testing for genetic diseases. It occurred to me that we might take the labs public.

This is a very good case of how biotechnology can build a business. Prenatal testing is a \$250 million marketplace divided up among five hundred labs all around the country. They have no science and no real quality control. These labs are mostly not-for-profit and located in hospitals or associated with them. Today they service about ten percent of the OB-GYN practices in the country. The demand is growing, as older women have babies, and as more people know about this option.

Biotechnology can improve on how that demand is met, improve on standardization and quality control, improve the turnaround cycle, and lower the price. By using DNA hybridization, we will reduce a process that now takes several weeks to two days, and maybe one. We're also working to make it possible to obtain fetal cells from the expectant mother's blood, rather than fetal fluid.

That will reduce the discomfort and risk enormously. It will become a simple blood test.

We are now the best capitalized effort in this field. There's no patent uncertainty. The FDA controls only the facility and laboratory procedures. The Integrated Genetics people already knew this. They helped me understand that the marketplace is already there and really accessible to being served better through biotechnology.

Integrating an Acquisition

E&Y: Does IG Labs signal a change in your business strategy from, say, a year ago?

Mr. Termeer: There is definitely a change in operating strategy, but not in our strategic philosophy, which has been to be pragmatic about the business opportunity, and not be bound by conventions in figuring out how best to finance it. We identify a niche, define a program for the niche, create a financial vehicle around the program, and then stick with it.

E&Y: Genzyme and Integrated Genetics were two Boston-based companies that had been somewhat competitive. You do not seem to have gone through a lot of wear and tear in melding the two companies into one. How did you accomplish that?

Mr. Termeer: It came together very quickly. Part of it, I think, is because the people essentially were from the same schools—mostly out of Boston, all young, and many knew each other. Also, Genzyme is spread among Boston, Cambridge, and England. There was not an overwhelming Genzyme presence in Boston. We had roughly the same number of people here as Integrated Genetics, so that was pretty even-handed.

Integrated Genetics had created many valuable programs, and we did not destroy their momentum. We also made many of the Integrated Genetics people part of the momentum around Genzyme programs that were growing very fast,

like Ceredase. That gave large groups within Integrated Genetics a destiny, a product with which they knew they were going to be number one. If you have been struggling in a number two, three, or four position for a long time, it's like coming into the light.

We deemphasized programs that we were doing just to create research income, and assigned people to programs that were more uniquely Genzyme. For instance, we now have a very active program in cystic fibrosis, with as good a shot at coming up with a solution as anyone. That builds a lot of excitement.

Visions: Present and Future

E&Y: The market has certainly endorsed the progress and changes of this year. What is the vision behind it?

Mr. Termeer: The vision, and the goal, is the creation of a major, vertically integrated, health-care products company. We are very pragmatic about our vision. Yesterday, after I gave a presentation to some analysts, somebody said me, "It all sounds so easy when you explain it. What keeps you awake at night?" My answer? "Everything keeps me awake." Genzyme has done well and will continue to do well. We also will have major headaches. We will not take anything for granted.

I worry about a lot of things, but not in a way that becomes obsessive. If I believe any one thing, it is that the effort must be fun. I always emphasize to our people that it is important to feel good about what they are doing and how we are creating the company together. We each, individually, make the decision to build a major company and, individually, make a contribution to it. If people no longer feel satisfied, I encourage them to consider leaving. Nobody needs to put out an effort such as these companies require if it is forced, if it is not fun. The fact that we have a lot of people who are happy to be part of our effort creates the confi-

dence to make reprioritization and redeployment decisions.

E&Y: The industry appears to be entering a period of consolidation. What do you expect the shape of the industry to be five years from now?

Mr. Termeer: It won't be dramatically different from today. Some names will be different, some will be the same. The number of companies will be comparable, because every time one company disappears, a new one is created. That's the richness of this technology. It is still innovating so fast, and giving so many opportunities to create value, that people will continue to find money and encouragement to start new companies.

*When large companies combine,
they divest market share along
their fringes*

Companies like Genzyme will grow not only through internal development and acquiring other technology companies, but also by acquiring pieces of the large companies. When large companies combine in mega-mergers, they divest market share along their fringes—divisions in which they don't have strong products for an encore or which are trailing in the marketplace. They will not maintain those lower-margin businesses.

Some of that market share will end up in the emerging companies. This will enable us to enter a market with mature products, while our innovation will provide the encore. We can build up the critical mass we need to have the chance to become a reasonably sized company. Acquiring the base market share in this way eliminates the need to have to fight to remove that market share from someone else's pocket. That's very expensive and inefficient.

E&Y: Conversely, do you envision first-tier companies being acquired by the larger companies?

Mr. Termeer: Absolutely. All of these companies are going to be reviewed. Over the next five-year period, I would expect more than half of the top-tier companies to be acquired. It's a very efficient acquisition for a large company, if it brings a reasonable pipeline.

It also is efficient from the point of view of some of the biotech companies. Unless they are able to claim a share of the marketplace, they always will be vulnerable to being picked up, because they are floating on the basis of their market valuation. It's a purely financial calculation.

E&Y: How do you stake out a share of the marketplace when you may be in a race with ten companies to develop a product?

Mr. Termeer: The first responsibility to your shareholders and your own people is not to engage in a race that you can't win. When 18 companies were engaged in interleukin 2, you knew that at least 16 of them would lose. This is a tremendous waste of capital and science resources, and is simply bad management.

You can argue that biotechnology is not an industry at all, but just a group of small companies using a tool called biotechnology to make interesting products. The way to make these companies economically viable is to keep the focus on creating value that would not otherwise be there. We have an historical opportunity now to build major new companies, but we have to be realistic and pragmatic in how we go about it.



Edward E. Penhoet, Ph.D.
Vice Chairman and
Chief Executive Officer
Chiron Corporation

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"We're hybrid companies right now,
.....
partially mature and partially
.....
early-stage."
.....

During 1989-1990, Chiron Corporation kept its name in the bio-headlines. Physicians and blood banks around the country heralded the May, 1990 FDA approval of Chiron's hepatitis C blood-test, already on the market in Japan, Canada, and Europe. Chiron and its diagnostic-products joint-venture partner, Ortho Diagnostic Systems of Johnson & Johnson, had taken the test from development to the marketplace in just two years. Several months earlier, Chiron/Ortho locked in the platform for marketing its blood-testing technology by purchasing Du Pont's blood-screening business, placing Chiron/Ortho in the number two market position worldwide.

A bold move to acquire a major vaccine company brought Chiron and its vaccine-products joint-venture partner, Ciba-Geigy, to the brink of acquiring Canada's Connaught BioSciences. Their bid came a cropper on a higher bid from France's Institut Merieux, but Chiron again had demonstrated its resolve to link, license, and acquire—upstream, downstream, and sideways—to leverage its technology and broaden its penetration of target markets.

Chiron's early-stage products include human growth factors, superoxide dismutase (SOD), and anti-tumor necrosis factor. To fund continuing development, Chiron issued \$121.5 million in convertible subordinated debentures in June, 1990.

CEO Edward Penhoet, one of the company's co-founders in 1981, served as its President, CEO, and a Director until 1989, when he was named Vice Chairman and CEO. Dr. Penhoet has been on the faculty of the biochemistry department of the University of California—Berkeley for seventeen years, currently as adjunct professor.

Dr. Penhoet was interviewed by Kenneth B. Lee, Jr., National Director of Ernst & Young's Life Sciences Industry Services, at Chiron's headquarters.

Managing Corporate Partnerships

Mr. Lee: Does the Roche/Genentech deal set a new model that will be played out by others? By Chiron?

Dr. Penhoet: This is an acquisition of Genentech by Hoffmann-La Roche. As a result, the two companies will have to work out a number of issues concerning the ways in which their two cultures will work together and affect each other.

Chiron is trying to maintain a group of corporate partnerships where both companies work as collaborators, with no reason to try to manage each other's business in any significant way. A lot of other companies' partnerships have come and gone, but almost all of ours have lasted and seem to be working. We probably are the company that has been most committed to corporate partnering as a fundamental commercial strategy.

Mr. Lee: What makes your partnerships work so well?

Dr. Penhoet: As much as anything, it's an attitude. Many companies view corporate partnerships as a necessary evil to bridge the gap from start-up to the time they are fully independent. From the beginning, we viewed corporate partnerships as a productive way of doing business.

Parochial interests can sandbag a corporate partnership

A couple of other elements are important. First, we get as close to equal participation in the relationship as we can, so that both parties have real standing. Second, we work at developing a positive understanding in both companies about the relationship. Partnerships are hardest to implement at the middle-management level; that's where parochial interests can sandbag your shared interests.

Mr. Lee: Pharmaceutical companies themselves seem to be increasingly oriented towards co-marketing and partnering arrangements.

Dr. Penhoet: I put together a slide about the growth of corporate partnerships among traditional pharmaceutical companies for a recent talk. If you go back fifteen years, there were almost none. Now there are at least as many of these relationships between the large companies as there are between large and small, if not more.

Generally, the bulk of the profitability in almost all of the pharmaceutical companies today comes from a handful of products. That can mean a bumpy road in terms of financial results from year to year, because the fortunes of those products are so crucial in driving the performance of their companies. We saw this in Hoffmann-La Roche with

Valium, SmithKline with Tagamet, and are seeing it now in Glaxo with Zantac.

Having a great product is both a blessing and a curse. It's like the Spanish Empire: They had all the gold in the world for a long time. They didn't have to develop anything else. But history passed them by. All companies today are seeking to broaden their bases by accessing new products from a variety of sources.

Mr. Lee: In 1989, in partnership with Ciba-Geigy, you bid to acquire Connaught BioSciences of Toronto. In 1990, with Ortho Diagnostic Systems, you purchased Du Pont's blood-screening products business. Will we see more of these moves?

Dr. Penhoet: Our technology had driven a fundamental change in the industries of those two companies, vaccines with Connaught, blood testing with Du Pont. That provided us opportunities to make purchases under advantageous terms. Strategically, without our going downstream with our technology in both of those businesses, we would be vulnerable.

Acquisitions should not be a one-way street where the big guys buy the small

Connaught was one of those momentary opportunities that we continue to seek. I hope and expect we will see more acquisitions by technology-driven companies. Acquisitions should not be a one-way street where the big guys buy the small. Companies like ours should be aggressive about using the leverage associated with new technology to make acquisitions as a forward-integration strategy. We expect to do more in the future.

Moving Into the Marketplace

Mr. Lee: You're shifting quickly from an R&D orientation toward having products in the marketplace. How do you assimilate this?

Dr. Penhoet: The biggest danger in this period is the opposite of what people might normally think. There is a tendency to believe that the technology-driven companies will stumble in commercialization because they haven't had the marketing and sales experience. I see an equal danger of them becoming so enamored with the issues involving marketing and sales that they let their research organization become less effective than it should be. For us, right now, a crucial issue is to become a commercial organization while not forgetting that technology is the real engine.

We have to stay plugged-in to the university system. We have to continue to generate new technology, because that's the real value we supply. It's tempting for management to focus on the commercial side of things and take the research organization for granted. That's a strategic mistake.

Mr. Lee: Are you looking outside as well as inside for new technology?

Dr. Penhoet: There's a complex dynamic between marketing and the product stream. We're firmly convinced that you have to make a commitment to a marketplace, not solely to your own research organization, in terms of the products you are going to sell. Our marketing and sales strategy is customer-based, not technology-based.

In Chiron Ophthalmics, as an example, we're building a broad-based business focused around the product needs of the ophthalmic surgeon. While we have a strong foundation of technology, for market presence we have to augment our products with products we get elsewhere. You'll never invent everything the ophthalmic surgeon needs in a single organization.

We're developing wound-healing products and some vision-correcting products as our key proprietary positioning. But to build a successful long-term business, we have to have a broader, deeper portfolio. So we license in other products. Recently, we licensed a technology from Staar Surgical for foldable, single-incision intraocular lenses. We're trying to build a platform from which the wound-healing agents we're developing can make a big impact in ophthalmology—ultimately, replacing sutures in cataract surgery. For that to happen requires surgeons to make the smallest possible incision. So from a market-positioning point of view, the foldable lenses are right in the mainstream of our business strategy.

Two ways to go in marketing and sales of pharmaceuticals: high-tech or high-touch

There are two ways to go in the marketing and sales of pharmaceuticals: high-tech or high-touch. We're in the high-touch segment, where you sell innovative products through knowledge, relationships, and service. In selected niches, we think small companies can be very effective at doing that. The high-tech route involves massive sales of products to many and often diverse organizations. Small companies are not going to be effective in that kind of marketplace. The consolidation of the major pharmaceutical companies probably provides more niche marketing opportunities for smaller companies. The vast size of the conglomerates that are emerging will leave open niches that they're not going to cover.

Generating Value vs. Generating Earnings

Mr. Lee: Has the public market's interest in financing biotech companies returned this year?

Dr. Penhoet: There are always two sides to the financial markets. People used to come to me from Europe to try to understand how they could create a venture capital-based entrepreneurial business climate. Well, they had two problems: they didn't have any entrepreneurs and they didn't have any venture capital.

The financial markets are not roaring like they were in 1983, but capital is reasonably available for good companies and technologies. As far as IPOs go, I actually think there are fewer companies ready to go public than there is a willingness to fund them. Chiron had some difficulties with financing in the past because of wide swings in the market perception of our company, but it hasn't been a problem in the last few years. Capital is available to us for our needs, and our recent debenture offering was quite well received.

Mr. Lee: How do you react to the new SWORD method that's been used by Centocor with Tocor, for example, to finance development of a new technology through a public offering?

A new product creates an exaggerated effect in a company's earning curve

Dr. Penhoet: We're hybrid companies right now, partially mature and partially early-stage. The most significant issue that we face as a group in the next five years is to manage the potential conflict of building long-term value versus generating short-term earnings.

Ten years from now, new products will be coming along on a regular basis to provide steady increments to earnings. Right now, a new product creates an exaggerated effect in a company's earning curve over the short term. But time can pass before the next important product comes out. During that period, earnings growth flattens. That can have an exaggerated effect on valuation—although it shouldn't, as long as you're making significant progress.

Our hepatitis C test, for example, will take us from losing \$16 to \$20 million a year to break-even in a very short period of time. That's an enormously rapid growth in earnings, but the rate of change in earnings can't be maintained over five years.

Two years from now, we'll have a relatively mature diagnostic business, but we'll be an emerging vaccine and pharmaceuticals company. We have to keep the financial community focused on the value that we're building at Chiron during this period of time, but there still will be a certain amount of focus on earnings.

Off-balance sheet financing mechanisms exist to partially address that issue. I think they're a perfectly legitimate way of sharing new technology with a new set of investors, while minimizing the current effects of R&D spending on the company's earnings. It's inherent in a growth company that you have to keep investing in your technology to build value.

Mr. Lee: The Japanese seem to take a much longer-term view with developing companies. Now that they are zeroing in on biotechnology, will they have an impact on Wall Street's short-term outlook?

Dr. Penhoet: Wall Street seems to be more willing to learn from the Japanese than they are from us. They can see how the capital market functions in Japan. Multiples are much higher, because the Japanese investor focuses on value rather than current earnings. There's a reward system for building

value. Somehow, we have to arrive at a reward system like that here. Otherwise the Japanese can capture our technology at a discount from true value.

Wall Street seems more willing to learn from the Japanese than from us

As competitors, the Japanese are tough. There's absolutely no question that their pharmaceutical industry has to enter the U.S. market. They're being squeezed unmercifully in Japan by their own government. Increasingly, foreign pharmaceutical companies are marketing directly in Japan, rather than through local companies, so Japanese companies can't count anymore on access to American and European products. The major Japanese companies will be here in a significant way. Lyphomed and Gen-Probe were certainly not the last acquisitions.

Competition and Patents

Mr. Lee: Do you look at competition with the Japanese as a U.S. versus foreign issue?

Dr. Penhoet: We really enjoy working with the Japanese as a group of people. They're our partners in some businesses, for example, Daiichi in DNA probes, and Takeda in SOD. They hold up their end of the deal. When they say they're going to do something, it gets done. But we also have to recognize that they are our competitors, and quite serious ones.

The basis on which we should compete with the Japanese is who invented things first. We have to make sure that the Japanese respect our patents in Japan, which is still a problem. I think we have to be very firm with the Japanese about respecting intellectual property.

The most positive thing that has happened for the competitive position of U.S. biotech companies in recent times has been the degree to which patents are being issued and upheld as valid. I think all the recent decisions have been very pro-patent.

Mr. Lee: Even the EPO decision?

Dr. Penhoet: Amgen's patents are being upheld. The court did not rule them invalid, which is the crucial issue. It simply ruled that GI also has a valid claim, different from Amgen's. The reverse could have occurred—neither of their patents being upheld, and then any company could get into the erythropoietin game.

Mr. Lee: How are you coping with the bottleneck in the Patent and Trademark Office? Does it force you to expose your technology before you have patent protection?

Dr. Penhoet: The PTO has become more efficient in the last several years. I think the level of understanding of the examiners has been increased substantially. We'd still like to see more high-quality examiners, but the system's starting to function the way it should.

However, it is still taking too long to issue patents. There are patents just issuing now for inventions made a decade ago. That's tough from two points of view: First, products are commercialized before the patents issue, and it's hard to sort things out afterwards. Second, the technology changes so much in a ten-year period that it's difficult to go back and evaluate what constituted an invention in 1980. That's important because inventions have to be seen somewhat in context. A lot of key patents are going to issue soon. We're going to have to be sensible about paying each other. One way or another, everybody's going to be playing in somebody else's sandbox, patent-wise. People need to be paid for inventions that help create value.

Actually, I think the litigation is a sign of the health of the patent situation. The way our legal system functions, you have to test cases in court before they become truly inculcated. It's a predictable, necessary stage to go through. There'll be many more court battles before this is all over. It's not fun, but it's healthy for the industry and for our value.

The Myth of the Entrepreneur

Mr. Lee: Looking back over your ten years in building one of the major biotechnology companies, are there things you would like to have done differently?

Dr. Penhoet: I'm a firm believer that if you make 51 percent of the calls right, over time you're going to win. We've made our share of mistakes—any organization that's aggressive is going to. But I can't think of any strategic areas where we would have done things differently. On a project basis, there are some decisions that I'd reverse with hindsight.

Any organization that's aggressive is going to make mistakes

We were criticized early on for the degree to which we relied on corporate partnering as a strategy, but we're still very comfortable with that way of doing business. We haven't done any significant amount of off-balance sheet financing. In some periods that was painful for us, because our losses were bigger than those of some other companies, but we don't have any share overhang from it.

One of the most destructive things that's happening is this myth of the entrepreneur-as-hero we're creating in this country. It's a disservice to individuals who are starting new ventures to have them think that their predecessors who've made it walk on water. I'm thinking of the books that are written by "gurus" who seem to have the answers to everything. I know all the people in this business. We're very human, we all make a lot of mistakes, and we've worked very hard to get that 51 percent right. One CEO once said to me, "Penhoet, if we ever make a dime in this business, we'll deserve every penny of it."

The notion that somehow the successful companies decide to finance at just the right moment and make all their decisions in a totally rational way—it's a fantasy. For people in companies starting out, it's very important to realize that the process is not programmed. It's daily living, thinking, and decisions. There's no mystery about it—and ordinary guys do quite well at this from time to time.



Jeffrey Casdin
Senior Vice-President
Biotechnology Investment
Research
Oppenheimer & Co.

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“I would say that we’re at an
.....
incredibly buoyant period in the
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markets for biotech.”
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Jeffrey Casdin is a biotech analyst who makes news. He is respected for the depth of his knowledge of the industry, and his stock recommendations have clout. In addition to his research responsibilities for the investment firm, Oppenheimer & Co., Mr. Casdin assists the firm’s health-care investment banking and venture capital groups. Mr. Casdin has been active in the securities business for more than 20 years. Prior to joining Oppenheimer, he was the publisher of Biotech Investor. The interview with Mr. Casdin was conducted by Kenneth B. Lee, Jr., National Director of Ernst & Young’s Life Sciences Industry Services, at Ernst & Young’s National Office in New York.

Mr. Lee: We seem to be at a new watershed in biotech financing. You are a part of it—Chiron’s stock jumped about two points on your buy recommendation yesterday.

Mr. Casdin: This new Chiron financing represents in microcosm the things I think are important to focus on in this industry. (*Chiron Corporation issued a convertible subordinated debentures offering just prior to this interview.*) Companies that have a broad scientific foundation and a blockbuster-

type proprietary product on the market, or are about to, are bringing the future value they have been creating much closer to the present, because they are generating the wherewithal to develop it. Now that cash flow is streaming through their companies, they can leverage it in the financial markets—which is precisely what Chiron is doing.

Mr. Lee: What’s your advice to CEOs on financing in this market?

Mr. Casdin: It’s hard to generalize. Every biotech company is unique, and there’s a spectrum of situations from the top tier down to the development-stage companies. I would say that we’re at an incredibly buoyant period in the markets for biotech. It’s spreading from the top-tier companies into some of the better secondary companies and the more interesting venture-capital financed companies. IG Labs, Immune Response, and Gensia have put out IPOs. We’re seeing what I would call the second generation of biotech companies coming along and going public.

The markets seem inclined to speculate on biotech again, but in a more discriminating way than in 1986 and ‘87. My advice to biotech executives—and this is probably not news—is to identify the product they believe in the most and focus their resources on it, both financial and management. The markets are very receptive to that kind of product, even when it has a way to go, if there’s enough data to show that it has a reasonable chance of success.

Mr. Lee: What about an IPO of a company that has been through two or three rounds of venture capital, and still has a long way to go to products?

Mr. Casdin: That sort of public venture-capital financing is very difficult to do. Raising equity and burning it, then coming back and raising more equity and burning it, and so on, is a tough sell.

Mr. Lee: In the surge of 1986 and '87, there were roughly 1 to 1.2 billion dollars worth of offerings, about half IPOs and half secondaries. In 1989, there were under \$100 million worth of IPOs, but a high level of secondary deals. You're saying that we will see an improved scenario for IPOs in 1990.

Mr. Casdin: In 1989, we saw, basically, the top ten companies loading up again. The strong were getting stronger. That trend is still under way. In January and February of 1990, the public market was terrible. However, biotech held up, foreshadowing that this group of strong companies is going to remain strong, even in a fair to down market.

*This group of strong companies
is going to remain strong*

Since that time, the markets have recovered. We're at new highs, and the leading biotech stocks are roaring. While a rising tide doesn't necessarily lift all boats, it does tend to lift some of them. The surge is broadening out.

Mr. Lee: When we've had falling tides, high tech often has been the first sector left high and dry. Is high tech precarious relative to the Dow?

Mr. Casdin: I think we've seen a shift in the overall market which is favorable to biotech. The tremendous market we had in the 1980s consisted primarily of asset-transfer stocks that were being taken out through LBOs and corporate raids. That game is pretty well over. Investors are now looking for some other way to get appreciation. The focus is shifting toward companies that are not caught up in the economic cycle, that have a unique, proprietary way to grow. Hence you're getting a shift toward

technology companies—both computer-related and biological science. It's a major shift that I think is going to stay with us for some time.

Mr. Lee: Always looming, however, is the impact of Wall Street's short-term view. That's a trite phrase, but a useful shorthand for the performance pressures that growing U.S. companies face. Do you support the need for change, and do you have any ideas for bringing it about?

Mr. Casdin: The main reason for the short-term focus is the fact that so much of individual savings are now tied up in corporate pension plans. These huge blocks of capital are being directed by a relatively small number of money managers who are, first of all, constrained to put most of that money to work in the big companies and, secondly, called upon, every quarter, to justify their contracts with the pension plans. A proposal that appeals to me is to make the funds' short-term gains taxable.

Mr. Lee: Cost containment is surely the theme in health care for the 1990s. How does it affect the financial market's perception of the earnings potential of the biotech companies engaged in that arena?

Mr. Casdin: Drugs get beat up on this cost-containment issue much more than they should, considering they represent only a small share of the total health-care bill. But many individuals get practically everything reimbursed except drugs, so it becomes a pocketbook question for a large constituency. Also, doctors and hospitals have enormous political clout to defend their costs. A few drug companies that are perceived to be oligopolistic do not.

When you get down to it, however, people appreciate that a good drug is still the most cost-effective way of dealing with an illness. Congress may do a lot of grandstanding for political reasons, but usually ends up with sensible solutions. I'm not

terribly concerned about the pressure on drug pricing in general. Biotech drugs, which in most cases are breakthrough products for problems that previously couldn't be solved, should be relatively immune. I really think that the only choice for biotech companies is to price their products for what they're worth, even if it seems extraordinarily high relative to some other drugs.

Mr. Lee: What does, or should, the Hoffmann-La Roche/Genentech transaction mean to the biotech CEO considering his financing options?

Mr. Casdin: That transaction should encourage some of the smaller and mid-sized biotech companies with real products in their portfolio, but insufficient resources to develop them, to seriously consider merging with some of the leading companies. It's a way for them to maximize the capital appreciation of their ownership of their company, and it accelerates the process of bringing their products to the market. We saw an excellent example of that in the merger of Integrated Genetics into Genzyme. The appreciation in the stock of Integrated Genetics is about 100 percent from the time the deal was done last August.

In 1985-87, a freak number of companies went public, many of which probably shouldn't have

We're still working through the effects of a unique confluence of events in 1985-87. It kicked off in late '85, when Lilly bought Hybritech. Next, Genetic Systems was bought by Bristol-Myers. In those days, those \$300 million price tags were fantastic numbers. Genentech's t-PA started to look very good and that stock took off. At the same time, there was this incredible liquidity-driven stock market. All this resulted in a euphoric sense about

biotechnology that probably never will be repeated. A freak number of companies went public, many of which probably shouldn't have. They're the ones that should seriously consider the merger option.

Mr. Lee: Despite the number of companies that have been burning without earning, we haven't seen many mergers or, for that matter, bankruptcies. What is keeping these companies afloat?

Mr. Casdin: It is amazing how long these companies are able to hold on and create real value in their technology. Look at the price that Gen-Probe got from Chugai. (*Gen-Probe was acquired for \$110 million.*)

Strategic alliances are a significant factor. There are 350 to 450 a year with the big drug companies, both domestic and foreign. Then there's the National Institutes of Health—most people don't appreciate the extent of the venture capital-like money that's available from NIH. A good deal of the roughly \$8 billion a year in NIH funding trickles down to biotech companies directly, and considerably more to universities that form alliances with them. A good percentage of the drug companies' spending on R&D—which is about equal to NIH's funding—also ends up in biotech companies.

This ties in to what happened with Roche and Genentech. That transaction reiterates that the big drug companies are still having trouble getting this technology to produce dividends for them internally. It's very hard, within the bureaucracies of big drug companies and their traditional chemistry mind set, to keep anything creative going. They increasingly go outside for innovation and allow it to stay outside, while they arrange to reap some of the dividends. Hoffmann-La Roche demonstrated that dramatically when it plain bought Genentech.

I think Genentech is going to be a source of considerable financing to small and medium-size companies. They will have \$700 million in cash. I believe a lot of that is ear-marked for product

acquisition, company acquisition, licensing, and so on. That puts a lot of pressure on the top five to 10 companies. Now there is a very knowledgeable competitor with huge resources competing for technology; before they had to be concerned only about the big drug companies, which aren't as knowledgeable.

In terms of financing, it's hitting on all cylinders now for biotech. The big drug companies are pouring in money and buying biotech firms. The markets are increasingly receptive. It looks like the venture capitalists will be bailed out with a new generation of IPCs. As they get refunded, they'll start seeding more companies.

The situation is much healthier than it was back in 1986-87, when there was an almost mindless speculation going on. The investment community now is much more informed.

Mr. Lee: Most of what you're saying applies to the companies engaged in health care. What is your outlook on other biotech segments?

Mr. Casdin: On the agricultural side, the pricing pressures are immense. Farmers are extremely sensitive to price, and the companies producing huge volumes of pesticides and seeds will do anything to maintain their markets. It will be hard for biotech companies to get the value for their technology in that kind of marketplace. Also, it's a very cyclical market.

Regulation is another problem. Health-care companies complain about the FDA being slow, but at least it has decided that biotech drugs will go through the same process as other drugs. The EPA, USDA, and even the FDA on the agricultural side, do not yet have a coherent regulatory scheme. That creates an awful lot of uncertainty.

Wall Street likes nothing better than to see targets being hit

Mr. Lee: If you were going to advise a CEO on how to establish a good relationship with Wall Street, what would be your Do's and Don'ts?

