

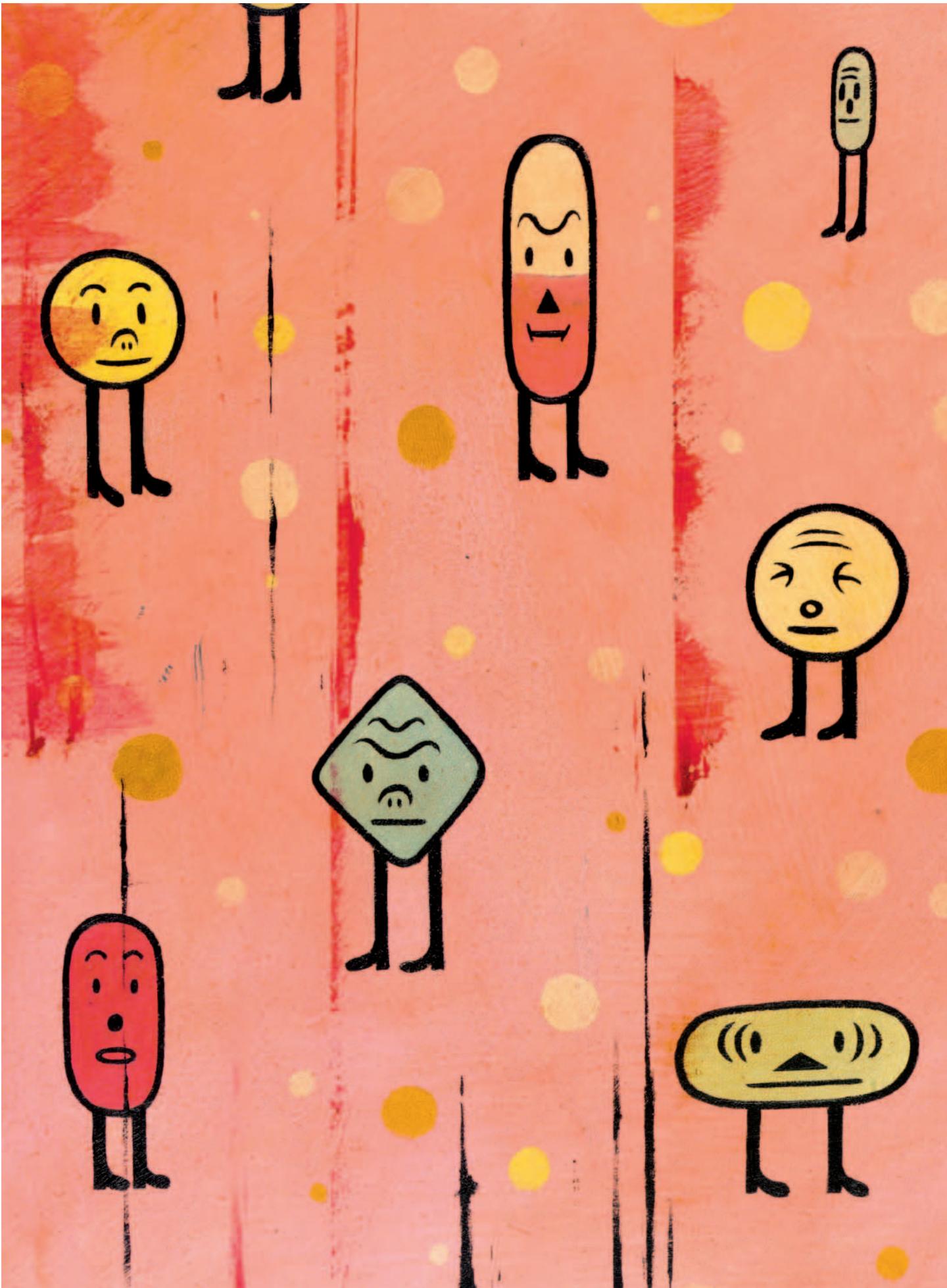
LIKE MANY things in life, some cholesterol is good, but **TOO MUCH OF A GOOD THING CAN BE BAD.** Cholesterol is necessary for producing the bile that helps digest the fats in our food. It also helps stabilize and protect cells, and it plays a key role in the production and use of vitamin D and certain sex hormones. But extra cholesterol can build up and constrict or block arteries, leading to angina, heart attacks, and stroke. ¶ Doctors had suspected for years that cholesterol played a role in heart disease. But their suspicions weren't confirmed until 1984, when a national study demonstrated that cutting cholesterol significantly reduced the risks of heart attacks and death from coronary heart disease. On this news, doctors rushed to help their patients with high cholesterol find a way to bring it under control. But at the time, the available treatments were only mediocre. A few anti-cholesterol drugs such as Lopid, Cholybar, and Questran were on the market, but none were very effective and patients complained about their flavor and gastric side effects. The other proven remedy, diet and exercise, was as unpopular, difficult, and frequently unsuccessful then as it is now. Yet the potential market for a new anti-cholesterol treatment was huge, since about one-half of Americans have cholesterol levels above the magic number of 200 milligrams per deciliter. The drug race was on. ¶ Just three years later, Merck Pharmaceuticals introduced Mevacor, a blockbuster new drug that promised to cut cholesterol levels by 30 percent with minimal side effects. In less than 18 months, Mevacor had

