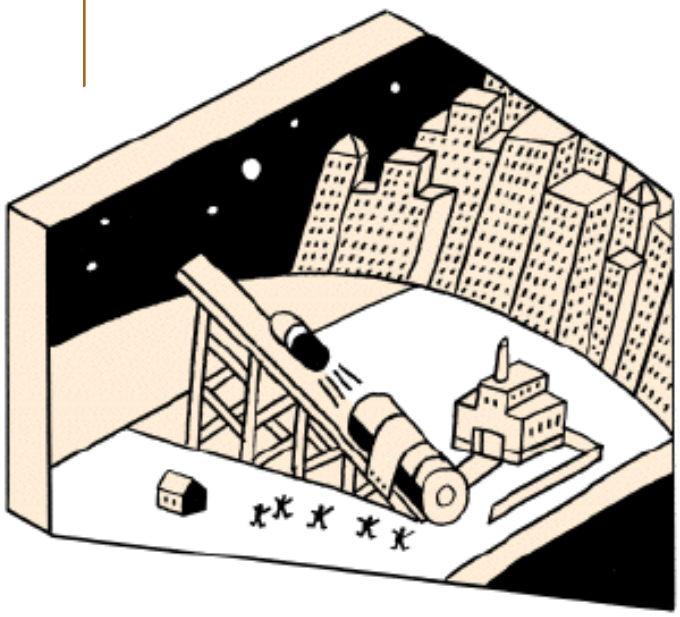
THE ROCKY ROAD FROM STARTUP TO BIG-TIME PLAYER: BIOGEN'S TRIUMPH AGAINST THE ODDS



BY LAWRENCE M. FISHER

How does a fledgling company become an industry powerhouse? By managing itself professionally and betting on the right products. The case of Biogen shows how it can be done.

FROM A DISTANCE, the biotechnology industry appears unique, based on arcane science, with outsize capital requirements and a daunting ratio of risk to reward. But up close, as in Biogen Inc.'s successful introduction of its first product, a drug for the treatment of multiple sclerosis, one sees an implementation of best practices with more universal applicability, based on a clearly articulated strategy and sound management principles.

To be sure, there were twists and turns in Biogen's road to commercialization that could occur only in a company balanced on the leading edge of science. But the company's successful navigation of that journey reflects many more pragmatic disciplines: the timely addition of senior management, the willingness to make tough decisions without flinching, the balancing of internal capabilities and outsourcing and an early devotion to customer service. Within seven months

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of its introduction, Biogen's first drug had captured more than a 50 percent share of its target market, and Biogen is now the second largest independent biotech company, behind Amgen Inc.

For any business, in any competitive industry, the transition from research organization to operating company is critical. James L. Vincent, Biogen's chairman, calls it "transforming knowledge into product." Like adolescence, this corporate coming of age is rarely painless or predictable; at Biogen, the challenge was heightened by a cash crisis brought on by the profligacy of its early management.

Founded in 1978 by a group that included two Nobel laureates, Biogen was perhaps the most ambitious of the pioneering group of biotech companies that also included Amgen, the Cetus Corporation and Genentech Inc. Incorporated in Luxembourg, with its headquarters and research staff split between Geneva, Switzerland, and Cambridge, Mass., Biogen had a vision of remaking and dominating both medicine and industrial chemistry. In the go-go financing climate of the early 1980's, the company raised, and consumed, vast amounts of equity capital.

But there were no products, only a thin royalty stream derived from some early discoveries in immune-system proteins called interferons, which had been licensed to the Schering Plough Corporation. By 1985, when Mr. Vincent was recruited as president and chief executive, Biogen was teetering on the brink, with mounting losses and no way to raise more money. There seemed to be few options but to clean it up and sell the scientific assets to a larger company.