Mr. Casdin: Let the Street worry about the stock price. Devote your entire energies to building your company. Come out with a clear, coherent, conservative business plan. Communicate that plan and then perform to it. If performance falls short of the plan, communicate that, too. Wall Street likes nothing better than to see targets being hit.

Mr. Lee: Have biotech companies been good at this drill?

Mr. Casdin: They're always in need of money, so they have tended to serve up what they think the Street wants to hear. A lot of companies became more sensible after Genentech's fall from grace in 1988 after the deflation of the expectations that had built up about t-PA. Right up until the Roche acquisition, Genentech never really recovered from that crash. Since then, companies like Amgen and Chiron have been ultra-conservative in a lot of their projections. The surprises now are on the up side, not the down side. One of the reasons why I recommended Chiron yesterday was the fact that their hepatitis C business is coming through a lot sooner and stronger than they had forecast. That really is the right way to go about it.

Mr. Lee: Will any of these companies be able to become large pharmaceutical companies?

Mr. Casdin: The acquisition of Genentech by Roche prevented that company from answering your question. Pioneers break an awful lot of ice, sometimes with their heads. They can create something that has a lot of value, but they also have a legacy of pain. Is it surprising that they might want to cash in and relax for a while?

You can argue that's myopic. It may be that some of the newer companies that are just going public will go the furthest, because the way has been paved, more or less, by some of these earlier companies. That's an open question.

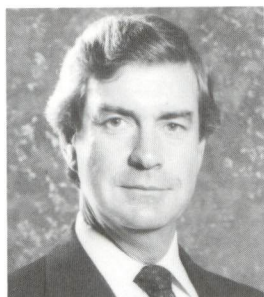
Mr. Lee: How big do you have to be to make it into the big leagues? The smallest of the large com-

panies is Syntex, at about \$1.5 billion in sales. Genentech was at roughly half a billion. Everybody would agree that Syntex is successfully independent.

Mr. Casdin: Right, they've done it. Interestingly, if you look back at Syntex's history, they went through a very difficult period. Like the t-PA situation, their birth control pills panned out to be less for them than they had expected. It wasn't until they came up with their arthritis product that they took off again. They persisted through a rather long, difficult trough of the sort that Genentech chose not to go through.

Can any of these companies do it? I certainly hope that some of these managements will stick it out.

Large and Small Companies: The View from Both Sides



George W. Ebright
Chairman and
Chief Executive Officer
Cytogen Corporation

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"Biotech companies enjoy a
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vitality not seen in the larger
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pharmaceutical companies."
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In January 1989, George Ebright ended a 26-year career with SmithKline Beckman that included planning the worldwide launch of the blockbuster product, Tagamet, turning around the company's animal health business, and becoming President and Chief Operating Officer. In February 1989, Mr. Ebright joined Cytogen Corporation as its President and Chief Executive Officer. His charge: to transform the company from a prestigious research boutique to a solid commercial enterprise. Mr. Ebright's first year at the helm brought the filing of two Product License Applications with the Food and Drug Administration, a marketing and distribution agreement with EuroCetus, a \$17.25 million preferred stock offering, and equity infusions from Eli Lilly & Co. and Bracco Industria Chimica S.p.A. of Italy. A year after joining the company, Mr. Ebright was elected Chairman. Cytogen's proprietary technology links therapeutic and diagnostic agents to monoclonal antibodies that target human cancers.

The interview with Mr. Ebright was conducted by Kenneth B. Lee, Jr., National Director of Ernst & Young's Life Sciences Industry Services, at Ernst & Young's National Office in New York.

Turnaround and Tough Decisions

Mr. Lee: There is quite a history of turnaround management in your resumé—in various divisions put under your charge at SmithKline and now with Cytogen. What are the most important things a CEO has to do, walking into that kind of situation?

Mr. Ebright: One truth I've learned over some twenty-five years is that it is easier to work with a turnaround or troubled situation than to run a company where everything is going well. In a problem situation, you usually can figure out two or three key things that need to be done. If you do those things well, you can perform a lot of other managerial functions less well and still be successful. In a well-running situation, the key things may not be so clear. Yet if you do them badly, you can do everything else well and probably still will not make it.

What I typically do is look for the pressure points—the things that absolutely must be dealt with. It's always just a few—if your list has more than four or five, then you don't have the right list yet.

In the case of Cytogen, the company was approaching ten years old. We had a lot of good people, sound technology, and interesting projects. But the organization seemed unfocused, and we had not yet demonstrated to ourselves and the world that we could take a product through clinical trials, bring it to the FDA in a scientifically sound and well-presented filing, get an approval, and become a commercial company. So, the first essential item was to focus on products which we could commercialize in a reasonably short time.

Secondly, we needed more partnering. A biotech company cannot go from start-up to a fully integrated health-care company without agreements for sharing the technology in return for financial support. So we spent a lot of time locking in corporate relationships.

The last thing was the ongoing challenge of any biotech company—raising the capital and minding the cash.

We have started to experience success in each area, and now are seeing some reflection of that in the price of our shares. In the early part of 1989, our shares were close to \$3; they were at \$9 on the day of our shareholders' meeting this spring. The encouraging part is that our increase in valuation has come up in steps; it hasn't leaped and then fallen back. We seem to be able to establish a resistance point, and then, as we continue to realize our objectives, the price of our shares respond.

Mr. Lee: I take it you feel your financing options are dramatically improved from a year ago?

Mr. Ebright: There are more options available to us. The market's appetite for investing in biotech is coming around again. By my reckoning, it's just a little bit late. I've been developing a theory that the market for biotech revives every second year. On that basis, 1989 should have been an "on" year, because 1987, '85, '83, and '81 were. As it turned out, 1989 was a difficult year. But now I'm beginning to feel sort of a sixth sense that it might not be a bad idea to go back to the market sometime soon. *(A few weeks after our interview with Mr. Ebright in May, Cytogen announced a public offering of 3 million shares of common stock, which raised \$39 million.)*

Raise your capital when the market has an appetite to give it to you

Another thing I've learned in my year or so in this industry is that a smart person does not go to the market to get money when he needs it. You stay prepared to raise your capital when the market has an appetite to give it to you.

Mr. Lee: You went to the market in 1989, which, by your account, was not a good year.

Mr. Ebright: Right. We did a \$17.25 million public offering of convertible exchangeable preferred. The market was the worst it had been for five or six years for raising money for a small biotech company. People ask me every once in while about the differences between running a \$4.5 billion pharmaceutical company and a small biotech firm. Well, up until a year and a half ago, my idea of raising \$20 million to make an investment was to get up from my chair on the 24th floor, go down to see my treasurer on the 23rd floor, and tell him what I needed. The most demanding function of a CEO in a biotech company is keeping up the funding.

Mr. Lee: How do you decide the type of financing to do? What led you, for instance, to choose convertible exchangeable preferred last year?

Mr. Ebright: It's less a matter of what we prefer, as of what we realistically can do. Last year, we would have been happier to do a plain vanilla common-stock offering. But it was not in fashion, not by any stretch of the imagination. Several investment bankers advised that, for a company like ours, the best way to raise money in that particular investment climate would be to do a convertible exchangeable preferred offering. So we did that.

Given my druthers, I would design different instruments for different stages of a company's life. A good base of common equity is very important. There is a place at certain times for the well-thought-out use of debt. Partnerships are a great idea. A unit rights offering is extremely useful at certain times.

Large and Small Companies: Comparative Strengths and Needs

Mr. Lee: You've had in-depth, high-level experience at both large and small health-care companies. What are the differences?

Mr. Ebright: The overriding need to always look at the cash and funding simply isn't there in a big health-care company. It's an industry that generates cash very well.

A second major difference plays more positively to the strengths of biotech companies. Large health-care companies are loaded with cumbersome policies and procedures, and make decisions very slowly. As a result, the process of taking a new compound through a major pharmaceutical company is torturous.

These roadblocks are absent in a small biotech company. At Cytogen, we can move products from the pre-clinical animal stage into an IND stage, and through the clinics, at a much greater speed than the typical pharmaceutical company. We make decisions much faster. We change directions much faster. Biotech companies enjoy a vitality not seen in the larger pharmaceutical companies.

There's greater risk, but proportionately greater reward if the risk pays off. At SmithKline, I was instrumental in the launching of Tagamet, the first billion-dollar pharmaceutical product. That moves even a big company—but you don't get many of those. A \$100 million product would have a similar impact on the typical biotech company. So the risk and funding problems, in my mind, are more than offset by the flexibility, the ability to make decisions, the lack of bureaucratic overload, and the fact that when you do have a success, it is usually very significant for the company.

I think the alliances between large and small companies are essential. My view is that no more than two or three biotech companies could ever become stand-alone, fully integrated health care companies. Anybody who's lived in the health

care industry knows that until you're in business for about 25 years, you can't say that you've got it made, because the dry periods will test you unbelievably.

Until you're in business for about 25 years, you can't say that you've got it made

The biotech industry fills a vital niche and performs an exceedingly vital role. We work on things that large, established companies probably would not. Neither the feasibility nor commercial viability of the products we are developing can be demonstrated early on with the certainty that the large companies require.

Mr. Lee: But you think the acquisition of these companies is inevitable.

Mr. Ebright: Acquisition is an honorable end. I have total admiration for what biotech companies do. They manage to get financing in a free market society. They bring together ingenious, aggressive, entrepreneurial people who take a chance on developing a new technology to where its value is recognized by the more staid, but wealthy, health-care companies. Acquisition by a larger company is a perfectly honorable end as long as the management of the company looks out for three things: the employees who created the value, the shareholders who put up the money, and the technology itself, so that society benefits from it.

Now, you don't necessarily have to be purchased by a large pharmaceutical company to arrive at that end. I am a champion of the idea that biotech companies ought to stop suing each other and look at how they might work together in a complementary fashion. It's an alternative way to create

some of the critical mass that otherwise would be accomplished by being bought by a large pharmaceutical company.

That's one reason why I am delighted that Cytogen has the opportunity to work with Euro-Cetus as our European distributor. Cetus had strategically chosen to put a marketing and sales infrastructure in place in Europe. We had a rapidly approaching product, but didn't have the resources to go into Europe. It's a great complementary fit that will benefit and more effectively utilize the resources of both Cetus and Cytogen.

Mr. Lee: I take it that a deal with a Cetus would have a different flavor from a deal with a major pharmaceutical company.

Mr. Ebright: Yes, because biotech companies like Cetus share with us the attributes of flexibility, urgency, and vitality. It didn't take our negotiating teams more than 50 days to move the arrangement with Cetus from conception to contract, and it's a pretty substantial agreement for both sides. That's not to say we didn't do the necessary due diligence or consider and cover the important points—but we can do these things much more quickly.

Mr. Lee: When you're doing a deal—whether with a Cetus or one of the large pharmaceutical companies—how do you decide on the value of what you are trading and what you need to get for it? Do you predetermine values that you feel are appropriate? Or do you work these out through negotiation?

Mr. Ebright: It's an imprecise art, as far as I'm able to ascertain. The best measure that anybody has is what they teach you when you get your M.B.A.—to run out a string of expected cash flows from product sales and then discount it back by some factor to allow for the risk. But, as I described

earlier, most of what the biotech companies are working on is so conceptual in nature that pharmaceutical firms haven't been able to come up with projections that satisfy them. Therefore, in terms of valuation, it gets down to judgment and feel on both sides of the table.

The biotech company wants to get as much as it can for what it gives up. The partner would like to get as many rights as it can for as little as possible. And both sides are handicapped by the inability to prove definitively what the product or technology might be worth. If you are negotiating with a large company whose management does not have the ability to stand back and create a vision, then you have a real hard sell.

In our case, we recognize that we have to give up some of the applications of our technology in order to make a successful deal. We are carving out a franchise in *in vivo* imaging for cancer and cardiovascular diseases, and have products that can be used both in imaging and therapeutics. At this stage, we are willing to give up some of the therapeutic applications for funds that will help us build our imaging franchise.

An arrangement not good for both parties, will not be good for either party for long

One other thing that is exceedingly important is that if the arrangement is not good for both parties, it will not be good for either party for long. Both parties have to envision, without being able to quantify it, what the arrangement could bring, and be committed to their continuing mutual benefit from it.

The Next Hurdle: Reimbursement

Mr. Lee: Do you think the biotech companies are dealing with reimbursement issues with foresight?

Mr. Ebright: I suspect that many of them don't think about it until they have a product very close to release. In our society where, more and more, health care is paid for by somebody other than the person who receives it, the question of reimbursement is vital. I think the industry ought to be doing more to educate HCFA about the worth of our products. If we can't prove that our products are worth what we're asking, then the products probably shouldn't be reimbursed.

Mr. Lee: When should a company start getting serious about reimbursement?

Mr. Ebright: By the time you take it to the first patient. As soon as you have characterized what you think you have, it is time to start talking to the people who are going to have a lot of impact on its future. It's sort of a parallel to the concept of designing in quality, rather than trying to inspect it in after the fact.

Mr. Lee: At what point, if ever, would you put on your own reimbursement people?

Mr. Ebright: In a sense, we have them now. In a small biotech firm, you quickly realize that everybody has more than one job. So our reimbursement people are really our business development and marketing people. At this stage, rather than have a team of strictly reimbursement people, it makes more economic sense for us to hire a good outside consulting firm to work with us, which we have done.

Looking Forward, Looking Inward

Mr. Lee: What do you believe the biotech industry's priorities should be for the next six months or even five years?

Mr. Ebright: Right now—and rightly, because this industry is old enough—investors are expecting us to start to deliver commercial products. My concern is that companies don't neglect to make provision for tomorrow's technology while they concentrate on bringing out the product that the world has been waiting for.

My feeling is that this industry will be much more quick-moving than the pharmaceutical industry. With our ability to tailor-make the sorts of products that are going to be needed and useful, product life cycles are going to be shorter. The biotech company that's not going to be a flash in the pan has to keep up its allocation of resources to develop its technology. The best way to do that is to build on your accrued, paid-for experience, as opposed to trying to be expert in a half-dozen unrelated areas.

Mr. Lee: One final question—how has the change from a large company to a small one affected you personally?

Mr. Ebright: I will say this—I've had more fun in the last year at Cytogen than I had in the last 10 or 15 years of my career at SmithKline. It's out on the edge, and you can see what you're doing right or wrong very quickly. You can cause things to happen.

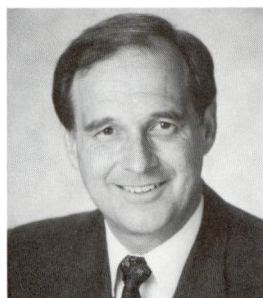
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“The term, biotechnology,
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encompasses too much for the
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to understand.”
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Does being outside the mainstream of what we call the biotechnology industry leave a company swimming against the tide or relegated to the shallows? What do 1990's controversies over the introduction of bovine somatotropin and herbicide-resistant plants portend about the prospects for public acceptance of genetically engineered agricultural products and organisms? The special situation, problems, and potential of biotechnology companies developing products for markets other than human health care were the topic of a discussion with three CEOs conducted by Kenneth B. Lee, Jr., National Director of Ernst & Young's Life Sciences Industry Services.



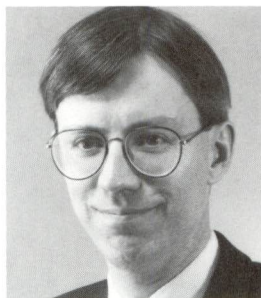
Louis Fernandez, Ph.D.
Chairman
Celgene Corporation

Louis Fernandez, Ph.D. started as a chemist with Monsanto Corporation in 1949 and retired as its Chairman in 1986. That same year, he became President and CEO of Celgene, a new Warren, NJ, company employing biocatalytic technology to develop industrial products. In June, 1990, shortly after his participation in our roundtable discussion, Dr. Fernandez stepped up to Chairman of the Board, and was succeeded as President and CEO by another senior executive from a major chemical products corporation, John L. Ufheil, previously of Mallinckrodt. Celgene is developing pharmaceutical chemicals, such as high-purity chiral intermediates, and specialty chemicals, such as high-performance polymers. In the area of bioremediation, the company is developing systems using naturally occurring microorganisms to destroy hazardous chlorinated compounds produced by industrial processes. Celgene's corporate partners include Schering-Plough.



Roger Salquist
*Chairman and Chief
Executive Officer*
Calgene, Inc.

Roger Salquist, Chairman and CEO of Calgene (Davis, CA), is one of the more quoted and quotable CEOs in the business. Calgene's announcement this year of its success in developing a bromoxynil-resistant cotton plant brought virulent criticism from groups opposing herbicide use and vociferous responses from Mr. Salquist. Calgene is an agribusiness company developing genetically engineered crops for improved processing characteristics and resistance to herbicides, insects, and disease. Its corporate partners include Central Soya, Campbell Soup, Kirin Brewery, Bayer USA, and Rhône-Poulenc. Before joining Calgene in 1983, Mr. Salquist had served as chief financial officer of Zoecon Corporation and president of a division of Occidental Petroleum.



Jonathan MacQuitty, Ph.D.
*President and Chief
Executive Officer*
GenPharm International, Inc.

Although it is only two years old, privately owned GenPharm International has an impeccable heritage. Its investors and partners include Genencor International, Leiden University (Netherlands), and a number of venture capital firms, including Kleiner Perkins Caufield & Byers. GenPharm's Leiden subsidiary is developing genetically engineered cows that will produce high-value proteins in their milk for pharmaceutical and nutritional uses. GenPharm's Mountain View, CA, operation is developing transgenic mice for use in research related to AIDS, cancer, and other immunological diseases. Before joining GenPharm in 1988 as President and CEO, **Jonathan MacQuitty, Ph.D.**, was Vice President of Commercial Development at Genencor and, earlier, manager of industrial products for Genentech.

The Shadow of the Health-Care Companies

Mr. Lee: Health-care companies dominate the biotech industry. How does this affect your strategies and the way the financial markets perceive you?

Dr. Fernandez: We call Celgene a chemical biotechnology company. That's our way of saying that we are focusing on the use of biological as well as chemical processes to develop products that otherwise would be made by classical organic synthesis. In that sense, we are partners in what would broadly be called the biotech industry.

However, for the most part, the analysts who follow the biotech industry don't understand our company. Their focus is on the companies that are working on the blockbuster therapeutic products. They throw up their hands with us, rather than try to dig in. Of course, there are exceptions, which are always a pleasant surprise.

Mr. Salquist: We started out calling Celgene an agricultural biotechnology company to gain recognition and raise money. Calling ourselves an agribusiness biotechnology company would be more to the point. However, what we really are—and ultimately will be judged as—is a seed, food, and specialty chemical company that happens to employ genetic engineering of plants.

In financing, we're the tail and they're the dog

We have the same problem Lou does in being understood. This haunts companies outside the human health area in raising funds and getting appropriate valuations for the quality of their technology and their business plans.

When it comes to financing, we're the tail and they're the dog. If the market is down on the health-care biotechnology stocks, no matter how attractive the product opportunities we're working on, we take the hit, too. Conversely, we have been able to raise money only when the biotech industry in general has.

Dr. MacQuitty: The extent to which the share prices of biotech stocks track with each other is remarkable. They move up and down largely together, despite the fact that the companies have very different targets, even within the health-care field.

Mr. Salquist: We can all list the six or eight companies that get 80 percent of the analysts' coverage. That's the influence of the investment banking side. They've set in motion a self-fulfilling prophecy: Investment bankers think they can raise money only for these eight popular companies, so they tell the analysts to write only about those companies. As a result, the only companies that can raise money are those eight popular companies.

Mr. Lee: What will it take to separate the individual companies from the pack in the public's perceptions?

Dr. Fernandez: The term, biotechnology, encompasses too much for the investment community and public at large to understand. I believe that's going to change, although I wouldn't predict how fast. As this industry starts to mature, analysts and investors will view it less homogeneously, and look more closely at its pieces.

At Celgene, we're trying to serve the chemical industry. I'm not competing with other biotechnology companies. I keep my eye on the chemical companies and their technologies to make sure I'm not deluding myself as to the economics of the biological approach vis-à-vis classic organic chemistry.

*There may be value in retaining
the biotech epithet*

Dr. MacQuitty: As companies start developing their products and selling them, they will be seen more clearly as a seed or therapeutic drug or specialty chemical company. But when times are good for biotechnology stocks generally, or for the health-care stocks that represent biotechnology in the public's mind, I suspect we'll continue to nestle under the biotechnology umbrella because it will improve our cost of capital. There may be value in retaining the biotech epithet for quite some time.

Mr. Salquist: The alliance among these diverse companies gets very weird. We're all aware of strains within the IBA and between the IBA and other trade associations. (*Jerry Caulder, chairman of the Industrial Biotechnology Association, is interviewed beginning on page 159.*) These are not just based on the question of whether you're a food company or a pharmaceutical company. It's a big-company/small-company issue, too.

The pharmaceutical companies are consumed with the Orphan Drug Act and HCFA reimbursement. These issues dominate 80 percent of the time that we spend in industry associations. But companies like ours are a lot more concerned about the guys carrying signs saying, "Save the cows in Wisconsin."

My guess is that we're moving toward a situation where companies that are regulated primarily by the EPA and the USDA (which would mean chemical and ag-type companies) are going to be in one sector or trade association, or at least act collectively; and the pharmaceutical companies, which are regulated by a selective function within the FDA, will do their things in concert. FDA regulation of food kind of falls in the middle, but the food companies' concerns are very separate from the pharmaceutical concerns.

Financing Options and Resource Decisions

Mr. Lee: What are your financing options today, and how do these affect your strategy?

Dr. MacQuitty: The financing climate is not easy, currently, for companies like GenPharm that are backed by venture capital. If I remember my figures correctly, the amount of fresh venture capital coming in was about \$4 billion three years ago, and down to about \$2 billion last year. The IPO market, if not completely dead, definitely has been weak since 1987. We're trying to build as much flexibility as we possibly can into our financial strategy, and are looking at strategic alliances and other kinds of equity arrangements.

Mr. Salquist: We've raised about \$125 million from outside sources since I joined Calgene in 1983—I can't complain, I guess. On the other hand, what we're doing takes a long time and a lot of money. The markets definitely are not as good as they were pre-October, 1987. In my mind, there really hasn't been a window for secondaries and IPOs since then.

The climate for money from Europe for non-health care companies is decidedly less favorable than it was two to three years ago, with the possible exception of Germany, because the environmental movement is so strong there. The only hot market for potential new deals appears to be the Far East, especially Japan. If you look at the last 36 months, the number of new corporate partnerships is very small, and I would bet maybe 80 percent of them are with Japanese companies.

Dr. Fernandez: It's tough to find the investor who'll say, "Great technology, great management. It's going to take three years for the product to come, but I can wait." That climate doesn't exist anymore. We've taken a hard look at everything we're doing and are redeploying resources to put greater intensity behind those products that we can bring to the market at an earlier date.

Redeploying resources behind products we can bring to the market earlier

Mr. Lee: Every biotech CEO has to grapple with the issue of deploying resources. What methods or tactics do you use?

Dr. Fernandez: My approach is to work very closely with my senior subordinates and make sure that everybody who has a point of view gets an opportunity to express it on these matters. You might call it consensus-building. The CEO has to make the ultimate decision, but the technology issues and marketing issues are complex. You have to get the commercial development people and the R&D people to talk to one another and understand each other's capabilities. You have to create a climate that allows them to bring their ideas and concerns to the table.

Mr. Salquist: A lot of our decision process about deployment of resources is ingrained in our structure. We obviously have quarterly milestone meetings with each of our corporate partners, where a large number of our projects get a thorough going-over. We have intense internal peer review sessions where each project is reviewed by the scientists at large on a rotating basis. Then, just as part of your budgeting and strategic planning process, you are forced to deal with these resource issues.

Dr. MacQuitty: There is no better way of evaluating the prospects for a project than having somebody willing to put a lot of money behind it—that's one of the side benefits of trying to put together strategic alliances. Also, the partners' funds reduce the amount of equity funds going in, which means that the company's resources tied up in the project are reduced. So, one has to think, when one makes a resource decision, what are the real resources we're putting into this on a net basis? And what will the real rewards look like?

To go back to your original question about financing, I'd like to gaze into the tea leaves and make a prediction. The secondary market has come back to life this spring. If you look at the biotechnology stock index, the big eight biotechnology firms that we grumble about have put on a lot of muscle over the last year. These developments suggest to me that the financing window is opening up again, and quality firms which have been waiting for the opportunity are going to hustle toward an IPO.

Mr. Salquist: Let me interject that every biotech CEO should always have a draft prospectus in his top drawer. If Jonathan's window opens, you don't want to sit around for two months drafting a prospectus, because those windows can slam shut very quickly.

Windows of financing opportunity slam shut very quickly

Dr. MacQuitty: A pet idea of mine—which I think should get congressional support and would really aid the biotechnology industry as a whole—is to bring back the idea of R&D tax credits that would be saleable to limited partners and individual investors. It seems to me a much better political

concept than capital gains relief. It's tied directly into building the technology infrastructure of this country vs. the alternative of going abroad and, in some measure, selling off the technology. It would help attract venture capital by presenting alternative financing sources for long-run ventures. Because you can run the R&D partnerships through the revenue account, it would help the profitability of biotechnology companies, and make a big difference in getting out IPOs. And it would provide support for all of the biotechnology companies involved in late-stage development and clinical trials.

Facing the Critics

Mr. Lee: All three of you are working in areas that evoke a degree of emotional response from the general public—genetically engineered foods, transgenic animals, and environmental release of microorganisms. How does that affect your strategies?

Dr. Fernandez: We are especially sensitive to the public relations aspects of the bioremediation segment of our business. As a matter of fact, we deliberately avoided getting into genetically engineered microorganisms. We're a small company, and I don't think we can hang in long enough and tough enough to battle the forces that would line up against us any time we talked about an environmental release of a genetically engineered microbe.

Mr. Salquist: There are a large number of people in the United States and the world who simply are philosophically opposed to genetic manipulation—be it with bacteria, plants, cows, or humans. I believe there's an even larger group of people who are philosophically opposed to the free enterprise system. And I believe those people are using fear of the unknown and fear of technology to forward their own beliefs.

That's not to say there aren't huge numbers of truly committed environmentalists. There are, I respect them—I count myself among them. But I believe that the vocal part of the environmental movement has been preempted by people who have a larger agenda. This creates a serious problem, not just for biotechnology, but for U.S. economic growth and international competitiveness.

Business has to stand up to make sure that good science is not degraded as being bad. We have to communicate the economic benefits of our products and the idea of risk/reward. I spend probably 20 to 25 percent of my time participating in the external organizations and in lobbying and public relations for this purpose.

Business has to make sure that good science is not degraded as being bad

Dr. MacQuitty: We will be releasing genetically engineered organisms into the environment—transgenic dairy cattle. True, they're fairly large, so they're not going to wander around without people knowing.

We have met with groups of all persuasions in Holland, from the young Christian Farmers Union to people who are against the use of animals for farming altogether. It has been quite an educational experience.

Many of the people we talked with thought that ethics didn't make a difference to us. Over a period of time, I think we have been able to demonstrate that we care about ethics a great deal, and that our approach in using this technology, for both commercial and ethical reasons, is focused on very beneficial things.

In the United States, we face the same kinds of issues with our transgenic laboratory animals. There are people who are against the use of any kind of animal for research purposes. We have to get through to them that the use of transgenic animals drastically will reduce the number of animals that researchers will need. In AIDS research, the transgenic mouse we're developing will provide researchers an alternative to chimpanzees and monkeys, which are endangered species.

The animal rights groups are not the same as the animal welfare groups. We are in complete accord with the animal welfare groups which recognize that the research must take place, but are concerned that it is conducted humanely. What the animal rights groups don't bother to tell you is that people will die because of their actions. Human rights have to be built into this assessment.

Dr. Fernandez: You're preaching to the choir with us, Jonathan. But when you get ready to put a product on the market, will talking to people on a rational, intellectual level get you anywhere? Look at bovine somatotropin. The governors of Wisconsin and Minnesota won't allow it to be sold, although there is no evidence of human or environmental hazards.

Dr. MacQuitty: Economic considerations, not safety, are driving that resistance. Just as we deal with the questions of safety, efficacy, and good manufacturing practices, we now will have to address the socioeconomic impact of our technology. In Europe, it's referred to as the fourth hurdle.

Let me give you an example. Although the Dutch dairy community has mixed feelings about bovine growth hormone, it has supported our work on transgenic dairy cattle. Why? Because we can demonstrate that we're making a high-value product from which even a small farm can make good money. BST is a pocketbook issue to dairy farmers, and it needs to be dealt with on that basis.

