10

Magic Bullets and Patent Wars: New Product Development and the Evolution of the Biotechnology Industry

❖

WALTER W. POWELL AND PETER BRANTLEY

Biotechnology was in many respects *the* hot industry of the 1980s. At the decade's outset, venture capitalists and Wall Street investors poured money into the field, lured by the promise of new wonder drugs and magic bullets. But by the time of the stock market crash of 1987, many "gene dreams" had come face to face with the reality of biotechnology: Drug development is an extraordinarily expensive and protracted process. Yet just as the investment community soured on biotech, large pharmaceutical companies became active participants in the field. Although many established pharmaceutical companies initially looked askance at the new field, no major pharmaceutical or chemical corporation can ignore biotechnology today. Most large companies now have active research programs of their own and multiple ongoing strategic alliances with various smaller biotech companies. Indeed, the pattern of interfirm collaboration in biotech is probably more extensive than in any other industry (Powell and Brantley, 1992; Barley and Freeman, 1992; Kogut, 1990; Arora and Gambardella, 1990).

In part because of fruitful collaborations among large firms, small companies, and universities, and due to the maturation of research efforts, a number of biotech products had become part of established medical practice by the end of the 1980s. Many more new drugs are now in various stages of development. The industry came of age in the 1980s. In our view, the critical lesson of the past decade is that biotechnology is a fundamentally new technological regime (Dosi, 1982), one that builds on a different scientific basis (molecular biology and immunology) and requires creative kinds of organizational arrangements to exploit

these novel developments (Powell and Brantley, 1992; see also Abernathy and Clark, 1985; Tushman and Anderson, 1986). As the industry developed, it became clear that the full range of skills (e.g., basic research, applied research, clinical testing procedures, manufacturing, and marketing and distribution) could not be easily assembled under one roof. While the basic and applied research skills needed to create new products were based in universities, research institutes, and biotech companies, the cash necessary for product development, the experience required in launching extensive clinical trials, and the established, worldwide marketing channels were located in large chemical and pharmaceutical companies. So the participants in this field have turned to joint ventures, research agreements, minority equity investments, licensing, and various kinds of partnerships to make up for their lack of internal capabilities.

But it is not only corporate relationships that have been redefined by biotechnology. With the development and elaboration of this field we have seen either critical changes or contentious debate in a number of other areas: (1) industry-university relationships, (2) the federal regulatory approval process for new drugs, and (3) patent law and intellectual property rights. In perhaps no other industry are there such close linkages between basic science done in universities and R&D in company laboratories. The cross-traffic is so constant and reciprocal that it is appropriate to consider universities and firms as part of the same technological community (Nelson, 1991). The development of biotechnology has reshaped university policies regarding relations between professors and private companies and altered both the traditional means of funding biomedical research and the opportunity structures for basic scientists. Professors now take sabbaticals at biotech companies, and postdoctoral fellows as well as senior scientists move back and forth between universities and biotech firms.

The U.S. Patent and Trademark Office, which has a backlog of thousands of patent applications (and currently has much longer than average delays with biotech applications), is only beginning to come to grips with patenting in this rapidly developing field. In science-based industries, researchers race toward similar objectives. Consequently, a good deal of scientific developments are "in the air" and the contribution of an individual researcher or a single firm may be small. Legal and economic theorists argue that under these circumstances patents should be awarded narrowly (Merges and Nelson, 1990), although that has not yet become the norm. Biotechnology has posed novel and thorny problems for the courts on issues of patent scope and validity. In a similar fashion, the U.S. Food and Drug Administration's (FDA) approval process has felt the winds of change ushered in by biotechnology. Critics have charged that extensive delays threaten lives. The FDA has responded with several steps to shorten its lengthy review process with respect to drugs that offer hope to patients with deadly and/or exotic illnesses. The FDA has also been the target of harsh attacks by the press and the financial community because of its stringent requirements, illustrated best by the *Wall Street Journal*'s editorial crusade in 1987 against the FDA over its initial turn-down of tPA.

In this chapter we depart from our previous work on biotech, in which we focused on interorganizational relationships, and instead concentrate on product development. The process of creating new biotech drugs is research intensive and costly. Yet the subsequent stage of clinical trials and obtaining regulatory approval is often even lengthier and costlier. It presently takes at least 6 to 9 years to successfully bring a new drug to market. By the end of the 1980s, 10 biotech products were approved by the FDA. At the close of 1991, more than 100 products based on genetic engineering were in various stages of testing or human clinical trials, and some two dozen drugs awaited FDA approval (Gibbons, 1991:369–370; Thayer, 1990:17–19), but of the 10 drugs approved in the 1980s, only three were both developed and marketed by a new biotech company. The other products were typically developed by a biotech company and then licensed to an established firm for sales and marketing (e.g., alpha-interferon, developed by both Biogen and Genentech and licensed to Schering-Plough and Hoffmann-LaRoche, respectively). The three biotech-produced and marketed drugs are

hgh (human growth hormone)	Genentech	FDA approval 1985
tPA (tissue plasminogen activator)	Genentech	FDA approval 1987
EPO (erythropoietin)	Amgen	FDA approval 1989

EPO and tPA generated intense competition among a handful of companies that raced to bring them to market. The stories behind the creation of these drugs are fascinating and complex. Yet we chose them as cases, not because they are interesting, but because with the development and marketing of these drugs, many of the "rules of the game" in biotechnology became elaborated. In short, we are describing a process of coevolution of technology and institutions.

Technological Change and Product Development

Technological change is a moving target. What is striking about the process is that markets, technologies, and institutions are continually changing. As Freeman (1982:111) suggested, "a kaleidoscopic succession of new combinations" emerges. What is technically impossible at one point may be eminently feasible a year hence because of scientific advances. But ideas can lie fallow because of the lack of supportive institutions. Scientific progress is continually generating new technical possibilities, yet only some breakthroughs lead to the creation of new products or, more fundamental, new industries. Innovations in plastics, aluminum, and recycling have expanded the container industry rather than creating separate fields for plastics, aluminum, and paper. Microwave technology was readily assimilated into the kitchen appliance field. Yet solar technology has not transformed the construction industry, nor has solar really taken off as a new burgeoning industry.

An important feature of technological progress is its uneven impact and rate of advance from firm to firm, and across industries. There is a wide disparity in

the rate at which different firms and institutions pursue and capitalize on technical advances. Managers have different perceptions of the risks and opportunities associated with a new technology. Although those perceptions are strongly shaped by one's position, they are also influenced by timing and a host of external factors. Technological change can be thought of as a bundling process. New fields emerge and established boundaries are redrawn only when there is a particular combination of perceptions, pressures, and felicitous events. Markets, institutions, and technologies must somehow align. This clustering is not purely serendipitous—it is a socially constructed process. There are very few opportunities lying around awaiting discovery and exploitation. As our cases of new biotech drugs illustrate, it is only through the concerted collective action of opportunistic actors that the biotech field emerged.

Technological advances often build upon existing know-how. Typically, established firms reap the bulk of the benefits of competence-enhancing innovations. Consequently, new fields do not emerge and established domains are not reshuffled. In some cases, however, innovation constitutes a radical break from previously dominant technologies. Biotechnology is a dramatic case of a competence-destroying innovation because it builds on a scientific basis (immunology and molecular biology) that differs significantly from the knowledge base (organic chemistry and its clinical applications) of the more established, mature pharmaceutical industry. At the forefront of product development in biotechnology are young research-driven companies, long on scientific expertise but short on business experience. Over the past two decades, hundreds of new biotech firms have been founded, but in the process of moving from the laboratory to clinical trials to regulatory approval to the medical marketplace, many firms have stumbled. Scientific acumen has not readily led to business success. Product development in biotechnology requires scientific, financial, legal, and medical know-how, and a good deal of luck and propitious timing. The cases of tPA and EPO provide apt illustrations.

This chapter briefly describes a stylized series of steps through which a new drug must pass before it can be released on the market. Turning to tPA and EPO, we then provide detailed histories of each drug. The messy reality of product development is vastly more protracted and conflictual than a simple stagelike model suggests. We then attempt to draw lessons from these two case histories.

Product Development: A Stylized Account

Research

The stated goal of most biotechnology firms is to produce biopharmaceutical products using the science of genetic engineering. A company's research agenda is set by a combination of factors: its scientific competence and focus, its notion of what is an attainable market, and its sense of a "doable" area of research

(Fujimura, 1987). In fields such as biotech, where knowledge is advancing rapidly, companies invest in research to know "what to make of the news" (Nelson, 1990; Rosenberg, 1990; Cohen and Levinthal, 1989). Technical prowess is a competitive weapon for young biotech companies. But "highly productive R&D operations have a nasty habit of running off in every direction at once," according to the former president of Cetus (Fildes, 1990:67). Basic science research guarantees many more ideas and potential products than a firm can possibly pursue. As a consequence, firms are involved in all kinds of collaborative relationships to attempt to exploit their "surplus" of good ideas.

