BY MARCIA ANGELL
The Truth About Drug Companies
Science on Trial
Basic Pathology

~The Truth About Drug Companies
HOW THEY DECEIVE US
AND WHAT TO DO ABOUT IT
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RANDOM HOUSE TRADE PAPERBACKS
NEW YORK
AS YOU WILL DISCOVER, THIS BOOK IS VERY CRITICAL OF THE PHARMACEUTICAL INDUSTRY. I SHOW THAT, CONTRARY TO ITS PUBLIC RELATIONS, THE INDUSTRY DISCOVERS FEW GENUINELY INNOVATIVE DRUGS, SPENDS LESS THAN HALF AS MUCH ON RESEARCH AND DEVELOPMENT (R&D) AS ON MARKETING AND ADMINISTRATION (THESE TWO ITEMS ARE INEXPLICABLY COMBINED IN DRUG COMPANY ANNUAL REPORTS), AND CONSISTENTLY HAS PROFIT MARGINS FAR ABOVE THOSE OF MOST OTHER FORTUNE 500 INDUSTRIES. THE ARGUMENT THAT IT NEEDS TO CHARGE EVER-HIGHER PRICES TO COVER ITS RESEARCH COSTS IS SIMPLY NOT TRUE. I ALSO SHOW HOW DRUG COMPANIES PUT MOST OF THEIR EFFORTS INTO TURNING OUT HIGHER-PRICED VERSIONS OF EXISTING MEDICINES (CALLED “ME-TOO” DRUGS) AND PERSUADING US TO TAKE MORE AND MORE OF THEM. AND I DESCRIBE HOW THE PHARMACEUTICAL IN-
The industry uses its immense wealth and power to co-opt nearly every institution that might stand in its way—including the U.S. Congress, the Food and Drug Administration (FDA), and the medical profession itself. Finally, I propose reforms that might restore this industry to its original purpose of discovering innovative drugs and making them available at reasonable prices.

Predictably, the industry was not happy with my book when it was published in August 2004. The Pharmaceutical Research and Manufacturers of America (PhRMA), the industry’s trade association, promptly prepared a long response, which it posted on its website. It contained the usual rhetoric about how the industry works day and night to discover miracle cures, and the usual thinly veiled threats that if we try to regulate it further we will cut off those miracles. But it disputed very few of the essential facts I presented. One that it did dispute was the contention that the industry spends much more on marketing than on R&D. However, the industry's rebuttal depended on ignoring the billions of dollars drug companies spend on “educating” doctors—expenditures that come out of their marketing budgets and are probably their most effective means of promotion.

By happenstance, around the same time this book was published, several other books appeared that were also critical of the industry. They included Merrill Goozner’s The $800 Million Pill, Jerry Avorn’s Powerful Medicines, John Abramson’s Overdosed America, and Jerome Kassirer’s On the Take. Although our books focus on different aspects of drug company behavior, the facts in them are remarkably consistent, and it is clear that we are all talking about the same industry. Anyone wishing to delve deeply into the subject might want to read all of them.

With few dissents, public response to my book has been positive. I was invited to appear on a large number of radio and television shows, many with call-ins, and it was clear that I had touched a deep well of resentment among ordinary people. They were angered by drug-company price-gouging, incessant television ads urging them to “ask your doctor” about this or that drug, and the fact that the same brand-name drugs are much cheaper in Canada but it is illegal for Americans to buy them there. They were clearly skeptical about drug company protestations that all this was for their own good. These people reflected a growing public restiveness about the pharmaceutical industry that is starting to show itself in Congress and, even more, in state capitals, although it has yet to yield any important legislative reforms.

Since this book was published, two events concerning prescription drugs captured front-page attention—one dealing with drug safety, the other with costs. In September 2004, the drug giant Merck suddenly withdrew its blockbuster arthritis drug, Vioxx, from the market, because it was found to double the risk of heart attacks and strokes. (Blockbusters are drugs with sales of over a billion dollars a year.) Vioxx is one of a class of drugs, called COX-2 inhibitors, that includes two other blockbusters, Celebrex and Bextra. The withdrawal of Vioxx, and subsequent
indications that Celebrex and Bextra were also unsafe, led to a widely publicized hearing by an FDA advisory panel.

The panel ultimately recommended that all three COX-2 inhibitors be allowed on the market. The FDA, however, did not take the panel's advice. Instead, it decided that Bextra should be withdrawn and Celebrex should carry a strong warning, and left open the question of whether Merck would be allowed to resume selling Vioxx. I tell this story in detail in an Epilogue added for this paperback edition, because it illustrates in a nutshell most of the problems discussed in the book.

The second event was the spectacular upward revision of the estimated cost of the Medicare prescription drug benefit, passed into law in late 2003 and described in Chapter 11. When Congress passed the bill, the price tag was said to be about $400 billion over ten years. Within weeks, it was upped to $534 billion. Then, in February 2005, the White House released budget figures that revealed a new estimate of over $1.2 trillion (which would drop to $720 billion if projected offsets were realized).* Despite administration assurances that this wasn't quite as bad as it looked, because the new estimate was for a later ten-year period, not many people were mollified. This was, in the immortal words of the late Senator Everett Dirksen, "real money"—real money that the government doesn't have, nor is likely to have anytime soon, given its huge deficits.

