Knocking on Opportunity's Window

Amgen's master builder remembers what it was like to build the first start-up pharmaceutical company since Syntex

GEORGE B. RATHMANN

10 CELEBRATING A DECADE OF EXCELLENCE

In January 1980, Biogen (Cambridge, MA) announced the cloning of alpha-interferon—and the production of this long-awaited molecule. The announcement lent credibility to enthusiastic projections that molecular biology could lead the way to new pharmaceutical discoveries. That June, the U.S. Supreme Court decided that Ananda Chakrabarty could indeed patent a living organism—in this case, a bacterium that could consume oil. Most people interpreted this as a clear sign that gene companies could afford to invest in developing new organisms to produce pharmaceuticals—and could be assured that their rights to these organisms would be protected.

Within three months, Genentech (S. San Franscisco, CA) filed for its landmark initial public offering. In early October, the first publicly traded biotechnology company exploded onto Wall Street. During that same month, a number of biotechnology companies—including Genetics Institute (Cambridge, MA), Bio-Technology General (New York, NY), Chiron (Emeryville, CA), Applied Biosystems (Foster City, CA), and, of course, Amgen (Thousand Oaks, CA)—were moving from wishful thinking to reality.

As the new CEO of Amgen, my job was to prepare and file an offering memorandum that would raise enough capital to begin operations. We decided that staying power was vital to survival: We would try to raise $15 million dollars so that we could produce some tangible results before the money ran out and we had to go to the well again. Genentech's dramatic debut assured us of investor interest. So did a strong, active scientific advisory board (active scientific boards, unlike "window-dressing" boards, contribute ideas, review scientific progress, and help with recruiting. Ours drew on the abilities of John Carbon, Norman Davidson, Leroy Hood, and Winston Salzer, with consulting from Gene Goldwasser and Irv Weissman). And two big company investments helped sway venture capital opinion: Tosco, an oil shale company that was interested in microbial-enhanced oil recovery generally and shale-digesting organisms in particular, invested $3.5 million, and Abbott Laboratories (Abbott Park, IL) (interested in a "window" on biotechnology) put up $5 million. (Whatever else Abbott gained from the relationship, stock appreciation alone made their $5 million investment worth over $200 million when it sold its holding in 1991.)

By early February 1981, Amgen had completed its first financing and had $18.9 million in the bank. This was the largest initial equity financing in history, a record that would stand until ICOS (Bothell, WA) raised $33 million in 1990. (At the time, $19 million seemed like all the money in the world. It was barely enough.) In April, Amgen became the first of the '80s generation to begin operations.

The large bolus of capital was crucial in many ways. It permitted Amgen to concentrate on research and development: For two years, management could "stick to its knitting" without having to spend time courting new investors or corporate partners. The clear appearance of financial stability made it easier to recruit good people. That critical task went rapidly and smoothly—in memory, anyway.

Though some companies were predicting product sales and even income within four years, we knew it would take much longer to bring products to market. The Pharmaceutical Manufacturers Association's (Washington, D.C.) figures from the time made it clear that we would need $94 million over eight to ten years to bring a product from its first clinical trials to market. And $19 million could only begin to cover that.

Investor Confidence Roller Coaster

By early 1983, Amgen's original cash hoard had dropped to a few million dollars, but the general enthusiasm for initial public offerings had risen to new heights. When Biogen (again a bellwether) completed its public offering that spring, it was clear to us that this was the time for Amgen to access the public markets to meet its financing requirements. On June 17, Amgen raised $43 million at $18 a share (equivalent to just $3 a share today, after a three-to-one and a two-to-one split). Amgen's staff watched in dismay as the stock price slid to $9 a share within three months. We were one of the many companies Wall Street hindsightedly criticized for deciding "to go public without even a single product in human test-

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ing." But the proceeds financed the cloning and expression of the genes for erythropoietin (EPO) and granculocyte colony stimulating factor (G-CSF). These then-potential products met many of the criteria we had set for projects warranting a major share of Amgen's resources:

- our best chance for strong patents;
- a critically ill patient population for which an injectable product—the only option for a protein therapeutic—might be justified;
- a small, addressable target group of physicians and institutions;
- rapid success in product development;
- significant therapeutic gain, which should lead to a significant market opportunity.