The basic science that is at the heart of product development may be carried out by university scientists, with funding or technical assistance from a biotech company, or the work may go on in a company's own labs, where it might be supported by an R&D partnership with a large pharmaceutical company. To give the reader a better sense of how this process takes place, we use a hypothetical example of how a project on tumor necrosis factor (tnf) might be carried out.

A scientist at a top research university worked on the identification of lymphokines (such as tnf produced by T-cells in the body's immune system) for a number of years. She described some of the biological activity of a lymphokine and the cells that produced it, but lacked the technological capability to rapidly identify the gene. The lymphokine was produced in very small amounts by the cells that expressed it. Scientists at a biotech company were interested in the lymphokine because some of its properties suggested it could be used as a cancer therapy drug. They provided the professor with the necessary technology and reagents to clone the gene and identify its chromosomal location. A joint paper was published, and the professor received academic and scientific recognition. The company then went on to produce large amounts of both human and murine (mouse) forms of the lymphokine, using recombinant DNA technologies. This product was tested in clinical trials on cancer patients. The university scientist retained loose control of the molecular reagents of the murine form of the lymphokine, and for a short period of time the company consulted with her. Eventually the company released the genetic probes to other scientists. The firm subsequently pursued development of the human form of the lymphokine and produced an anticancer drug.

Patent Law and Intellectual Property Rights

Once a research program has generated potentially innovative ideas or products, a firm will attempt to secure patent protection. Simply put, a patent is a formal grant from the U.S. government, giving an inventor the right to exclude others from making, using, or selling the invention within the United States for 17 years. In exchange for these rights, the patentee is required to disclose the invention in sufficient detail to enable those of ordinary skill to make and use it. The principal requirements for a patentable innovation are that it is new, useful, and nonobvious.

The first step in obtaining a patent is to do a feasibility search to make sure the invention is novel. If it appears to meet this test, then an application is filed with the Patent and Trade Office by a registered patent agent. Foreign filings must also be considered, but requirements vary greatly from country to country. Time is critical because, even though the approval process is slow and cumbersome, there is a 1 year grace period rule that is strictly enforced. For example, if a paper explaining a major breakthrough is published in January 1991, a patent for that innovation must be filed by January 1992 or all proprietary rights are forfeited.

The power to exclude others from making, using, or selling one's invention also includes the right to license others to do these things. In biotechnology, licensing and cross-licensing are critical strategies in product development. Firms generate extensive patent portfolios in order to have technology to trade in the event of patent infringement problems or blocked paths of development. In biotechnology, patents not only protect a market niche or a company's research lead, they also establish reputations as technology leaders and allow companies to use patents strategically for defensive purposes.

The emphasis of patent protection for recombinant products has shifted from "composition of material" patents, describing chemical configuration, to patents covering the genetic sequence of recombinantly produced substances, such as protein hormones, and the technical processes used to synthesize them. These process patents are emblematic of the transformation wrought in the pharmaceutical industry by biotechnology, which has encouraged a shift away from chemical synthesis of biologically active compounds to the recombinant reproduction of previously known biological products. Process patents provide greater protection against importation of competing materials and prevent legal battles from developing over small changes in the genetic makeup of biologically active pharmaceuticals. Arguments over the extent to which small alterations in molecular composition constitute justification for patent extension, approval, or change in regulatory status frequently hinge on the extent to which significant changes in activity are effected. These confusions currently lie behind suits involving Glaxo's Zantac, a traditional pharmaceutical, and Genentech's and Lilly's human growth hormone.

Regulatory Approval

The FDA is justifiably renowned for its labyrinthine approval process for new drugs. (The following description of the review process is substantially derived from Thayer, 1991:30.) The same drug that requires a decade or more to win marketing approval in this country may receive approval in 2 years or less in the European Community's Committee on Proprietary Medicinal Products (CPMP). But the FDA's rigorous and lengthy reviews are a potential buffer to a fairly loose implementation regime: Once a drug has received approval, even for the narrowest of applications, it can be legally prescribed by doctors for any treatment they deem fit.

By the time final approval is sought, a drug must have undergone a three-phase human clinical trial process. First, an investigational new drug (IND) application is filed, which becomes active in 30 days unless denied by the FDA. It is based on results from preclinical laboratory and animal tests for biological activity and safety, and also includes information on drug manufacture.

Phase I of clinical trials consists of profiling the safety and pharmacological activity of a drug. Using a small number of healthy volunteers—not patients—Phase I trials are estimated to take less than a year to complete. Safe dosage amounts are determined, as well as how the drug is absorbed, distributed, metabolized, and excreted. Phase II studies are the first step in efficacy tests on patients. Controlled studies on a population of about 200 to 300 volunteer patients are conducted along with coincident animal and human studies for safety. Such trials are expected to require about 2 to 4 years to complete.

With as much as 10 times the test population as in Phase II trials, Phase III trials are generally the most extensive of clinical studies, running for about 3 years at great expense. The aim is to confirm prior efficacy results in patients afflicted with the specific disease. In addition, low-incidence adverse effects must be identified.

Upon completion of clinical trials, a Product License Application, or PLA as it is known by the FDA's Center for Biologics Evaluation and Review, which handles most biotechnology drug products, is filed. Containing all the data collected in preclinical and clinical studies, along with information on chemical structure, scientific rationale and purpose, and formulation and production details, PLAs can be thousands of pages long. Amgen's EPO application was over 19,000 pages long and weighed over half a ton. The subsequent FDA review and approval process takes an average of 2½ years to complete. Consequently, the entire formal clinical testing and approval process can last between 6 and 10 years.

Due to widespread criticisms over delays, the FDA began a program for expedited drug approval in 1989. Its aim is to decrease the approval time for drugs for serious or life-threatening diseases. Based on promising results from Phase I trials, Phase II and Phase III studies may be combined, saving about 2 to 3 years. Another program, called treatment IND, was started in 1987 in order to make promising investigational new drugs available to seriously ill patients early in the drug development process prior to the granting of marketing approval. To qualify for this status, no comparable or satisfactory therapy or drug can be available, the drug must have already completed or currently be in controlled clinical trials under an IND, and the sponsor of the trials must be seeking marketing approval. The overall review process is not affected.

A company may also apply for an orphan drug designation from the FDA under the 1983 Orphan Drug Act. The act was passed to encourage the development of drug products for rare diseases, defined as those affecting 200,000 or fewer individuals in the United States. Although the drug approval process is unchanged, it provides tax incentives and 7 years of marketing exclusivity to the first company receiving FDA approval for a designated orphan drug. Since the act

was implemented, approximately 60 orphan drugs have been approved and more than 180 are in clinical testing or pending review (Pharmaceutical Manufacturers Association, 1992).

Product Development: The Messy Battlefield

tPA

It is estimated that 1½ million people have heart attacks in the United States each year, and approximately 1 million people are hospitalized. Heart attack, or acute myocardial infarction, is the number one killer in this country, taking more than half a million lives annually (Schmeck, 1988; Sun, 1988). Over the past decade, a wide range of new treatment regimes have become available, ranging from coronary surgery to angioplasty to the use of thrombolytic drugs, such as streptokinase and tPA, or tissue plasminogen activator. Clinical studies differ, but there is clear evidence that thrombolytics can save lives, reducing mortality rates of in-hospital heart attack patients by at least 25 percent (Dalen et al., 1988; Wilcox et al., 1988; White et al., 1989).

Streptokinase, made from streptococci bacteria, was used for 25 years for other conditions before it was licensed for heart attacks in late 1987. It is produced by Hoechst AG of Germany, and the Swedish firms AB Astra and Kabivitrum AB. Activase, Genentech's tPA, is a genetically engineered human protein, and Eminase, produced by SmithKline Beecham (U.K.), is a derivative of human blood. TPA was discovered in the late 1940s, but like EPO, it is a protein found in the human body at concentrations far too low to generate enough protein for distribution. Thrombolytic drugs are known as "clot-busters" because they dissolve blood clots and restore blood flow to the heart.

Within a short time of their release on the market, thrombolytic drugs have become a key part of worldwide cardiological treatment. In 1990, Activase maintained a two-thirds share of the U.S. market for patients being treated with thrombolytic therapy. In dollar terms, Activase had sales of $210 million. That is an impressive figure, but behind these numbers is a complex story of competition, political wrangling, legal battles, and controversial medical research. At the center of the story is the largest and most publicized biotechnology company, Genentech.