By Carrie Conaway

THE PROS AND CONS OF PHARMACEUTICAL PATENTS

Illustrations by Gary Taxali

Patents can yield more and better drugs for society by protecting the economic value of drug research.



captured 42 percent of the market for cholesterol-reducing drugs. Through the success of Mevacor and a follow-on product, Zocor, Merck would dominate the anti-cholesterol pharmaceutical market for almost a decade.

But don't let this fast timeline fool you. By the time of the 1984 cholesterol study, Merck was already well on its way to putting Mevacor on the market. The research behind the new class of drug Merck discovered, known as statins, originated decades earlier when scientists began to uncover how cholesterol was produced in the body. It took many years and thousands of rejected compounds to move statins from research idea to the drugstore shelf, even after the basic science of cholesterol was known.

The payoff on this investment of time and resources has been huge, for Merck and for society. Today cholesterol-reducing drugs are the nation's pharmaceutical sales leaders, with more than \$11 billion of sales per year in the U.S. alone, and physicians have rated statins the fourth-most-important medical breakthrough of the last 30 years after magnetic resonance imaging, ACE inhibitors, and angioplasty.

The cost and uncertainty of the drug development process mean that pharmaceutical firms need to receive large returns on any successful drug in order to counterbalance the failures along the way. Yet the products they make, once discovered, are extremely easy for other firms to copy. Without some kind of legal right to the economic returns from their research findings, pharmaceutical companies would have no incentive to develop new drugs—and society would miss out on the new and improved treatments for disease and illness that the companies would discover. To solve this problem, the government grants drug manufacturers patents—short-term monopolies that limit competition and thus help ensure that companies receive a return on their research. But this benefit to inventors comes at a social cost. The shield from competition that patents provide gives manufacturers the economic power to set prices higher than competitive markets would allow, on the very goods that society regards as critically important to make available.

There is no doubt that patents foster innovation, especially for pharmaceuticals. But it is harder to know whether their current structure has struck the right balance between their costs and

benefits for society. With drug patents, as with cholesterol, too much of a good thing may be bad.

LONG TIME IN COMING

Research and development is critical to the long-term health of any pharmaceutical firm, as these companies live and die on their pipeline of new drugs. Without a steady stream of new products on the horizon, a drug company will falter as its older products are superseded by other companies' inventions. But new products are not easy to find. Only 10 percent of potential drugs advance to the human trial stage, and only a small fraction of those tested ever make it to market.

The first steps towards what ultimately became Mevacor were taken in the early 1950s, when a Merck scientist isolated mevalonic acid from a yeast extract and demonstrated that it could be converted into cholesterol. But Merck didn't make much more progress with cholesterol drug development until 1973, when researchers at the University of Texas uncovered critical details about the chemical reactions behind cholesterol production in the liver (where 70 percent of the body's cholesterol is made).

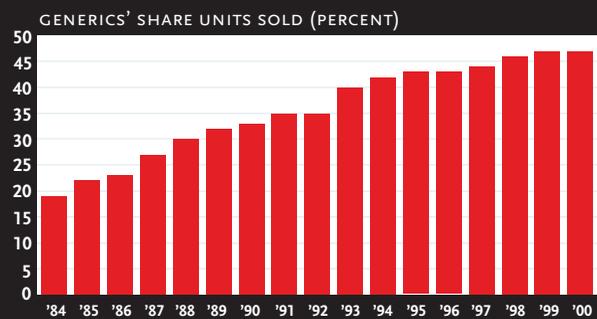
Three years later, scientists at Sankyo, a Japanese pharmaceutical firm, found a fungus-derived compound that could block the activity of HMG CoA reductase, an enzyme at the head of the cholesterol production chain. By looking at similar fungi, in 1978 Merck zeroed in on another compound, lovastatin, which successfully blocked cholesterol production in animals. They were now ready to take the next step in getting the drug on the market—obtaining approval from the federal Food and Drug Administration (FDA).