Many of today's top-selling drugs are variations of innovative drugs that came on the market in the 1980s or earlier. In the seven years 1998 through 2004, only 22 percent of new drugs were judged by the FDA to offer improvements over drugs already on the market to treat the same condition, and most of those were not made by major American drug companies.* In 2004, for example, of the twenty-five drugs classified as likely improvements, only four came from one of the top nine American drug companies.

Since stock prices reflect the promise of an industry, not just its current performance, it should be no surprise that pharmaceutical stock prices are generally lower, despite some blips here and there. Clearly, the industry's future is uncertain. There is growing talk of mergers and acquisitions involving some of the more troubled companies, such as Merck, Bristol-Myers Squibb, and Schering-Plough. Increasingly, this is how the big drug companies acquire new drugs—by buying the smaller companies that develop them. Many of the latter are start-up biotechnology companies. Mergers between giants accomplish much the same thing—they combine marketing forces and permit some economies of scale, but mainly they combine pipelines of new drugs.

Nevertheless, despite its difficulties, this industry remains hugely profitable.* In 2004, Pfizer, the largest drug company, had a profit margin of nearly 22 percent of sales (which were $53 billion). The same year, it spent 32 percent of sales on marketing and administration and only 15 percent on R&D. Altogether, the nine U.S. drug companies listed in the Fortune 500 had a median profit margin of 16 percent of sales in 2004, compared with just over 5 percent for all the industries listed.

Sadly, there is little sign that the pharmaceutical industry is responding to its current difficulties by changing its behavior. It continues to make me-too drugs as its major product, to use its massive marketing muscle to promote them relentlessly, to charge prices as high as it can get away with, and to act as if it puts short-term profits ahead of everything. It doesn't have to be that way. Drug companies could be what they once were—businesses that were quite profitable, yes, but also sources of cutting edge research that produced real medical miracles. For this reason, my book was intended to show the pharmaceutical industry as it actually is, in the hope that I can contribute constructively to its much-needed reform.


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Introduction:
Drugs Are Different

Every day Americans are subjected to a barrage of advertising by the pharmaceutical industry. Mixed in with the pitches for a particular drug—usually featuring beautiful people enjoying themselves in the great outdoors—is a more general message. Boiled down to its essentials, it is this: "Yes, prescription drugs are expensive, but that shows how valuable they are. Besides, our research and development costs are enormous, and we need to cover them somehow. As 'research-based' companies, we turn out a steady stream of innovative medicines that lengthen life, enhance its quality, and avert more expensive medical care."
Drugs Are Different

You are the beneficiaries of this ongoing achievement of the American free enterprise system, so be grateful, quit whining, and pay up.” More prosaically, what the industry is saying is that you get what you pay for.

Your Money or Your Life

Is any of this true? Well, the first part certainly is. Prescription drug costs are indeed high—and rising fast. Americans now spend a staggering $200 billion a year on prescription drugs, and that figure is growing at about 12 percent a year (down from a high of 18 percent in 1999).\(^1\) Drugs are the fastest-growing part of the health care bill—which itself is rising at an alarming rate. The increase in drug spending reflects, in almost equal parts, the facts that people are taking a lot more drugs than they used to, that those drugs are more likely to be expensive new ones instead of older, cheaper ones, and that the prices of the most heavily prescribed drugs are routinely jacked up, sometimes several times a year.

Before its patent ran out, for example, the price of Schering-Plough’s top-selling allergy pill, Claritin, was raised thirteen times over five years, for a cumulative increase of more than 50 percent—over four times the rate of general inflation.\(^2\) As a spokeswoman for one company explained, “Price increases are not uncommon in the industry and this allows us to be able to invest in R & D.”\(^3\) In 2002, the average price of the fifty drugs most used by senior citizens was nearly $1500 for a year’s supply. (Pricing varies greatly, but this refers to what the companies call the average wholesale price, which is usually pretty close to what an individual without insurance pays at the pharmacy.\(^4\)

Paying for prescription drugs is no longer a problem just for poor people. As the economy continues to struggle, health insurance is shrinking. Employers are requiring workers to pay more of the costs themselves, and many businesses are dropping health benefits altogether. Since prescription drug costs are rising so fast, payers are particularly eager to get out from under them by shifting costs to individuals. The result is that more people have to pay a greater fraction of their drug bills out of pocket. And that packs a wallop.

Many of them simply can’t do it. They trade off drugs against home heating or food. Some people try to string out their drugs by taking them less often than prescribed, or sharing them with a spouse. Others, too embarrassed to admit that they can’t afford to pay for drugs, leave their doctors’ offices with prescriptions in hand but don’t have them filled. Not only do these patients go without needed treatment but their doctors sometimes wrongly conclude that the drugs they prescribed didn’t work and prescribe yet others—thus compounding the problem.