In 1973 Stanley Cohen at Stanford and Herbert Boyer at UCSF created the first recombinant DNA clone, thus giving birth to the science of gene splicing. The world did not exactly beat a path to their door. Indeed, most people felt the first uses of this technology would be in agriculture. But a young entrepreneur, Robert Swanson, had other ideas, and after a 1975 meeting with Boyer, Genentech was born. Backed by venture capital funds, Genentech, Inc. was established in April 1976, with Boyer as an independent consultant to the company and a member of the board of directors, and Swanson as CEO. Perhaps no other start-

up company has vaulted into the corporate big leagues as rapidly and dramatically (see Teitelman, 1989:11–20).

Swanson and Boyer convinced young scientists that Genentech could offer the prestige and flexibility of the university as well as the financial rewards of business. New hires were guaranteed research funds, autonomy, minimal corporate bureaucracy, and the right to publish their work (in marked contrast to the policies of established pharmaceutical companies). Genentech pioneered the use of profit sharing and stock options, practices that are now commonplace in high-technology firms. All work is organized into project teams, with non-R&D personnel fitting into a matrix structure. Success came fast to Genentech. On October 14, 1980, the company went public in a widely anticipated stock offering. Within a minute, all of Genentech's shares were sold, and in a trading frenzy the share price climbed as the day wore on from $35 to $89, before falling back to less stratospheric levels. Swanson, at age 32, made half a billion dollars that day. When he returned from his honeymoon later that week, he bought his wife a new car—a Volkswagen.

A distinctive R&D-based corporate culture emerged. The company has routinely plowed 40 percent of revenues back into R&D, and Swanson has consistently touted the goal of becoming an integrated pharmaceutical corporation, built from the ground up, from the research lab to the drugstore counter. TPA was to be the company's flagship drug, the product that would enable Genentech to fulfill Swanson's dream of becoming a billion dollar company by 1990.

The concept of dissolving clots in the heart is not new, but the translation of the idea into practice has been revolutionary.[1] Initially, clot dissolution was effected by injecting streptokinase directly into the heart. This procedure required use of a heart catheter and had to be done at the onset of an attack. At Genentech, a huge research program was under way to mass produce tPA and test it as an intravenous heart attack treatment. Scientists at Genentech isolated the human gene that constitutes the body's own instructions for making tPA and modified it so that mammalian cell cultures would execute the gene's instructions. The modified cells were then grown in fermentation tanks and produced in large quantity.

Genentech knew that dozens of other corporations were pursuing tPA, but it was cocky enough to believe that its research capability would allow it to crack what it thought was a huge market first. Genentech encouraged the National Institutes of Health (NIH) to sponsor an extensive study to evaluate tPA and streptokinase. The research found that tPA was twice as effective as streptokinase in reopening fully closed arteries in the heart. The results were so dramatic that the trials were halted, preliminary results published (*New England Journal of Medicine*, April 4, 1985), and plans for a large nationwide study canceled.[2] Soon after, an independent research team in Europe reached the same conclusion.

Based on the superiority of tPA for dissolving clots, expectations soared. Genentech and Wall Street produced a vision of a blockbuster drug—with antici-

pated annual sales of $400 to 800 million (*Wall Street Journal*, Oct. 11, 1988). Genentech argued that it would be unethical not to use this drug to treat heart attacks. It launched a crusade to win fast approval of tPA from the FDA (Mahar, 1988).[3] Investor confidence skyrocketed, and Genentech's stock reached $80 a share as analysts claimed tPA might even be the industry's first billion-dollar drug (*Wall Street Journal*, Oct. 28, 1986). Researchers involved in trials of tPA joined the bandwagon too, purchasing shares of Genentech stock in anticipation of tPA's launching (*Washington Post*, Sept. 30, 1988). Genentech's stock soon split two-for-one.

By early 1987, it appeared to many people in the industry that Activase was assured of imminent FDA approval. Genentech was stockpiling its product in anticipation of large orders from hospitals. More than 4,000 patients had been treated with tPA in clinical trials, and cardiologists such as Dr. Eric Topol of the University of Michigan, the first physician to use tPA with patients, compared tPA's importance to penicillin. Dr. Eugene Braunwald, chairman of Harvard Medical School's Department of Medicine and director of the NIH trials, called tPA a drug that could save the lives of millions. Moreover, tPA had already been approved for use in France, New Zealand, and the Philippines. So on May 27, 1987, when a FDA Cardio-Renal Advisory Committee turned down approval for tPA, the medical community, the biotech industry, and Wall Street were stunned. The FDA voiced concern over the safety of the drug, proper dosage levels, and the adequacy of the manufacturing process, and required further data documenting that tPA would in fact save lives (see "The FDA Cardio-Renal Committee Replies," letter to the editor, *Wall Street Journal*, Aug. 12, 1987).[4] The incredulity generated by the ruling was aptly expressed by an editorial in *Science* (July 24, 1987, p. 341), which said, "[A] drug that dissolves blood clots should no longer have to answer whether such an action prolongs life."

A firestorm of controversy ensued. Genentech's stock dropped 25 percent the day following the announcement, and the company's market value fell $928 million (*Wall Street Journal*, June 2, 1987). Critics of Genentech emerged, charging it with arrogance in its presentation to the FDA and questioning its extensive preapproval publicity campaign. Some argued that Genentech's failure reflected the young biotech industry's inexperience and naiveté in dealing with the regulatory process, and wondered whether larger, established companies should be preferred with drugs of this importance (see Mahar, 1988; Westphal and Glied, 1990).

Criticisms of Genentech paled in comparison to the attacks on the FDA. The *Wall Street Journal* and *Science* magazine led the campaign. The *Journal*, in a long series of editorials with titles such as "Human Sacrifice" (June 2, 1987) and "The Flat Earth Committee" (July 13, 1987), charged the FDA with incompetence and needless delays, and suggested its "pedantry" was responsible for the loss of lives. *Science*, in its July 24, 1987, editorial, charged that the FDA might not only have "egg on its face, but blood on its hands." Clinical trials on tPA continued.

Approval for sale of tPA was received in West Germany and South Korea over the summer, with approval in Austria and Brazil soon following.

In the fall of 1987, Genentech submitted more data to the FDA. On November 13, 1987, the FDA finally granted a license to Genentech, concluding that Activase was safe and effective.[5] Genentech had been rather quiet between May and November, but upon securing approval it launched a massive campaign to promote Activase and scaled up its sales force. The subsequent marketing of tPA was masterful; brand loyalty among cardiologists was readily established, helped in no small part by glowing endorsements from leading practitioners. By this time, nearly every major teaching hospital in the country and every highly regarded cardiological group had been involved in experimental work with tPA. Later, in February 1989, Genentech was to secure FDA approval for the claim that Activase "saves lives." And in 1990, the FDA extended Activase's scope to the treatment of pulmonary embolism.

Although Genentech did a convincing job of garnering the medical community's support for tPA, other battles, besides the FDA approval process, remained to be fought. Genentech found itself engaged in extensive legal action over patent rights to tPA, slugging it out with large pharmaceutical companies' competitors to Activase, and doing damage control over, and interpretation of, numerous clinical studies of the efficacy and risks of thrombolytic drugs with respect to saving lives.

Genentech has tried to aggressively pursue exclusive broad-based patent rights for tPA, but the rancorous disputes over patents are not due solely to Genentech. In 1980, a Belgian research team purified human tPA isolated from tumor cells and filed for a patent in the United States. A U.S. patent was granted to the University of Leuven, and Genentech, which had facilitated the work of the research team, soon became the exclusive licensee. Innovi, the Belgian company that handles the University's patents, and Genentech have consistently maintained rights to the gene-splicing process, and the substance tPA itself. By trying to enforce property rights for the genetic engineering process, the natural substance tPA, and all synthetic variations on it, they have aimed to shut out competitors.

Genentech filed for patent rights in the United States, the United Kingdom, and Japan. They initially won exclusive rights for tPA in the United Kingdom in 1986, but Wellcome plc sued, and a British court ruled in July 1987 that the patent was too broad. Initially, Genentech feared that this ruling might have wide international precedence, because it was the first court in the world to deal with biotech patents. Instead the ruling turned on a particular interpretation of patent law (Tang, 1988). The British court ruled that tPA was a naturally occurring compound and that Genentech had only discovered a particular route to tPA production. It was therefore not entitled to broad proprietary rights. The British High Court decided not to treat recombinant products any differently than conventional drugs. Wellcome plc, whose version of tPA was at least a year away from market status, also challenged Genentech in the U.S. courts.