The FDA requires that any consumer pharmaceutical product go through a series of rigorous clinical trials to demonstrate the drug's safety, efficacy, and proper dosage in humans. Once Merck knew its new compound worked in animals, it launched into human testing. But worries about a potential cancer risk in Sankyo's similar compound halted the trials for almost four years, and they weren't resumed in full force until May 1984. Lovastatin turned out not to be carcinogenic and in fact had very few side effects, leading the FDA to approve the drug only 10 months after application—near-record time. Merck received final approval to put lovastatin, trade-named Mevacor, on the market on September 1, 1987.

The length of the research and development process for Mevacor—two decades before the initial research on cholesterol production led to a target for a potential drug, and another 11 years before Mevacor went on the market—is not at all atypical for the pharmaceutical industry. And companies can invest years in searching for a drug treatment and still find nothing at all. As a result, pharmaceutical development is extremely expensive. The Pharmaceutical Research and Manufacturers of America, the pharmaceutical industry's trade association, estimates that the U.S. pharmaceutical industry spent over \$30 billion just on research and development in 2001. This amounts to almost one-sixth of their sales revenue, near the highest among high-technology industries. In total, each new drug that makes it to market can cost half a billion dollars to develop from beginning to end, including the cost of all the wrong turns along the way.

THE GROWTH OF GENERICS

The Hatch-Waxman Act of 1984 eased many restrictions on developing generic drugs. As a result, the percentage of prescriptions written for generics has more than doubled in the last two decades, saving consumers billions each year.



SOURCE: IMS Health

It can take years to develop a chemical into a marketable drug, and thousands of possibilities are discarded along the way.



TAXALI



Patents keep competitors at bay. During a patent's 20-year lifespan, no one else can make the same product without a license or permission.



THE HATCH-WAXMAN ACT: R_x FOR THE GENERIC DRUG MARKET

Until 1984, federal regulations made it extremely difficult to get a generic drug on the market. Generic manufacturers had to perform the same safety and efficacy testing required for brand-name drugs, even though they were producing a drug chemically identical to one that had already been approved. Few companies were willing to take on this costly process unless they knew their generic would capture significant market share, so manufacturers made generic equivalents only for the most popular and effective drugs. In 1984, less than 20 percent of pharmaceutical prescriptions were written for generics.

But spiraling drug costs in the early 1980s spurred Congress to pass the Hatch-Waxman Act, with the hope of fostering the generic drug market while also protecting brand-name drugs. Generic manufacturers would no longer have to repeat the safety and efficacy tests; they would only need to demonstrate that

their product was bio-equivalent to its trade-name counterpart. The legislation further laid out criteria under which generic manufacturers could challenge a patent's validity and thereby start making a protected product before its patent actually expired. They also received additional protection from patent infringement lawsuits brought by brand-name drug companies.

In exchange, brand-name manufacturers were granted five years of guaranteed market exclusivity before any generic competitor could challenge a patent, along with patent life extensions to compensate them for the time lost between patent filing and FDA approval. These changes added an average of about three years to the effective life of pharmaceutical patents.

In addition, unlike any other patent owners, brand-name drug makers were also guaranteed 30 months of protection from generic competition for each time a

generic manufacturer filed a suit over a patent's validity, to allow time to sort out the competitor's claims before any economic damage was done. (In other industries, if a competitor claims a patent is invalid, the patent owner must obtain a preliminary injunction from a court to prevent the competitor from making its product, and this injunction is not guaranteed.)

In the two decades since the Hatch-Waxman Act was passed, the generic market has opened up considerably. Today nearly half of all prescriptions are written for generics, saving consumers and insurers billions of dollars each year. And the Act appears to have had little impact on pharmaceutical innovation levels. While it didn't solve every problem in the pharmaceutical market, most observers agree that the Hatch-Waxman Act has struck a good balance between protecting intellectual property and promoting market entry for generics.