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But Mr. Vincent, who had previously built successful businesses within the corporate confines of Bell Telephone of Pennsylvania, Texas Instruments, Abbott Laboratories and Allied Signal, had a different plan. "I came here to build an operating company," he said in an interview at Biogen's offices overlooking the Massachusetts Institute of Technology. He began by evaluating the company's science. "It was deep, broad and sound; it had just been misguided," he said. To help him think through his options, Mr. Vincent brought in Booz-Allen & Hamilton, the consulting firm, to conduct a complete strategic review.

That analysis and the assurance that he had the backing of Biogen's board in any decision, no matter how distasteful, gave Mr. Vincent the confidence to proceed. But that confidence would soon be tested. "Vincent is a very strong C.E.O., and he is right most of the time. But he really needed to bring the organization together," said Joseph Nemec Jr., a senior vice president in Booz-Allen's New York office.

"If you look at the founders, you would expect them to hire great scientists,"' Mr. Vincent said. "It was also pretty clear that the staffing outside of science was not of the caliber needed to create an operating company. In the previous four times when I built businesses, they were from scratch or from something smaller. I had not dealt with something like this, where you had to take it apart first."

With the benefit of hindsight, Mr. Vincent said there are two classic mistakes made by development-stage companies regardless of industry, and Biogen had made both of them. One, he said, is that "an organization begins to believe its own press notices, overcommitting on expenses before revenues, and they go over a cliff." Second, he added, "they undercall the management capacity needed to build at very high rates of growth. They miscall the timing badly, thinking that there is plenty of time to bring these people on."

So Biogen had to raise money, cut expenses and build a senior management team. Wall Street had written off Biogen, but Mr. Vincent's track record in his previous jobs gave the company a chance to have its proposals heard, said Frederick Frank, an investment banker with Lehman Brothers, who represented the company.

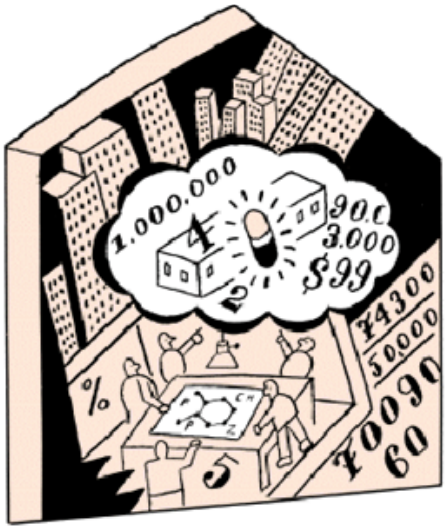
Mr. Vincent's credibility, coupled with an innovative convertible preferred offering that allowed investors to receive a dividend that was sheltered from taxes by Biogen's losses, allowed the company to raise $65 million in the tough market of 1986.

Mr. Vincent "realized that what appeared to be the assumption of the founders was fallacious — that they would have unlimited access to capital so they could take off on many different scientific endeavors," Mr. Frank said. "He didn't bring any science to the party; he just brought focus."

Focus meant eliminating dozens of research projects, selling Biogen Geneva to Glaxo, selling the company's Belgium operations to Roche and closing a lab in Zurich. "We killed about 85 percent of what we were working on when I came," Mr. Vincent said. In short order, the company shrank from 500 employees to 225, and it was not a happy time. "The insecurity level here was so high," he said. "You had so many talented people here; they had been winners all their lives, and this was really their first experience with losing."

Painful but necessary, the shrinkage reduced Biogen's burn rate, that quaint term high-tech startups use for cash consumption. But with product revenues still a distant promise, Biogen needed a revenue source more secure than its repeated sales of equity. So Mr. Vincent spent the latter half of 1986 and all of 1987 renegotiating the licensing deal the company had previously signed with Schering Plough, for the interferons, on more favorable terms. He also signed new deals with Merck, Smith Kline Beecham and Abbott for the use of patented Biogen discoveries in making hepatitis vaccines and diagnostic kits. The royalty stream, just $1.7 million a year in 1986, grew to $150 million by 1996.