The socioeconomic impact of our technology is the fourth hurdle

Mr. Salquist: BST was a soft target for the anti-technology groups in a number of ways. Just yesterday, the House Agricultural Committee agreed on the 1990 Farm Bill. They froze all other farm subsidies except milk, where they added another \$1.5 billion. That makes it hard to argue that we need to produce more milk, even if we can produce it more cheaply.

Mr. Lee: You're all saying that biotech companies need to take the offensive in public relations. What are some of the specific things they should do?

Mr. Salquist: The first rule is secure your home base. Make sure that the local population and infrastructure know and support what you're doing. There's nothing more embarrassing than not having the people where you work and live on your side.

In 1984, two years before we did a field trial, we were bringing in schoolteachers one day, ministers the next day, the Audubon Society and Sierra Club people the next week, and all the people active in local politics. Also, a CEO should know his state and federal legislators on a first-name basis.

Secondly, you need to go out and meet with each of the groups that are likely to be poised against you. You probably won't change anybody's mind, but you have to go on record. If you haven't sat down with the critics and tried to answer their concerns, it's hard to be self-righteous later when you're defending yourself against their attacks.

I also think you have to be active in the industry associations. The fragmentation and splintering of the various trade associations right now is a big negative. The industry's got to pull together. If a congressman sees three different industry groups coming in with three different positions, how can he know what to believe?

Finally, I believe the salvation is a knowledgeable media. There are a limited number of writers who write consistently about biotechnology. The absolute single biggest leverage of a CEO's time is getting to know those writers personally. That will take you a long way toward being able to manage your public image. They'll print what your opponents say, but they'll give you equal coverage.

Dr. Fernandez: I would add that talking to the editorial boards or editorial writers at the principal newspapers is also highly desirable. This often is best done through a trade association, if it is cohesive and professionally staffed.

Dr. MacQuitty: Public relations is one area of a CEO's activities that is non-delegatable, in my opinion. If you have, or are likely to have, issues with interest groups, you need to be comfortable putting your case forward yourself.

I share Roger and Lou's views about the importance of industry groups. We are involved in building a pan-European association of firms that are working with bovine embryology and transgenic cattle. In my talks with other U.S. firms that are working on transgenic animals, we've also agreed that we need to stay in touch with each other to deal with our common interests in this area.

Patents: To Fight or Deal?

Mr. Lee: As more products enter the marketplace, we're seeing more and bigger patent suits. What are your patent strategies? How vigorously do you think you should defend patents, as opposed to cross-licensing?

Mr. Salquist: I believe in cross-licensing. Every time we see a potential patent problem, we try to figure out how to make it a plus by putting our technology together with theirs. I have a pathological dislike of legal bills, unless there is an absolute, ironclad, clear product patent.

When we see a potential patent problem, we try to make it a plus

We try to file very early on. We try to make sure we have defensive patent positions in lots of areas. We don't try to block people, but we want to make sure that if somebody tries to block us, we have a patent on which to base a reasonable discussion with them.

Dr. Fernandez: The patent litigation that's going on is a sign of the industry's immaturity. I saw a lot of this after World War II in the chemical industry. After you get into a couple of those fights, spend a lot of money, end up at the mercy of some judge who doesn't really understand your arguments, and lose or half-lose, you see the sense of the thinking that Roger just described. File widely for defensive purposes, sure; but don't sit there thinking, "I'm going to kill that guy because I've got a patent." Cross-licensing makes a lot of sense.

Mr. Salquist: This is almost in the category of minutiae, but one of the things to keep constantly in mind is notebook maintenance and notebook policy. I'm unpleasantly surprised at least once a year with a scientist's notebook that hasn't been properly witnessed or has some other problem. As an organization grows, if the head of R&D doesn't rigidly enforce notebook policy, you really put yourself at risk.

International Competitiveness

Mr. Lee: It's fairly well-known that Japan has identified biotechnology as a priority industry. Is it a concern? Or is it an opportunity for American companies seeking investors and alliances?

Dr. Fernandez: In 1989, I visited a number of industrial biotechnology companies in Japan to determine whether they had any technology that might be of interest to us, or vice versa. I came away frankly shocked at the amount of work going on, as compared to what I think is going on in this country and in Europe. Companies you wouldn't imagine being involved in biotechnology, like Nippon Steel and Nippon Mining, have programs.

I came away shocked at the amount of work going on in Japan

When you ask why, you learn it's national policy—they've been subsidized to some extent. That scares me. If they're putting that much effort into it, something is going to come out of it.

Mr. Lee: Would you want to see that kind of fostering of the industry here?

Dr. Fernandez: It goes against my grain. What's appropriate in a culture that has the strong nationalism they do, may not work very well over here. But I would favor some of our home-grown kinds of government support for the industry, such as R&D tax credits.

Dr. MacQuitty: Japan is not particularly active in transgenic animals. As they tend to pick up their pharmaceutical products from outside, rather than develop them, they have had no great need for sophisticated research animals. However, they are clearly interested in moving into both of these areas, and we expect to have relationships with Japanese and other Asian companies as a matter of course over the next few years.

GenPharm is very much a transnational operation. Fifty-five percent of our current activities are in Holland; we're not at all negative about international transfer. We have to remember that if a technology is going out of the country, it will be offset by situations where it comes back in. Companies these days have to consider setting up relationships, even early in their lives, to get access to foreign technology, capital, and markets. The integration of the European market makes this even more important.

Mr. Salquist: Our strategy to build businesses in North America makes us very receptive to licensing our product rights elsewhere. To the extent people like the Japanese are interested, that's positive.

In our most recent deal with Kirin, besides paying cash for an equity interest in one of our businesses, they also put their technology into it. From my standpoint, that is the best of all worlds.

We Americans are not as effective at probing and pulling technology from Japan as they are in getting it from us. One reason is that they have a lot more people who speak English than we have speaking Japanese. A concerted national effort to find out about Japanese technology might help.

The cost of capital in the U.S., as we've all been saying, is the central issue where the government can help. Whether it's giving the tax credits for R&D LPs, capital gains relief, or lowering the interest rate or whatever, we have to lower the cost of capital for this industry.

In a companion area, the federal government is spending about \$3 billion a year through NIH on research. That's the lifeblood of a lot of companies, but a couple of negative things are happening. One, we're giving it away as freely to the Japanese as we are to U.S. companies in many respects. Secondly, policy guidelines have been proposed that would severely restrict researchers with NIH funding from interacting with U.S. businesses. That's thankfully on the shelf for now—but if you want to talk about shooting yourself in the foot, the federal government has got a shotgun about two inches from its big toe on that one.



Senator Albert Gore
(D-Tennessee)
United States Senate

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"The progress of the human mind
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has been truly staggering, but
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our laws and institutions lag
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far behind."
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Albert Gore was elected to the U.S. Senate in 1984. Earlier, he served for eight years in the House of Representatives. As a member of the House Science & Technology Committee, he chaired the first comprehensive series of hearings on biotechnology policy. Senator Gore currently is Chairman of the Senate Science, Space & Technology Subcommittee, which has jurisdiction over the Office of Science and Technology Policy, the Biotechnology Science Coordinating Committee, and the Coordinated Framework for Regulation of Biotechnology.

The interview was conducted by G. Steven Burrill, National Director of Ernst & Young's High Technology Industry Services, in Senator Gore's office in the Russell Senate Office Building.

Mr. Burrill: We hear a lot of rhetoric from Washington about the importance of biotechnology to American competitiveness and science leadership. But many in the industry believe that government policy and procedures present many hurdles and uncertainties, and little support. Is Washington really on the industry's side?

Sen. Gore: People in Washington who understand the importance of America's biotechnology industry have been trying to create a coherent policy to encourage the development of this industry, while simultaneously encouraging a responsible effort to deal with the questions raised by the underlying science. We have seen, at best, a limited success on both fronts.

Our efforts have been made more difficult by the obstacles placed in our path by the Reagan and Bush administrations. Their *laissez-faire* religion might be a respectable intellectual approach in a world of free markets. However, it seems to me to be naive and unrealistic in a world dominated by foreign competitors who actively support their domestic industries by spreading risk broadly and focusing effort on priority objectives.

Mr. Burrill: Is that an argument for a more active government role?

Sen. Gore: One of my favorite quotations from Thomas Jefferson is, "Our laws and institutions must move forward hand-in-hand with the progress of the human mind." In biotechnology, the progress of the human mind has been truly staggering, but our laws and institutions lag far behind.

Biotechnology will be a cornerstone industry of the twenty-first century. It began here in the United States; most of the key discoveries have been made here. We are still significantly ahead, but the trends are not presently in our favor. Unless we take action, we will see this industry slip from our grasp over the next two decades.

So, yes, I believe there should be government encouragement. I hasten to add that it's not an either/or question—an all-out industrial policy or a complete *laissez-faire* approach. There are things we can do that dramatically will help biotechnology without trying to pick winners and losers among competing technologies. For example, we must increase our support of education in science and engineering. That will strengthen the most important resource drawn upon by our biotechnology firms—well-educated young men and women who are eager and capable to take on the challenge of the industry.

Neither an all-out industrial policy nor complete laissez-faire

Mr. Burrill: The National Science Foundation study says we're failing to do that.

Sen. Gore: We're going in the wrong direction now. There have been some increases in spending on education in the United States in real terms, but compared to the dramatic increases in spending for education, training, and research and development in Europe and Japan, we're falling behind.

Mr. Burrill: We also are failing to encourage capital formation.

Sen. Gore: That's a major problem for all American industries, but it's especially acute in capital-intensive emerging technologies. A well-focused capital gains measure, which is targeted on long-term investment and does not suffer from perverse income-distribution effects, is a piece of addressing this issue. Measures to increase the domestic savings rate should also play a role.

A capital gains measure targeted on long-term investment

Mr. Burrill: To move to what you described as the second part of government's role, dealing with the questions raised by genetic engineering in the public mind, how effective has government been in creating a climate for reasonable discussion?

Sen. Gore: The federal government has failed to conduct a dialogue with the public on the questions raised by the basic science. Often, alarms are set off that are wildly inappropriate, tensions are exacerbated, and progress on the underlying issues comes to a halt. The irony is that frequently the questions causing the most public concern ought to really cause no concern at all, while the questions which actually deserve close attention are virtually ignored.

When there is no responsible effort to address the pertinent questions, a vacuum results, which becomes filled by the shrillest, most vitriolic critics. They are very skilled at raising the questions most calculated to hit a raw nerve and to draw the attentions of the networks.

Mr. Burrill: Who should be setting the framework for the real discussion? Should it be Washington? Should it be the industry?

Sen. Gore: Ideally, elected representatives of the people should structure that dialogue. I've tried to do that. I succeeded in creating the Biomedical Ethics Board, for example, but it has been hamstrung by the Right to Life movement. I've undertaken a number of other efforts to create that dialogue, but the administration has not been willing to pull its share of the weight. For these and other reasons, the dialogue has not really been

successful. In light of this failure by government, industry trade groups have to attempt to fill that vacuum with a responsible, open-minded effort to focus on the legitimate questions.

Mr. Burrill: What role do you personally wish to play in support of biotechnology or technology-based industries?

Sen. Gore: I'm interested in playing whatever responsible role I can. I have in the past, and will in the future, have hearings in my subcommittee on the prominent issues. At times I've been able to contribute to the resolution of these issues. However, I can't do it alone, and I can't provide the kind of forum that I think is really needed.

Congress finds it difficult to lead on questions as complex and novel as biotechnology

Congress, as an institution, finds it difficult to lead on questions as complex and novel as those presented by biotechnology. In novel areas, leadership has to come disproportionately from the executive branch—where it is presently lacking.

Congress can do better, and we're trying to do better; but it takes teamwork. The industry also could do more. There are opportunities for the industry to open a dialogue with a broader segment of Congress and the public.

For example, we are in the midst of an unprecedented assault on bio-diversity in the world today. Biologists are saying that in the lifetimes of our children we will witness, at current rates, the loss of more than half of all the genetic information which now exists on planet Earth. Why doesn't the

biotechnology industry speak out about the destruction of half its potential raw material on this planet? In the process, it could bolster its credibility and credit with people who might not otherwise pay attention to the industry's concerns. It might also learn skills relevant to conducting a dialogue with the public and the Congress which can be useful on issues of more immediate financial import.

Mr. Burrill: Entrepreneurial companies that are focused on survival might regard becoming engaged in broader issues as a luxury they cannot afford. You are suggesting that they cannot afford not to be engaged.

Sen. Gore: The industry complains that government takes a myopic, short-term view and doesn't address the long-term interests. Should the industry not then be prepared to take a longer-term view itself, even though it faces short-term pressures? I think that is the imperative the industry faces.

Mr. Burrill: The federal regulatory structure has a lot to do with the success of this industry. One could argue that the gatekeeper functions of the FDA, USDA, and EPA, as well as HCFA's influence on product pricing, are impediments and even anti-biotechnology. Are our regulatory processes appropriate, or do we have major problems there that need fixing?

Sen. Gore: Seven years ago, following a series of hearings, I released a report detailing steps the administration should take to provide a solid regulatory foundation for biotechnology. A year and a half later, in November, 1985, the administration responded by establishing the Biotechnology Science Coordinating Committee. Seven months after that, they published the coordinated framework for regulation.

Now, three and a half years later, it's time to pronounce at least a major part of that experiment a failure. I am embarking on another series of hearings to try to spell out where the project went wrong and how it can be fixed.

The BSCC was supposed to ensure that different government agencies worked from similar key definitions. Today, the agencies can't even agree on the definition of genetic engineering or deliberate release. The committee was supposed to resolve disputes between agencies, but instead has actually fueled disputes. It promised Congress that it would stick to questions of science and not policy,

but it has become mired in politics. It promised to play a key role in foresight, but it has utterly failed at that mission, as well. I had hoped it would foster public participation, but it has discouraged it. The whole effort has been seriously flawed and needs to be reexamined.

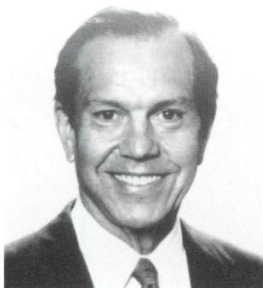
We need to enable American companies to succeed. One way we can help them is by paying attention to the infrastructure essential to their success. That includes a government infrastructure that is predictable, reliable, efficient, and stable. It doesn't exist today. We need to make sure that it will exist in the near future.

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“What should the federal
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government do on behalf of
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individual industries?”
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Search the White House, Congress, the federal regulatory infrastructure—you will not turn up anyone who does not speak in favor of the development of a strong U.S. biotechnology industry. But how does the intent translate into policy? Does the rhetoric match the reality? And what should a pro-industry policy entail?

A group of eminent Washington hands met with G. Steven Burrill, National Director of Ernst & Young’s High Technology Industry Services, for a far-ranging discussion covering the need for government regulation, the nature of government regulation, the public’s concerns about new technology, and the effects of overall government policies on the industry. These issues—much debated within government and the industry generally—were examined by our pundits from divergent points of view.

The discussion was held in the offices of Fox, Bennett & Turner, a Washington, D.C., law firm specializing in health and environmental policy.



James B. Wyngaarden, M.D.
*Foreign Secretary
National Academy of
Sciences*

James B. Wyngaarden, M.D. was the Director of the National Institutes of Health (NIH) from 1982 to 1989, following which he served as the Associate Director for Life Sciences in the White House Office of Science and Technology Policy (OSTP). Shortly after this roundtable, he was named the Foreign Secretary of the National Academy of Sciences.



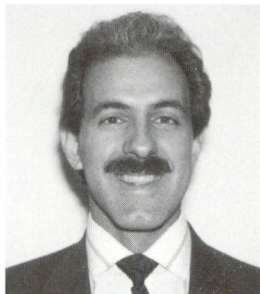
Rachel E. Levinson
*Senior Policy Analyst for
Biotechnology
Office of Science and
Technology Policy*

Rachel E. Levinson is Senior Policy Analyst for Biotechnology in the OSTP. From 1988 to 1989, she was Deputy Director of NIH’s Office of Recombinant DNA Activities (ORDA), and earlier was a program analyst for the Science Policy Analysis Branch at NIH’s Office of Science Policy Legislation.



Henry I. Miller, M.D.
Director
Office of Biotechnology
U.S. Food & Drug
Administration

In August, 1989, **Henry I. Miller, M.D.** was appointed Director of the new Office of Biotechnology of the Food & Drug Administration. Previously, he was Special Assistant to the FDA Commissioner with responsibility for biotechnology issues.



Gregory Simon
Staff Director/Counsel
Subcommittee on
Investigation and Oversight
House Committee on Science,
Space and Technology

Gregory Simon is Staff Director/Counsel of the Subcommittee on Investigation and Oversight of the House Committee on Science, Space and Technology. He and his staff organized a series of subcommittee hearings on biotechnology issues that culminated in the 1986 Committee report, "Federal Issues in the Regulation of Biotechnology: From Research to Release."



Charles E. Hess, Ph.D.
Assistant Secretary for
Science and Technology
U.S. Department of
Agriculture

Charles E. Hess, Ph.D. was named Assistant Secretary of Agriculture for Science and Technology in 1989. Earlier, he was Dean of the College of Agricultural and Environmental Sciences at the University of California—Davis and Associate Director of the California Agricultural Experiment Station. He served on the National Science Board from 1982 to 1988.



Allan M. Fox
Partner
Fox, Bennett & Turner

Allan M. Fox is a partner in Fox, Bennett & Turner. Earlier, he was Chief of Staff to the late Senator Jacob K. Javits, and Counsel to Senator Edward M. Kennedy on the Senate Subcommittee on Health and Scientific Research.



Nicholas W. Allard
Partner
Fox, Bennett & Turner

Nicholas W. Allard is also a partner in Fox, Bennett & Turner. Earlier, he was Chief of Staff to Senator Daniel Patrick Moynihan and Minority Counsel to Senator Edward M. Kennedy on the Senate Judiciary Committee.

Is Washington Biotech-Friendly?

Mr. Burrill: One could argue that there is a gap between Washington's pro-biotech rhetoric and the reality of our policies in the areas of capital formation, taxation, technology transfer, regulation, and patents. One could also argue that the complexity and delay in the Washington regulatory environment maintains a certain competitive advantage for large pharmaceutical companies, and works against small, less richly-capitalized biotech firms. Against these background arguments, which I am sure you all have heard, I would like to have a candid discussion on whether Washington is working for or against the biotechnology industry. What is the relationship of the rhetoric to the reality?

Dr. Miller: The FDA probably has more experience with the evaluation and approval of individual product applications than all other U.S. agencies combined. I'm not going to judge the quality of our rhetoric, but I believe our record is good, albeit not perfect.

From our first contacts with biotech products more than a decade ago, we have maintained the view that the techniques of biotechnology represented extensions or refinements of other tech-

niques of genetic manipulation with which industry, government, and consumers all had a great deal of experience. We saw no need for new procedures or requirements for new biotech products and, in fact, they've been treated no differently from similar products produced in other ways.

We saw no need for new procedures or requirements for new biotech products

Mr. Fox: Has there not, in fact, been confusion within the FDA as to who is going to approve biotech products? And isn't your role evidence that biotech has taken on a special domain?

Dr. Miller: More than half of all investigational new drug applications for biologics are now for products made through new biotechnology. But the number of jurisdictional questions has been no greater than for non-biotech products. It is often difficult to distinguish whether a product is a medical device or a drug when it has characteristics of both.

The Biotechnology Office operates mainly as FDA's interface with other agencies and with our various constituencies—regulated industries, professional and trade associations, consumer groups, and so on. It has relatively little function within the agency. Regulation occurs largely autonomously in our Center for Drugs, Center for Biologics, Center for Food Safety and Nutrition, Center for Devices, Center for Vet Medicine, and so forth.

The only special treatment biotech products have received has been an increase in activity—commensurate with increases in submissions—to direct resources to moving these products through the agency expeditiously and with a good-quality review. They have not received undue scrutiny or delay.

Mr. Burrill: Is the FDA trying to help the biotech industry, or is it indifferent to the biotech industry vis-à-vis all the industries that come under its jurisdiction?

Dr. Miller: User-friendliness toward biotech companies, fair and scientific review, and good communication have been our highest priorities for interactions with companies that use new biotech techniques. (We avoid the term “biotech industry,” which we don’t find meaningful.) The bottom-line demonstration of the effectiveness of our approach has been that our marketing approval times for new biotech products have been substantially less—about half as long, in fact—than for new molecular entities produced in other ways.

Dr. Wyngaarden: When I arrived at the White House Science Office in October, 1989, I was assigned to chair a working group on biotechnology under the Council on Competitiveness, which is chaired by Vice President Quayle. The overview presentation I attended made it clear that the council, and the Vice President, in particular, are concerned about the health of the biotechnology industry. They want to make sure that it doesn’t go the way of computer chips and consumer electronics.

Our working group has appointed subcommittees on research and training; on regulatory issues, including patent-issue problems; and on the economic climate. We are now preparing the report. I think this attention is an indication that the

administration feels that this extraordinarily promising industry is perhaps at a shake-out phase. The sale of Genentech to Roche, I think, was a light bulb that went off in everybody’s head.

The Council on Competitiveness is concerned about the health of biotechnology

Regulation involves maintaining a balance among protecting public health and safety, being as light-handed as is adequate to the task, and encouraging the industry to the extent possible. I would say there’s a great deal of interest in the biotech industry in Washington, for both its actual and symbolic importance. It is peculiarly an American industry that is predominantly an outgrowth of NIH-supported research. It’s an industry we don’t want to lose.

Mr. Burrill: Yet one could argue, Jim, that we are well into the process of losing it. There’s plenty of evidence that we, in this country, are playing with a different set of rules from the rest of the world. Our capital cost is a great deal higher and our focus more short-term. And, therefore, we may end up exactly where we are in the computer chips arena.

Dr. Wyngaarden: I’d say there’s wide recognition of the points that you’re making. The question is what can we do about it?

Mr. Burrill: People generally give the NIH high marks for funding the “R” side of the R&D equation, without which the “D” side would never have happened. Will the NIH’s continuing investment be readily available?

Dr. Wyngaarden: The extent of NIH support, as well as support from Agriculture and other agencies, depends on the availability of unearmarked funds for research. The politics of research support have gotten much more intense than they used to be. While NIH's budget has gone up quite well in the last decade—from \$3.6 billion in 1982 to \$7.9 billion in 1990—the vast majority of the incremental funds are pretty tightly assigned. Federal support for non-defense R&D has declined in the past 20 or 25 years from 2.8 percent of our GNP to about 1.5. During the same time span, government support in West Germany and Japan has increased from 1.5 to 2.8 percent. If we really want to support the biotechnology industry, we have to increase the federal support for non-defense R&D.

Mr. Burrill: Two government policies seem to be on a collision course. A series of legislative events in the last decade have been intended to promote technology transfer from the government-supported scientist in the university or the national laboratory. Coming in the other direction, is a speeding locomotive called conflict of interest, and the notion that no scientist should personally profit from any research that is federally supported. Some of the giants in this field have said publicly that had these proposed NIH conflict-of-interest guidelines been in effect in 1974, we would have no biotech industry.

The politics of research support have gotten much more intense

Dr. Wyngaarden: The proposed guidelines that NIH put out in the fall of 1989 were much broader than anything that I had intended. They were an attempt to address the issue of scientists conducting clinical trials and device evaluations on products of

companies with which they have a relationship. My recommendation all along has been that we should ask for disclosure up front from the scientists. Some relationships might be disqualifying; others would not. It was never my intention to limit the interaction of basic scientists and industry representatives.

The proposed regulations would have gone into effect had not Dr. Bromley and I gone over to see Secretary Sullivan in late December. The Secretary withdrew the proposal and ordered a much more restricted approach. He also has said that the regulations will have to go through the rule-making process, which is an enormous safety factor, requiring one to define the problem and then adjust the remedy to that problem.

Mr. Burrill: Charley, how does the relationship between government and biotech look on the agricultural side?

Dr. Hess: Agriculture definitely sees the tools of biotechnology helping us address some of the major challenges that we face in regard to food safety, environmental impact of current agricultural technology, the nutritional quality of products, and so forth. We provide support through research and education programs. We're working on guidelines for field testing genetically modified organisms with the goal of having experiment design approved at the local level by institutional biosafety committees, with the Department getting involved only in cases of high risk.

This past year, APHIS (Animal and Plant Health Inspection Service) cleared some 60 field trials of transgenic plants, some of which had insect resistance incorporated into them using a gene from a bacterium. The recent success in engineering rDNA into monocots like corn and wheat was a collaborative effort between Monsanto and the Plant Gene Expression Laboratory in Albany, CA, using research that came out of Cornell. There is also collaborative work between Calgene and the

University of California—Davis on using the anti-sense gene to improve the quality of tomatoes.

The President's 1991 budget proposal included the first phase of a \$500 million increase in agriculture research proposed by a National Academy of Science study. Of the \$100 million that will go into our competitive grants program, \$15 million will be used for plant-genome mapping for resistance to drought, insects, and diseases. I see us providing the fundamental information on the germ-plasm that the private sector could then take and convert into new crop varieties.

The social and economic impact of a product should be assessed during research

The problem area that both the government and industry have to work on is negative public perception of biotechnology. The reaction to bovine somatotropin (BST) is a classic example. In Europe, a proposal has been made to regulate the release of new products on the basis of their social economic impact. There been suggestions that this be done here, too.

I don't believe that this belongs in the regulatory scheme. The social and economic impact of a product should be assessed during the research stage. Strategies should be developed at that time to address any negative impacts of new technology, rather than regulating a new technology out of existence.

Mr. Fox: To a large extent, the BST problem resulted from a lack of vision on the part of the companies. They should have figured out the economic impact and done some public education in advance, instead of just assuming that the product would be accepted.

Dr. Hess: There is some truth to that. And the industry could have picked less of a sacred cow than milk to launch the technology. It might have been better to begin with porcine somatotropin and be able to argue the advantages of producing leaner meat.

However, an anti-science attitude is spreading, witness the attempts to ban research that would lead to herbicide-resistant plants in the current farm bill. There's also language in there that would dictate the purposes of research. This is earmarking research to the extreme.

Industry and government have to work together to educate people. People don't understand this area; they don't know who to trust. The media are being manipulated by some very clever groups. If we want more balanced reporting, we have to help the media understand the science underlying the issues.

Mr. Simon: Instead of developing models for dealing with the issues those products raised, Washington has maintained an attitude of business-as-usual that ignores the clamor outside the belt-way, both in the industry and the environmental community. However, is government the key player in determining the success of biological products and winning public acceptance? Being on the inside of government, I feel that people look to us far too often to make things happen.

The Relationship Between Government and Industry: Can We Agree?

Mr. Burrill: To the broader issue then, what is the ideal relationship between our government and this industry? And how do we get there from here?

Mr. Simon: Government and the industry are not the complete picture. Government has a direct relationship with the public that is often ignored in these discussions. If I may rephrase your question,

what is the role of the government in helping the industry relate its products to the public?

With BST, and earlier with Ice-Minus, did the government reach out to the public to understand its concerns so the government could create models for putting those products on the market? No, it did not. If we hold the public at arm's length, we can't be astounded when it doesn't embrace us.

Ms. Levinson: Educating the public is crucial. If you don't have public acceptance, our discussions about tax incentives or regulatory procedures or other policy questions become academic.

Dr. Hess: At the very beginning of the recombinant DNA industry, the scientific community and government—in this case, NIH—had a conference which established the RAC (Recombinant DNA Advisory Committee). This set aside some initial public concerns and gained public confidence as time went by. Maybe that should be a model to use to move into the future.

Dr. Miller: The flip side of that, Charley, is that by circumscribing recombinant DNA as something requiring an entirely new paradigm for its oversight, we've burned into the public mind and the minds of some regulators that it's something very different and presents significant risks.

Dr. Hess: I agree that the ideal would be to not single out recombinant DNA as being any more risky than any other technique. However, I think there was already a public concern, which the scientific community decided to address in a public conference. And I think it worked.

Dr. Wyngaarden: I don't think the public was particularly concerned about genetic experiments at that time. The scientists recognized the potential for public concern and decided to think it through. It was an affirmation that scientists do not live outside society, and has served me well in a number of

Congressional hearings. Memories are short, and congressmen and congressional staffs come and go. Being able to cite that history has prevented some restrictive legislation.

An affirmation that scientists do not live outside society

Dr. Hess: The dimension that has come into play since the establishment of RAC are the single-interest groups, which have great skills in getting their particular point across. The Alar decision clearly was driven by a special interest group.