When a pharmaceutical company thinks it has identified a possible winner, then, it begins to worry about how to protect its research investment. And that was exactly Merck's situation in 1979. It had a promising molecule in hand and knew it was facing competition, especially from Sankyo, in turning the chemical into a marketable drug. So on June 15, 1979, the company applied for a patent with the U.S. Patent and Trademark Office.

THE ECONOMICS OF SECRETS

For firms in which research drives growth, nothing is more valuable than the knowledge they create—their intellectual property. The longer they keep their trade information secret from their competitors, the more money they make. This is why many companies require employees to sign noncompete contracts preventing them from jumping ship to work for a competitor, and it's why they spend billions of dollars each year to keep their research and product designs from being stolen by computer network attacks, reverse engineering, and industrial espionage.

But while keeping this information secret may reward inventors, it doesn't always benefit society. If no product designs were ever publicly released, innovation would stagnate. Inventors would be forced to start from scratch on every new product and would wastefully duplicate others' efforts. Knowing a product's design also helps to accelerate the use of the new technology and to improve the quality of future innovations, especially in cases where the new product must be compatible with earlier versions.

To adjudicate between inventors' interest in maximizing the return on their investment and society's interest in disclosing product designs, the U.S. Constitution provides for patents: exclusive time-limited property rights granted to inventors in exchange for their publishing information about how they design and make their product. During the life of the patent (currently 20 years from the date of application filing), no other manufacturer may make the same product without first obtaining a license or other permission from the patent owner. Once the patent has expired, the product is fair game for anyone to copy.

Since there are almost always competing—though possibly inferior—products on the market when a new design arrives, patents do not typically create true monopolies. But they do limit the competition a product will face during the life of its patent, since no other company can make an exact copy. This is the social tradeoff of patent protection. The very shield from competition companies need as an incentive to innovate can translate into higher prices and reduced access for the rest of society while the patent is in effect. In many cases, patented products turn out to have limited commercial value, mitigating this problem. But for the few especially successful products, the economic value of their patents—and the potential impact on society in terms of price and access—can be quite large.

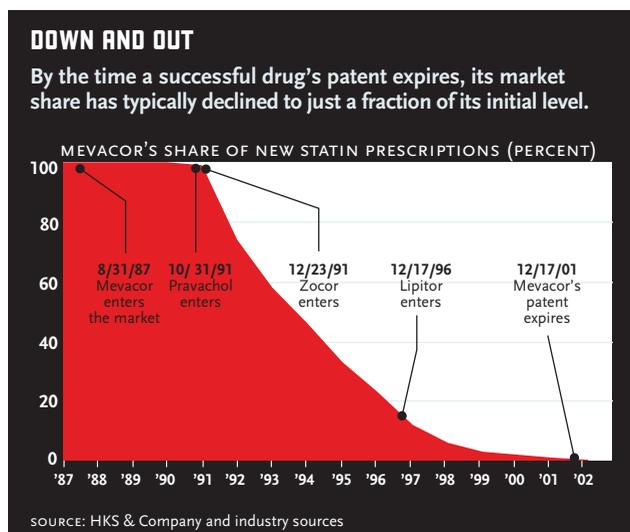
Empirical estimates of this value are hard to come by, since it is not easy to determine what a company's prices or profits would have been were it not for its patent protection. But there is no

doubt that the value of patent protection is higher for drugs than for most other high-tech products. While other companies can rely on inventive lead time and employee secrecy to keep competitors at bay, with pharmaceuticals the cat is out of the bag once the product hits the market. With only the pill itself in hand, it can take just weeks for a competitor to replicate it, a trifle compared to the years of work invested in its discovery. Copycatting is made even easier by the FDA approval process, since the application itself discloses key details about how the drug is manufactured. And the potential payoff to copying is especially great because drugs work by themselves, instead of being just one element of a complex machine (think of all the innovations that go into the average DVD player or computer).

To be sure, patents are by no means the only reason why pharmaceutical prices are high. As noted earlier, the process for discovering and developing drugs is quite time-intensive and expensive. Furthermore, consumers and even doctors are often not well informed about prescription options and prices and often choose brand-name products marketed to them by pharmaceutical companies, rather than the cheapest drug that will treat their problem. Those with insurance coverage for drugs don't pay the full cost of their prescriptions, reducing their incentive to shy away from the most expensive brand-name products. And regulated drug prices overseas mean that pharmaceutical companies must charge more in the unregulated U.S. market to make up for losses elsewhere. Notwithstanding these and other issues, patents are a significant factor in pharmaceutical prices, since they leave the door open for drug companies to restrict competition and raise prices.