"In the first half of 1988, I could finally see we were going to survive financially," Mr. Vincent said. "That's when I started to build the management team to have an operating company. I replaced everybody on the senior management team in a four-year period."



This was another challenge, another source of emotional trauma for the company. The departing executives formed a support group called Biogones. Although operating results were still some distance in the future, it was critical to have senior management in place well in advance, Mr. Vincent said. "To really hire 'A' people is hard," he said. "And you don't want to still be hiring and dealing with the culture when you've shot off the gun. You're in trouble then, not focused."

During this same period, Biogen's scientists zeroed in on two drug candidates. One, which was ultimately named Hirulog, was an anticoagulant, meant to be given to heart patients to prevent blood clotting. The drug was meant to replace heparin, an older drug that is inexpensive and effective but has problematic side effects, including bleeding. Biogen's scientists believed Hirulog would be both safer and more effective.

The other promising molecule was beta interferon, which Biogen had originally licensed to Schering Plough along with its better known relative, alpha interferon. Beta had sat on the shelf while alpha became a successful therapy for hep-atitis and various leukemias; the prevailing belief was that the two molecules were too similar to warrant developing both. Cetus had developed a slightly different form of beta interferon, but it had not shown much promise.

But Biogen's lead scientists were convinced both that beta acted differently in the body than alpha and that their formulation of beta was superior to the Cetus molecule. "Based on their view of the world, I went off to get beta back," Mr. Vincent said.

At such points, the trajectory of Biogen, or that of any drug company, diverges from the path of other development-stage businesses. Drugs that show potential benefits in test tube or

animal studies must all weather a sequence of human clinical trials designed to demonstrate safety and efficacy before they can be submitted for marketing approval by the United States Food and Drug Administration or equivalent foreign agencies. But while this costly and time-consuming regulatory process is unique to drugs, Biogen's management of it still has lessons for other companies.

With Hirulog in clinical trials for multiple heart disease indications and beta interferon beginning trials against hepatitis B, the small company was strained. A smaller parallel trial of beta interferon against multiple sclerosis was financed by the National Institutes of Health, but it was considered a long shot by all concerned. It soon became clear that the company had to either add staff or contract out to manage the multiple trials.

To maintain flexibility, Biogen chose to outsource trial management, using so-called contract research organizations, or C.R.O.'s. "We get C.R.O.'s to do the brute-force stuff — getting the data in, cleaning it up, cranking it out," said Irving Fox, Biogen's vice president for medical affairs. "We work on data analysis, the creative part, in house. That way we don't have to hire armies of people. It isn't easy to outsource; you have to have in-house people who are talented to oversee it. But it gives you the leverage to compete in major markets, not just niches."

But while going outside for help with the heavy lifting, Biogen's management also looked inside during this pivotal period. At many larger drug companies, the leading scientists have little to do with a molecule once it passes from discovery to the trial process and ultimately to market, as it ceases to be a matter of science and becomes an engineering problem and a marketing issue. Not so at Biogen.

"Everybody has to be involved in moving the process along," said Dr. Phillip A. Sharp, a co-founder of Biogen and chairman of its scientific board as well as the head of the department of biology at M.I.T. "It's true that drug development becomes an engineering problem, it becomes a marketing problem, but to the day our first drug was launched, a leading scientist in the company made calls to the regulatory agencies that were critical to the product's acceptance. In a small company, that integrated knowledge and expertise is critical."

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Drugs typically go through three phases of clinical trials before they are submitted to the F.D.A. The first phase, often on healthy volunteers, is to determine safety; the second, on a small number of patients, is to show efficacy; the third, on a large group of patients at multiple sites, is to confirm that the drug is safe and effective. Drugs can fail at any stage, and historically, about nine out of ten do. Nevertheless, optimism is the real dominant gene in the biotech firmament, and most managements believe their molecule will be the one in ten that succeeds.