Ms. Levinson: But the critics aren't the ones who came up with BST. While the critics seem to be driving the agenda, the fuel is coming from the industry. The food companies, in particular, might take a page from the book of the pharmaceutical companies, which in their early product introductions did not stir up the same problems of public acceptance.

Human growth hormone produced by recombinant techniques was an excellent product pioneer because it replaced the natural product that had been found to be contaminated. The risk/benefit equation was totally different, and it obliterated any issue of public acceptance.

Recombinant drugs don't have the economic dimension that BST did. But if the food industry's first product had been something for which there is a clear need; and if the industry had looked for ways to minimize any potential risk that people might rightly or wrongly associate with it; and if it had approached the product launch as an industry-wide public information issue—there might have been a happier result.

Mr. Allard: You're not going to find anybody on Capitol Hill who in principle won't say they're sup-

portive of a successful American biotech industry. Despite that, it is hard to think of anyone who is a champion of the biotech industry, who is concerned enough to launch an initiative to answer the questions we've been discussing.

The industry has presented a confused agenda to Congress. The notion of competitiveness is usually driven by individual companies, as when Senators Cranston and Wilson intervene with the FDA on behalf of Genentech, or when Boucher and Wilson introduce a bill on the process patent. It becomes a question of ensuring that particular companies are being competitive.

On the regulatory side, we're seeing a variety of state laws proposed on biotech issues. It would be desirable for federal regulation to preempt the arena and prevent companies from having to deal with 50 different sets of regulations. The critics are driving the issues at the state level, and the industry and federal government are letting them take the lead.

Mr. Fox: The people who work in the government agencies spend their days, in effect, being responsive to the crises of those days. They are dealing with many industries, companies, and issues. None of them has the job of making this a successful industry. That's the industry's job.

Mr. Simon: I would disagree that the government is doing its job. Part of the government's job is to regulate when it's appropriate. We didn't spend this long trying to regulate lead or infant car seats or cigarettes. The industry will suffer without these guidelines. Last year, Steve, in *Biotech 90*, you said, "The U.S. biotech industry has been something of an economic miracle based on consecutive acts of confidence." I would argue that the next acts of confidence have to come from the market and the public. And until the government does its job, the next acts of confidence won't happen.

The next acts of confidence have to come from the market and the public

Mr. Burrill: Is the confidence there? Wall Street is unsure. Pressures from HCFA and public attacks on drug pricing may cut profitability way down. Roche/Genentech has taken away some of the belief in this industry. And at the same time, government and the industry haven't articulated a policy that we want. We can say it's the industry's problem, but it's also Washington's problem and our country's problem. The real question is, are we going to do anything about it?

Mr. Allard: I don't quite understand the alarm about the Roche/Genentech deal. Is it necessarily bad that a multinational company has determined that it's useful to build its pipeline by acquiring rights in Genentech? Genentech presumably will continue to make its products available in the United States and have additional resources to develop a full line of products.

Mr. Burrill: I don't disagree, Nick. I think it's a good event for Genentech and not a bad event for the industry or the consumer. What's troubling a lot of people is that the buyer is foreign.

Mr. Fox: But, in purely economic terms, can these small companies really become big companies? A tremendous worldwide consolidation is taking place in the pharmaceutical industry. Companies might do well to focus on their logical strategic alliances and combinations.

Mr. Burrill: The concern is that the United States may be losing its historical ability to grow companies and industries. A big part of the issue is that we don't have a level playing field—capital forma-

tion, industrial incentives, trade policies, regulation, and accounting and tax policies differ around the world.

Mr. Simon: If Dr. Hess, Dr. Miller, or Dr. Wyngaarden mentioned the words “industrial policy” where they worked, they would be out of a job. Our government does not allow its agencies to talk about industrial policies. When the Department of Transportation wanted to have a transportation “policy,” they knocked the name down. “Policy?” No. “Plan?” No. “Agenda?” They ended up with a transportation “proposal.” We don’t talk “policy” in this country.

Our government does not allow its agencies to talk about industrial policies

We won’t bring on government support for new industries, not directly anyway. If you brought industry people together, they would say the biggest area in which they need help is the scaling-up technologies—the pre-competitive research to help small companies learn how to make products for large markets. But we don’t allow ourselves a policy of doing that. On the other hand, when an orphan drug makes \$200 million and serves 100,000 people, I’d say someone is getting help from the government.

Dr. Hess: Attitudes about the role of the federal government in supporting industry seem to be cyclical. Fifty years ago, the Agriculture Department established four regional laboratories to convert agricultural commodities into non-feed, non-food uses. In the late ‘70s and ‘80s, we went into a period in which we looked at the involvement of the public sector with the private sector as something bad.

By 1986, we saw all too clearly that Japan was taking our basic research, converting it into products, and selling it back to us. We were going to change that with the Technology Transfer Act. And in the past few years, there have been at least five bills in Congress on, again, developing non-feed, non-food uses of agricultural commodities, looking at alternative fuels and biodegradable plastics—a whole spectrum of things. This year, after a fair amount of arm-twisting with the Office of Management and Budget, we included a section on commercialization in our Farm Bill, because I thought that we should work together with Congress in trying to develop an approach. And in the last Competitiveness Council meeting, the Vice President said he was going to establish a work group on commercialization of technology.

I recognize that there isn’t complete agreement within government on this direction. Messrs. Darman, Sununu, and Boskin take a different view. But I do see a change in attitude in Congress and some shift in the administration.

Mr. Simon: Our committee, in particular, has promoted technology transfer legislation. However, we still have problems creating the technologies that we can transfer. It’s not unique to biotechnology—we get letters every week from the computer industry, semiconductor industry, and fiber optics people. If biotech could shake loose a policy, it would help everybody.

It would help if the industry acted like an industry, instead of components of one. It is very difficult to deal with the industry as an industry if every bill that we’re asked to pass on the Hill is directed to a specific company.

Mr. Fox: In other industries, there have been companies that have taken it upon themselves to be leaders and inform government policy on industry-wide issues. Leadership has to emerge from the industry.

Ms. Levinson: It's a traditional problem that scientists are not particularly politically active as a group. More often than not, that leaves the door open for the critics. In the health area, at least there are the patient constituency groups.

Mr. Burrill: Let's stipulate, for a minute, that it's in the public interest that this industry does not disappear as, perhaps, some others have. Doesn't Washington, driven by its role of protecting the public interest, need to take leadership above anything the industry is able to muster?

Mr. Simon: What you have to realize is that the public thinks the government is taking the industry's part—not the public's—and protecting the industry. That's why we've seen a surge of state legislation. Until there is a visible, well-working federal regulatory system, the federal government will be viewed as a non-player in the interchange between the industry and the public.

Dr. Miller: Greg, you've alluded a couple of times to the absence of federal legislation and regulations. The Food, Drug and Cosmetic Act; the Noxious Weed Act; the Public Health Service Act; the Plant Pest Act; and FIFRA—these encompass aspects of biotech. Somebody who wants to put out irradiated Dutch elm fungus for a field trial is captured by the Plant Pest Act. Somebody who wants to put a recombinant rabies vaccine into you comes to the FDA. I'm not aware of a paucity of regulations or of any gaps in their coverage.

There is a political need at the community level

Mr. Simon: But what about herbicide-resistant plants, or genetically engineered fish? Monsanto and other companies express a desire for regulations. Why?

Dr. Hess: There is a gap in the guidelines in terms of field testing genetically modified organisms that do not fall under existing regulations.

Mr. Fox: Monsanto wants the government to do whatever it can do to make sure the public is comfortable. There is a political need at the community level.

Dr. Miller: I'm not sure that public perceptions, or government perceptions of public perceptions, should, by themselves, drive policy. Rather, people need to be educated to have an appropriate perspective on the existing regulation and where there are gaps, if any.

The fact is, there are vast numbers of transgenic microbes and plants. Many are tested every day in the absence of federal, state, or local regulations. Every year, hundreds of thousands of new transgenics are out there, and, predictably, with no unforeseen consequences. To treat a small subset in a discriminatory fashion only because they are manipulated with the newest, most precise techniques, is in no one's best interest.

Mr. Simon: We're creating a circle. Educate the public, yes. But if you don't involve the public, how are they being educated? The public should be part of the regulatory debate, and they haven't been. Not surprisingly, they assume the government is hiding something from them.

Mr. Fox: And the critics are telling them what to think.

Can We Define the Direction?

Dr. Wyngaarden: Among those of us who have been struggling with the wording of the next round of regulations, there is full agreement that they need to be risk-based and grounded in the best science available, as well as workable for the regulatory agencies on a practical level. There is a general sense that we are at a very crucial point in the scheme of things.

There is a general sense that we are at a crucial point

In 17 years under RAC, we've not had a single adverse public health event involving people, animals, or plants. There is no unique risk involved in rDNA-derived organisms or genetically modified organisms. A real problem in drafting the regulations is getting the wording to match this scientific understanding. We're having great difficulty describing how to regulate genetically modified organisms in such a way that it doesn't reinforce the notion that genetically modified organisms are a special class that needs special regulations because of special hazards. If we can't find the appropriate way of defining the situation, then we may be trapped in misstatement for all the future.

Dr. Miller: Overall, I disagree with the view that the industry is in peril. In pharmaceuticals, the record has been impressive and favorable. NIH funding has provided a good pre-competitive substrate. Biotech companies spend vast amounts on R&D. While some would consider that the FDA process has not been rapid in absolute terms, approval times have averaged only about half of the mean 32 months required for non-biotech products.

A number of products have been approved, and many more are in the pipeline.

In other industry sectors, there hasn't been quite as much nourishing of the pre-competitive substrate, nor as much going into R&D from the private sector. The regulatory interface has been a problem. There is discriminatory treatment of agricultural products manipulated with the new techniques. These regulatory disincentives have caused some companies to go back to using less precise, less powerful, pre-recombinant DNA techniques. That's what regulation can accomplish when it's applied in a non-rational, discriminatory fashion, and is driven by governmental perceptions of public perceptions.

Mr. Simon: The industry has to be forthright. New biological technology raises new concerns. The industry has to address these squarely.

This is a new era. We're talking about gene therapy and genetically engineered food. For biotechnology to succeed, we have to frame the discussion around those points. At the same time, these bright new products have shadows— orphan drug policy, drug pricing policy, the ethics of gene therapy, the environmental and economic impacts of agricultural products, and people's fear of the unknown. We can't dispel the shadows if we don't address them.

If we had decided five years ago to regulate releases, monitor the data, and create a data bank that could be disseminated across the country, we could be talking about deregulating the industry in the agricultural area right now. If we do something now, five years hence we'll have the data to convince the public that we have found out what they wanted to know. However scientifically correct your position may be, Henry—and I would argue that it's not—this is a democracy, not a scientocracy. If we relied only on science, we'd outlaw tobacco and alcohol. We have to win the minds of the public.

Dr. Miller: I still affirm that good science dictates a path at odds with the one you espouse.

Mr. Fox: I remain convinced that important new technology will make it. If this requires strategic alliances or combinations, so be it. I question whether federal policy should be directed specifically to help small biotechnology companies. I would look more favorably on policies that help small, scientific companies across the board. That's different from the biotech policy the industry seems to be asking for.

The people who are driving this industry are wonderful, but I don't think they understand Washington. Their expectations of what the government should be doing for them are unfounded. I think they have to do a lot more for themselves.

Dr. Wyngaarden: The public needs to have more confidence in the regulatory apparatus, or the states will go their own way. This is one area in which the federal government can do something relatively soon.

Many of the problems of industry fall under the rubrics of tax policy, fiscal policy, or simply giving the regulatory agencies enough resources to do their job. There's a trend in that direction—the FDA and Patent Office have received some additional funds.

But underneath all that we've been discussing today, is the general question of what, in a democratic and predominantly capitalistic society, should the federal government do on behalf of individual industries. That is far from resolved.



Jerry D. Caulder, Ph.D.
*Chairman, President and
Chief Executive Officer
Mycogen Corporation*

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“We have different opinions or two
.....
or three issues—even a dozen.
.....
But there are hundreds of issues
.....
on which we agree.”
.....

*Businessman, scientist, industry leader—
Jerry Caulder met with G. Steven Burrill, National
Director of Ernst & Young’s High Technology
Industry Services, in Mycogen’s headquarters to
discuss the issues confronting the CEO of a devel-
oping company, the trials in winning acceptance
for new technology, and the overriding concerns of
the biotech industry at large. Long a spokesperson
for the biotechnology and agriculture industries
before policy and business forums, Dr. Caulder
is currently the Chairman of the Industrial
Biotechnology Association (IBA).*

*The son of a Missouri cotton farmer, Dr.
Caulder has focused his education and career on
agronomy and agribusiness. For fifteen years, he
held positions of increasing management respon-
sibility for Monsanto Corporation’s agricultural
products. While involved in Monsanto’s biotech-
nology thrust, Dr. Caulder urged the company to
acquire a position in several emerging agriculture
companies, especially Mycogen. When his recom-
mendation was turned down, Dr. Caulder continued
to strongly believe that the future of agriculture lay*

*in biotechnology. Eventually he joined the firm he
had identified as a comer.*

*Founded in 1983, Mycogen develops, manu-
factures, and commercializes biological pesticides
as alternatives to chemical insecticides and her-
bicides. Its proprietary CellCap™ encapsulation
system has disarmed the critics of genetically engi-
neered microorganisms by delivering active toxins
within a dead bacterium, a format which also
improves the crop-protection performance of the
Bacillus thuringiensis-derived biotoxins.*

Stages of Development

Mr. Burrill: Talking both as the chairman of the IBA and a CEO who has just finished a very effective road show for a \$50 million equity offering, what is your view of the state of the biotech industry?

Dr. Caulder: Anytime you’re changing a basic industry like the ag-chemicals or pharmaceuticals, you and the world are waiting for the answers to three basic questions. First, can you do it, that is, is it technically feasible? Secondly, how effectively can you do it? And, finally, how big is it going to be?

Today the industry is moving from being technology-driven to being market-driven. We’ve shown that the technology works. We’re developing effective products. And as we move more and more products into the market, we’ll determine how big these products will be. It’s a fairly normal progression of new technology and products moving into the marketplace.

Mr. Burrill: Most other technologies don’t grow up with as much emotion around them as biotech has, with people focusing on what they perceive as the religious, ethical, and environmental implications of the processes and products of this technology. While this industry has gone through some fairly normal stages of development, doesn’t it also have some unique problems?

Dr. Caulder: It's very difficult to assess the external factors when you're living among them. Some of the problems that we're having now are no different from those people have faced in other times and other industries. I don't remember the exact quote, but I came across a reference that said, basically, we are manipulating living matter in a way that was never intended by nature. That sounds like something we're discussing today. Actually, it was a criticism of Luther Burbank's work around 1906, when he was just learning to hybridize plants to create new varieties. There was tremendous opposition to using threshing machines and other machines when they were first introduced. Some people said that God didn't mean us to use machines; the Amish and the Mennonites still believe that. Every new technology has been met with an emotional reaction of some type.

Ethics, beliefs, and values change. If you look at the adoption of a technology on a snapshot basis you're not seeing the whole picture. The only thing that has been consistent over the last few hundred years has been the scientific method. The scientific method does something very important—it allows for change. Morals and ethics on a snapshot basis don't.

We live in a society that is dominated by science and technology. Yet not five percent of the population is equipped to understand scientific reasoning. This leads to a blurring of the distinction between science and technology. Science is the production of new knowledge; technology is the application of knowledge to some product. Most people do not distinguish between the two.

Science, in itself, is more or less innocuous. But as soon as it leads to technology, it is not necessarily innocuous. Herein lies the dilemma—there are inherent risks to the pursuit of new knowledge. The risks are greater, however, if we don't continue the pursuit.

Mr. Burrill: A good deal of the public discussion of the technology is driven by the critics. How can the industry gain greater control over the dialogue and put it on a more rational footing?

Dr. Caulder: Nay sayers deal in absolutes. Scientists know there are no absolutes. If you asked whether I could assure you that the release of a genetically engineered organism will never cause any problems, as a scientist, I would have to say, no. The nay sayers want absolute assurance that there is zero risk. Well, we don't live in a zero-risk society—not in any respect. In fact, striving for a zero-risk society is the greatest risk of all, because it stops innovation.

In their desire to give a balanced picture, the press often gives an unbalanced one. Every time they write an article about biotech, they want to give the other side of the story, so they quote one of the critics. What comes across is that half the people are against biotech, when, I believe, you probably can identify thousands of people who are for the technology and what it can produce, for every person you can find who opposes it.

*We don't live in a zero risk society
—not in any respect*

In the end, nothing succeeds like success. As we continue to bring out the t-PAs and the biopesticides that replace chemical pesticides (or at least reduce the pesticide load), these products will prove so valuable, and their risks so negligible, that everybody will be able to see that.

Think about it being plotted on a graph, with anxiety measured along the vertical axis and knowledge on the horizontal. The lower people's knowledge, the higher the anxiety curve. As people understand more, the curve comes down very rapidly. We're moving down that curve now because products are there. T-PA, gamma interferon, interleukins—people understand that these are good products. Mycogen's products, the bio-pesticides, are working through that acceptance curve now.

*The lower people's knowledge,
the higher the anxiety curve*

You're never going to make everyone understand genetic engineering or gene splicing—and you don't have to. I don't understand very much about electricity, which is a powerful and dangerous technology, but I'm comfortable with its products. Our goal should be fairly simple—to put together a regulatory framework that gives us reasonable assurance that the science can progress, while giving the public reasonable assurance that the products are safe and effective. We don't need new legislation to do this. The agencies are in place—the EPA, USDA, and FDA. Let's let them work.

Mr. Burrill: Accomplishing that requires enough industry cohesion so that the principal companies in the industry speak with one voice. This is a key issue you've been struggling with in your role in the IBA. Is there a hope that the industry can put the interests of individual companies aside and speak cohesively?

Dr. Caulder: I think the industry does speak cohesively. The attention given to a few areas of difference is rather like the coverage our critics get—our disagreements are considered more newsworthy than the things we agree on. When a couple of people resign from the IBA because they disagree with the majority on a couple of issues, it gets attention. Does that mean we as an industry are divided? I don't think so. It means we have different opinions on two or three issues—even a dozen. We're still working them through. But there are hundreds of issues on which we agree. Why don't we get coverage on those issues? Disagreement is a sign of a healthy organization—it means that the members feel that a forum exists that allows them to openly air their beliefs.

The Washington Agenda

Mr. Burrill: There is a cry that biotechnology needs certain things from Washington—regulatory effectiveness, incentives for capital formation, and funding of basic research, for example. But when I talk to people in Washington about the relationship between this industry and the government, they say they can't figure out what the industry needs—that the ABC says this, the IBA says that, and the PMA says something else. Washington is saying that it can't be any more effective in addressing the industry's issues than the industry is. Do you think that's a fair assessment?

Dr. Caulder: For people in government to say that we have to have unanimity in opinion before they can act is a copout for not doing their job. Whether or not we agree on every issue is irrelevant to the kind of regulatory structure we need to bring these products to the marketplace, in an orderly fashion, that assures safety and quality.

Take the broad issue of intellectual property rights. There's no disagreement in the industry that you need strong protection for patent rights. There is some disagreement on how you implement it. We see Genetics Institute looking at it one way, and Amgen another. But why accent this when everyone agrees that we need faster reviews of patents so that we understand what our asset basis is?

If Congress were willing to sit down with the IBA and ABC and discuss intellectual property rights, I don't think they would see much disagreement. Instead, they look at the Boucher bill and say we disagree on this. Yes, we do—on a narrow aspect of it.

On orphan drugs, one group wants the Orphan Drug Act to stay unchanged and the other wants to change it. But both groups are willing to look at what the bill does and what it should do. If the law is written badly, we ought to change it, as long as we do not retroactively penalize companies that have made investments based on that law as it stood. We should be able to find the compromises.

Whether we agree on every issue is irrelevant to the kind of regulatory structure we need

There is no disagreement in the industry that small companies have been unduly punished by the capricious change in the capital gains law. I hired a lot of people based on the premise that they would own stock in Mycogen which, sooner or later, would represent a significant capital gain for them on which they would get a tax break. Overnight, the government made me a liar, and put a small company at a drastic disadvantage in recruiting talent. I want the people I hire to take equity in the company, but the stock I give them is restricted to a point in time. Monsanto and Du Pont can hire them for cash. The net effect is that I have to hire

new people at the same salary they do. I have to compete with the resource of which small companies have the least—cash.

Small companies have been unduly punished by the capricious change in the capital gains law

Mr. Burrill: The bottom line, then, Jerry—what does the industry want from Washington? Where is there total agreement?

Dr. Caulder: What we need from Washington centers around two areas. The first is patents. A small company's asset base is formed around intellectual assets. Unless we have a patent system that protects our intellectual property rights in the U.S. and abroad, we have a problem. We need to strengthen our patent system to account for the fact that, in a highly regulated industry, you chew up a lot of your patent time getting your products approved, leaving you fewer years than you need to recoup your investment and to plough profits back into R&D.

The second area is regulatory procedures. We don't need a special function to regulate biotechnology products. Biotechnology is merely the process by which we get products that are already regulated by the EPA, USDA, and FDA. Do the laws and the regulations that are currently on the books cover every aspect of biotechnology? No. But do they need a major overhaul? Absolutely not. They just need some tweaking. Someone within the regulatory structure has to provide the leadership. The industry can't do it—as soon as you have the regulators and the regulated working together, third parties yell collusion.

Mr. Burrill: What about a capital gains tax differential?

Dr. Caulder: That's fundamental to our ability both to attract capital and attract and retain key people. As a society, we benefit from giving people incentive to take risk. Historically, we've invested a tremendous amount of money in basic research. I know of no other area where we have gotten so great a return on our investment as the monies we've put into basic research over the last 200 years. The second thing we've done very well is capitalize industries to convert new knowledge into technology. A capital gains tax differential is just a way of subsidizing this science/technology interaction for the good of our society. It defrays the cost of the risks over a larger base.

I'm concerned that we're not funding science as we should. In agriculture, we're living off investments in research that were made years and years ago. Our government now is funding only those things that show the promise of a product—a cure for cancer or something. I'm sure that, in 1896, when we discovered the electron, not too many people ran out in the streets yelling, now we can have television! We don't know where science is going to take us. That's why we have to continue to make basic discoveries. In the early 1970s, had Senator Proxmire known that Boyer and Cohen were working on what was basically the sex life of bacteria, he would have given them the Golden Fleece Award. No one knew that their work would create a whole new industry.

Mr. Burrill: Foreign governments and financial markets take a long-term perspective on this transformation of knowledge into technology. In effect, they subsidize their industries through the cheaper cost of capital. U.S. technology companies are not competing on a level playing field.

Dr. Caulder: Absolutely. My father, a good old cotton farmer who has more common sense than most people I know, always told me that things that get rewarded get repeated. Well, what have we been rewarding in the United States for the last few years? We've been rewarding people to become investment bankers and move money around. We've been doing deals, while the Japanese have been making products. We've been rewarding the wrong things.

Things that get rewarded get repeated

Three hundred years ago, countries built empires by colonizing areas that could provide raw materials. They brought those materials back to the home country, added value to those materials, and then sold the products back to the colonies. It seems to me that the United States is becoming the colony for the rest of the world in technology. We discover the science. They take it home, add value to it, and then sell it back to us.

Mr. Burrill: So what's the answer?

Dr. Caulder: We have to add value to our science ourselves—true value. If you look at why we lost leadership in the automobile industry, it's because the value that we were putting into cars wasn't as good as the value others put in theirs. We have to spend more resources on converting our science into technology and adding that value.

Managing Mycogen

Mr. Burrill: Mycogen is working with several foreign partners. Why is that more attractive to you than working with U.S.-based international companies?

Dr. Caulder: A small company needs to stay highly focused, not only in its research and technology, but also in what it does with its products geographically. Southeast Asia is a big market. It makes sense to establish partnerships with companies that are strong in that part of the world, as we have with Kubota and Japan Tobacco. Their difference in outlook—that long-term perspective you referred to—also is important.

On the other side of the world, we're working with Royal Dutch Shell as a partner in Europe for many of the same reasons. They appreciate the long-term prospects for biotechnology in agriculture, and have the marketing expertise in Europe that we need. These are strategic partnerships rather than revenue-creating situations.

Mr. Burrill: With Lubrizol increasing its equity investment in Mycogen during these past months, and your recent equity offering, you have a large capital base to invest in developing intellectual property. Does Wall Street's quarter-to-quarter focus hold you back in any way? How do you make the trade-off between the Street's short-term requirements vs. your perspective on the really long-term game that you're in?

I am not going to focus on a given quarter to the detriment of our long-term success

Dr. Caulder: I don't make that trade-off. As far as I'm concerned, I run this business to make it successful. I am not going to focus on a given quarter to the detriment of our long-term success. When you're changing an industry and trying to build a business at the same time, you have to be in it for the long haul. We've put together a strong capital base precisely because we don't want to be forced to manage quarter to quarter to raise money. That can happen to you all too easily in this business.

Mr. Burrill: You are still beholden to some extent to the capital markets. If your earnings go down after a couple of quarters that were up, you trade off real flexibility.

Dr. Caulder: You're going to have ups and downs, but if you manage consistently over time, I don't think you're going to have violent swings. I don't know what our stock is trading at today; I don't watch it on a daily basis. It's probably somewhere around \$17 or \$18. It may go down to \$13; it may go up to \$23. I am not going to be overly concerned about any swing in a short period of time. My focus is to build the base for Mycogen's products to enter the marketplace in an orderly fashion so that they have staying power.

I told the world that my objective is to try to break even this year. But if I see that it will force me to bring a product into the marketplace before the market is ready, I'll choose to lose money for another year. If you put money into Mycogen at \$17 and, let's say, it's now \$14, and you're dismayed—I'll be the first to say that if you bought this high-risk stock to hold only for six months, you probably shouldn't be investing in Mycogen. If you put money in us, you have to be willing to hold it for a period of time to see our business plan develop, not to see how our quarter develops. Agriculture is a seasonal business and can also be cyclical. Therefore, there will be quarter-to-quarter variations and some yearly variability as well. Do I ignore what

the financial markets think? No. Do I cater to them? Only when it isn't detrimental to the overall plan.

Mr. Burrill: Year after year, our survey shows us that most of the companies in the industry remain driven by their financial strategy, which is a function of the capital they can raise, whether through venture capital, partnering, or the public markets. How do you deal with the need to carve out a meaningful business strategy against the reality of having to finance this company—day one, day 100, day 1000?

Dr. Caulder: When I sat down with the venture capital people seven years ago, I told them I felt it was important to maintain ownership of our technology and not give up our products to generate royalties and short-term revenues. They thought I was crazy; they said no one does it that way.

But you cannot build a business on royalties. The big companies aren't going to buy your poor products; they're going to buy your best products. We took the risk early to reduce our science and technology to practice. Only then were we able to deal with the big companies on a partnership basis, rather than a royalty basis. Young companies have to be recalcitrant toward the venture capital people. They're looking for exit strategies. Don't give them one! They have to know that this kind of business takes a certain time to develop.

So, finance your technology early, reduce it to practice early, and do one thing right. At Mycogen, we centered on a pesticide product, our M-One bioinsecticide and the technology, CellCap. We put the product through the regulatory system. This allowed us to test the distribution system and to start hiring sales and marketing people. M-One is probably a \$10 million product. Is that big enough to build a company with? Absolutely not. But it tested every one of our systems to make sure they were functioning. It put in place the foundation

on which we are bringing our CellCap technology and other products to the marketplace for a much larger payback. It gave us the cash to buy Safer's agricultural product line which we can exploit in our markets.

An Ag Frog in a Health-Care Pond

Mr. Burrill: The pharmaceutical side of biotechnology got the big dollars early. Ag-biotech companies still aren't getting the attention, the understanding, the capital base, and perhaps the valuations that they would like. How has life been on the less visible side of the industry?

Dr. Caulder: The good news about being in agriculture is that people leave you alone. Also, the bad news is that people leave you alone. Languishing in the shadow of human health care has kept us from being under a microscope all the time, but none of our valuations has ever approached the Genentechs and Amgens of the world.

What is going to get the bigger headline—someone working out a cure for cancer or someone learning how to kill bugs in a more efficient manner? The world overlooks the fact that if we can eliminate the need for certain chemical pesticides, we can improve human health as well as protect the environment.

In the United States, we've gone from an agrarian society to an agrarian-dependent society. Less than two percent of the folks out there keep the rest of us well fed. And the rest of us are absolutely ignorant about it.