In June 1988, Innovi and Genentech were awarded a broad patent for tPA in the United States. Genentech responded immediately by filing a patent infringement suit against Burroughs-Wellcome, the U.S. subsidiary of Wellcome plc, and its partner, Genetics Institute. Wellcome pledged a worldwide fight against Genentech. Nearly 2 years later, the U.S. district court in Wilmington, Delaware, ruled that Genentech's patents were valid and that its patent had been infringed by its competitors, blocking Burroughs-Wellcome and Genetics Institute from marketing tPA in the United States. The U.S. court adopted a very different logic from the British court, taking into account the enormous amount and cost of research needed to develop new drugs and arguing that patent protection was necessary as an incentive to R&D. Shortly after the patent ruling, Philadelphia-based SmithKline, a year before its merger with the Beecham Group (U.K.), producer of Eminase, canceled its codevelopment agreements on tPA with Biogen and Damon Biotech (*European Chemical News,* July 18, 1988). After 6 years of costly research, Wellcome halted work on tPA, ceding the field to Genentech (*Wall Street Journal,* May 11, 1990). In October 1991, the Osaka District Court, in the first biotechnology patent case in Japan, ruled that Japanese companies had infringed Genetech's tPA patent. The court blocked further sale of tPA by Toyobo, and court bailiffs seized the tPA at Toyobo's plant. Genetech's tPA is now the only tPA sold in Japan, where it is marketed by the Mitsubishi Kasei Corporation and the Kyowa Hakko Company.

In its first 12 months on the market, Activase had sales of $190 million. This was a highly successful launching by most standards, with Activase achieving the largest first-year market sales of any new drug in history, but Genentech and Wall Street considered these results disappointing, at least 50 percent less than what they had anticipated. Although Activase sales were initially red hot, racking up $58 million during the last 6 weeks of 1987, once hospital shelves were stocked, orders slowed. Genentech misjudged the speed with which physicians would use Activase. By fall 1988, when Genentech had to halt production of Activase because of oversupply, its stock value had fallen 70 percent to $16 a share (*Wall Street Journal,* Oct. 11, 1988).

What happened to render a new drug that in fact was highly successful a disappointment? Genentech was a victim of its own extraordinarily high goals, which were uncritically embraced by Wall Street and which in turn further fueled the biotechnology community's expectations. Genentech also faced competition from other thrombolytic drugs. Finally, Genentech, and others, underestimated the inherent difficulties in creating a medical market for a novel treatment for a disease that occurs unexpectedly.

One of the critical decisions Genentech faced involved pricing. With Activase, Genentech needed to recoup both its $200 million development costs and the expenses of building the organizational capability to market it. It also needed revenues to fund its new product development. Genentech adopted the view that physicians do not prescribe drugs on the basis of price, but rather on the basis of

merit and familiarity. The press regularly made much of Activase's steep cost of $2,200 a dose, and the company has encountered some difficulty with large insurers, such as Medicare, but remarkably, the price of Activase has held despite competition from lower-priced rivals. The battle among thrombolytics is keenly fought, and rival SmithKline has complained that Genentech's tactics go "beyond the spirit of competition" (see *Business Week*, Nov. 30, 1989; *Wall Street Journal*, March 8, 1990).

Streptokinase, marketed under the trademark Streptase by Hoechst-Roussel Pharmaceuticals, a unit of Hoechst AG, costs less than $300 per course of therapy. In November 1989, SmithKline Beecham won U.S. approval for Eminase, which it priced at $1,700 a dose. SmithKline enlisted Upjohn, which had more experience selling to hospitals, to give the marketing of Eminase a boost in order to catch up with its rivals. Eminase differs from Activase in one significant way—it can be administered in 2 to 5 minutes with a single injection. Activase and streptokinase are given intravenously over several hours. Genentech counters that if complications such as bleeding develop or if surgery is required, Activase (and streptokinase) can be easily discontinued.

To meet the challenges of Eminase and Streptase, Genentech's marketing has switched to emphasizing the benefits of thrombolytics in general, hoping to reach a wider market. To complement its 300-person sales force, Genentech teamed up with Boehringer Ingelheim GmbH of Germany, whose 450-person force put them on more even terms with the SmithKline–Upjohn team. Boehringer has also launched tPA under the name Actilyse in at least 20 more countries, while co-promoting with Genentech in the United States (Genentech, 1989; Thayer, 1991).

Price and organizational capability have not as yet proven to be critical weapons. Activase retains a dominant place in the U.S. market. The growth in the market for thrombolytics has possibly been curbed by the very muddy picture that has emerged from numerous clinical tests of the clot-dissolving drugs. One fairly common theme in these studies is that although all the clot-busters are highly effective in treating heart attack victims, there are minimal differences among the drugs. That conclusion is much debated because ideal comparisons, using commonly practiced treatment regimens, have not been carried out (*Science*, Dec. 16, 1988; Kidder Peabody & Co., March 11, 1991). What is striking to a nonmedical observer is the complexity and scale of these clinical trials. The initial tests were based on small samples and inappropriate comparisons, but the most recent trials are massive undertakings. The GISSI trials in Italy, comparing tPA and streptokinase, involved 12,490 male heart attack patients in 233 coronary units. The researchers found no statistical differences save for a potential for streptokinase to produce allergic reactions. But this study did not use tPA in conjunction with a blood thinner in the same manner as is done in the United States. The HART studies in the United States combined tPA with heparin and found it to be superior. The ISIS trials conducted by a British team, involving

46,000 patients at 936 hospitals (and underwritten by Burroughs-Wellcome and SmithKline Beecham to the tune of $8 million), again found little difference. The study concluded that the three drugs were equally effective, reducing deaths by about 27 percent. There was no doubt that tPA was fastest at dissolving clots, but doing so did not appear to save more lives. Because the version of tPA used in this research was Wellcome's Duteplase (now no longer produced), Genentech is currently cosponsoring, at an expected cost of $40 million, the GUSTO trials on 33,000 patients to compare Activase, streptokinase, and a combined dose of tPA and streptokinase.[6]

The stock prices of biopharmaceutical companies have gyrated with every news of a new clinical trial, but the U.S. medical community's reaction appears to be one of diffidence. Out of an estimated potential 450,000 to 600,000 treatable patients, only about 150,000 to 200,000 are being treated (*Wall Street Journal,* Oct. 11, 1988, Nov. 29, 1989; *New York Times,* March 4, 1991). In contrast, in Europe it is estimated that 90 percent of patients receive clot dissolvers; Eminase is even administered to victims in ambulances (*Business Week,* Aug. 13, 1990). Why has this therapy not been more widely embraced in the United States, particularly given the wide endorsement of tPA by leading cardiologists?

Thrombolytics must be administered within hours of a heart attack. During that time a number of key decisions must be made. Gorlin (1988:351) summarizes aptly:

> The patient must be informed, aware and willing to react and not deny the nature of a symptom. The physician, too, must be alert and responsive, and not necessarily just give an antacid or nitroglycerin and ask for a report in a couple of hours or, worse still, "in the morning." And finally, the system must work. The transport mechanism and staff involved must be prepared; there must be an institutional protocol ready with the hospital staff well apprised when patients reach the emergency room so that a formal plan goes into effect involving the decision for and application of thrombolytic therapy.

These remarks suggest the necessity of having a wide range of people receptive to and informed about clot-dissolving therapy—patients, ambulance teams, emergency room doctors and staff (few of whom are cardiologists), insurance providers, and so on. The fact that the U.S. health care delivery system involves great discretion, boasts a vast array of alternative treatments, and is very sensitive to litigation mitigates against rapid adoption of new treatments (Weisbrod, 1991).

Activase, Genentech's crown jewel, has not proven to be the dramatic success the company had anticipated. To be sure, intensive research efforts and clinical trials are under way to expand its usage to the treatment of strokes, unstable angina, and peripheral arterial occlusion. Genentech also has a research pipeline filled with promising drugs, but in early 1990 its executives decided it could no longer afford the huge development and marketing costs required by their products. Hoffmann-LaRoche, the Swiss pharmaceutical company known for the drug

Valium, was attracted to Genentech's research prowess, and on February 2, 1990, it offered to purchase 60 percent of Genentech for $2.1 billion, with an option to acquire the remainder of the company. Genentech sacrificed its dream of independence, but it has poured the Roche money into its own research and into an internal venture capital unit that now seeds technologically advanced biotech start-ups. In 1992, Genentech expects to plow 50 percent of its revenues into drug research and development (Genentech, 1992).

EPO

In early 1987 a report was published in the *New England Journal of Medicine* concerning the effects of a hormone, erythpoietin (EPO), on anemic dialysis patients suffering from renal failure. EPO increases the supply of red blood cells in the bloodstream, obviating the need for constant transfusions. Although a naturally produced hormone, EPO is not generated by patients with malfunctioning kidneys.