By the early 1990's, as Hirulog and beta interferon, now known as Avonex, proceeded through the various phases, the ground was littered with wounded biotech companies that had built vast manufacturing, marketing and sales infrastructures for drugs that ultimately failed. Biogen held off, adopting a just-in-time approach.

But at the same time, applying his maxim of adding management capacity in advance of growth, Mr. Vincent was already searching for an executive who could become his successor, someone with experience running a major operating company. He had met and been impressed by James R. Tobin, president and chief operating officer of Baxter International Inc., his direct competitor from his days at Abbott. But Mr. Tobin, who was widely considered a leading candidate to become Baxter's chief executive, turned down an offer to join Biogen.

Months passed. "It was one of the most arduous, intense and far-reaching searches I've ever done in my career," said Frederick Wackerle, a partner in

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WHERE BIOGEN WENT FOR HELP

Small companies with large competitors must ever seek leverage. As Biogen approached the introduction of its first drug, the company found some areas of expertise were too costly or time-consuming to build internally. Biogen turned to outside consultants for matters as diverse as strategic planning and systems implementation. And for one critical process, the company even tapped the expertise of large pharmaceutical companies.

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Biogen executives knew their first drug, Avonex, created to treat relapsing and remitting multiple sclerosis, would face competition right out of the gate, with the prospect of additional competitors in the near future. The Berlex Laboratories division of Schering A.G. was already marketing a similar drug for the disease, and at least three companies — Pharmacia & Upjohn, Autoimmune and Teva Pharmaceuticals — had potential M.S. drugs in the late stages of clinical trials.

For help in planning a competitive strategy, Biogen turned to Joseph Nemec Jr., a senior vice president in Booz-Allen & Hamilton's New York office, who had been a consultant to the company since 1985, when he was brought in to conduct a complete strategic review for James L. Vincent, Biogen's chairman.

Mr. Nemec devised a "war game" to explore the likely outcomes of different competitive scenarios. Biogen's senior executives were divided into teams devoted to each of the competing products, plus a neutral control group to act as umpires, briefed on each company's strengths and weaknesses, and turned loose to compete in a virtual market.

"The war game is a very powerful, albeit elaborate, tool," Mr. Nemec said. "It allows a management team to put themselves in the shoes of their worst enemies, and everybody learns from that. It allows an understanding of market action and reaction in a very compressed time.'"

The primary issue examined in the war game process was pricing. Biogen executives believed they had a better drug than Berlex; should they charge more for Avonex? But Betaseron was already costly, at about $8,500 a year per patient. Should they charge less to grab market share, or would a lower price undercut the claim of superiority? "We worked all night and did an assessment of how the market would accept each product," Mr. Nemec said.

"The key thing that made it work was that once you were on that team, you were as committed to Betaseron as Berlex was," said James Tobin, Biogen's president and chief executive. "All of a sudden that product didn't seem so bad."'

The war games persuaded Biogen to price Avonex the same as Betaseron. A higher price might have created roadblocks for patients trying to get reimbursement from Medicare and insurers unless Avonex's superiority could be proved, which would be a scientifically onerous task. And a lower price was unlikely to generate enough additional volume to offset the lower profit margins. Biogen executives say the war game

proved a fairly accurate predictor of how Berlex would compete.

The war game practice "brings a live-bullet kind of attention and focus to the world you're going to face out there," said Mr. Vincent, Biogen's chairman. "On a global basis we were going into a market with multiple competitors on the horizon. The action and reaction of competitors is where the process has the most value," he said.

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On a more pragmatic level, when Biogen executives realized they had an approvable drug, they also realized they had no systems in place to begin commercial operations. "Had we wanted to take an order, we would have had to write it on a piece of paper," Mr. Tobin said. "We had no inventory control system, no manufacturing system, no receivables, no customer interface."

Yet those systems had to be up and running before the expected Food and Drug Administration approval of Avonex came through, so Biogen turned to the Computer Sciences Corporation, a consulting and systems integration company based in Newton Lower Falls, Mass. "They put on a Biogen shirt, suited up and played," Mr. Tobin said. "We started out without a contract, but at each level of detail of the project, they were right there."