DISTINCTION WITHOUT A DIFFERENCE

With a patent in hand by 1980 and FDA approval for Mevacor in 1987, Merck was ready to take on the anti-cholesterol market. Thanks to an easy-to-use product with a large potential audience—and to the success of its direct-to-consumer advertising, one of the first times a drug company used this approach—Mevacor quickly became one of Merck's biggest sellers. In Mevacor's first year on the market, it earned an estimated \$260 million, the highest sales ever for any prescription medicine to that date.



In response, other pharmaceutical companies ramped up their efforts to find a drug that could compete. They could not literally replicate the molecule Merck had patented; that could only come once the patent expired. But they could design around it, using the knowledge Merck had gained to find a similar, but not identical, compound that generated similar results.

This approach makes sense in an environment in which intellectual property is protected with patents. Short of inventing an entirely new product, designing around an existing product is the quickest and easiest way for manufacturers to enter a market. Indeed, it can take as little as one year before the first design-around products make their way to store shelves. The strategy is to capture market share either by pricing the product at a discount or by improving on the original in some way. These new products will be fighting an uphill battle to gain sales, since the name recognition and familiarity of the original product will help the innovating firm to maintain its revenues. But design-arounds can often make a significant dent in market share—sometimes as much as 15 or 20 percent in their first year on the market.

From a social perspective, though, there's a tradeoff. The incentive to design around an existing product is also an incentive to create products with distinctions that make no difference. Products that make substantial improvements to the original design—in the case of pharmaceuticals, perhaps drugs that are more effective or easier to tolerate—are always welcome. And these improved products carry the added benefit of increasing competition, which tends to hold the line on prices. But design-arounds can also be "me-too" products with little to no advantage over the original. While they might help increase competition, this benefit may not outweigh the cost of discovering the copycat drug. Furthermore, it would be less socially wasteful if the effort that went into developing me-too drugs had instead gone toward truly novel innovative activity, which could have had greater benefits in terms of quality or cost.

Because of its unprecedented success and large potential audience, Mevacor was a natural target for me-too drug development. The first on the market, in October 1991, was Bristol-Myers Squibb's pravastatin sodium, sold as Pravachol. Pravachol is a classic me-too drug. It is less effective at reducing cholesterol than Mevacor, but it is also priced 5 to 10 percent lower, making it attractive to managed care plans and others looking to cut prescription costs. Pravachol's price advantage was enough to capture 20 percent of the statin market by 1994.

But Merck had another trick up its sleeve. During the period when human testing on lovastatin was halted, Merck scientists continued to look for another agent that blocked HMG CoA. They came up with simvastatin, which turned out to cut cholesterol more effectively than either Mevacor or Pravachol. Trade-named Zocor, simvastatin entered the market at the end of 1991 and quickly outstripped both Mevacor and Pravachol in sales and new prescriptions. Zocor and Mevacor continued to dominate the market for the next six years, even as two more copycat drugs entered the market. Only in late 1996 did a product finally appear that significantly improved on Zocor. Both cheaper and more effective than any other statin, Pfizer's Lipitor vaulted into first place in sales by 1998 and has remained there ever since.

Successful drugs attract competition from copycats as well as products that substantially improve on the original formulation.



THE GENERIC THREAT

Competition from copycat drugs had been cutting into Mevacor's market share for years. But its patent expiration on December 17, 2001, was its death knell. The axe had been slated to fall the previous June, but at the last minute, the FDA granted Merck an additional 6 months of market exclusivity in exchange for studies on Mevacor's safety and effectiveness in children. The very day that extension expired, seven separate generic manufacturers put generic lovastatin on the market at around \$1 per pill—half the cost of Mevacor.

What makes generics so threatening to brand-name drug companies is that they are exact copies of an FDA-approved drug that can be sold at a much lower price since they cost much less to develop. Federal legislation passed in 1984 helped open the markets for generics, which prior to that point had comprised only about 20 percent of prescriptions (see sidebar on page 15). Today nearly half of all prescriptions are written for generics (see chart on page 12), and they cost an average of 70 percent less than trade-name drugs. Generics typically capture almost half of the market for their brand-name equivalent within their first year of availability, substantially cutting consumers' prescription costs. A 1998 Congressional Budget Office study showed that using generics saved consumers \$8 billion to \$10 billion in 1994 alone.