We have about a 60-day supply of food in the world, and call it a surplus. We have a 200-year supply of oil and call it a strategic reserve. Why do we look at those things differently? Because we have never known shortages of food. The farmers in the U.S. have done a better job than anyone else in the world.

People view agriculture as slow growth, low-tech, and stoical. Yet our products should have gross margins that approach pharmaceuticals. Pesticides comprise a \$20 billion business. Almost 25 percent of the gross national product is still associated with agriculture. About one out of four workers in the United States is still associated with agriculture. These things get lost in the shuffle.

Our products should have gross margins that approach pharmaceuticals

Agriculture is a very efficient business that needs a lot of inputs and technology to keep going. It's a national shame that we haven't put any more

money into basic research in agriculture than we have. Since 1968, the budget has stayed flat, absolutely flat. We are consuming our seed corn.

Mr. Burrill: It's interesting, though, that you, an agriculture guy, are chairing the IBA.

Dr. Caulder: When I was asked a couple years ago if I would become chairman, my first inclination was to say no, because I didn't want to spend much time away from Mycogen. The more I thought about it, though, I reasoned that if the Bob Swansons, George Rathmans, Will Carpenters, and Gabe Schmergels of the world are confident enough to let a small-company, agriculture guy be the chairman, I could not afford to turn that down. It could do nothing but good, I thought, to raise the profile of agriculture in the biotech community.

Biotech and The Health Care Agenda

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"The market is primed to gravitate
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toward products and procedures that
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are directed to producing
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better outcomes at lower cost."
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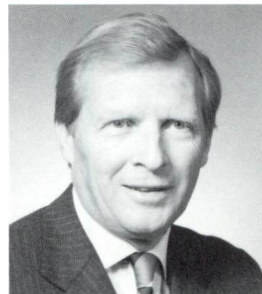
Genetically engineered diagnostic and therapeutic products are flowing into the pharmaceutical mainstream at a time when employers and government are trying to assert greater control over the escalating costs of health care. While drugs represent only six percent of total health-care costs in the United States, the pricing of breakthrough products like Burroughs Wellcome's AZT and Genentech's Activase have been subjected to scrutiny and attack.

G. Steven Burrill, National Director of Ernst & Young's High Technology Industry Services, met with leaders of Ernst & Young's Health Care Industry Services to explore how biotechnology companies can communicate the value of their products, and contribute to resolving our society's need to better manage health-care costs, while making quality health care available to all.



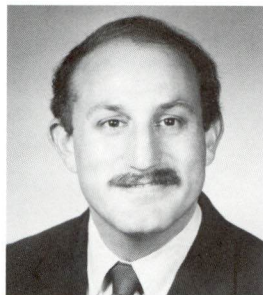
Richard L. Marrapese
National Director
Health Care Industry Services

Richard L. Marrapese is the National Director of Ernst & Young's Health Care Industry Services. He is a member of the Healthcare Financial Management Association, the American Hospital Association, the Ohio Hospital Association, and the Health Care Administrators' Association. Mr. Marrapese is based in Cleveland, OH.



J. Robert Holt
Partner
Health Care Industry Services

J. Robert Holt is a partner in Ernst & Young's Health Care Industry Services in Los Angeles, CA. Earlier, he was founder and President of The Brighton Consulting Group, a health-care consulting firm with a special focus on managed care; and Vice President and a Director of Beverly Enterprises, the largest nursing-home operation in the United States. Mr. Holt has served as a Director of the Watts Health Foundation and United Health Plan.



John G. Nackel, Ph.D.
*Regional Director
Management Consulting
Health Care Practice*

John G. Nackel, Ph.D., is the Regional Director of Ernst & Young's Great Lakes Region Management Consulting Health Care Practice, based in Cleveland, OH. Dr. Nackel holds an M.S. degree in public health and a Ph.D. in health-care systems design. He is a Fellow of the Healthcare Information and Management Systems Society and the American College of Healthcare Executives, and a senior member of the American Institute of Industrial Engineers (Health Services Division).



Carolyn K. Davis, Ph.D.
*National/International
Health Care Advisor*

Carolyn K. Davis, Ph.D., is National and International Health Care Advisor to Ernst & Young. From 1981 to 1985, Dr. Davis served as the Administrator of the Health Care Financing Administration (HCFA), overseeing the functions of the Medicare and Medicaid programs. Dr. Davis holds a nursing degree, an M.S. in nursing education, and a Ph.D. in administration. She serves on the Board of Directors of the American Red Cross, Beckman Instruments, The Prudential Insurance Company of America, Merck & Co., Flying Nurses, and the National Museum of Health and Medicine Foundation.

The New Gatekeepers

Mr. Burrill: From your perspective of being closely aligned with the health-care sector and yet sufficiently outside it to take a broad, objective view—what are the issues in health care today that affect the way the new biotechnology products are regarded and received?

Mr. Marrapese: We are experiencing a multiplicity of crises in health care. An aging population is shifting the patient and disease demographics. There are significant gaps in our health-care delivery system—some people simply cannot access appropriate care. There is a strained and decreasing supply of care-delivery professionals. The biggest crisis is economic. In everyone's mind in this country, health-care costs are out of control.

All the forces are aimed at creating cost-effective delivery in health care. This has primed the market to gravitate toward products and procedures that are directed to producing better outcomes at lower cost. An example is the push toward less invasive surgery, such as angioplasty, in which you're cleaning out arteries as opposed to doing a surgical bypass.

Mr. Burrill: How do we determine where the greatest leverage points are in the cost/benefit equation?

Mr. Holt: Those judgments are evolving on the purchaser side, where we are moving toward a system characterized by third-party management of health care. The purchasers today—HCFA, the insurance industry, and the benefits managers of large employers—are shifting away from determining coverage on a cost-management basis and heading toward a utilization-management approach.

They are moving toward dictating the appropriateness of care—the procedures that ought

to be performed, and how they are to be performed. When someone is going to be admitted to a hospital, a utilization manager will lay out the length of stay, the discharge date, and the treatment plan, and then monitor the patient to make sure the treatment is appropriate. The provider is expected to manage the patient against the plan.

Mr. Burrill: Is there a way to measure the value of health care? Let's suppose we save my life. To me, that's worth a lot. How do we measure what it is worth to society?

Transforming horizontal care into vertical care

Dr. Nackel: Measuring value has both short- and long-term considerations. The short-term value issue centers on transforming horizontal care, where the patient is flat on the hospital bed, into vertical care, where treatment is given on an outpatient basis, at home, or even on the job site. Anything that moves us toward vertical care yields a dramatic result in cost savings and value.

The long-term value issue relates to the aging of the population. With better treatment, we may be able to halve the cost of cancer to society. But as we save people from cancer, we are creating an Alzheimer's cost that may be five times as high, because it's a longer-term illness with severe societal and family costs.

A fairly significant amount of health care costs are incurred in the last six months or year of a person's life. Extending what is now a six-month or one-year cost into a multiple-year cost can have a dramatic effect. The cost and quality-of-life implications of extending average life expectancy through new technology are important issues for biotechnology and society.

Mr. Burrill: You're saying that the long-term values are very difficult to measure because of the multiplicity of pieces of the equation.

Dr. Nackel: Exactly. If you cut cancer costs by fifty percent, that may not be a fair assessment of the ultimate value to society.

The long-term values are very difficult to measure

Dr. Davis: There's another dimension that relates to cost containment—the question of who's there to give the care. Health-care organizations simply can't find all the people they need—the nurses, physical therapists, right down the line. They are looking for products and technology to be not only cost saving, but also personnel saving. If companies can develop products that need less human intervention or monitoring, that's an additional benefit.

Mr. Burrill: We are seeing the emergence of some gatekeepers who were not factors before—benefits managers, HCFA, and the insurance industry. In the absence of sufficient information to make the value tradeoffs, I would imagine the greatest contribution those gatekeepers can make is in the short-term comparison of one set of cost dynamics against another.

Dr. Nackel: Those are very measurable. For example, we did an engagement for a large pharmaceutical company where we compared the cost-benefits of pre-packaged syringes versus having the nurse fill the syringe at the medications counter. You can translate the amount of time it takes for each modality into a dollar value.

Dr. Davis: HCFA always looks at the question of benefit. It is true that, to some degree, a benefit in one area can be a cost item in another. But HCFA is also dealing with society's demand for products that are benefits because they cure. There may be fiscal pressures coming from OMB (Office of Management and Budget) and others related to the longer-term, indirect costs. But, generally, HCFA will yield on the societal value side. It may take a couple of years, but as societal pressure builds up—and it can be orchestrated to build up—HCFA usually responds.

There are a number of experiments going on at HCFA that deal with how to quantify and measure quality of life. They started during the 1980s when the agency was dealing with the question of kidney transplants versus sustained dialysis. They saw that with kidney transplants, not only was the cost lower, but the quality of life was better. After they added those two together, they started promoting kidney transplants over dialysis every way they could.

HCFA always looks at the question of benefit

Mr. Burrill: How broad is physicians' control today over incurred health-care costs?

Mr. Marrapese: The physician admits the patient, orders the diagnostics, orders the treatment regime, and orders the discharge. Those are the major sets of activities that affect the hospital's cost, and the physician has control over all of them. However, managed-care plans are placing limits on what physicians control and how patients access the system. Thus they are starting to really manage delivery as well.

Dr. Nackel: The fallacy of that approach is that medicine is not all science. Some portion of medicine is an art. There are intuitive sides to patient care that can't be written up. For many diseases, we can get fairly well-defined protocols for hospital admission—the criteria that determine whether a patient should be admitted. Likewise, for discharge. However, this cannot be accomplished for all diseases and conditions. Determining diagnosis and treatment isn't always clear-cut.

Mr. Holt: But product manufacturers are going to have to make explicit statements of value, cost, and benefit. The FDA is looking for more formatted, electronic, transaction types of information, even back to Stage I, II, and III clinical trials. That spells the need for companies to arm themselves with information systems or interact with the systems of the institution that is carrying out the trials. We're also seeing trends to monitor post-approval drugs.

Dr. Nackel: An important issue, too, is that we're moving as a society towards a wellness rather than a disease focus—witness our emphasis on fitness, nutrition, exercise, stop-smoking programs, alcohol and chemical dependency treatment, and preventive care. We'll always be dealing with the treatment of illness, but there is a growing focus on keeping our work force well, keeping people out of the hospital, and identifying disease early rather than when it has progressed to a stage where treatment is extremely costly and the disease may be irreversible. Products that address the wellness and preventive side of the market may be just as important to develop as those that address the disease side.

Mr. Marrapese: In Cleveland, where I live, a coalition of the top 50 CEOs in the city formed a group called Cleveland Now to try to do something to control their health-care costs and make sure they're getting cost-effective, quality care for their health-care dollar.

Before you could blink twice, the hospital association wanted to be a part of the effort. Imme-

diately behind them was the Cleveland chapter of the American Medical Association. These organizations recognize that business as usual is no longer acceptable to the folks who are paying the freight, and they would rather be a part of the change process than have the change imposed on them.

Why should double inflation be acceptable in health care?

Groups like this are coming together around the country, because the health-care industry has not demonstrated that it can manage itself within a reasonable cost-increase framework. Double inflation isn't acceptable in other industries. Why should it be acceptable in health care?

Mr. Burrill: Does all of this translate into a more opportunistic marketplace?

Mr. Marrapese: Absolutely. Assuming that we do the best we can from a prevention perspective, technology that aids early diagnosis is critical because it substantially reduces cost. And anything that gets the patient out of the hospital faster and back to work sooner gives the employer a double benefit.

Mr. Holt: The payers are really gearing up to measure those things. A few weeks ago, I was talking with the manager of information systems at a national HMO, who was working furiously to develop a system that would provide information on patient utilization. Why? The insurance brokers were pushing it. If the HMO doesn't provide that kind of information, the brokers won't let it bid on accounts with their clients. Then, the brokers and clients use that information to negotiate tighter contracts and fees.

Mr. Marrapese: Today we have some 31 million Americans covered by managed care—about 20 percent of the population. It's suggested that in the next five to 10 years, 60 to 70 percent of the population will be covered under some form of managed-care programs.

Mr. Burrill: That also means concentration of control. I would think that companies that can make the cost-benefit case for a new technology or product can get much more rapid acceptance than if they had to deal with 50,000 individual doctors.

Dr. Nackel: I think the pharmaceutical and therapeutic committees of the hospitals will become the first-line buyers of drugs. In effect, these committees will be setting the protocols for drug distribution within an entity or a hospital system.

This is an opportunity. You generally can change physicians' practice patterns if you explain the ramifications of their current protocols and can demonstrate that you are not impairing the quality of their care. A group of physicians within our health-care practice who work with hospitals to improve clinical performance are evaluating some of the productivity and cost-reducing benefits of pharmaceutical products and addressing product alternatives to providers.

The HCFA Response

Mr. Burrill: Carolyne, from the perspective of your insights into HCFA, what are the forces that you see driving new drugs and medical technologies?

Dr. Davis: There's going to be less and less payoff for, say, the third me-too drug, or the fourth one. The question becomes, when do drug companies cease research of a drug that may have promise, if they know it's going to be out much later than numbers one and two?

Secondly, drug companies really have to look at how they position themselves to sell their products. A critical piece of that will be their cost-benefit analysis. A price may at first appear high, but if the product reduces patients' hospital stay or, better yet, prevents their having to go in to begin with, the payers will look again at that payback. The drug manufacturer may well get a bigger volume of sales if it can demonstrate that the product really produces better outcomes. It helps to have objective data developed by an independent source that has credibility in that type of analysis.

Another factor to consider in developing products is the effect on productivity. Any product that saves labor will look increasingly attractive. If it's a scanning technology that requires less allied health-care input, if it's an oral drug rather than an intravenous drug—these features result in productivity savings.

*Any product that saves labor
will look increasingly attractive*

Mr. Burrill: Down the road, as we start containing the costs and managing the cases better, will the payers actually be designating the preferred drugs? Because of the aging population, HCFA conceivably could end up with almost dictatorial power.

Dr. Davis: It is true that once something gets through HCFA and achieves pretty stable acceptance, the private sector frequently will piggyback and buy in. They find comfort in being behind the government shield. HCFA can set a trend.

I would not go so far as to say that HCFA calls all the shots. You still have your large multi-group organizations—the Fords, IBMs, and other large companies. As long as they are paying the bills for their employees, they're going to be pretty active in managing utilization.

Mr. Marrapese: Also, the unions are spending a lot of time lobbying for health benefits. It's a major issue because corporations, having taken a look at their rising costs, have tried to scale back benefits.

Dr. Davis: What Ford Motor Company can tell you about the provider community is awesome. In Michigan, a couple of years ago, they called together all the hospitals. They laid out which were the highest-cost hospitals for each type of case, and communicated, very nicely and quietly, that if those hospitals maintained those prices, they would not be on Ford's preferred list the next year.

Mr. Burrill: Historically, the large pharmaceutical companies had their enormous market franchises and economic resources working for them. Suddenly, it seems, a small company with a good cost-benefit story, can go to HCFA or the payer community and be heard. Have the probabilities or prerequisites for market success changed?

Dr. Davis: My reservation about that scenario is that it takes an enormous amount of money to bring a new drug to fruition. The ability of small companies to sustain themselves through that process is questionable.

What is more likely is that the big drug companies will continue to watch these new developments and, as they reach a certain point of promise, pitch an alliance, which the small companies will take up because they don't have the marketing and sales organizations. It's happening all over. Not only are the drug firms consolidating and merging, the number of alliances they're forming with each other, as well as smaller companies, is huge. On the development side, each is still targeting specific areas; but on the marketing side, they're all enlarging their spectrum through these relationships.

The FDA Bottleneck

Mr. Burrill: Biotech companies will tell you that it is taking longer today, in relative terms, and too long, in absolute terms, to get their products through the FDA. Is there a way to eliminate this obstacle that the industry believes government is placing in its path?

The FDA gets a schizophrenic message from Congress

Dr. Davis: You have to start with the premise that the FDA, like any other bureaucracy, serves its masters, which are Congress and the administration. Secondly, it serves the general public.

The message the FDA gets from Congress is schizophrenic. One week Congress wants the FDA to hurry up the process of review; the next week it's holding a hearing to determine how all this "junk" got through. And now we have a new GAO (Government Accounting Office) report on post-approval problems. Like true bureaucrats, the people in the FDA are going to protect themselves and slow the process even more.

Mr. Burrill: So the FDA doesn't know at its most fundamental level whether it's in the business of getting reasonably safe things onto the market, or keeping reasonably unsafe things off. Is that going to change?

Dr. Davis: There is an FDA advisory committee being formed that is supposed to look at how to change the FDA. Its report should come out in 1991. I would say there is at least a 60 percent chance that

the review may be able to initiate some significant changes in light of 1992 and the European economic harmonization. The European Community really has moved on the drug-approval process. To the degree that the EC's Committee for Proprietary Medicinal Products (CPMP) provides either a model or a threat, we will be taking notice. There is a chance, then, that those two forces together can mandate some change.

To the degree that the CPMP provides a model or a threat, we will be taking notice

Mr. Burrill: You're saying that if the Europeans succeed in getting their act together, we in the United States will be more concerned about getting our act together.

Dr. Davis: We will be concerned if they, or the Japanese, cut into our marketplace because they have succeeded in getting products out faster.

Dr. Nackel: There's a third force, besides the European Community and the review of the FDA, that may even be more important—the consumer in the United States. AIDS has galvanized that force and made a major issue of the FDA approval process. AIDS activists are saying they're willing to take their chances on anything that could halt the course of a fatal disease. The other force that might also have an impact is the American medical community. At some point the university-based research physicians will start pushing and say we've got to be competitive internationally or we will lose our edge in the world marketplace in medical treatment.

A Demographic Imperative

Dr. Davis: Earlier, we were referencing the fact that the population is aging. That fact is not being reflected enough in new product development in medical technology or pharmaceuticals. Everybody is looking for the wonder drug, the breakthrough. There's not nearly enough work on the chronic conditions.

I don't know of anybody, for example, who's working on problems of incontinence. If one-quarter of the research dollars being spent on heart valves were devoted to urinary sphincters, we could deinstitutionalize one-quarter of the patients sitting around in nursing homes.

At some point, we have to focus more on the problems of the elderly. People are still uncomfortable in this area. They don't find it a glamorous field. Curing cancer, AIDS, or heart disease is big stuff. But what about just making people feel better when they walk?

There's not nearly enough work on the chronic conditions

I think the breakthrough will come by the year 2000. Some bright people are going to finally figure out that this is an area where they should be dumping major, and I mean major, dollars. I'm not talking about token research.

Value and Economics

Mr. Burrill: Somehow the public and, perhaps, Congress have come to hold the perception that new products and technologies are a big cause of the explosion of health-care costs, and that drug companies, basically, are ripping-off the consumer. How can the industry bring about a greater aware-

ness that better technology and drugs are the solution to the problem, rather than its cause?

Dr. Davis: Part of it is the fault of the companies themselves. They have not positioned themselves to talk about the cost benefits and enhanced productivity. To change that, the companies are going to have to make a major investment in telling the story. I don't think the umbrella industry organizations are effective at telling it. I think it has to be the individual companies, as they get out a new product. It links back to what we said earlier about communicating the real benefits of their products to the payers in a different way than they did in the past.

Mr. Marrapese: It goes back to the true crisis underneath all the other crises—the increasing cost. Health care now consumes 11.4 percent of the GNP. In a few years, it's projected to take 15 percent. We're going to be spending \$1.5 trillion on health care in the year 2000. We cannot afford to spend that kind of money and not have demonstrably better outcomes.

The costs keep going up, while the outcomes are not really better

Dr. Davis: That's the key. If society would hold still for our spending 25 percent of the GNP, we could cure every disease we have and have marvelous access to health care. The problem is that the costs keep going up, while the outcomes are not really better.

I think over time we will be able to quantify quality-of-life and some of these other long-term values that are now so hard to define. Then as we pay the costs of health care, we'll be far better able to determine whether it is worth it.

Appendices

A. The Year's Financings (July '89-July '90)

(in millions of dollars)

Company	Date	Government Grants	Venture Capital	Private Equity	Public Offerings	Debt Financings	Creative Financings, (Units, Warrants, R&D Partner- ships, etc.)
Affymax, Inc.	Jan., '90			\$25			
Agouron Pharmaceuticals, Inc.	Aug., '89	\$1					
Agouron Pharmaceuticals, Inc.	Oct., '89				\$15		
Alcide Corp.	Oct., '89				4		
Allelix Biopharmaceuticals, Inc.	Feb., '90		\$10				
Alpha 1 Biomedicals, Inc.	Jan., '90			1			
American Bionetics, Inc.	Jul., '90			1			
Amylin Corp.	Nov., '89		10				
Bio-Technology General Corp.	Jul., '90			5			
Bio-Vascular, Inc.	Jan., '90			1			
Biogen, Inc.	Jul., '89				60		
Biomira, Inc.	Oct., '89			4			
Biopure Corp.	Apr., '90		17				
Biosys, Inc.	Oct., '89		7				
Biotech Research Labs, Inc.	Aug., '89	1					
Biotechnica International, Inc.	Jan., '90				23		
Calgene, Inc.	Jul., '89				25		
Calgene, Inc.	Jan., '90					\$10	
Cambridge Neuroscience Research, Inc.	Oct., '89	1					
Cambridge Neuroscience Research, Inc.	Apr., '90	1					
Centocor, Inc. (Tocor, Inc.)	Jul., '89						\$31
Centocor, Inc.	Dec., '89			11			
Centocor, Inc.	May, '90				47		
Cetus Corp.	Mar., '90				41		
Chemex Pharmaceuticals, Inc.	Sep., '89			2			
Chiron Corp.	Jun., '90					122	
Collaborative Research, Inc.	Apr., '90	2					
Columbia Labs, Inc.	Jul., '90		3				
Cortex Pharmaceuticals, Inc.	Jul., '90				7		
Corvita Corp.	May, '90			6			
Creative Biomolecules, Inc.	Aug., '89			8			
Crop Genetics International Corp.	Jun., '90				20		
Cytogen, Inc.	Dec., '89				14		
Cytogen, Inc.	Jan., '90			3			
Cytogen, Inc.	Jun., '90				25		
CytRx, Inc.	Jan., '90		1				
Embrex, Inc.	Oct., '89		5				
Enzon, Inc.	Mar., '90			26			

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.

Company	Date	Government Grants	Venture Capital	Private Equity	Public Offerings	Debt Financings	Creative Financings, (Units, Warrants, R&D Partner- ships, etc.)
Fountain Pharmaceuticals, Inc.	Mar., '90				\$4		
Genelabs, Inc.	Sep., '89			\$14			
Genentech, Inc.	Aug., '89						\$73
Genetics Institute, Inc.	Jul., '90				49		
Genpharm International, Inc.	Sep., '89		\$6				
Genpharm International, Inc.	Jul., '90		4				
Gensia Pharmaceuticals, Inc.	Sep., '89		11				
Gensia Pharmaceuticals, Inc.	Jun., '90				31		
Genta, Inc.	Oct., '89		7				
Genzyme Corp.	Nov., '89						37
Genzyme Corp.	Dec., '89				39		
Genzyme Corp (IG Labs)	May, '90				14		
Glycomed, Inc.	Apr., '90			16			
Hologic, Inc.	Mar., '90				15		
ICOS, Inc.	Jun., '90			33			
Imatron, Inc.	May, '90			2			
Immulogic Pharmaceutical	Oct., '89		28				
Immune Response Corp.	May, '90				15		
Immunex, Inc. (Receptech, Inc.)	Nov., '89						30
Immunogen, Inc.	Nov., '89				14		
Insite Vision, Inc.	Oct., '89			5			
Integrated Labs, Inc.	May, '90				14		
Interneuron Pharmaceuticals, Inc.	Sep., '89		2				
Interneuron Pharmaceuticals, Inc.	Mar., '90				9		
Jackson Laboratory	Nov., '89	\$25					
La Jolla Pharmaceutical Co.	Nov., '89			12			
Lidak, Inc.	Jan., '90				5		
Liposome Technology, Inc.	Mar., '90			3			
Marrow-Tech, Inc.	Dec., '89						11
Martek Corp.	May, '90		2				
Matritech, Inc.	May, '90		3				
Matrix, Inc.	Jun., '90		8				
Medicis Pharmaceutical, Inc.	Feb., '90				7		
Microprobe Corp.	Feb., '90		8				
Molecular Devices Corp.	Dec., '89		6				
Mycogen, Inc.	Apr., '90			6			
Mycogen, Inc.	Jun., '90				51		
Neurex Corp.	Nov., '89		11				
Neurogen, Inc.	Oct., '89				6		
Nova Pharmaceutical, Inc.	Oct., '89	2					
Oncor, Inc.	Jan., '90			2			
Organogenesis, Inc.	Feb., '90			5			
Perseptive Biosystems, Inc.	Dec., '89		3				
Personal Diagnostics, Inc.	Jan., '90				3		

<u>Company</u>	<u>Date</u>	<u>Government Grants</u>	<u>Venture Capital</u>	<u>Private Equity</u>	<u>Public Offerings</u>	<u>Debt Financings</u>	<u>Creative Financings, (Units, Warrants, R&D Partnerships, etc.)</u>
Pharmakinetics Labs, Inc.	Apr., '90			\$3			
Procyte, Inc.	Nov., '89				\$9		
Quadra Logic, Inc.	Dec., '89				23		
Repligen Corp.	Dec., '89			9			
Repligen Corp.	Jun., '90				30		
Response Technologies, Inc.	Jan., '90					\$3	
Roberts Pharmaceutical Corp.	Jan., '90				10		
Somatogen, Inc.	Mar., '90			16			
Synbiotics Corp.	Oct., '89			2			
Synergen, Inc.	Feb., '90				19		
T Cell Sciences Corp.	Feb., '90						\$3
Tanox Biosystems, Inc.	May, '90	\$1					
Teva Pharmaceuticals, Inc.	Jan., '90						21
TNI Pharmaceuticals, Inc.	Mar., '90			1			
Transgenic Sciences, Inc.	Jun., '90						4
Transgenic Sciences, Inc.	Jul., '90	1					
U.S. Bioscience	Aug., '89			15			
Vertex Pharmaceuticals, Inc.	Jul., '89		\$6				
Vestar, Inc.	Jun., '90			7			
Zynaxis Cell Sciences, Inc.	May, '90			7			
Totals		\$35	\$150	\$264	\$648	\$135	\$210

B. The Year's Alliances

Company	Company	Type of Alliance*	Date
Abbott Laboratories/ Chiron Corp.	Johnson & Johnson	R&D	Aug., '89
Advanced Magnetics, Inc.	Eiken Chemical Co.	Marketing/Distribution	Mar., '90
Advanced Polymer Systems, Inc.	Scott Paper Co.	Marketing/Distribution	Jan., '90
Advanced Polymer Systems, Inc.	Pfizer, Inc.	Marketing/Distribution	Apr., '90
Alcide Corp.	Ciba-Geigy AG	Marketing/Distribution	Jan., '90
Allelix Biopharmaceuticals, Inc.	Biotech Research Institute	R&D	Nov., '89
Allelix Biopharmaceuticals, Inc.	Eli Lilly and Company	R&D	Jun., '90
Allergan, Inc.	Chesapeake Biological Labs, Inc.	License	Apr., '90
ALZA Corp.	Procter & Gamble Co.	Marketing/Distribution	Feb., '90
American Bionetics, Inc.	AKZO	Marketing/Distribution	May, '90
American Cyanamid Co.	Praxis Biologics, Inc.	Marketing/Distribution	Aug., '89
American Cyanamid Co.	Quadra Logic Technologies, Inc.	R&D	Nov., '89
American Cyanamid Co.	Elan Corporation PLC	Marketing/Distribution	May, '90
Amgen, Inc.	Enzon, Inc.	R&D	Jan., '90
AMS Biotechnology Ltd.	Medicorp, Inc.	Marketing/Distribution	Nov., '89
Applied Biosystems, Inc.	Perkin-Elmer Corp.	License	Mar., '90
Bio-Response, Inc.	Baxter Healthcare Corp.	Equity	Jan., '90
Bio-Technology General, Inc.	Duphar, Inc.	License	Jul., '89
Bio-Technology General, Inc.	JCR Pharmaceuticals	R&D	Sep., '89
Biogen, Inc.	New York Life	Equity	Sep., '89
Biogen, Inc.	Abbott Laboratories	License	Apr., '90
Biogen, Inc.	Merck & Co., Inc.	License	Apr., '90
Biomara, Inc.	Ribi Immunochem Research, Inc.	R&D	May, '90
Bios, Inc.	Soviet Ministry of Health	R&D	Nov., '89
Biotech Research Labs, Inc.	Ortho Diagnostics Systems, Inc.	Marketing/Distribution	Jan., '90
Biotechnica International, Inc.	Abbott Laboratories	R&D	Sep., '89
Biotechnica International, Inc.	Wacker-Chemie GmbH	R&D	Apr., '90

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.