Computer Sciences had considerable experience working with large pharmaceutical companies, but discovered that a small biotech concern was something else. "This is a small rapid-growth company, so we had to adapt the way we did things to fit its culture," said James Kenneally, a partner in Computer Sciences. "That meant coming down off the methodology and all those things you should do to what you have to do given limited time and resources."

Limited resources meant Biogen chose whenever possible to use off-the-shelf software, primarily from the Oracle Corporation, rather than build custom applications. One exception was "Integrated Customer," a custom database combining commercial third-party data with Biogen's own sales figures. "That was very important for them, to get a picture of how the market was responding," Mr. Kenneally said.

One measure of the market's response took Biogen by surprise. After Avonex was introduced in the United States, large numbers of multiple sclerosis patients called the company directly, seeking advice. In most diseases, drug companies rarely have contact with patients. But Biogen executives say M.S. primarily strikes relatively young, affluent and educated white women, and the loss of control associated with the disease seemed to prompt many patients to seek greater understanding of the drug.

"M.S. patients call in droves," said Burt Adelson, Biogen's vice president for development operations. "That has posed a unique challenge to this group for which you couldn't look back at the annals of pharmaceutical history."

Nevertheless, Biogen turned to large established drug companies, which collectively have more experience dealing with patients, and found them willing to share advice. As a result the company hired pharmacists and nurses to field calls from patients and potential patients alike. "Big pharma was very willing to share the information," Mr. Adelson said. "It's the industry's image. It's our responsibility." SB

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McFeely, Wackerle, Shulman, a Chicago-based executive search firm that more typically works for Fortune 500 companies. "We had three candidates from three industries, but Tobin remained our first choice." The next time Mr. Vincent called, Mr. Tobin accepted the position of president and chief operating officer, with the understanding that he would ultimately be chief executive.

Mr. Tobin said that he had grown disenchanted with Baxter's strategic direction and that Biogen's $150 million a year in royalty revenues made the company a more attractive prospect than other biotech concerns that depend on repeated infusions of cash from equity offerings. The risk was lower, but the potential reward — with two drugs in multiple clinical trials — was comparable to other opportunities he considered.

"Biogen was right at the cusp of its curve," said Mr. Tobin, who joined the company in 1994. "They said, 'We need to transition from research to operating company in three to four years.' Jim Vincent saw all of that and personally was planning to change his involvement and had enough foresight to understand the transition was real, it was different, it was hard; it was not a lay-down hand."

While Biogen's royalty revenues mitigated its risk — the company would not die if one or both of its lead drug candidates failed — tough decisions lay ahead. As the data began to trickle in from the trials of Hirulog in heart disease patients and Avonex in hepatitis, it appeared that both worked well enough and were safe enough to gain F.D.A. approval. But the question still loomed, did they work enough better than alternatives — heparin in heart disease and alpha interferon in hepatitis — to succeed in the market? That was less clear.

Complicating matters, the Chiron Corporation, which had acquired Cetus in 1991, completed clinical trials of its form of beta interferon, which it called Betaseron, in a form of multiple sclerosis called relapsing and remitting. Although the data were not particularly strong and the drug had a

range of nasty side effects, the trials showed it reduced the number of flareups suffered by patients. Biogen's Avonex was still at an earlier stage in clinical trials.

With no other effective therapies for M.S., the F.D.A. in 1993 approved Betaseron, which Cetus had licensed away to the Berlex Laboratories division of Schering A.G., a German company not related to Schering Plough. Berlex marketed the drug, paying Chiron a royalty and manufacturing fees. But because it had been considered such a long shot, neither Chiron nor Berlex was ready to manufacture Betaseron in large quantities, and for many months patients had to endure a lottery to determine who got the drug and who waited.