By the fall of 1984, we thought we would file a number of investigational new drug applications (INDs) and would begin four—probably five—clinical studies during 1985. But this promise of progress was not enough to shore up investor confidence. By November, Amgen stock had fallen to $3.75 (63¢ before splits), but that was the bottom. A slow recovery followed. Still, more public financing was out of the question. At this juncture, many other companies sold rights to their key products. For some (like Biogen) this strategy succeeded, though it was hard to see that at the time. For others, like Chiron (Emeryville, CA), it meant selling part of their birthright to stay alive. For some companies, the compromise meant gaining continued life at the cost of as much as a decade of slowed growth. We decided to hold on. We cut expenses, maintained a constant headcount for the next year-and-a-half, and kept the key rights to our product pipeline.

We made it. Five products entered the clinic during 1985, just as we had predicted. That success is testimony to a creativity and energy that characterized not only our company, but many or most of the new generation of biotechnology companies then fighting for survival.

By the spring of 1986, it appeared that the biotech public-offering window had opened again. Our early clinical results were still inconclusive, but we took what we had and went to Wall Street again. We needed to start immediately investing in an EPO plant that would cost $20 million, and we had just a little over half that in the bank. Our second public offering raised $43 million that April (at $15 a share, almost the price it had commanded three years before). But the aftermath was very different. Within two months, the stock price had risen 60 percent—and in fact has yielded a 20-to-1 return for those investors who still hold their stock from that offering.

In 1987, with G-CSF entering the clinic, and with strong clinical results for EPO, Amgen was able to carry out two more rounds of financing, raising $150 million more. Production yields were improving. Our first production plant was becoming a reality. We had enough money for the first time. And excellent clinical results continued to come in. For a moment, the future looked rosy.

Amgen and its investors were thus totally unprepared for the patent dispute that threatened the company's technical foundations. To be sure, other biotechnology companies had endured some proprietary disputes. English courts had rejected Genentech's broad claims on tissue plasminogen activator in the summer of 1987, and battles over monoclonal antibodies, factor VIII, and interferon flared up periodically through the end of that decade and into this.

Many felt that the courts were the wrong place to settle these disputes and that any settlement would be better than hazarding litigation. Others felt that firm precedents would finally define this murky corner of intellectual property law, and would, in fact, reduce the level of uncertainty, the number of disputes, or at the very least lead to some future resolution. Amgen management, including me, felt that any settlement should be appropriate to the relative contributions of the disputing parties. Amgen management and its board of directors reluctantly entered the courts to resolve the issue.

The suits and countersuits with Genetics Institute dragged on for four years, distracting managers of both companies, and running up very large legal bills (which were, nevertheless, modest compared to the values at stake).

The last few years of the 1980s witnessed some striking biotech successes—especially the launches of human growth hormone, hepatitis B vaccine, alpha-interferon, tissue plasminogen activator, and EPO. As was the case in 1984, when Amgen's stock dropped to its all-time low in the face of generally good news about EPO, investors continued to be apathetic to biotechnology stocks. The media made solemn pronouncements about "faded genes" and "clouds over biotechnology." Few companies managed to brave the prevailing winds and consummate new financings between 1988 and the end of the decade.

Some attributed the problems to patent uncertainties. Others blamed the biotechnology companies' meager product pipelines. Still others worried that there were too many companies competing for primacy on too few viable products. Odd mixtures of public opinion—polls showed that about 80 percent of the U.S. population expected personal benefit from biotechnology, while 80 percent feared some unspecified harm—slowed commercialization of agricultural and environmental products. And perhaps some of that public uncertainty filtered into biopharmaceuticals. Few companies were profitable.

The '90s Bring New Technologies

The 1990s dawned a bit brighter. At Genentech and Amgen, sales and profitability both grew. Various courts issued favorable patent decisions on rDNA products and processes. Neupogen (G-CSF) and Leukine (GM-CSF)—both offering great promise for cancer patients with compromised bone marrow—were launched. With the almighty window opening again in 1991 and 1992, the older biotechnology companies strengthened their balance sheets, and new companies managed to raise more money during those fifteen months than the first generation had raised in the previous decade. Most of these new companies were built on technologies unknown in the mid-1980s: signal transduction, antisense, cell trafficking, carbohydrate chemistry, gene therapy, humanized antibodies. All of these represent advances in the molecular understanding of physiological path-

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ways. In many cases, the new companies followed Amgen's early concept, looking for large sums in first-round financing to ensure financial stability over what could be lean years ahead.

As of 1993, commercial biotechnology is center-stage with respect to several of the key issues of our time—including the cost and quality of health-care, international competitiveness, and the creation of new jobs in the United States and around the world.