*As discussed in Chapter 3: Corporate Development Strategies, strategic alliances are usually formed for a number of broad reasons. The simple classifications here are provided to present the overall basis for relationships formed in the past year.

<u>Company</u>	<u>Company</u>	<u>Type of Alliance*</u>	<u>Date</u>
Calgene, Inc.	Gustafson	R&D	Oct., '89
Calgene, Inc.	Suntory	R&D	May, '90
Calgene, Inc.	Sakata Seed Corp.	R&D	Apr., '90
California Biotechnology, Inc.	Bayer AG	Marketing/Distribution	Dec., '89
California Biotechnology, Inc.	Merck & Co., Inc.	Marketing/Distribution	Jul., '89
Cambridge Bioscience, Inc.	Hauser Bioscience Research	Manufacturing	Aug., '89
Cambridge Bioscience, Inc.	Pasteur Diagnostics, Inc.	Cross-Licensing	Dec., '89
Cambridge Bioscience, Inc.	Hoechst AG & Pharmacia AB	License	Feb., '90
Cambridge Bioscience, Inc.	Noctech Ltd.	Equity	May, '90
Celgene Corp.	Schering-Plough Corp.	R&D	Dec., '89
Cephalon, Inc.	Boehringer Mannheim GmbH	R&D	Nov., '89
Cephalon, Inc.	Schering-Plough Corp.	R&D	Jun., '90
Cetus Corp.	Cytogen, Inc.	Marketing/Distribution	Oct., '89
Cetus Corp.	Quest Biotechnology Corp.	License	Sep., '89
Cetus Corp.	Hoffmann-La Roche, Inc.	Marketing/Distribution	Apr., '90
Cetus Corp.	Genetics Institute, Inc.	Cross-Licensing	May, '90
Cetus Corp.	Masonic Labs	R&D	May, '90
Chiron, Inc.	Ciba-Geigy, Inc.	R&D	Oct., '89
Chiron, Inc.	Daiichi Pure Chemicals, Inc.	Marketing/Distribution	Nov., '89
Clonetics Corp.	Charles River Labs	Marketing/Distribution	Nov., '89
Collagen, Inc.	CR Bard	Marketing/Distribution	Aug., '89
Cygnus Research Corp.	Nichiban Ltd.	Joint Venture	Jun., '90
Cytel, Inc.	Sandoz AG	R&D	Sep., '89
Cytogen, Inc.	Bracco Industria Chimica SpA	R&D	Oct., '89
Cytrx Corp.	Wellcome PLC	License	Apr., '90
DNA Plant Technology	DuPont & Co.	Marketing/Distribution	Jan., '90
DNX Corp.	Genezyme Corp	License	Feb., '90
Ecogen, Inc.	Gujarat State Fertilizers	R&D	Oct., '89
Endotronics, Inc.	Ventrex Labs, Inc.	Marketing/Distribution	Sep., '89
Enzo Biochem, Inc.	ESBE Laboratory Supplies	Marketing/Distribution	Jan., '90
Enzo Biochem, Inc.	Biolyn Corp.	Marketing/Distribution	Mar., '90
Enzon, Inc.	Schering-Plough Corp.	License	Apr., '90
Epitope, Inc.	SmithKline & French Labs	R&D	Dec., '89
Escalon Ophthalmics	The Liposome Company	License	Jul., '89
Escalon Ophthalmics	The Purdue Frederick Company	Marketing/Distribution	May, '90
Gene-Trak Systems, Inc.	Nissui Pharmaceuticals, Inc.	Marketing/Distribution	Nov., '89
Gene-Trak Systems, Inc.	Orion Biotechnology Corp.	License	Nov., '89
Genentech, Inc.	Behringwerke	Marketing/Distribution	Nov., '89
Genentech, Inc.	Biogen, Inc.	Cross-Licensing	Jan., '90
Genetics Institute, Inc.	Hoffmann-La Roche, Inc.	R&D	Mar., '90

<u>Company</u>	<u>Company</u>	<u>Type of Alliance*</u>	<u>Date</u>
Genetics Institute, Inc.	Yamanouchi Pharmaceuticals	Joint Venture	May, '90
Gensia Pharmaceutical, Inc.	Marion Merrell Dow, Inc.	R&D	Feb., '90
Immucor, Inc.	Diagnostic Transfusion, Inc.	Cross-Marketing	Oct., '89
Immulogic Pharmaceutical Corp.	Merck & Co., Inc.	R&D	Oct., '89
Immune Response Corp.	Rorer Group	Marketing/Distribution	Oct., '89
Immunex, Inc.	Syntex USA	License	Sep., '89
Immunex, Inc.	Hoechst AG	Marketing/Distribution	Dec., '89
Immunogen, Inc.	Takeda Chemical Industries Ltd.	R&D	May, '90
Immunomedics, Inc.	Merck & Co., Inc.	Regulatory	Feb., '90
Immunomedics, Inc.	Immunogen, Inc.	R&D	Jun., '90
The Inference Company	Pierce Chemical	Marketing/Distribution	Jul., '89
Insite Vision	Santen Pharmaceutical	Marketing/Distribution	Sep., '89
Interferon Sciences, Inc.	The Purdue Frederick Co.	Marketing/Distribution	Oct., '89
Interferon Sciences, Inc.	Amarillo Cell Culture, Inc.	License	Apr., '90
Ivax Corp.	Carter-Wallace, Inc.	Marketing/Distribution	Jan., '90
Life Technologies, Inc.	Genelex, Inc.	License	Dec., '89
Liposome Technology, Inc.	Erbamont, Inc.	R&D	Apr., '90
Marrow-Tech, Inc.	Bristol-Myers Squibb	R&D	Nov., '89
Microgenics Corp.	Boehringer Corp.	R&D	Nov., '89
Microgenics Corp.	Yamanouchi Pharmaceutical	Marketing/Distribution	Jan., '90
Molecular Devices Corp.	Abbott Laboratories	License	Feb., '90
Mycogen Corp.	S.C. Johnson & Son	R&D	May, '90
Mycogen Corp.	Monsanto Co.	R&D	Jun., '90
NeoRx, Inc.	Invitron, Inc.	License	Jul., '89
Nova Pharmaceutical Corp.	SmithKline Beecham PLC	Marketing/Distribution	Apr., '90
Oncogenetics, Inc.	Applied Biotechnology/ DuPont	Joint Venture	Jul., '89
Organogenesis, Inc.	Mary Kay Cosmetics	R&D	Jul., '89
Organogenesis, Inc.	Applied Biotechnology, Inc.	R&D	Oct., '89
Organogenesis, Inc.	Helene Curtis, Inc.	R&D	Dec., '89
Organogenesis, Inc.	Original Bradford Soap Works	R&D	Dec., '89
ProCyt Corp.	Ono Pharmaceutical Corp.	Equity	Apr., '90
Quadra Logic Technologies, Inc.	Baxter Healthcare Corp.	Manufacturing	Feb., '90
Quest Biotechnology Corp.	Hemosol, Inc.	License	Dec., '89
Quidel Corp.	Beckton Dickinson, Inc.	Marketing/Distribution	Jul., '89
Quidel Corp.	Takeda Chemical Industries	Marketing/Distribution	Jan., '90
Quidel Corp.	Altana AG	Marketing/Distribution	Feb., '90
Quidel Corp.	Photest Diagnostics, Inc.	Marketing/Distribution	May, '90
Repligen, Inc.	Merck & Co., Inc.	R&D	Sep., '89
Roberts Pharmaceutical Corp.	Sinclair Pharmaceuticals	Marketing/Distribution	Apr., '90
Synbiotics Corp.	Telios Pharmaceuticals, Inc.	Marketing/Distribution	Jan., '90
Syncor International Corp.	Squibb Diagnostics	Marketing/Distribution	Jun., '90

<u>Company</u>	<u>Company</u>	<u>Type of Alliance*</u>	<u>Date</u>
Synergen, Inc.	Syntex, Inc.	R&D	Feb., '90
Synergen, Inc.	Ciba-Geigy AG	License	Feb., '90
Syngene, Inc.	Life Technologies, Inc.	Marketing/Distribution	May, '90
T Cell Sciences, Inc.	SmithKline Beecham PLC	R&D	Nov., '89
T Cell Sciences, Inc.	Yamanouchi Pharmaceutical	Regulatory	Jan., '90
Tanox Biosystems, Inc.	Ciba-Geigy AG	R&D	May, '90
Telios Pharmaceuticals, Inc.	Ono Pharmaceutical Co.	Joint Venture	May, '90
Teva Pharmaceuticals Ltd.	Imre Corp.	Marketing/Distribution	Mar., '90
Teva Pharmaceuticals Ltd.	U.S. Bioscience	Marketing/Distribution	May, '90
Transgenic Sciences, Inc.	Boston Biomedica, Inc.	R&D	Mar., '90
Transgenic Sciences, Inc.	Toray Industries, Inc.	R&D	Apr., '90
Unigene Laboratories, Inc.	Schering AG	R&D	Dec., '89
Unimed, Inc.	Boehringer Ingelheim GmbH	R&D	Apr., '90
Ventrex Laboratories, Inc.	Biostar Medical Products, Inc.	R&D	Jan., '90
Verax, Inc.	Green Cross	License	Nov., '89
Wellcome PLC	Genetics Institute, Inc.	License	Jan., '90
Xenova, Inc.	Organon, Inc.	R&D	Jul., '89
Xenova, Inc.	FMC Corp.	R&D	Oct., '89
Xoma Corp.	Ortho Biotech (J & J)	Marketing/Distribution	Mar., '90

C. The Year's Consolidations

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-Haematol, Inc.	Acquisition	Mar., '90
Cambridge Bioscience Corp.	Angenics, Inc.	Acquisition	Aug., '89
Cambridge Bioscience Corp.	Biotech Research Labs, Inc.	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.	Genencor, Inc.	Acquisition	Jan., '90
Eli Lilly and Company	Pacific Biotech, Inc.	Acquisition	Apr., '90
Hoffmann-La Roche, Inc.	Genentech, 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, Inc.	Acquisition	Dec., '89
Life Sciences International, Inc.	International Equipment Company	Acquisition	Apr., '90
Life Technologies, Inc.	Waitaki International Ltd.	Acquisition	Jul., '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 Biologicals Ltd.	Acquisition	Jan., '90
Orion Pharmaceutical, Inc.	KSV Lipids	Acquisition	Aug., '89
Porton International, Inc.	Hazelton Biologicals, Inc.	Acquisition	Dec., '89
Porton International, Inc.	Sera-Lab, Ltd.	Acquisition	Dec., '89
Quidel Corp.	Monoclonal Antibodies, Inc.	Merger	Jul., '90
Sanofi Pharma SA	Genetic Systems, Inc.	Acquisition	Apr., '90
Schering AG	Codon Corp.	Acquisition	May, '90
Synbiotics Corp.	Cryschem, Inc.	Acquisition	Feb., '90
Transgenic Science, Inc.	Mason Research Institute	Acquisition	Dec., '89
Union Carbide Corp.	Vitaphore Corp.	Acquisition	May, '90
Ventrex Labs, Inc.	Cambridge Medical Technology	Acquisition	Aug., '89
Xoma Corp.	Ingene Corp.	Merger	Nov., '89

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Based upon a philosophy of integrated service—wherein the needs and requirements of each client are met with a combination of skills and capabilities customized to the client's unique business issue and environment—Ernst & Young has long been the recognized leader in serving high technology industries. Ernst & Young led the way with biotech pioneers such as ALZA, Cetus, Genentech, Amgen, Chiron, and Immunex—and today we work with many large, established life sciences/health-care industry leaders, including Eli Lilly, Becton Dickinson, Glaxo, Marion Merrell Dow, and Hoffmann-La Roche. We also work with high tech leaders in semiconductors, telecommunications, software, computers and peripherals, and aerospace and defense.

The Life Sciences Industry: A Strength of Ernst & Young

The Leader Serving the Biotechnology and Health-Care Industries

Since the industry's inception, Ernst & Young has consistently met the changing business needs of biotechnology companies, helping them face the classic challenges of financing, managing, commercialization, globalization, and rapid technological innovation. Our biotech teams include professionals with extensive industry-specific backgrounds in finance, tax, accounting, manufacturing, management, and systems. We provide knowledgeable support in regulatory matters relating to the FDA, USDA, EPA, and other government agencies.

In addition to being a leader serving life-sciences companies, Ernst & Young provides services to more health-care clients than any other accounting or consulting firm. Working with medical products companies, our professionals have assisted in strategy development, product quality-of-life and cost-effectiveness, market positioning, and organization of clinical trials. Our work with health-care delivery networks positions us well for conducting product demand analysis and assessment of alternative distribution networks to the market. With physician groups, we have helped resolve issues surrounding cash flow, malpractice insurance costs, reimbursement, and clinical practice patterns. We also work with more than one-third of the hospitals in the United States and over 150 managed-care organizations.

Serving Clients: Industry-Focused Capabilities

At Ernst & Young, we take a solution-oriented approach, focusing on problems that are strategically important to our clients. Our assistance frequently cuts across both functional and management lines in the following areas:

Financing and Strategic Business Combinations

Whether you're looking for venture capital, public or private equity, debt capital, or strategic alliances, the professionals at Ernst & Young have years of experience helping high tech companies determine their best financing alternatives and assisting in their effective implementation. We help large and small life sciences companies achieve their goals through strategic partnering, and we can also help with mergers and acquisitions, corporate alliances, joint ventures and other types of business combinations.

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Our clients benefit from the capabilities of our worldwide network of professionals serving high tech and other manufacturing businesses in Eastern and Western Europe, the Soviet Union, the Pacific Rim, and throughout the world. Ernst & Young can help with decisions about the forms of organizations most advantageous for companies with international operations, and our consultants can assist in planning international tax strategies, currency and reporting, custom and duties, market entry options and transfer pricing.

World-Class Manufacturing

Ernst & Young has a premier consulting capability to help high tech companies become world-class manufacturers. Design for Manufacturing, Total Quality Management and Just-in-Time address key areas of manufacturing where our know-how can help you achieve lower cost while maintaining quality. Our Good Manufacturing Practices (GMP) and our Good Laboratory Practices (GLP) services can help your organization meet the requirements of the FDA—and facilitate more rapid introduction of products into the market. And through our international practice, we can help you understand the complexities of offshore manufacturing and how to appropriately set up and manage operations in foreign countries.

Actuarial, Benefits, and Compensation

The Ernst & Young Actuarial, Benefits and Compensation Groups consists of professionals in all aspects of actuarial analysis, benefits, and compensation. Our executive compensation consultants review and advise on all aspects of compensation packages for executives and directors including base salary, annual and long-term equity-based incentives and comprehensive employment agreements. Our services cover all stages of a project, from design through administration. These services help develop a comprehensive and efficient benefits and compensation program that supports a company's business objectives.

Integrating Information Systems

Information is useless unless it is processed to yield business solutions or competitive intelligence. Ernst & Young information systems specialists work with major companies in every high technology segment, creating targeted information strategies from clinical trials management and analytical data management to distribution and after-sale service. Our professionals have also consulted on networks and communications, technical systems and database software.

Management Systems and Skills

As life sciences companies grow, Ernst & Young can help management address increasingly complex issues and new challenges by providing consulting support in areas such as strategic business planning and management systems development and implementation. We also help companies establish performance measures and provide systems to track results.

Accounting, Audit, and Tax Services

Ernst & Young advises biotech companies in accounting and tax practices, planning, and regulatory compliance. Our industry professionals are up-to-date and knowledgeable about the accounting and financial reporting techniques and requirements unique to life sciences companies. Ernst & Young professionals also conduct efficient, quality audits and provide guidance for tax compliance and planning.

Office Listing

Akron, Ohio	(216) 253-9150	Dayton, Ohio	(513) 223-2000
Albany, New York	(518) 434-4600	Daytona Beach, Florida	(904) 255-1981
Albuquerque, New Mexico	(505) 884-3700	Denver, Colorado	(303) 297-9500
Anchorage, Alaska	(907) 279-1411		(303) 534-4300
Atlanta, Georgia	(404) 658-9400	Des Moines, Iowa	(515) 243-2727
Atlanta (Overlook)	(404) 431-3300	Detroit, Michigan	(313) 259-4200
Atlanta (Perimeter)	(404) 395-2700		(313) 259-9600
Austin, Texas	(512) 478-9881		(313) 355-3690
Bakersfield, California	(805) 328-1221	Erie, Pennsylvania	(814) 454-2423
Baltimore, Maryland	(301) 539-7940	Fairfax, Virginia	(703) 352-9700
Baton Rouge, Louisiana	(504) 383-0166	Fort Lauderdale, Florida	(305) 763-7500
Berwyn, Pennsylvania	(215) 640-1700	Fort Wayne, Indiana	(219) 424-2233
Birmingham, Alabama	(205) 251-2000	Fort Worth, Texas	(817) 335-1900
Boston, Massachusetts	(617) 725-1100		(817) 335-2700
	(617) 266-2000	Fresno, California	(209) 431-1315
Buffalo, New York	(716) 854-5897	Grand Rapids, Michigan	(616) 774-0710
Burlington, Vermont	(802) 865-1110	Greensboro, North Carolina	(919) 665-3200
Canton, Ohio	(216) 455-5555	Greenville, South Carolina	(803) 242-5740
Cedar Rapids, Iowa	(319) 363-1090	Hackensack, New Jersey	(201) 343-4095
Century City, California	(213) 551-5500	Harrisburg, Pennsylvania	(717) 232-7575
	(213) 553-2800	Hartford, Connecticut	(203) 247-3100
Charleston, South Carolina	(803) 577-0414	Honolulu, Hawaii	(808) 521-4545
Charleston, West Virginia	(304) 343-8971		(808) 531-2037
Charlotte, North Carolina	(704) 372-6300	Houston, Texas	(713) 751-1200
Chattanooga, Tennessee	(615) 756-2461		(713) 653-6000
Chicago, Illinois	(312) 368-1800	Houston (Galleria)	(713) 871-2200
Naperville	(708) 505-8600	Huntsville, Alabama	(205) 551-2000
Schaumburg	(708) 240-5560	Indianapolis, Indiana	(317) 634-9700
Wabash	(312) 645-3500		(317) 236-1100
Cincinnati, Ohio	(513) 381-3995	Inland Empire East	
	(513) 621-6454	Riverside , California	(714) 682-5500
Ft. Mitchell, Kentucky	(606) 331-9004	Inland Empire West	
Cleveland, Ohio	(216) 861-5000	Rancho Cucamonga , California	(714) 944-2000
Cleveland Lander Circle	(216) 861-5000	Jackson, Mississippi	(601) 948-6600
Columbia, South Carolina	(803) 254-4700	Jacksonville, Florida	(904) 358-2000
Columbus, Georgia	(404) 327-2311	Kalamazoo, Michigan	(616) 349-6671
Columbus, Ohio	(614) 222-3900	Kansas City, Missouri	(816) 474-5200
	(614) 224-5678	Knoxville, Tennessee	(615) 637-4161
Corpus Christi, Texas	(512) 883-1871	Lansing, Michigan	(517) 487-5000
Dallas, Texas	(214) 969-8000	Lexington, Kentucky	(606) 253-3200
	(214) 979-1700	Little Rock, Arkansas	(501) 370-3000
		Long Beach, California	(213) 590-8011

Long Island, New York	(516) 752-6100	Reston, Virginia	(703) 648-2360
Los Angeles, California	(213) 977-3200	Richmond, Virginia	(804) 775-4400
	(213) 621-1666	Roswell, New Mexico	(505) 622-8500
Louisville, Kentucky	(502) 585-1400	Sacramento, California	(916) 443-6756
	(502) 583-0251	Saddle Brook,	
Madison, Wisconsin	(608) 257-0030	New Jersey	(201) 843-7200
Manchester,		Saginaw, Michigan	(517) 754-8471
New Hampshire	(603) 625-9601	St. Louis, Missouri	(314) 259-1000
Memphis, Tennessee	(901) 526-1000	St. Paul, Minnesota	(612) 291-1822
MetroPark, New Jersey	(201) 906-3200	St. Petersburg, Florida	(813) 822-4021
Miami, Florida	(305) 358-4111	St. Thomas, U.S.	
Milwaukee, Wisconsin	(414) 273-5900	Virgin Islands	(809) 776-1350
Minneapolis, Minnesota	(612) 343-1000	Salt Lake City, Utah	(801) 350-3300
Mobile, Alabama	(205) 438-6158		(801) 363-3995
Nashville, Tennessee	(615) 252-2000	San Antonio, Texas	(512) 228-9696
	(615) 255-5800	San Diego, California	(619) 236-1100
New Orleans, Louisiana	(504) 581-4200	San Francisco,	(415) 951-3000
New York, New York	(212) 773-3000	California	(415) 981-8890
Metropolitan New York	(212) 773-3000	San Jose, California	(408) 947-5500
New York Financial		San Juan, Puerto Rico	(809) 759-8212
Services	(212) 773-3000	Seattle, Washington	(206) 623-9000
Newark, New Jersey	(201) 624-3737		(206) 621-1800
Norfolk, Virginia	(804) 622-0422	Spartanburg,	
Oklahoma City,		South Carolina	(803) 573-7801
Oklahoma	(405) 278-6800	Stamford, Connecticut	(203) 326-8200
Orange County,	(714) 863-3010		(203) 348-3700
California	(714) 850-9500	Syracuse, New York	(315) 425-8011
Orlando, Florida	(407) 872-6600	Tacoma, Washington	(206) 597-7550
Palo Alto, California	(415) 496-1600	Tallahassee, Florida	(904) 224-7194
Philadelphia,	(215) 864-3300	Tampa, Florida	(813) 225-4800
Pennsylvania	(215) 561-4800	Toledo, Ohio	(419) 244-8000
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Actuarial Services	(215) 246-2780	Tulsa, Oklahoma	(918) 560-3600
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Pittsburgh, Pennsylvania	(412) 644-0600	California	(415) 977-2900
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Portland, Oregon	(503) 225-1700	West Palm Beach,	
	(503) 221-1450	Florida	(407) 655-8500
Princeton, New Jersey	(609) 243-0303	White Plains, New York	(914) 761-7888
Providence,	(401) 457-3700	Wichita, Kansas	(316) 265-9537
Rhode Island	(401) 331-7000	Winston-Salem,	
Raleigh, North Carolina	(919) 787-3110	North Carolina	(919) 725-0611
	(919) 833-7301	Woodland Hills,	
Durham,		California	(818) 703-4700
North Carolina	(919) 493-8416	Worcester,	
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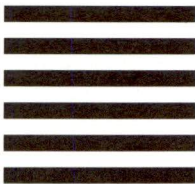
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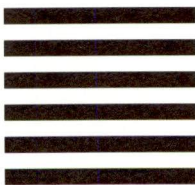
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Licensing and Corporate Development
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Gaining Ground: Comparison of US & Japanese Technology

George Gamota

MITRE CORP CHIEF SCIENTIST

17 January 1991

MITRE

The Final Frontier

- In the Beginning the Japanese made things cheaper, but we derided the stuff as junk
- Later, in the 60's and 70's, they started to make things cheaper and better and we began to worry - with good reason: cameras, calculators and cars weren't junk
- All the while, we had one consolation - the Japanese were essentially copycats - we had our new ideas, our Nobel Prizes, and we could always stay ahead by climbing to a higher technology
- ALAS - Japan is challenging us even here, they caught up to us in older technologies and want to pass us in new ones!

The Final Frontier (concluded)

- In this new phase
 - Japan will still depend on the US and Europe, but its technological borrowing will be mostly at the pre-commercial stage
 - Japanese visitors don't come to the US to photograph American factories anymore
 - They come to visit American professors
 - They invite our brightest students to do their research in Japan and hire our best people to work in Japanese research facilities in the US
 - They come to make deals with national laboratories
 - They bankroll Silicon Valley start-ups

Outline of My Talk

- Credits
- Introduction to Japan
- Japan's science and technology infrastructure
- Examples:
 - HDTV
 - Superconductivity
 - Space technology

Credits

- Beginnings of JTEC
- Current Program & NSF Pivotal Role
- Approach

Beginnings of JTEC

- Started by DOC & Interagency Group in 1983
- Purpose:
 - Assess Japanese Technology using best US minds
 - Contribute to a more balanced Tech Transfer
 - Help disseminate information

Current Program & NSF Pivotal Role

- NSF funded since 1985, with DARPA, NASA, DOE, DOC and ONR
- A total of 23 panels completed or started

Approach

- Assessments done by US experts
- Based on literature, lab visits and personal interactions
- Reports are widely disseminated through NTIS
 - Presentations made at workshop and technical conferences
 - Articles in Technical and Popular Journals, and the Press

US vs. Japan at a Glance

- United States

- Population ('88) 246M
- Land area 9.4M square kilometers
- GNP per capita ('87) \$18.6K, growing at 4.2% per year
- R&D expenditures \$482 per capita, 48.2% publicly financed

- Japan

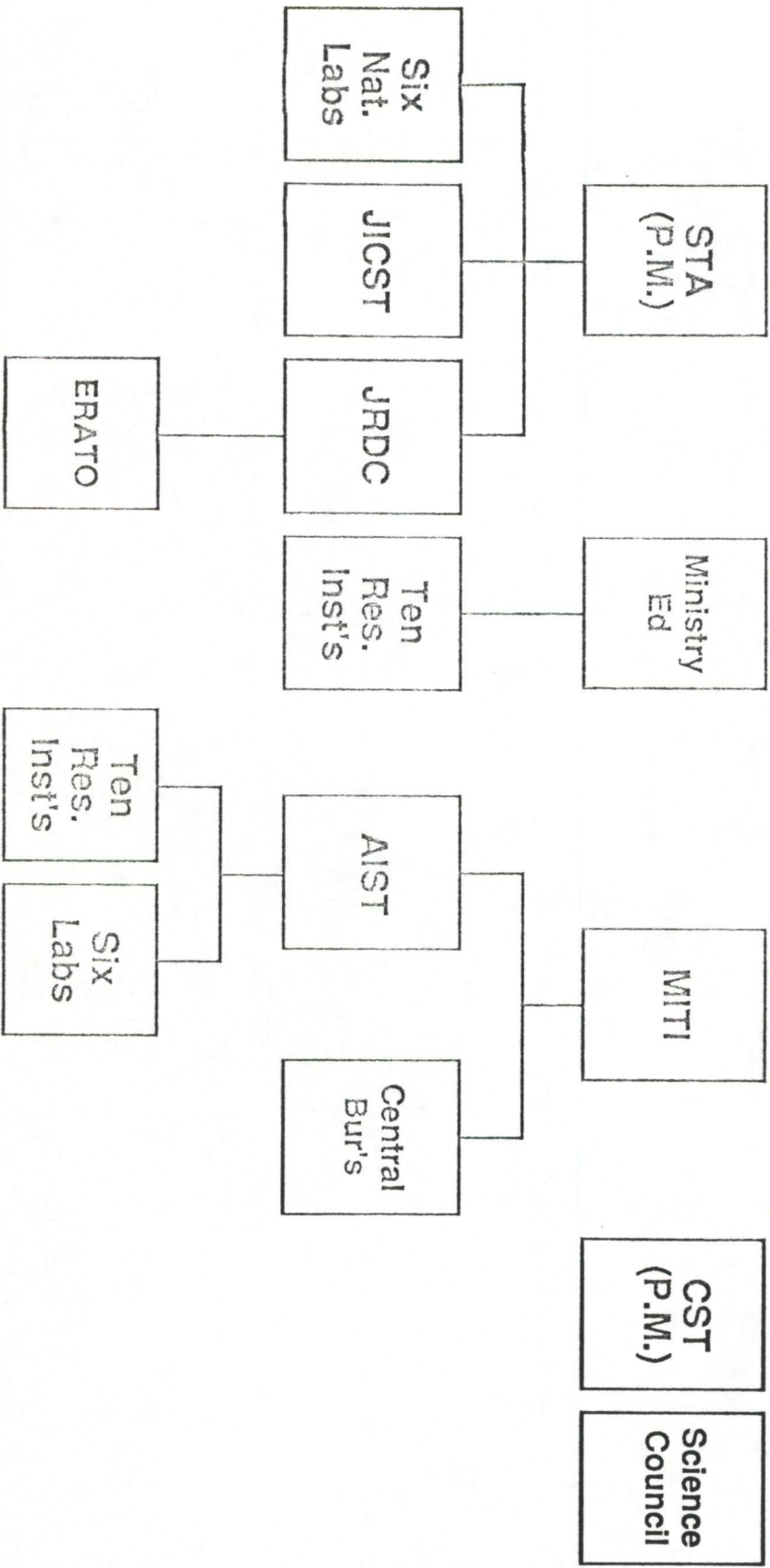
- Population ('88) 123M
- Land area 0.38M square kilometers, about size of California
- GNP per capita ('87) \$19.6K, growing at 4.5% per year
- R&D expenditures \$506 per capita, 19.9% publicly financed