That stumble, plus the multiple side effects of Betaseron, created an opening, and Biogen seized the opportunity. Biogen's scientists convinced Mr. Vincent and Mr. Tobin that Avonex, which more closely mimicked the natural beta interferon protein than Betaseron did, would both be more effective against multiple sclerosis and have fewer side effects than the Chiron-Berlex product. They designed a third clinical trial, intended to show that the drug actually slowed the progression of the disease rather than just reducing flareups.

At the time, almost nobody outside Biogen and its academic collaborators believed this. The prevailing thought was that the two forms of beta interferon were essentially similar and at best Biogen might get F.D.A. approval only to fight a bruising marketing war with Berlex for half of a relatively small market. "Wall Street doubted Avonex," said Jeffrey Casdin, an investment banker with Hambrecht & Quist, who has followed Biogen closely. "I don't think anyone counted on its working."

But Biogen's management did count on it, sufficiently so that trials of Avonex in hepatitis were suspended. This decision was as much strategic as medical, Mr. Tobin said. Although Avonex appeared to be a better drug for hepatitis than alpha interferon, it was only modestly so. Moreover, hepatitis is a huge market, primarily Asia-based, where Biogen would have to compete directly with its own far-larger marketing partner, Schering Plough.

drug Biogen had hoped for. It was time for another tough call.

"I said, 'Let's devote all of our resources to getting one thing right,' " Mr. Tobin said. But the decision to kill Hirulog was not popular. The drug was the company's first real invention — interferons had been discovered before Biogen was founded — and half the company's 414 employees were devoted to the Hirulog program. "Hirulog was the favored son; to put a bullet in that was

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"We chose a market where we were really adding value," Mr. Tobin said. "We chose a bite-size target for our first time out." The total number of patients in the United States with relapsing and remitting multiple sclerosis is about 100,000, easily reached by the kind of small sales force Biogen could afford to mount.

Hirulog was a drug aimed at a big market, the millions of heart disease patients who receive interventional therapy each year, and within Biogen, it was always considered the lead drug. So the company was devastated when, three months after Mr. Tobin's arrival, the clinical trial data on Hirulog showed it was somewhat safer than heparin, but no more effective. Hirulog could be an approvable drug, but probably not the billion-dollar

emotionally the most difficult thing the company had faced," Mr. Tobin said.

The decision was announced at a companywide meeting, and the Hirulog team moved to the Avonex program en masse. Although the company could have reduced costs by laying off some of these workers, it chose instead to retain everybody in the interest of maintaining morale and increasing the momentum of beta interferon.

"We made the decision right up front — we are not going to lose a single person," Mr. Tobin said. "We need everybody." Although Biogen could simply have put Hirulog on the back burner pending the outcome of the Avonex trials, Mr. Tobin and Mr. Vincent decided instead to license the drug to another company. "It made more sense to make a clean decision that you could get everybody behind," he said. "We had to manage expectations."

Expectations were about to go through the roof. The data on Avonex were surprisingly strong: they showed that it did slow the progression of multiple sclerosis to disability and that side effects were substantially reduced compared with Betaseron. M.S. newsgroups on the Internet were soon buzzing with trial patients' anecdotal reports of the new drug's superiority, creating an upswelling of demand even before Biogen submitted its marketing application to the F.D.A.

With the filing of its application, which occupied 32 feet of shelf space, Biogen entered a period of frenzied activity. Complicating matters, the German partner that had supplied beta interferon for the clinical trials declared bankruptcy, forcing Biogen to jump-start production in a pilot plant in Cambridge, at a cost of $10 million, and requiring another level of F.D.A. approval.

Construction began on a volume production plant in Research Triangle Park, N.C., consuming another $60 million. Computer systems for inventory, order entry and billing had to be built [see article, page 59], costing about $20 million. Filing simultaneously with regulatory bodies in Europe added $30 million more to expenditures.

And now the hiring of the long-deferred marketing and sales staff could be put off no longer. In the fall of 1995, Biogen hired a senior executive from Zeneca, the British pharmaceutical giant, and asked him to assemble a non-traditional team, emphasizing individuals with substan-

tial medical backgrounds.