The supplier of EPO for these trials was Amgen, a biotechnology company in Thousand Oaks, California. Amgen was founded in 1980 by George Rathmann, an Abbott Laboratories research chief who wanted into the emerging biotechnology field. Known as the "Golden Throat" at Abbott because of his ability to raise money, Rathmann raised $19 million for the new start-up, with $5 million coming from Abbott itself. Rathmann wanted his new company to succeed with recombinant engineering in a big way, so he was unwilling to commit resources on products such as bovine growth hormone and indigo dye, which had small but definable markets, or on such difficult and time-consuming projects as oncogene research. Early going was tough. Just 2 years after its incorporation, Amgen's funds were about to run out. Taking advantage of a favorable market in technology stocks, Amgen found underwriters, and rushing to file with regulators, went public at $18 a share in July 1983. Beating a sharp downturn in the market by a matter of weeks, Amgen netted $42 million (*Wall Street Journal*, June 2, 1989).

Rathmann coveted a drug that might propel Amgen into the ranks of established pharmaceuticals—something that had not been done since Syntex Labs catapulted into the big leagues after selling oral contraceptives under its own name during the 1950s. Although Amgen did not know it in the early 1980s, EPO was to be that drug (*Wall Street Journal*, June 2, 1989). When Amgen first initiated the pursuit of EPO's genetic sequence, and for a few years thereafter, it did not really know what it had on its hands. In its 1985 annual report Amgen presented EPO last among the five major pharmaceutical drugs it was developing, preceded by consensus interferon, gamma-interferon, interleukin-2, and hepatitis-B vaccine. By the next year the first trials had come in, and they were so strikingly successful that in 1986 Amgen listed EPO first among the same five drugs (Amgen, 1985; 1986). The potential attractions of EPO were clear enough that Amgen had a competitor—Genetics Institute (GI), a Cambridge-based company

founded by two Harvard scientists who were also researching EPO's genetic structure. In its own 1986 annual report, GI ranked EPO second, after GM-CSF, but before G-CSF, interleukin-3, Factor VIII, tPA, and GI's second-generation tPA (1986). By 1987 it was becoming clear that EPO would not only allow a biotech company to survive, it could generate enough income—at least $300 to 500 million—to allow it to become a major company.

Unlike the first generation of recombinant substances such as Genentech's tPA, an entirely new market and infrastructure did not have to be fashioned for EPO. It would find an immediate home in the dialysis market, be utilized among chemotherapy and AIDS patients to boost lowered red blood cell counts, and augment the ability of preoperative patients to donate as much blood as their procedures required.[7] In addition, since there were fewer than 200,000 dialysis patients, EPO would be granted orphan drug status under 1983 federal legislation, guaranteeing the marketer a 7-year monopoly.

Since both Amgen and GI lacked expertise in marketing and required financial and technical assistance to complete the work necessary to take EPO through the clinical trials mandated by the FDA, both signed marketing agreements with major pharmaceutical companies at an early stage. Genetics Institute licensed U.S. and Japanese rights to Chugai Pharmaceutical of Tokyo, and European rights to Boehringer Mannheim GmbH of Germany. Amgen granted nondialysis rights in the United States and all European rights to Johnson & Johnson's Ortho Pharmaceutical subsidiary, and signed a $24 million agreement with Kirin Brewing Company of Japan for development assistance, according Kirin marketing rights in Japan. Amgen kept the profitable—and manageable—U.S. dialysis market for itself. The nondialysis rights also subsumed a relatively small "predialysis" market, comprised of patients who suffered renal distress but not renal failure.

In the fall of 1983, working with the most complex possible combination of DNA sequences, a senior research scientist at Amgen beat GI to the punch by isolating the two parts of the hormone that unlocked the sequence of the gene encoding EPO (Lin et al., 1985). Amgen immediately filed for a patent, but patent examiners forced the company to file separate applications for the gene *and* the process of making recombinant EPO (Andrews, 1990:56). To a significant degree, this discrimination between product and process patents would not only critically slow the Patent Office's review, it would also introduce significant legal troubles for Amgen. Genetics Institute received the first U.S. patent on EPO from another section of the Patent Office in July 1987. This license, known as a "composition of matter" patent, covered only the naturally occurring form of EPO, isolated from the urine of a certain class of anemia patients, and had nothing to do with the manufacture of recombinant EPO. GI isolated the EPO gene 9 months after Amgen (Shoemaker et al., 1985), but that was too late for the company to receive a proprietary patent on the gene or its synthesis.

The incipient patent conflict signaled an implicit judgment on the valuation of pharmaceutical production via the genetic engineering of mammalian proteins.

Amgen argued that traditional interpretations of patent law were irrelevant for the fledgling biotechnology industry, where innovation consists not in discovering drugs (EPO was discovered in 1906), but in discovering and patenting the techniques for manufacturing them. An industry official involved in the Amgen-GI dispute commented, "As a matter of public policy, it doesn't make any sense to reward someone when all they've done is gathered together 1,000 cadavers and drained off the right proteins" (*Washington Post*, August 5, 1988).

Despite its lack of commercial or scientific relevance, GI's patent was a legal gold mine. In U.S. patent law, a patent covering a composition of matter applies to that substance regardless of its production method, potentially making Amgen's forthcoming patent much less proprietary. Conversely, having a patent solely on the pure form of a molecule might not allow its commercialization, since the patent on its synthesis could be needed as well. GI argued that Amgen would have to obtain a license from GI in order to recombinantly produce EPO, aiming to obtain a cross license against Amgen's own patent. Bruce M. Elsen, a vice president and GI's chief patent counsel, stated, "Amgen needs us. We may or may not need Amgen" (*Wall Street Journal*, July 2, 1987).

To enhance their legal position, GI knew that it would infringe Amgen's forthcoming recombinant patent only if EPO was assembled within the boundaries of the United States. According to U.S. intellectual property laws, EPO produced overseas and imported into the U.S. market would not constitute an infringement. GI exploited its marketing deal with Chugai by transporting the EPO gene and host cell used in its production to Japan prior to the granting of Amgen's license, enabling Chugai to manufacture EPO in Japan and export it to the United States. Presuming GI won marketing rights in the United States from the FDA for Marogen, its brand name for EPO, Chugai's Japanese-manufactured EPO could then be sold in the U.S. market (Andrews, 1990:57).

In October 1987, several months after GI was granted its patent on EPO, Amgen received a product patent for the DNA sequence, the vector used to carry the gene fragment, and the host cell. Thoroughly enraged by GI's legal moves, Amgen immediately sued GI for patent infringement and filed a complaint with the International Trade Commission against Chugai Pharmaceutical, aiming to prevent the importation of Chugai's genetically engineered EPO into the United States. GI countersued, arguing on a variety of technical grounds that Amgen's patent was invalid. Amgen's general counsel and a senior vice president, Robert Weist, contended, "Because we were first with the cloning of the gene, and expeditiously filed our patent application, we feel that the system is supposed to give us exclusive rights" (*New York Times*, Sept. 11, 1988).

The International Trade Commission (ITC) turned down Amgen's request to block imports of EPO into the United States by Chugai, GI's licensee. Since Amgen's patent was classified as a product, not a process patent, it was not covered under the 1930 Tariff Act, which prohibits only the importation of goods produced under valid process patents within the United States. However, the tac-

tics of GI and Amgen did not escape the notice of the presiding ITC judge, who wrote in his opinion, "It is clear that Chugai entered into a licensing agreement with Genetics Institute knowing that Amgen had cloned the gene first and applied for a patent first . . . and sought to escape from U.S. laws by manufacturing recombinant EPO abroad" (cited in Andrews, 1990:58). The ruling had another consequence: Congress initiated hearings on the impact of the Tariff Act on competition in innovation-driven industries.

The patent litigation did not interrupt EPO's passage through the FDA, and Amgen pushed its research and development lead over Genetics Institute and Chugai. Johnson & Johnson, Amgen's marketing partner, secured marketing approval in France, in Switzerland, and with the CPMP, the pan-European regulatory body. Amgen initiated talks with the U.S. Health Care Financing Administration, which was responsible for establishing Medicare payments for dialysis procedures, and rushed to assemble a 120-member sales force, hiring a vice president of sales and marketing away from G.D. Searle & Company. Amgen also initiated the use of the company trade name for EPO, Epogen, in all of its product literature (*New York Times*, Sept. 11, 1988).

In the midst of this patent ruckus, Johnson & Johnson, Amgen's own marketing partner, sued Amgen in U.S. District Court, charging Amgen with violating their 1985 marketing agreement. Ortho feared that due to the manner in which Amgen presented its clinical trial data, the FDA would grant Amgen approval to market to both dialysis *and* predialysis patients, who rightfully belonged to Ortho Pharmaceutical. Ortho alleged that Amgen could have filed the relevant information on predialysis patients supporting Ortho's own application (*Los Angeles Times*, Feb. 7, 1989). The federal court quickly ordered Amgen to submit data to the FDA that would aid Ortho in obtaining parallel approval for EPO. Ortho would be compensated in the meantime for Amgen's sales to the predialysis market (*Wall Street Journal*, Mar. 24, 1989). Ortho was also required to purchase all of its U.S. supply of EPO from Amgen.