Key Japanese Science & Technology (S&T) Organizations

- Japanese Government
- Japanese Corporations

Japanese Government

Selected Ministerial Offices Involved With Science & Technology



FY89 S&T Appropriations in Japan (Gov't)

AGENCY/MINISTRY	GENERAL ACCOUNTS	SPECIAL ACCOUNTS	TOTAL	% INCREASE From FY88
Ministry of Education	197	658	855	5.1
Science & Technology Agency	355	111	466	6
Ministry of International Trade & Industry	69	164	233	5.6
Defense Agency	93		93	12.5
Ministry of Agriculture, Forestry, & Fishery	64	3	67	1.6
Ministry of Health & Welfare	38	11	49	9.8
Ministry of Posts & Telecommunications	4	26	30	0.5
Ministry of Transport	15	1	16	11.4
Environmental Agency	8		8	1.7
Ministry of Foreign Affairs	6		6	0.1
Others	11	5	16	8
TOTAL	¥ 860 B	¥ 979 B	¥ 1,839 B	5.8

MITRE

The Science & Technology Agency (STA)

- Charged to promote S&T that contributes to the national economy
- Spends roughly one-fourth of the National Science budget
- Coordinates research activities of the industrial ministries, and funds projects too large or risky for industry to do alone
- Thrust areas include:
 - Nuclear power
 - Ocean exploration
 - Space technology
- Operates six national laboratories
- Administers two public agencies: JICST and JRDC

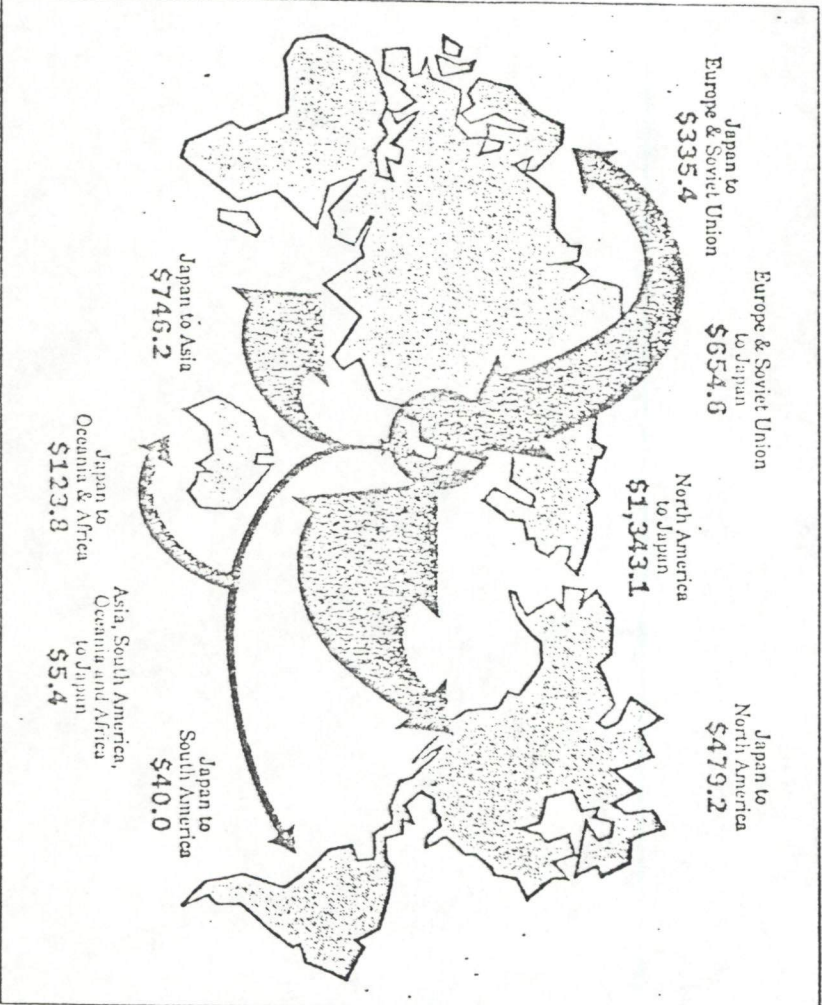
Science & Technology Agency (continued)

- Japan Information Center of Science & Technology (JICST)
 - Maintains a large database of Japanese and foreign S&T literature
 - Available to Japanese researchers
 - Available to US researchers through the US National Technical Information Service (NTIS)

Information Exchange Imbalance

Trade in Technology

Japan's purchase of technological information from North America totaled more than \$1 billion in the year ended March 31, 1987. North America purchased less than half that amount from Japan.
(In millions of U.S. dollars; ¥130=\$1.00)



Source: Central Asian Agency of Japan

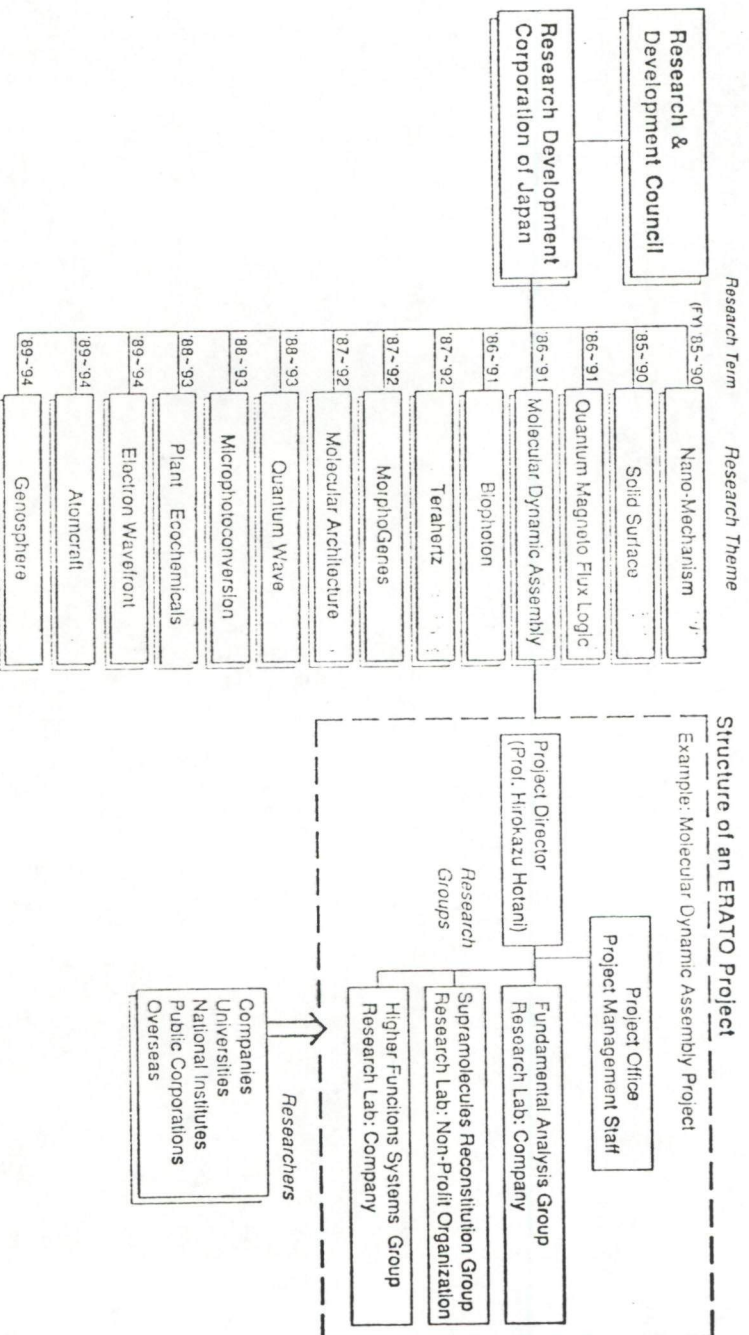
John P. Smith

MITRE

Science & Technology Agency (Concluded)

- Japan Research & Development Corporation (JRDC)
 - JRDC's objective is to commercialize government-sponsored basic research
 - Companies compete for funding (loans)
 - The loans must be repaid if a firm benefits commercially from the project
 - Companies retain exclusive rights to products and processes developed with JRDC money for 2-3 years
- Administers Exploratory Research in Advanced Technology Office (ERATO)

Organization of ERATO Projects



Currently 21 projects are funded at approximately \$10M for a five-year project lifetime

The Ministry of Education, Science, & Culture (Monbusho)

- Monbusho accounts for roughly half of the national spending on S&T
 - Two-thirds is allocated for science and education at 21 universities
 - Funds for primary, secondary, and university education
 - Formulate policies to meet manpower requirements for Japan
 - Japan's major corporations recruit mainly from the University of Tokyo and a few other prestigious universities
 - 80% of the government professionals come from the University of Tokyo
 - Japan awards about the same number of BS degrees in engineering as the US

The Ministry of Education...(Continued)

- Funds basic and applied research at universities
- Three funding channels
 - General-purpose research funds to chairman or division of a university department
 - Allocates special research funds for construction of new plants and purchase of new equipment
 - Administers a grant-in-aid program for researchers - approved by the Monbusho Science Council
- Administers 10 research institutes
 - Run by a board
 - Created for a wider user base
 - Hybrid between university centers and government research institutes

The Ministry of Education...(Concluded)

- Interested in fostering cooperative research BUT many disincentives exist
 - If a chairman accepts industrial funds, Monbusho subtracts equal amount
 - Professors can accept equipment BUT not consulting fees (illegal)
- Compared to the US, little cooperative work is seen between universities and industry BUT situation is being addressed

Example: Monbusho Special Project on Research on High- T_c Oxide SC

• Similar to the NSF S&T Centers (includes many institutions)

Table 1.2: Members of the Ministry of Education (Monbusho) Special Project on Research on High Temperature Oxide Superconductors (1987).

Member	Institution
Sadao Nakajima [†]	<i>Department of Physics, Tokai University</i>
Shoji Tanaka	<i>Department of Applied Physics, University of Tokyo</i>
Kazuo Fueki	<i>Department of Industrial Chemistry, University of Tokyo</i>
Hiroo Inokuchi	<i>Institute for Molecular Science</i>
Yasuo Endoh	<i>Department of Physics, Tohoku University</i>
Hidetoshi Fukuyama	<i>Institute for Solid State Physics, University of Tokyo</i>
Yoshio Muto [†]	<i>Institute for Materials Research, Tohoku University</i>
Koichi Kitazawa	<i>Department of Industrial Chemistry, University of Tokyo</i>
Humihiko Takei	<i>Institute for Solid State Physics, University of Tokyo</i>
Masayasu Ishikawa	<i>Institute for Solid State Physics, University of Tokyo</i>
Seichi Kagoshima	<i>Department of Pure and Applied Sciences, University of Tokyo</i>
Shinobu Hikami	<i>Department of Pure and Applied Sciences, University of Tokyo</i>
Kunisuke Asayama	<i>Faculty of Engineering Science, Osaka University</i>
Toshizo Fujita	<i>Department of Physics, Hiroshima University</i>
Masatoshi Sato	<i>Institute for Molecular Science</i>

[†] Chairman (1987)

[‡] Present Chairman

The Ministry of International Trade & Industry (MITI)

- Spends about one-eighth of the national S&T budget
- Sets the course for industrial research in Japan
 - Initially set up to identify, acquire, and disseminate foreign technology
 - Current focus is on:
 - Coordinating work of other ministries
 - Promoting and facilitating industrial research
- Operates national laboratories

The Ministry...(MITI) (Concluded)

- Uses a variety of mechanisms to promote industrial research
 - National research projects
 - e.g., Engineering Research Association (has special tax privileges) - the VLSI program
 - e.g., public corporations - Institute for Fifth Generation Computing (ICOT)
 - Funding comes in grants or loans to be repaid if project is successful
- Japanese corporations often assign their best people to work on MITI-sponsored work
- MITI bureaucrats are mostly lawyers or economists
 - Decisions are built by consensus through the Industrial Structure Council
- Example of MITI's role in superconducting generators

MIT's Agency of Industrial Science and Technology (AIST)

- Executes most of the R&D programs for MITI
- Provides technical advice
- Responsible for large-scale projects

MITI's New Energy & Industrial Technology Development Organization (NEDO)

● Large-Scale Projects

—	MANGANESE NODULE MINING SYSTEM → TECHNOLOGY RESEARCH ASSOCIATION OF MANGANESE NODULE MINING SYSTEM (TRAM)
—	HIGH-SPEED COMPUTING SYSTEM FOR SCIENTIFIC AND TECHNOLOGICAL APPLICATIONS → SCIENTIFIC COMPUTER RESEARCH ASSOCIATION (SCRA)
—	ADVANCED ROBOT TECHNOLOGY → ADVANCED ROBOT TECHNOLOGY RESEARCH ASSOCIATION (ARTRA)
—	NEW WATER TREATMENT SYSTEM → AQUA RENAISSANCE RESEARCH ASSOCIATION (ARRA)
—	INTEROPERABLE DATABASE SYSTEM → INTEROPERABILITY TECHNOLOGY ASSOCIATION FOR INFORMATION PROCESSING JAPAN (INTAP)
—	ADVANCED MATERIAL PROCESSING MACHINING SYSTEM → ADVANCED MATERIAL PROCESSING AND MACHINING TECHNOLOGY RESEARCH ASSOCIATION (AMMTRA)
—	FINE CHEMICALS FROM MARINE ORGANISMS → MARINE BIOTECHNOLOGY INSTITUTE CO., LTD (M3)
—	SUPER/HYPER-SONIC TRANSPORT PROPULSION SYSTEM → (NOW BEING PLANNED)
—	UNDERGROUND SPACE DEVELOPMENT TECHNOLOGY → (NOW BEING PLANNED)

The Council for Science & Technology (CST)

- Supraministerial organization - arm of the Prime Minister (he chairs it)
- Five appointed members, plus several ex officio members
- Formulates broad policy framework for S&T
- Defines long-range goals for scientific research

The Science Council of Japan

- Independent body of Japanese scientists who advise the Prime Minister
- Elected by the S&T community for three-year terms
- Prime Minister must review and accept proposals BUT can postpone indefinitely any action
- Influence has declined in favor of Monbusho Science Council - not to be confused with Prime Minister's Council for Science and Technology
- Typically is considerably to the left of the government - e.g., its antinuclear power stance

Japanese Corporations

- Critical to the national S&T because:
 - Corporate spending accounts for three-fourths of the total S&T budget, as compared to 50% in the US
 - Through MITI councils, corporations make critical investment decisions
 - Provide extensive training
- Scientists often work on projects from basic research to commercialization
 - Central research laboratory (generic work)
 - Divisional laboratory (product development and manufacturing)
 - Marketing or sales
- Transfers are a source of prestige and carry financial remuneration

Sample Technologies

- Source: NSF's JTEC reports
 - High Definition Systems ('89)
 - Superconductivity ('89)
 - Space technology
 - Propulsion ('90)
 - Space Robotics ('91)
- Advanced Complex Materials ('91)

JTEC High Definition Systems

- Trip to Japan: June 1989
 - Panel: Richard Elkus, Chair, Prometrix Inc.
 - Dr. Robert Cohen, Economic Advisor to NY State
 - Birney Dayton, NVISION
 - Prof. David Messerschmitt, UC Berkeley
 - Prof. William Schreiber, MIT
 - Lawrence Tannas, Tannas Electronics

HDTV or HIGH ANXIETY!

- Home TV IS NOT the reason behind the race for HDTV
- It IS the associated technology that will impact:
 - computers
 - instrumentation
 - defense industry
 - broadcasting
 - movie industry
 - computer chips

HDTV is Available in Japan Now

Sony to sell HDTVs for home use

Sony Corp. will market next month a wide-aspect 36-inch high-definition television receiver for home use in preparation for the start of HDTV broadcasts next fall.

The first consumer-use HDTV receiver will go on sale Dec. 1 for ¥2.3 million.

Sony first announced developing an HDTV for industrial use in 1981.

Company officials said the home-use HDTV lacks a decoder and will have to be fitted with one if it is to receive HDTV broadcasts.

They said the decoders will be produced to order, beginning in December for ¥1.8 million each. A decoder converts encoded data back into its original form.

The HDTV without the decoder is capable of receiving common and satellite TV broadcasts, as well as reproducing videodiscs, the offi-

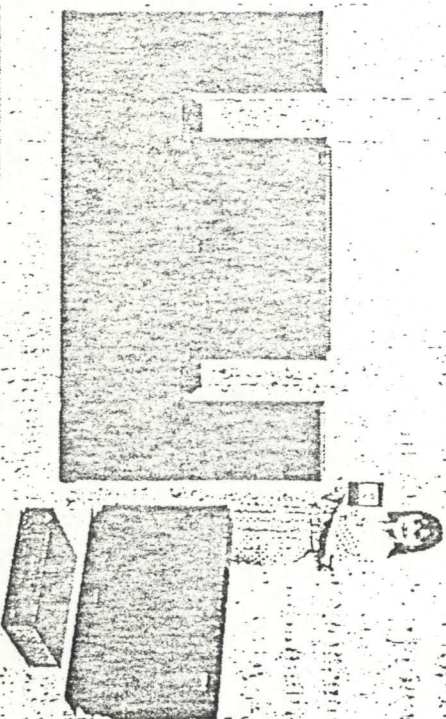
cials said.

A wide-aspect 16:9 ratio cathode-ray tube, compared with the conventional 4:3 ratio type, is a main feature of the new Sony product, they said.

NHK plans to start full-scale HDTV broadcasting in

autumn 1991.

Other consumer electronics giants, such as Matsushita Electric Industrial Co., Toshiba Corp., and NEC Corp., which have test-manufactured home-use HDTV receivers, are also preparing to enter the market soon.



A 36-INCH high-definition television produced by Sony Corp. will be the first home-use HDTV receiver to go on the market.

COMSAT Ready to Provide HDTV Service

- COMSAT says it is ready to provide commercial high-definition television transmission service over the 119 member-nation INTELSAT global satellite network

Historical Perspectives of Japanese R&D HDTV Activities

- NHK (Japanese public broadcasting organization) began work on HDTV in 1964 and spent \$133M for R&D from 1964 to 1989
- Japanese industry spent \$600M during those same years
- Key government ministries include: MITI and the Ministry of Posts and Telecommunications (MPT). MITI and MPT are setting up competitive efforts
- NHK continues to play a critical key role in technology development
- Today HDTV is market and politically driven, and not technology driven
- Between 1985 and 1995, Japan plans to spend \$1.6B on programs directly related to HDTV

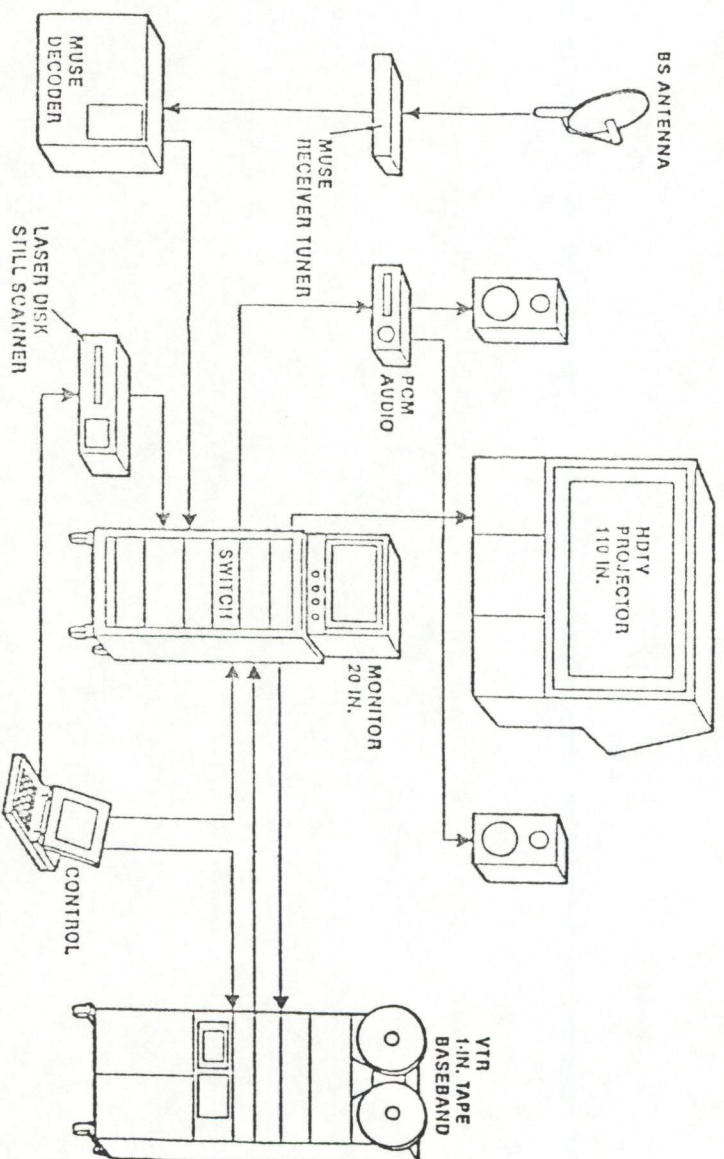
Regular TV to HDTV Progression

- NTSC is the regular television broadcast and reception used in North America and Japan
- IDTV (improved definition television) requires no changes to the transmitted signal, but improved signal processing in the receiver
- EDTV (enhanced definition television) requires changes to both the transmitter modulation and the receiver, but changes to the transmitter are constrained to enable NTSC and IDTV receivers to receive signals

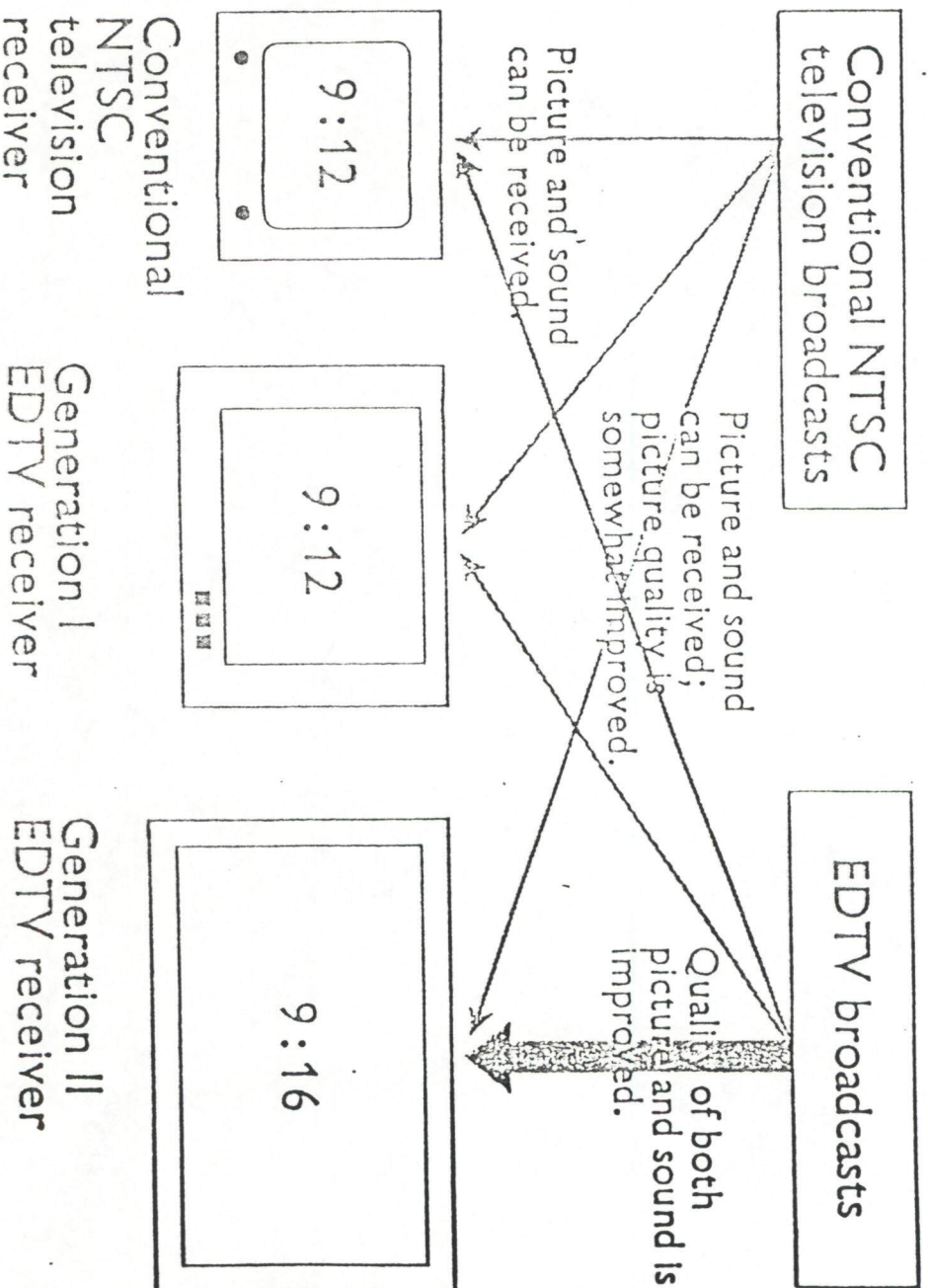
Regular TV to HDTV Progression (Concluded)

- HDTV (high definition television) provides dramatically improved quality, but the system is not compatible with the previous systems. It needs more bandwidth than is available for terrestrial broadcasting - a key sticking point with the US broadcasting companies
- MUSE (multiple sub-Nyquist sampling encoding) is a Japanese (NHK) proposed standard to transmit HDTV within a 27 MHz bandwidth satellite channel

Toshiba HDTV System (Studio Version)

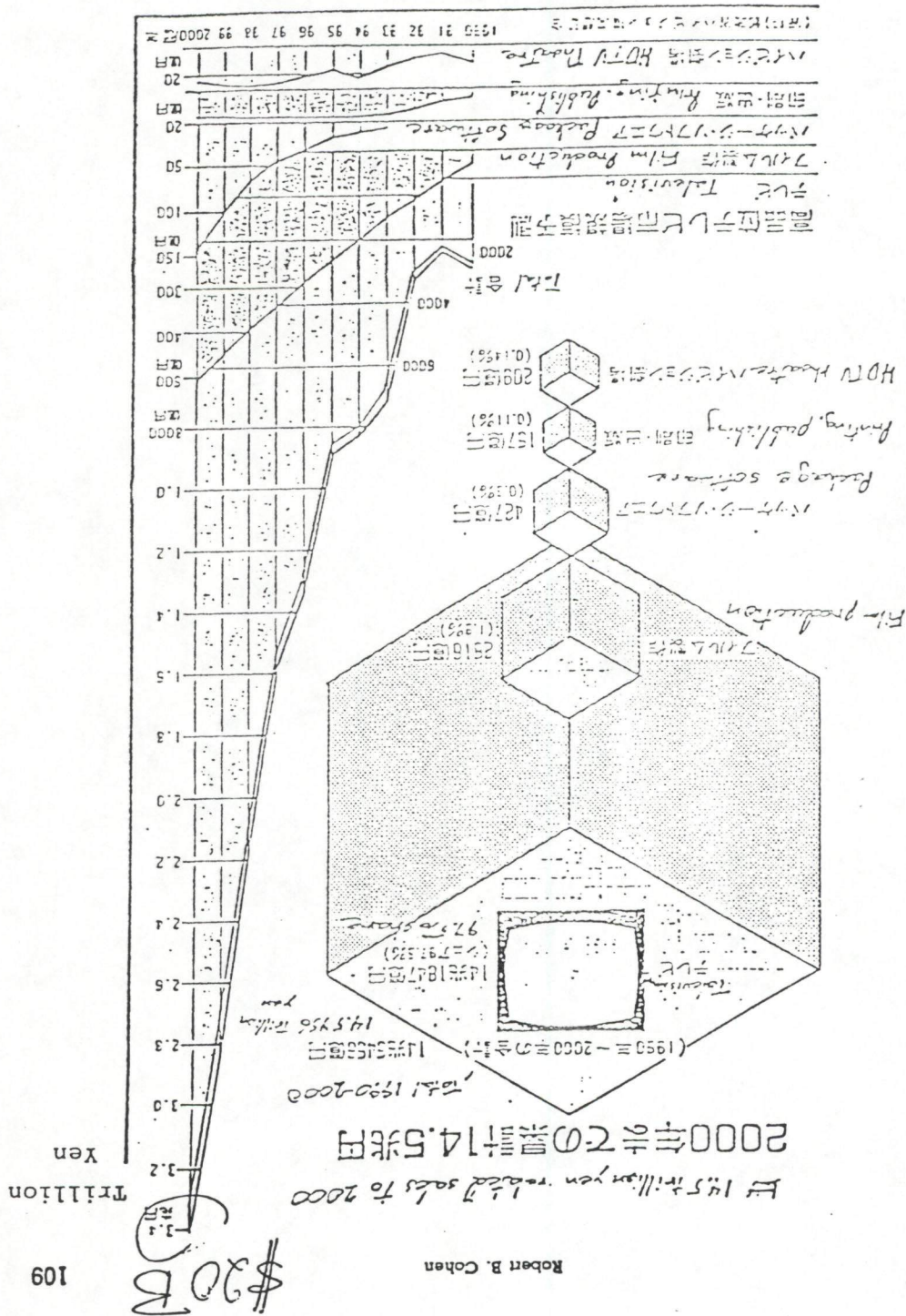


EDTV Compatibility



Source: MPT, HDTV Promotion Committee, provided to NSF JTEC members during meeting with MPT Staff in Tokyo, June 2, 1989.