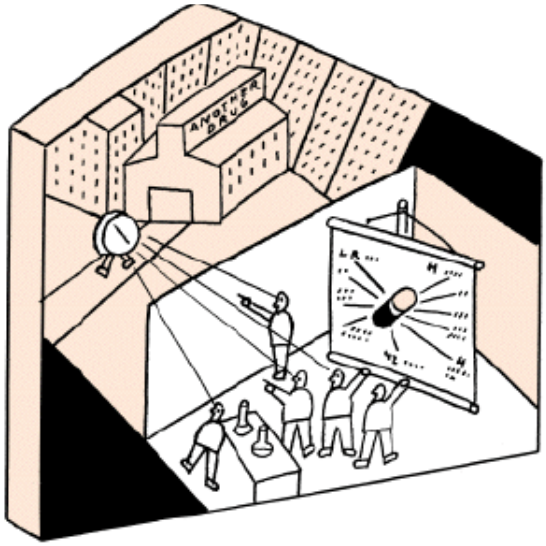
"They had to be the best," said Mr. Tobin. "It isn't often salespeople get to introduce a product. It was as close to just-in-time as you could get. We hired management in November, December and January and started hiring reps in January. We could have launched March 15; as it was we launched in May."

The delay was caused by a last-minute legal challenge from Berlex, which induced the F.D.A. to postpone approval. Because both companies held various patents covering beta interferon, Biogen had approached Berlex at one point about a cross license that would allow both products to coexist. Berlex rebuffed that overture and took the unusual step of suing the F.D.A., claiming that an approval of Avonex would violate the "orphan drug" status the agency had granted Betaseron.

An orphan drug is granted a seven-year pledge of exclusivity by the F.D.A. in return for treating unmet medical needs. For a similar drug to be approved, it has to show superior efficacy or greater safety, or it must prove that it is actually significantly different from the orphan drug. Biogen went to work with the agency to defend Avonex, with the bonus that the F.D.A. then went on record in court saying Avonex was a superior drug.

"Getting this over with promptly was a corporate goal because Berlex was using this to go to doctors and say Avonex would never come to market," said Michael Astrue, Biogen's vice president and general counsel. "So we went in there fast and forcefully." Although Berlex failed to block Avonex from the market, patent litigation continues between the two companies.

With the regulatory path cleared, the priority became to ship Avonex as soon as possible after F.D.A. approval.



"We had competition, and we as a company had zero commercial credibility, so we wanted to make a statement," Mr. Tobin said. In contrast with the lottery that had been set up to distribute the limited supply of Betaseron when it came to market, Biogen was determined "to be able to start shipping within 33 hours of approval, all the inventory you could want, and get it to you any way you wanted." He added, "That made a very strong statement to a tight community that had been irritated by the Betaseron experience."

Avonex was approved for sale in the United States on May 17, 1996, and the market battle with Berlex began in earnest. "It took us seven months to catch them, and two-thirds of that was market growth," Mr. Tobin said. "If all we had done was arm-wrestle Berlex for its 30,000 patients, we each would have wound up with 15,000. Now they have 20,000, we have 25,000 and everybody wins."

The success of Avonex is an ongoing story, as Biogen must find ways to increase its penetration of the 100,000-patient market in the United States and to expand the drug's reach in other ways, possibly by treating other diseases. Approval by the pan-European regulatory agency came this April, opening another market comparable in size to the United States and presenting fresh challenges: no other biotech company has introduced a major drug in Europe without a local partner.

And Biogen must produce more new drugs, whether through internal research or strategic alliances, to prove that Avonex was more than a one-time convergence of smarts and luck. "Of course the question now is, What's the encore," Mr. Vincent said. "Many companies have shown they can't do an encore. But nobody will ever convince me it's harder to do the encore than the orig-

inal performance. I'll take this hand any day over the one we had in 1986."

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