One might expect that drug companies would try to compete with generic equivalents by lowering their prices. But instead, they typically keep prices high, capitalizing on the fact that patients tend to be loyal to drugs that they have found effective. In a rare break with this practice, Merck once offered a two-week discount of about 4 percent off Mevacor and Zocor in 1993 in response to price competition from Pravachol. But prices quickly returned to their normal levels, and the discount was never repeated. Today, even though its patent has expired, a single Mevacor pill still costs around \$2—almost the same as its 1991 price in real terms.

BALANCING ACT

Merck certainly stood to lose financially when generic lovastatin hit drugstore shelves. But it's easy to forget that by 2001, Mevacor controlled less than 1 percent of the statin market. Mevacor had long ago lost the pole position, first to Merck's own Zocor and later to Pfizer's Lipitor. In general, competition from similar brand-name drugs can shave four times more off a drug's present discounted value than does generic competition. And truly innovative products can completely decimate a previously successful drug class, as Mevacor did for Lopid, Cholybar, and Questran in the late 1980s. For most drugs, the real revenue losses come not when they are copied, but when they are superseded.

Yet drug companies spend millions of dollars each year staving off generic competition at the end of their products' lives. They routinely sue generic firms for patent infringement. They separately patent the active ingredient of a drug, its form of administration, and even the by-products of its breakdown in the body to make it more difficult for competitors to design around the original product. They make the existence of some patents known only at the last minute, forcing potential generic competitors to go back and prove that they are not violating these "submarine patents." A few have even paid generic competitors not to make their drugs,

a tactic which has not won them friends with the Federal Trade Commission, the nation's antitrust enforcement agency.

Drug companies do this for two reasons: it pays off, and they can. Every year that drug companies add to a product's effective patent life increases the drug's expected return by an average of \$12 million, according to a 1990 Congressional Budget Office study; the figure would likely be significantly higher today due to pharmaceutical price inflation. This may not be much relative to the returns for finding a blockbuster new drug, but it's enough to justify the expense of litigating the patent violations. Plus this income is far more certain than the unpredictable returns from new product development. More important, while brand-name drug companies can't do anything about the me-too products that design around their patents, they *can* use their patent protection to limit the competition they face from exact duplicates.

The reason society grants patents, however, is to ensure a fair balance of returns for both inventors and society, not to keep competition at bay indefinitely. Inventors should be able to reap the rewards of their innovations, but so too should society be able to profit from product design disclosures and from the lower prices and increased access to products once the patents expire. Some are now arguing that in the case of pharmaceuticals, the scales may have tipped out of balance. One recent proposal to address this problem would limit drug companies to one 30-month extension of protection upon patent litigation versus the unlimited number of extensions available today. Another would disallow generics from being paid by brand names not to market their drugs.

An even more effective tactic would be to foster greater pharmaceutical innovation. Drug companies would not need to be so concerned with patent expirations if they had lucrative drugs waiting in the wings, and developing new drugs would also have the additional advantage for society of creating more and better treatments for disease. The pharmaceutical industry is already moving in this direction, using clues from basic science research to identify new treatments rather than relying on blind searches for pharmacologically active chemicals. This approach should lead to more efficient research processes and therefore greater innovation. Another way to promote innovation is to create a more competitive marketplace. Adjudicating more antitrust claims and reducing the restraints on generic entry, for example, would provide a greater incentive for drug companies to find new treatments.

Ironically, however, it may not make sense to try to encourage innovation by extending patent life or breadth. Patent protection is already strong in the United States. In this legal environment, adding on to the life of a patent or allowing patents to cover more aspects of a product's design could actually stall innovation by preventing later inventors from improving on the original design.

Nonetheless, patent law will always play a key role in protecting the rewards from discovery in the pharmaceutical industry. It has proven itself effective at ensuring both that inventors receive the economic benefits of their innovation and that valuable treatments see the light of day. But reaping the full social benefits of pharmaceutical invention, including fair drug prices and quantities and abundant treatment options, takes more than just patent protection. It takes more invention, and patents are only a piece of that puzzle. *