Only those unfamiliar with the marketing agreement originally signed between the two parties were surprised at the onset of litigation. In 1985, Amgen believed EPO was a relatively modest discovery and granted a healthy chunk of the potential market to Ortho in exchange for cash and technical assistance. It was not until the first test results came in a year later that Amgen understood EPO's importance. Not long after, both companies realized how inappropriate their agreement was for marketing a half-billion-dollar drug. In dividing rights between dialysis and predialysis patients, considered part of the nondialysis market, the firms inexplicably ignored the fact that drugs are not sold to patients but to doctors, and the same doctors treat both groups of patients. "The agreement gave the two companies virtually identical groups of customers. Instead of dividing the market for EPO, the arrangement all but guaranteed that the two firms would come into conflict" (*Washington Post*, May 11, 1989).

Amgen had developed some anxiety about the impact of Johnson & Johnson's huge sales force on its own sales efforts. Gordon Binder, Amgen's president, said, "We had some concern about why they were concentrating all their effort on a tiny market camped right on the edge of our territory" (*Washington Post,* May 11, 1989). Ortho alleged in its suit that Amgen deliberately withheld data to delay it from obtaining FDA approval. The presiding federal judge observed, "[Amgen] seems to have developed some paranoia with respect to its commercial relationship with Ortho" (*Washington Post,* May 11, 1989). Amgen officials claimed that they had never intended to split the kidney disease market, and had naively agreed to the use of the term "dialysis" instead of "chronic renal disease" in the agreement (*Wall Street Journal,* June 2, 1989).

With the dispute with Ortho entering arbitration, Amgen finally received some good news. In June 1989 the FDA approved Amgen's Epogen for use in treating anemia as a result of renal failure (*Wall Street Journal,* June 2, 1989). Simultaneously, Epogen was granted orphan drug status. Three weeks later, the Health Care Financing Corporation announced a very favorable Medicare payment schedule to reimburse the high costs of Epogen for dialysis patients.

The peace was short lived, with court rulings flying fast and furious. In December 1989, the federal district court in Boston issued a ruling in the patent dispute, determining that although Amgen and GI had infringed each other's patents, Chugai had not infringed Amgen's patent because that could be enforced only within the United States. Chugai was thus free to manufacture EPO in Japan and import it into the United States, but Amgen could not manufacture its EPO without violating GI's patent (*Wall Street Journal,* Dec. 12, 1989).

In January, GI asked the district court to grant an injunction to enjoin Amgen from infringing on its patent. Because Amgen was the only company to have achieved FDA approval, GI also asked the court to stay the injunction and to require Amgen to deposit its earnings from Epogen in an escrow account. Opening another front, GI and Chugai jointly petitioned the FDA to rescind the orphan drug status granted to Amgen's Epogen, which was blocking GI's ability to garner approval for its own EPO. In one day, Amgen's stock plunged $4.50, closing at $47.25 (*Wall Street Journal,* Jan. 1990). In March, the court ordered GI and Amgen to cross license their respective versions of EPO. Both parties appealed the order, and in April 1990 a Washington appeals court granted a stay against the lower court's injunction (*Wall Street Journal,* April 18, 1990). Amgen's stock, following a steady market upsurge, closed up $2 at $62.50 a share. In January 1991, the FDA denied GI's request that Amgen's orphan drug status be rescinded, and GI's stock price dropped $1.75 to $37.75 (*Wall Street Journal,* Jan. 15, 1991). Meanwhile, in March 1991, Ortho Pharmaceutical finally won FDA approval for its version of EPO, Procrit, to be marketed for all nondialysis uses (*Wall Street Journal,* Mar. 3, 1991). Amgen was later ordered, in July 1991, to pay Ortho $164 million for violating the terms of the 1985 agreement, due to its failure to help Ortho secure FDA approval.

In the spring of 1991, in a stunning development, Amgen decisively won its dispute against Genetics Institute when the appeals court reversed the lower court's ruling and granted Amgen a complete patent monopoly in the United States over the sale and marketing of EPO. The Court of Appeals ruled that GI had not proved it had isolated a protein with the biological profile described in its patent and rendered it invalid. Simultaneously, the court upheld Amgen's patent, dismissing GI's allegations of procedural violations. It also dismissed GI's claims that GI was first to demonstrate the genetic sequence of EPO. Amgen stock soared $12 to $113 while GI shares lost $21.75, falling to $40.25 (*New York Times,* Mar. 7, 1991). GI subsequently abandoned plans to sell 1.25 million new shares (*New York Times,* May 7, 1991).

In part, GI had sought to invalidate Amgen's patent on the basis that Amgen had not placed in a public depository a batch of the hamster ovary cells used in the "best mode" of manufacturing of EPO as disclosed under its patent. The Patent Office requires such deposits when a biological innovation cannot be adequately described in words. Amgen argued that the technology necessary for EPO's production was widely understood and publicly available by the research community. The appeals court agreed, writing that although biological deposits are required for new organisms isolated from nature, gene-splicing techniques are so widely diffused that they may be used by anyone skilled in the art. Attempting to overturn Amgen's patent validation, GI appealed this ruling to the U.S. Supreme Court, but on October 7, 1991, the Court let stand the earlier ruling, giving Amgen a complete domestic patent monopoly for EPO (Barrett, 1991; Genetics Institute, 1991e; Marshall, 1991b).

Consequent to the appeals court decision, Amgen charged that Genetics Institute had violated Amgen's patent rights by manufacturing EPO in the United States for distribution in Europe by GI's licensee Boehringer Mannheim. In mid-March, GI took a charge of $11 million to cover the costs of its unrecoverable EPO inventories (Genetics Institute, 1991a). In August 1991, a U.S. District Court granted an attachment to Amgen on real estate owned by Genetics Institute to cover any additional damages that might be assigned to Amgen (Genetics Institute, 1991c). Although Boehringer initially agreed to indemnify GI against damages, it later informed GI that it disputed the extent and scope of its obligation (Genetics Institute, 1991f).

There was yet a further wrinkle to the European market. Although Genetics Institute was awarded a European patent on the recombinant production of EPO in May 1991, it was notified a month later by Boehringer Mannheim that Ortho Pharmaceutical, the subsidiary of Amgen's marketing partner Johnson & Johnson, which had earlier received its own European patent, had filed suit for patent infringement in the Federal Republic of Germany. Boehringer Mannheim submitted a formal opposition, and the European Patent Office commenced a review (Genetics Institute, 1991b). In May 1992, a German court preliminarily enjoined

GI and Boehringer from selling EPO in Germany (*Wall Street Journal*, May 28, 1992).

Concurrently, Genetics Institute found its second major drug to enter the FDA review process, GM-CSF, marketed in conjunction with Schering-Plough and Sandoz under the brand name Leucomax, in a losing approval battle with Immunex's GM-CSF, marketed under the brand name Leukine, and a similar drug, G-CSF, marketed by Amgen under the name Neupogen. GI was also forced to cross license its rights to another drug under development, M-CSF, with Cetus because of patent overlaps (*Scientific American*, Feb. 1991). In June 1991, Genetics Institute was granted a separate patent covering the use of M-CSF for lowering cholesterol (*Wall Street Journal*, June 5, 1991).

But after having expended so much cash and energy on EPO, such small potential victories were far too little, too late for GI. In September 1991, it announced an agreement under which American Home Products (AHP) would acquire a majority ownership position in GI. AHP would purchase 40 percent of the common outstanding stock of GI for $50 a share, a total of $366 million. AHP would also acquire 9.5 million newly issued GI shares for $300 million. These acquisitions would leave AHP with 60 percent of outstanding GI shares. Finally, AHP would have the option to acquire the remainder of the common stock at any time over a 5-year period, ending in 1996, at an escalating share price (Genetics Institute, 1991f). This plan was approved by GI stockholders in January 1992.[8] Like Genentech, GI found that costly product development wars robbed it of its independence.

In contrast, Amgen was clearly on a different trajectory. By the third quarter of 1991, the company was so successful it came to be regarded as the bellwether stock for the industry. Epogen sales topped $300 million in 1990, and passed $400 million in 1991. An April 6, 1992, *Fortune* article touted the company's "hyper-growth," noting that over the past four years, its sales had grown by over 100 percent a year. Amgen's second big product, Neupogen, was launched after obtaining FDA approval on February 20, 1991. Its sales for 1991 exceeded $200 million. Suddenly, Amgen was no longer a biotech upstart; instead, its next challenge was to manage its rapid growth.