The Clinton administration has pledged to bring escalating health-care costs under control. The effects of such measures on biotechnology are hard to assess. Price controls, if imposed, should be directed only at those pharmaceuticals that:

- are priced higher than identical products overseas;
- have been subject to substantial year-by-year price increases;
- show only minor therapeutic benefit;
- duplicate other available products;
- or are clearly not cost effective.

Such measures would then have little negative impact on commercial biotechnology. Conversely, measures that indiscriminately target profitable products with substantial sales would seriously affect biotechnology: Price controls would shrink profit, and companies will be unable to sustain investor interest.

Action on the administration's other priorities should be positive for biotechnology. Biopharmaceuticals have touched, and improved, every branch of medicine, bettering the prospects for patients with hairy cell leukemia and other forms of cancer, heart disease, and genetic disease. The identification of the virus that causes hepatitis C made possible great strides in treating the ailment with another biopharmaceutical, alpha-interferon. Treatments for diabetes and anemia have benefited. Over the last four years, EPO has obviated the need for more than a million blood transfusions. Colony stimulating factors are mitigating the side-effects of chemotherapy and are clearly cost effective.

Since it is likely that these products represent only the beginning, quality health-care of the future could clearly depend on the health of the biotechnology industry. Commercial biotechnology offers the U.S. its best chance to maintain worldwide leadership in a key technology, to build a strong global trade balance while simultaneously creating high-quality jobs at home. The biotechnology industry now employs less than 100,000 people, but that is a poor measure of the total number of jobs created. Whole satellite industries have sprung up to produce the instruments, reagents, and equipment to supply the engines of discovery and manufacture.

The singular potential of a strong biotechnology industry has prompted the Industrial Biotechnology Association (Washington, DC), and many biotechnology executives, to urge caution and discrimination in enacting health-care cost-containment measures over the next four years.

As the number of biotechnology companies rose, the cost of bringing an "average" pharmaceutical to market began to approach $300 million per product. Investors began to wonder whether even the well-financed classes of '91 and '92 would have the resources necessary to bring products in. Estimates of 1000 products in the pipeline—requiring some $300 billion to bring to market—began to wilt even the most enthusiastic investors. With ten or a dozen companies all investing money in drugs for the same indication, the odds of backing the eventual winner seemed unacceptably slim. And the biotechnology product-development cycle has some very critical demands of its own: Researchers must unravel and understand basic physiological pathways before they can synthesize or screen the molecules necessary to alter them. This can slow the progress into the clinic and increase—not decrease—R&D time lags while increasing expenditures. At the same time, the administration and legislators have become increasingly insistent on health-care cost controls—an eventuality that could considerably diminish the investment incentives of even the most optimistic students of the field.

2000 and after

So, even as an accelerating pace of discovery has affirmed biotechnology's power and scope, the industry's viability again faces challenges. In 1993, the competing views are easy to enunciate, but difficult to assess. Many in the industry remain optimistic; they are sure that the basic science underlying biotechnology can reduce human suffering—and do it cost effectively. In virtually every major debilitating disease, the cost of failure to prevent morbidity—the cost of custodial care, lost productivity, lost taxes, lost life—far exceeds the cost of successful therapy. Well-conducted studies of such diseases as arthritis, for example, show that it costs U.S. alone some $50 billion a year. And as the population ages, the drain of such "hidden" costs will grow, and grow rapidly.

Clearly, therapies that address the root cause of such diseases would be cost effective. Unfortunately, even the most successful therapy envisioned to date may not reverse existing degeneration. Patients and society must bear the residual cost of past diseases even as they finance future cures.

Is it possible to sustain a thriving biotechnology industry if investors worry that cost controls will limit a return on even the very best products? Is the United States' current health-care delivery system spinning further and further out of control? Or is it reaching some favorable equilibrium? Equilibrium may indeed be possible, if the consolidation of purchasing power allows the laws of supply and demand to control health-care costs. Hospital buying groups, formularies, and emergent health-care delivery systems may reduce the need for government intervention, and yet reward innovators of successful products with incentives to continue discovering new therapies.

The hope of biotechnology is to find solutions for society's most pressing health-care needs—at a pace that will yield cost savings to finance still further discovery. By the year 2000, biotechnolgists' armamentaria will comprise trillions of compounds generated by random libraries and evolutionary biology. Couple these resources with a growing understanding of the genome as a whole and the burgeoning ability to construct molecules by computer, and the medicine of the 21st Century will bear little resemblance to its current practice.