Figure 5.2 MPT's Forecast for the Growth of HDTV



Robert B. Cohen

HDTV Issues in Japan

- Viability of the MUSE system, cost vs. quality
- Competition between EDTV and HDTV
- Desire to wait for the US FCC to decide on a standard, and thus allow the Japanese manufacturers to adhere to that system
- To really cash in on their investment in HDTV, the Japanese companies need the US market
- Despite some skepticism about the near-term potential of HDTV as a broadcast TV technology, most Japanese manufacturers favorably view HDTV in industrial applications

High Temperature Superconductivity in Japan (JTEC Report, November 1989)

- M.S. Dresselhaus, Chairman, MIT
- R.C. Dynes, AT&T Bell Labs
- W.J. Gallagher, IBM
- P.M. Horn, IBM
- J.K. Hulm, Westinghouse (ret)
- M.B. Maple, UCSD
- R.K. Quinn, ERDC Los Alamos
- R.W. Falston, MIT Lincoln Labs

Visits to Japan (June 1989)

- Government Laboratories
 - Electrotechnical Laboratory (ETL)
 - ERATO Program (Quantum Magneto-Flux-Logic Program)
 - International Superconductivity Technology Center (ISTEC)
 - Miyazaki Maglev Test Site (JR)
 - National High Energy Physics Laboratory (KEK)
 - National Institute for Research in Inorganic Materials (NIRIM)
 - National Institute for Research in Metals (NIRM)
 - Railway Technical Research Institute (RTRI)

Visits (continued)

- Universities
 - Institute for Solid State Physics - University of Tokyo
 - Tohoku University
 - University of Tokyo - Faculty of Engineering

Visits (concluded)

- Industrial Laboratories
 - Fujitsu
 - Furukawa Research Laboratory
 - Hitachi (Kokubunji)
 - Hitachi Research Laboratory (Ibaraki)
 - Matsushita
 - Mitsubishi Electric Corporation
 - NEC
 - NTT (Ibaraki)
 - NTT (Musashimo)
 - Sumitomo Electric
 - Toshiba

Comparison of Japanese & American R&D Trends in Low- T_c Superconductors

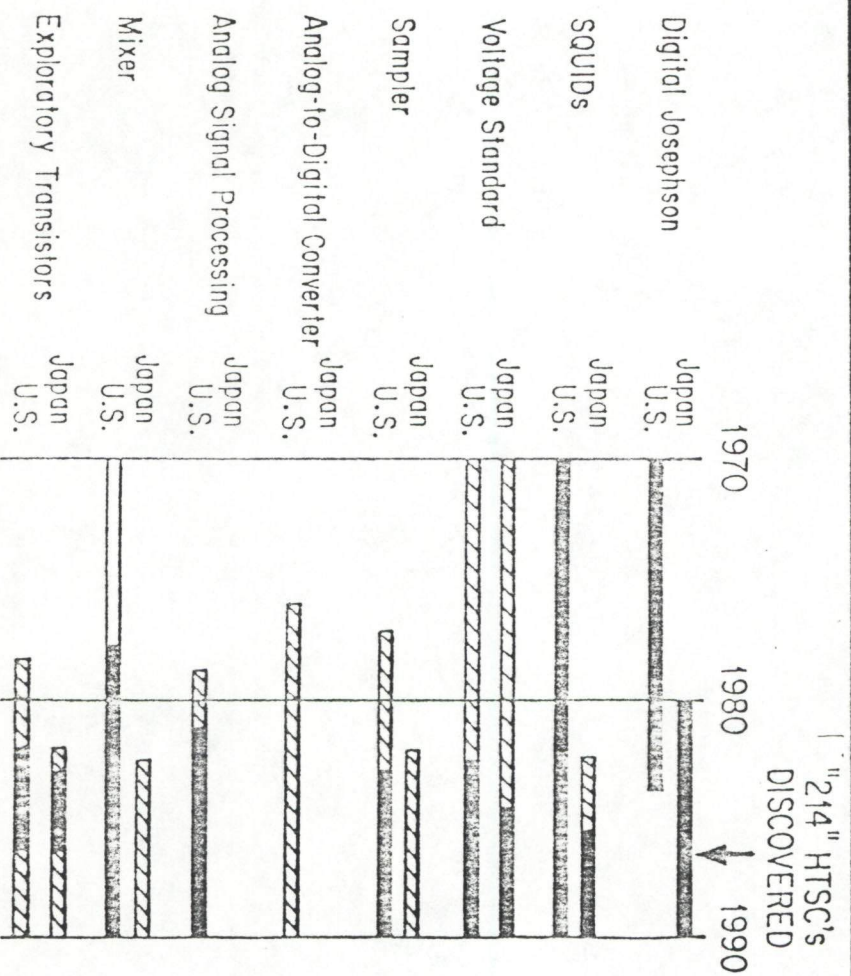


Figure 1.1: Comparison of Japanese and American R&D trends in low- T_c superconducting electronics. Schematic bar graph of the development of superconducting digital and analog electronics. The periods of most intense activity are indicated by the black regions of the bar, moderate activity is cross hatched and only small activity is unshaded.

Low- T_c Josephson Technology in Japan

Table 6.1: Low- T_c Josephson Technology in Japan

Institution	Application Focus	Junction	Lithography	Chip Density	Wiring Material	References
Fujitsu	Microprocessor	Nb/ Al_2O_3 /Nb	1.5 μm jnts 2.0 μm wire	3,056 gates (24,000 jnts)	Nb	[228]
	SQUID with integral feedback	Nb/ Al_2O_3 /Nb	—	4 jnts	Nb	[229]
	RAM DRO	Nb/ Al_2O_3 /Nb	2.5 μm	4 k bit	Nb	[230]
	Microprocessor	Nb/ Al_2O_3 /Nb	5 μm jnts 2.5 μm wire	2,066 gates	Nb	[231]
Hitachi	Quantum Flux Parametron	NbN/ NbO_x /Pb alloy	5 μm jnts	4 parametrons + 4 SQUIDs	Pb alloy	[232]
Goto/Hitachi	RAM	Nb/ Al_2O_3 /Nb	4 μm	1 k bit	Nb	[233]
NEC	Multi Chip Microprocessor					
ETL	- Arithmetic logic	Nb/ Al_2O_3 /Nb	3.0 μm	1273 gates	Nb	[234]
	- Control Unit	NbN/ MgO /NbN	2.5 μm	593 gates	Nb	[235]
	- Instruction ROM	NbN/ MgO /NbN	3 μm	1280 cells + 789 gates	Nb	[236]
	- RAM	Nb/ Al_2O_3 /Nb	3 μm	1 K cells + 1025 gates	Pb alloy	[237,238]
Voltage Standard		Nb/ Al_2O_3 /Nb	25 $\times$ 40 μm^2	2400 jnts	—	[239]
	SQUID Gradiometer	Nb/ Al_2O_3 /Nb	3.5 μm	—	Pb alloy	[240]
	10 K SQUID	NbN/ MgO /NbN	$\sim$ 5 μm	2 jnts/8 $\times$ 8 μm	NbN	[241]

Japanese-Sponsored Large-Scale Superconducting Projects

Agency	Co-ordinating National Laboratory	Superconducting Applications
Ministry of Education (Monbusho)	High Energy Physics (KEK)	Dipoles, Quadrupoles, Detectors, Microwave Cavities
Ministry of Trade and Industry (MITI)	Electrotechnical Laboratory (ETL)	Josephson Junction Circuits, Generators (Super GM*)
Japan Railways (JR)	Railway Technical Research Institute (RTRI)	Maglev Train*
Science & Technology (STA)	Japan Atomic Energy Res. Inst. (JAERI)	Fusion Magnets
	Natl. Res. Inst. Metals (NIRIM)	Advanced Superconducting Materials
	Natl. Inst. Res. Inorg. Mats. (NIRIM)	High-T _c Materials

• Major Projects

Basic Research Activity in High- T_c Superconducting

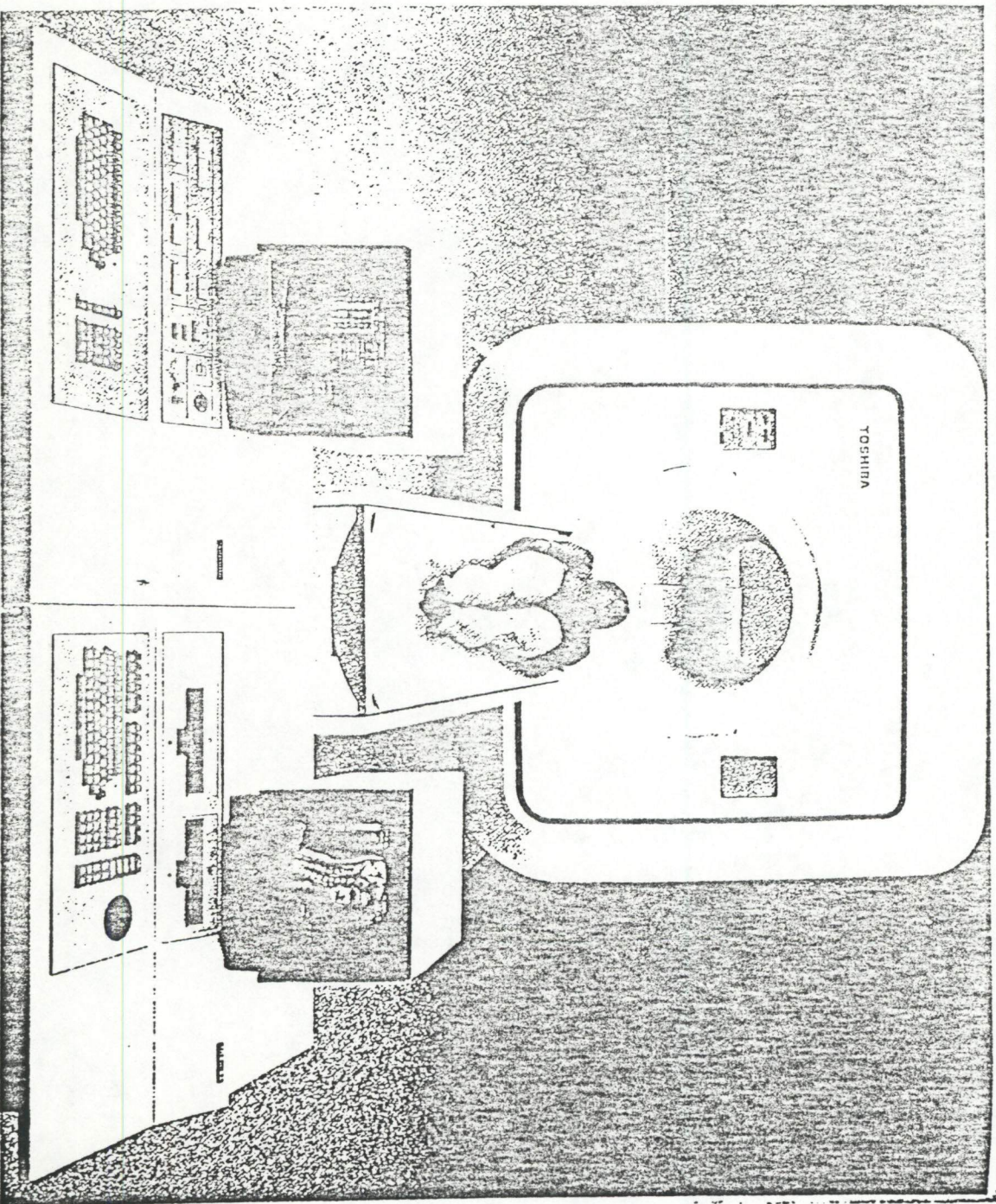
Table 2.1: Institutions visited with significant basic research.

University	Industry	Government Labs
Institute for Materials Research (Tohoku University)	Hitachi	ETL
ISSP (University of Tokyo)	NEC	NIRIM
U. of Tokyo	NTT (Ibaraki)	NRIM
	NTT (Musashino)	

Table 2.2: Major basic research accomplishments in high- T_c superconductivity from Japan

Accomplishment	Reference
Refined and legitimized original Bednorz and Müller result	[35]
High H_c2 measurements	[7]
Discovery of Bi materials	[11]
Large and high quality single crystals	[27,36]
Electron doped superconductors	[8]
High critical current films	[17]
Bi and Tl compounds with over four CuO_2 layers per unit cell	[12,32,33,34,37]

MRI Whole Body Scanner with Superconducting Magnet (Toshiba)



Digital Circuits - A Japanese Domain

- Since 1983, when almost simultaneously IBM, AT&T, and Sperry terminated their digital efforts, Japan has continued and has made substantial progress beyond IBM's level of 1000 gates-per-chip
- There has also been progress in memories, but progress has been less impressive as measured against semiconductor performance improvements

Selected Examples of Digital IC Developments at Fujitsu

Table 6.3: Selected examples of Nb/Al₂O₃/Nb digital integrated circuit developments at Fujitsu.

Year	Circuit	Speed	No. Gates	Junction Diameter	References
1986	16 bit multiplier critical path model	1.1 ns	828	2.5 μ m	[244]
1987	4 bit microprocessor	770 MHz	1841	2.5 μ m	[245]
1987	16 bit arithmetic logic unit	860 ps	900	2.5 μ m	[246]
1988	4 kbit static memory (destructive readout, random access)	590 ps	4k-bit	2.5 μ m	[230]
1989	4 bit microprocessor + 4 bit multiplier + 12 bit accumulator + 8 kbit memory read-only	1.1 GHz	3056	1.5 μ m	[228]

Overview of the Superconducting Technology in Japan

- Japan has a deep, long-term commitment to superconducting R&D in industry, universities, and national laboratories
- Number of researchers equal to that in the US
- A number of 5-10 year projects are sponsored by four agencies:
 - MITI - ISTEC Consortium, Josephson Computing System, and Superconducting Generator Project
 - STA - Multi-Core Project and ERATO Quantum Flux Parametron
 - Monbusho - High- T_c Oxides
 - JIR - Magnetic Levitation Program
- Superconductivity has been selected as a flagship for demonstrating commitment and capability in basic research

Overview...(continued)

- The Japanese have identified superior materials as a key to success in high-T_c technology, and have focused their work in materials synthesis and processing, including new materials research
- In basic science, the interaction between groups in industry, universities, and national laboratories is not as strong as in the US
- The equipment in industry is equal to or superior to the US: the equipment and infrastructure in the universities is steadily improving so that the best Japanese universities are equipped as well as in the US

Overview... (continued)

- The Japanese have developed a strong industrial base for the large-scale application of low- T_c work - government lead and collaborative work at national laboratories, electrical industries, and wire and cable companies
 - Large magnet systems for
 - Magnetic fusion
 - High energy physics
 - Magnetic levitation
 - Power generation
 - Medical applications - MRI
- Japanese capabilities in next-generation wire (> 15 tesla) exceeds the US, and the gap was widening before NSF's decision to close down MIT's Bitter Lab and start anew in Florida

Overview...(Concluded)

- Low- T_c Josephson digital capabilities exceed those at any US laboratories, while analog superconducting electronics in the US lead those in Japan
- Early high- T_c electronics applications are expected to be in analog devices, thus the US is well-positioned to lead in those areas

JTEC Space Technology Reports

- Space and Transatmospheric Propulsion Technology
- Space Robotics
- Advanced Complex Composites

Space and Transatmospheric Propulsion Technology

- Trip to Japan, October 1989
- Panel
 - Prof. Charles Merkle, Chair, Penn State
 - John McCarty, NASA Marshall Space Flight Center
 - Dr. Burton Northam, NASA Langley Research Center
 - James Brown, Pratt & Whitney
 - Dr. Louis Povinelli, NASA Lewis Research Center
 - Maynard (Joe) Stangeland, Combustion Devices & Rotating Machinery
 - Prof. Edward Zukoski, Cal Tech

Space Robotics

- Trip to Japan, June 1990
- Panel
 - William "Red" Whittaker, CMU Chair
 - Peter Allen, Columbia
 - Tony Bejczy, Cal Tech (JPL)
 - Jim Lowrie, Martin Marietta
 - Harry McCain, NASA's Goddard Space Center
 - Takeo Kanade, CMU
 - Tom Sheridan, MIT

Advanced Complex Composites

- Trip to Japan, March 1990
- Panel
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 - Bill Hillis, General Electric
 - Sal Grisaffe, NASA Lewis Research Center
 - Byron Pipes, U of Delaware
 - John Perepezko, U of Wisconsin
 - Jim Sheehan, MSNW Inc.

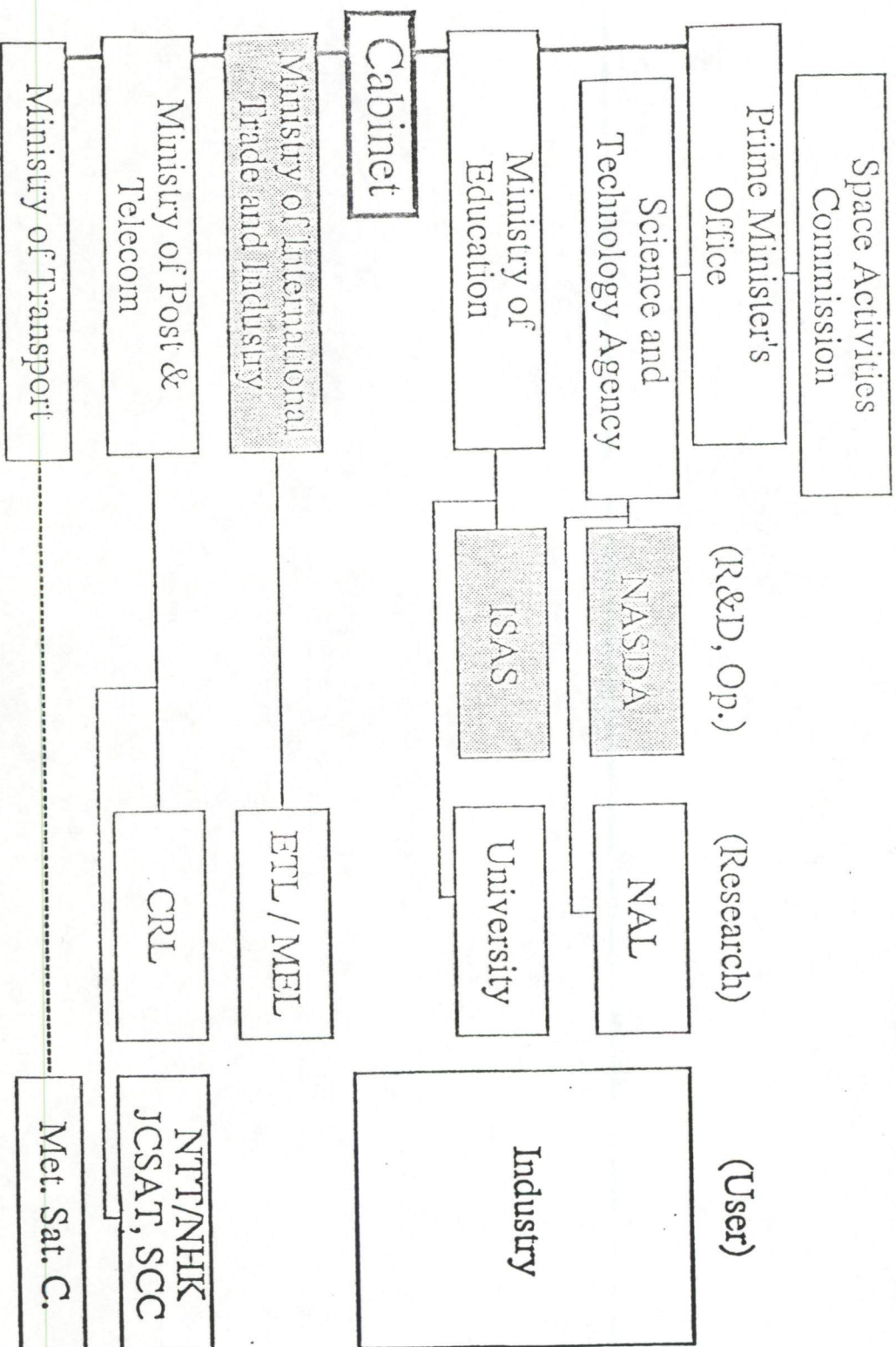
Overview of Japanese Space Development Activities

- Centerpiece
 - Japan's Tanegashima Space Center - launch capability comparable to the US Titan 34D and European Ariane-4 boosters
 - Took four years to build (\$330M) and is based on an operational approach similar to the space shuttle and Ariane 4
- Japan's space program, while advertised as basic in nature and involves space exploration, is focused on payback in telecommunications and other civilian applications

Japanese Space Technology Players

- SAC - Space Activities Commission, advises the P.M.
- STA - Science and Technology Agency, primary operative body under SAC, coordinates and oversees all space programs
 - NASDA - National Space Development Agency of Japan - Budget: \$1B per year - handles large boosters and applications satellites - although under STA, has quasi-government status
 - ISAS - The Institute of Space and Astronautical Science - Budget \$150M per year - develops medium boosters and science aircraft
- MITI - role is increasing, developing the 3.8 ton Space Flyer, Japan's first large retrievable satellite
- Industry - Mitsubishi, Kawasaki, Toshiba, Ishikawajima-Harima Heavy Industries, Nissan Motors, Nippon Electric, Fujitsu, and Japan Aviation Electric
- National research laboratories
- Universities

Space Development Structure in Japan



Japan's Space Technology - Observations

- Prime tenets of space policy:
 - To promote national space development in balance with national resources and social needs
 - To ensure autonomous space capability within Japan, so it can freely conduct various diversified space activities
 - To work in harmony and cooperation with international space activities in other countries
 - To develop its own launch capability so as not to be dependent on other countries

Japan's Space Technology - Observations (continued)

- The Japanese intend to become self-reliant in space
- Japan recognizes the enormous expense of manned space operations, and intends to minimize the cost by utilizing robots in space
- The Japanese are world leaders in non-space robotics, giving them invaluable help in space robotics
- The quantity and quality of Japanese space robotics is underestimated by the world
- In Japan, the government only provides seed money; the corporations carry most of the costs

Japan's Space Technology - Observations (concluded)

- Specific Projects for the 1990's
 - To encourage the commercial development and manufacture of communication, broadcasting, and navigation satellites
 - To continue development and operation of scientific satellites for meteorological, oceanographic, and earth observation purposes
 - To promote the utilization of space for scientific and technological experiments such as materials research and life science experiments
 - To develop the necessary technologies for autonomous manned exploration through international cooperative programs
 - To promote satellite technology development
 - To maintain and expand space transportation capabilities

The Real Challenge to American Power

"I am convinced that our policy should be to stake everything on the present opportunity, to conclude friendly alliances, to send ships to foreign countries everywhere and conduct trade, to copy the foreigners, to foster our national strength and complete our armaments, and so gradually subject the foreigners to our influence until in the end all the countries of the world know the blessings of perfect tranquility and our hegemony is acknowledged throughout the globe"

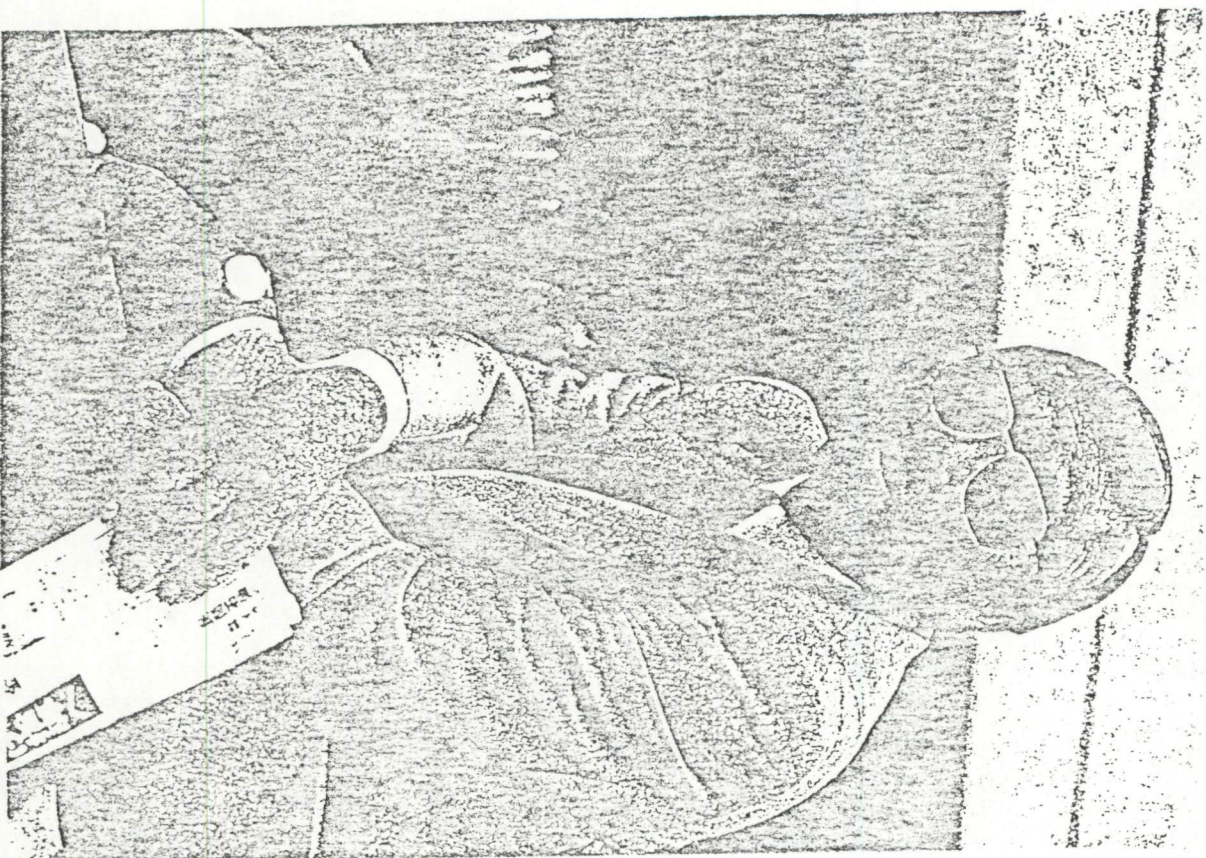
Masayoshi Hotta, Advisor to Shogun 1857

The Real Power Base in Japan

**"Prime Ministers Come and Go, But
We Ministry Officials Are Forever" -**

An Official in the Ministry of Posts and
Telecommunications, Spring 1985
(*Trading Places* by Clyde Prestowitz)

Competitiveness in Japan



Ishikawa drives a Buick for a good reason. Since he often meets traveling VIPs, Ishikawa doesn't have to worry about choosing between a Honda, Isuzu and Nissan, and possibly offending a client.

COMPASS readings
November 1990

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