Implications

It is clearly presumptuous, some would say rash, to talk about the evolution of an industry based on a mere two cases, and, on the surface at least, capriciousness and serendipity loom large in this new field. Witness the costs to Genentech of its unexpected failure to obtain FDA approval in May 1987, or the gains from its surprisingly broad patent victories, allowing it to vanquish numerous rivals, both giant multinationals and fellow biotech upstarts. Amgen's fortunes were almost irreparably damaged when Genetics Institute was awarded the first U.S. patent

on EPO, and then switched with equal drama and suddenness when a U.S. appeals court tossed out the same Genetics Institute patent only 4 years later.

We would remind our readers, however, of just how deep and extensive the involvement was with these two drugs on the part of a vast array of organizations. On the corporate side, tPA pitted Genentech and its subsequent partners Boehringer Ingelheim, Mitsubishi Chemical, and Hoffmann-LaRoche against Burroughs-Wellcome, SmithKline Beecham, Upjohn, and Hoechst along with smaller brethren Genetics Institute, Biogen, and Damon Biotech. EPO involved Amgen, Ortho (Johnson & Johnson), and Kirin Brewery against Genetics Institute, Chugai Pharmaceutical, and Boehringer Mannheim.

Critical decisions about both drugs were made by the FDA and the Patent Trademark Office, as well as parallel regulatory bodies in Europe, Japan, and elsewhere. The time spent in various courts of appeal, and the legal talent and fees, was considerable. EPO also touched on trade policy issues when Amgen appeared before the International Trade Commission. Legislative bodies in several nations debated the use of these drugs.

Coronary care units, kidney dialysis centers, and hospitals all over the world tested tPA and EPO. Tens of thousands of pages were devoted to them in leading medical journals. TPA necessitated the largest clinical trials ever and had the largest first year sales of any drug. And the sales of EPO in the United States surpassed those of tPA by over $100 million in 1991 (Thayer, 1991). All these actions were underwritten by investors, insurers—both private and public—and the financial community. Finally, even though they may be easily lost in the fireworks, there are millions of individuals to whom these drugs represent not corporate strategies but the hope of staying alive.

We stress the number and density of the participants in the development of these drugs for several reasons. One, major innovations are rarely the result of chance or the heroic efforts of single individuals. While the rewards often go to the individuals or firms who, in Rosenberg's (1982:49) felicitous phase, were "on stage at a critical moment," many more make critical contributions to the "cumulative accretion" of useful knowledge. Two, in the early stages of a new organizational field, many of the actions of the participants are symbiotic or mutualistic (Barnett, 1990; Van de Ven and Garud, 1991).[9] As tPA and EPO were brought to the market, extreme expectations about biotechnology were converted into more realistic assessments. It is not surprising that younger companies exploiting "second-generation" technologies are finding start-up and development funds easier to obtain, and they are less likely to be victimized by wild fluctuations in their stock prices as financial analysts and investors acquire the ability to better evaluate company goals. Finally, the experience of tPA and EPO illustrate that sustained cooperation between firms of unequal size can be both practical and rewarding—if both partners are explicit about obligations. One consequence of these two drugs, we suspect, will be to institutionalize various forms of strategic alliances to bring new drugs to worldwide markets.

At this stage in the development of the field, a certain set of skills are firmly in place. The new biotechnology companies know how to foster an internal climate and a set of interorganizational relationships that facilitate R&D and product development. Relational contracting with university researchers, hospitals, research institutes, and so on, has been honed to the level of an art. Companies organize themselves flexibly, with loose, overlapping project-team structures.[10] A set of informal rules is emerging as to how to make joint ventures and strategic alliances work in order to fund R&D or bring a product to the market. This organizational field is now rife with complex networks of both cooperative and competitive relationships (Powell and Brantley, 1992). There are even signs of private dispute resolution, as with the recent case of Genentech and Abbott Labs agreeing to drop lawsuits against one another and cross license in order to speed up the development of second-generation tPA. If we can draw lessons from tPA and EPO, these constantly changing and growing networks represent a new kind of industrial order, a form of organization that fits a field fraught with uncertainty and requiring vast amounts of expertise and capital.

Easy acceptance of ongoing ventures among basic scientists, entrepreneurial firms, and established multinational companies is not sufficient for the legitimation of this field, however. The commercial viability of biotechnology will depend on institutional accommodations to the new demands created by biotech innovations. The further development of biotechnology may depend upon the creation of a facilitative governance structure at the institutional level. As any new technology evolves, there is typically a sorting-out process—what things work, what practices endure? But the kinds of patent issues and the extensive litigation that characterized tPA and EPO suggest that a "normal" selection process might not suffice for biotechnology. Established pharmaceutical companies as well as dedicated biotech start-ups are both experiencing serious risks. Without widely standardized norms of patent protection and understandings about how to construct a patent policy, firms and investors may find it too daunting to support the enormous amount of research necessary to develop new drugs.

A September 1990 General Accounting Office report notes that the U.S. Patent and Trademark Office had more than 18,500 biotech patents pending (Thayer, 1991:34). The sheer volume is overwhelming, and the processing time—estimated at 26 months for biotech—puts product development on hold. The GAO went on to report that the time from original filing to final decision ran about 44 months for biotech patent applications. The overload of patent applications is exacerbated by legal and intellectual issues concerning the patent status of genetically engineered substances. While the PTO has improved its speed in handling patents in general, biotech patents take 40 percent longer than non-biotech patents (Marshall, 1991a). In this field it may not be feasible to wait until legal precedents become established, expensive lawsuits are resolved, and law firms develop extensive competence in the relevant science and technology. Just as product development required novel collaborations, similar institutional inno-

vations—such as sustained cooperation among universities, law firms, biopharmaceutical industry trade associations, and the government—may be necessary to provide a workable normative structure to the field.

Presently the biotechnology organizational field is only partially constructed. On the R&D and development sides, the boundaries of the field are clear and the practices routinized. Many companies are now in their third or fourth projects with collaborators, and although the boundaries of the field are international, they rarely extend outside the pharmaceutical and chemical industries. Professors and universities have also developed standardized policies that facilitate the transfer and commercial development of research ideas.

But the other side of the organizational field has not been created; indeed, all the necessary parts are not even visible, awaiting only some institutional entrepreneur to fashion them. Precisely because the commercial side of the industry is international, the regulatory infrastructure is disjointed, with multiple conflicting requirements and standards. Only in the European Community are there common regulatory policies that transcend national boundaries.

New technological regimes routinely pose key challenges to the capabilities of regulatory bodies. With biotechnology, a critical concern is the lack of relevant expertise to understand what it is that is new about this field. Under "normal" circumstances, a governance structure that legitimates and coordinates activities at the industry level would gradually emerge. In tandem, firms would develop their own skills at managing government relations, handling public affairs, and shaping public debate. But biotechnology faces several critical challenges—the extraordinary closeness of basic science to industry has allowed for exceptionally fast product development; yet given the concomitant high costs of R&D, it is extremely hard for firms to cool their heels while awaiting approval. The lengthy regulatory process is especially daunting for small firms that lack the resources to "hold them over" until approval decisions are reached. And when such decisions are forthcoming, the fortunes of small companies gyrate, going into a tailspin when approval is not received and climbing to new lofty levels when approval is obtained.

The general picture is one of an intense basic science race followed by a clinical trials relay, then slowed by a regulatory marathon. The kinds of firms equipped to run science "dashes" are not the ones capable of coping with grueling marathons. Two consequences result from this process. Few small firms survive intact from the product development process. Most find it essential to take on larger partners. Some even fail; others cease operating as independent entities. Second, under current circumstances, all biopharmaceutical firms opt to price new products extremely high, both to recoup steep development and testing costs and to compensate them for long delays in obtaining approval. But this pricing strategy threatens to run headfirst into the burgeoning demands for health care cost containment. If some kind of governance/regulatory structure that can reduce delays in obtaining patents and approvals, and thereby lower costs, does

not emerge, more coercive accommodations may be demanded by large insurers, governments with limited budgets, and patients faced with an infuriating inability to pay for new wonder drugs that could potentially offer them hope for healthier lives. Such strictures, however necessary from a financial or policy perspective, could well dampen the innovative ethos that gave birth to the new field of biotechnology.

Notes

1. We thank Donald Barr, M.D., for his extensive help in explaining to us the protocols of heart attack treatments and the workings of thrombolytic drugs.
2. Note that these studies compared the clot-dissolving abilities of the two substances, not their ultimate effectiveness in reducing deaths from heart attacks. The far more laborious and costly direct comparisons of the life-saving abilities of thrombolytic drugs would come several years later and be the subject of intense debate.
3. In retrospect, critics would charge that the "passion, politics, and pure hype surrounding the introduction of tPA has been unprecedented" (Mahar, 1988:8).
4. The FDA has two somewhat autonomous branches—one office concerned with biologics (living material) and another with drugs (synthetic compounds). Genentech had worked closely with the biologics office, where tPA was originally assigned. At the last stage of the process it was asked to submit its data to a drug advisory committee, whose requirements Genentech was less familiar with. Shortly before the hearing, the Cardio-Renal Committee requested mortality data, which Genentech was unable to present (*Washington Post,* July 28, 1987).
5. One FDA official quipped: "We are all glad that it's going to get on the market and off our backs" (*Washington Post,* Nov. 13, 1987). Lost in the furor over the FDA's initial rejection was recognition that the entire approval process for tPA was considerably shorter than the average drug review.
6. Note that although Genentech claims that Wellcome's tPA version used in ISIS is unlike Activase, several years previously Genentech did successfully sue Wellcome for patent infringement.
7. It also found a small but significant market among athletes who wanted to boost their aerobic performances. See "It Gives Athletes a Boost—Maybe Too Much," *Business Week,* Dec. 11, 1989, and "Stamina-Building Drug Linked to Athletes' Deaths," *New York Times,* May 19, 1991.
8. In a continuation of GI's litigious history, two class action suits were promptly filed by an aggrieved GI stockholder against GI and American Home Products in Massachusetts and Delaware, their respective incorporated residences. The suits alleged that stockholders of GI would not receive adequate consideration for their stock in the merger and that GI had breached its fiduciary responsibilities (Genetics Institute, 1991d).
9. A crude indicator of this is how closely the stocks of other biotechnology companies followed the movements of Genentech's. With the Roche–Genentech combination, Amgen, Centocor, and Chiron are now playing the role of leading indicators for the industry.
10. Although such skills may now seem commonplace, they are still not found in abundance in large pharmaceutical companies. One reason given for Roche's courting of Genentech was its inability to succeed at product development. From 1975 to 1985, Roche developed only three modestly successful drugs. And despite having two world-class

research centers, one in Basel and another in Nutley, New Jersey, rivalry and corporate bureaucracy have hindered the company's ability to transform ideas into products. See "Roche Is Reviving, But It Still Needs More Drugs," *Business Week*, Sept. 10, 1990.

References

Abernathy, W., and K.B. Clark. 1985. "Innovation: Mapping the Winds of Creative Destruction." *Research Policy* 14:3–22.

Amgen. 1985. *Annual Report.*

Amgen. 1986. *Annual Report.*

Andrews, E.L. 1990. "Mad Scientists." *Business Month* (May):54–58.

Arora, A., and A. Gambardella. 1990. "Complementarity and External Linkages: The Strategies of Large Firms in Biotechnology." *Journal of Industrial Economics* 38:361–379.

Barley, S., and J. Freeman. 1992. "Strategic Alliances in Commercial Biotechnology," in N. Nohria and R. Eccles (eds.), *Networks and Organizations*, Boston: Harvard Business School Press.

Barnett, W.P. 1990. "The Organizational Ecology of a Technological System." *Administrative Science Quarterly* 28:245–273.

Barrett, P.M. 1991. "Genetics Institute Appeal in Patent Case with Amgen Is Rejected by High Court." *Wall Street Journal* October 8:B4.

Business Week. Weekly.

Cohen, W., and D. Levinthal. 1989. "Innovation and Learning: The Two Faces of R&D." *Economic Journal* 99:569–596.

Dalen, J.E., et al. 1988. "Six- and Twelve-Month Follow-Up of the Phase I Thrombolysis in Myocardial Infarction (TIMI) Trial." *American Journal of Cardiology* 62(4):179–185.

Dosi, G. 1982. "Technological Paradigms and Technological Trajectories." *Research Policy* 11:147–162.

Fildes, R.A. 1990. "Strategic Challenges in Biotechnology." *California Management Review* 32(3):63–72.

Freeman, C. 1982. *The Economics of Industrial Innovation.* 2nd ed. Cambridge, MA: MIT Press.

Fujimura, J. 1987. "Constructing 'Do-able' Problems in Cancer Research." *Social Studies of Science* 17:257–293.

Gorlin, R. 1988. "Balancing the Benefits, Risks, and Unknowns of Thrombolytic Therapy in Acute Myocardial Infarction." *Journal of the American College of Cardiology* 11(6):1349–1354.

Genentech. 1989. *Annual Report.*

Genentech. 1990. *Annual Report.*

Genentech. 1992. *Second Quarter Report.*

Genetics Institute. 1986. *Annual Report.*

Genetics Institute. 1991a. *First Quarter Report.*

Genetics Institute. 1991b. "Genetics Institute Granted European EPO Patent." *News Release* May 2.

Genetics Institute. 1991c. "U.S. District Court Grants Attachment Against Genetics Institute in EPO Litigation." *News Release* August 16.

Genetics Institute. 1991d. "Class Action Suit Filed in Response to Proposed Genetics Institute/American Home Products Merger." *News Release* September 25.

Genetics Institute. 1991e. "Supreme Court Will Not Hear EPO Case." *News Release* October 7.

Genetics Institute. 1991f. *Third Quarter Report.*
Gibbons, Ann. 1991. "Biotech Pipeline: Bottleneck Ahead." *Science* (October 18):369–370.
Kidder Peabody & Company. 1991. Research report on clot-busters, March 11. New York.
Lin, F.K., et al. 1985. "Cloning and Expression of the Human Erythropoietin Gene." *Proceedings of the National Academy of Sciences* 82:7580–7584.
Los Angeles Times. Daily.
Mahar, M. 1988. "The Genentech Mystique: How Much Science? How Much Hype?" *Barron's* (January 11):8–9, 20–27, 30–31.
Marshall, E. 1991a. "The Patent Game: Raising the Ante." *Science* (July 5):20–24
Marshall, E. 1991b. "Court Leaves Patent Issue Unclear." *Science* (October 18):368.
Merges, R.P., and R.R. Nelson. 1990. "On the Complex Economics of Patent Scope." *Columbia Law Review* 90(4):839–916.
Nelson, R.R. 1990. "Capitalism as an Engine of Progress." *Research Policy* 19:193–214.
Nelson, R.R. 1991. "Technical Change as Cultural Evolution." Working paper, Columbia University, New York.
New York Times. Daily.
Pharmaceutical Manufacturers Association. 1992. "Orphan Drugs." Washington, DC.
Pisano, G. 1991. "The Governance of Innovation: Vertical Integration and Collaborative Arrangements in the Biotechnology Industry." *Research Policy* 20(3):237–249.
Powell, W.W., and P. Brantley. 1992. "Competitive Cooperation in Biotechnology: Learning Through Networks?" in N. Nohria and R. Eccles, (eds.), *Networks and Organizations.* Boston: Harvard Business School Press, pp. 366–394.
Rosenberg, N. 1982. *Inside the Black Box: Technology and Economics.* Cambridge: Cambridge University Press.
Rosenberg, N. 1990. "Why Do Firms Do Basic Research (with Their Own Money)?" *Research Policy* 19:165–174.
Schmeck, H.M. Jr. 1988. "The Revolution in Heart Treatment." *New York Times Health Magazine* (October 9):14–17, 32–34.
Science. Weekly.
Shoemaker, J.K., et al. 1985. "Isolation and Characterization of Genomic and cDNA Clones of Human Erythropoietin." *Nature* 313:806–810.
Sun, M. 1988. "The Coming Competition Among Clot-Busting Drugs." *Science* (June 3):1267–1269.
Tang, F.Y. 1988. "Recent Development of Patent Law Protection for Products of Genetic Engineering in Great Britain: Genentech's Patent for tPA." *Syracuse Journal of International Law and Commerce* 15:125–139.
Thayer, A.M. 1991. "Biopharmaceuticals Overcoming Market Hurdles." *Chemical and Engineering News* (February 25):27–48.
Teitelman, R. 1991. *Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology.* New York: Basic Books.
Tushman, M., and P. Anderson. 1986. "Technological Discontinuities and Organizational Environments." *Administrative Science Quarterly* 31:439–465.
Van de Ven, A.H., and R. Garud. 1991. "Innovation and Industry Development: The Case of Cochlear Implants." Working paper, University of Minnesota, Minneapolis.
Wall Street Journal. Daily.
Washington Post. Daily.
Weisbrod, B.A. 1991. "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment." *Journal of Economic Literature* XXIX(2):523–552
Westphal, C., and S. Glied. 1990. "AZT and tPA: The Disparate Fates of Two Biotechno-

logical Innovations and Their Producers." *Columbia Journal of World Business* (Spring/Summer):83–100.

White, H.D., et al. 1989. "Effect of Intravenous Streptokinase as Compared with That of Tissue Plasminogen Activator on Left Ventricular Function After First Myocardial Infarction." *New England Journal of Medicine* 320(13):817–821.

Wilcox, R.G., et al. 1988. "Trial of Tissue Plasminogen Activator for Mortality Reduction in Acute Myocardial Infarction." *Lancet* (September 3):525–530.