The people hurting most are senior citizens. When Medicare was enacted in 1965, people took far fewer prescription drugs and they were cheap. For that reason, no one thought it necessary to include an outpatient prescription drug benefit in the program. In those days, senior citizens could generally afford to
buy whatever drugs they needed out of pocket. Approximately half to two-thirds of seniors have supplementary insurance that partly covers prescription drugs, but that percentage is dropping as employers and insurers decide it is a losing proposition for them. At the end of 2003, Congress passed a Medicare reform bill that included a prescription drug benefit scheduled to begin in 2006, but as we will see later, its benefits are inadequate to begin with and will quickly be overtaken by rising prices and administrative costs.

For obvious reasons, senior citizens tend to need more prescription drugs than younger people—mainly for chronic conditions like arthritis, diabetes, high blood pressure, and elevated cholesterol. In 2001, nearly one in four seniors reported skipping doses or leaving prescriptions unfilled because of the cost. (That fraction is almost certainly higher now.) Sadly, the frailest are the least likely to have supplementary insurance. At an average cost of $1500 a year for each drug, someone without supplementary insurance who takes six different prescription drugs—and this is not rare—would have to spend $9000 out of pocket. Not many frail seniors have such deep pockets.

Furthermore, in one of the more perverse of the pharmaceutical industry’s practices, prices are much higher for precisely the people who most need the drugs and can least afford them. The industry charges Medicare recipients without supplementary insurance much more than it does favored customers, such as large HMOs or the Veterans Affairs (VA) system. Because the latter buy in bulk, they can bargain for steep discounts or rebates. People without insurance have no bargaining power, and so they pay the highest prices.

In the past two years, we have started to see, for the first time, the beginnings of public resistance to rapacious pricing and other dubious practices of the pharmaceutical industry. It is mainly because of this resistance that drug companies are now blanketing us with public relations messages. And the magic words, repeated over and over like an incantation, are research, innovation, and American. Research. Innovation. American. It makes a great story.

Rhetoric Versus Reality

But while the rhetoric is stirring, it has very little to do with reality. First, research and development (R & D) is a relatively small part of the budgets of the big drug companies—dwarfed by their vast expenditures for marketing and administration, and smaller even than profits. In fact, year after year, for over two decades, this industry has been far and away the most profitable in the United States. (In 2003, for the first time, the industry lost its first-place position, coming in third, behind “mining, crude-oil production” and “commercial banks.”) The prices drug companies charge have little relationship to the costs of making the drugs and could be cut dramatically without coming anywhere close to threatening R & D.

Second, the pharmaceutical industry is not especially innovative. As hard as it is to believe, only a handful of truly impor-
tant drugs have been brought to market in recent years, and they were mostly based on taxpayer-funded research at academic institutions, small biotechnology companies, or the National Institutes of Health (NIH). The great majority of “new” drugs are not new at all but merely variations of older drugs already on the market. These are called “me-too” drugs. The idea is to grab a share of an established, lucrative market by producing something very similar to a top-selling drug. For instance, we now have six statins (Mevacor, Lipitor, Zocor, Pravachol, Lescol, and the newest, Crestor) on the market to lower cholesterol, all variants of the first. As Dr. Sharon Levine, associate executive director of the Kaiser Permanente Medical Group, put it, “If I’m a manufacturer and I can change one molecule and get another twenty years of patent rights, and convince physicians to prescribe and consumers to demand the next form of Prilosec, or weekly Prozac instead of daily Prozac, just as my patent expires, then why would I be spending money on a lot less certain endeavor, which is looking for brand-new drugs?”

Third, the industry is hardly a model of American free enterprise. To be sure, it is free to decide which drugs to develop (me-too drugs instead of innovative ones, for instance), and it is free to price them as high as the traffic will bear, but it is utterly dependent on government-granted monopolies—in the form of patents and Food and Drug Administration (FDA)-approved exclusive marketing rights. If it is not particularly innovative in discovering new drugs, it is highly innovative—and aggressive—in dreaming up ways to extend its monopoly rights.

And there is nothing peculiarly American about this industry. It is the very essence of a global enterprise. Roughly half of the largest drug companies are based in Europe. (The exact count shifts because of mergers.) In 2002, the top ten were the American companies Pfizer, Merck, Johnson & Johnson, Bristol-Myers Squibb, and Wyeth (formerly American Home Products); the British companies GlaxoSmithKline and AstraZeneca; the Swiss companies Novartis and Roche; and the French company Aventis.7 (In 2004, Aventis merged with another French company, Sanofi-Synthelabo, which catapulted it to third place.) All are much alike in their operations. All price their drugs much higher here than in other markets. Since the United States is the major profit center, it is simply good public relations for drug companies to pass themselves off as American, whether they are or not. It is true, however, that some of the European companies are now locating their R & D operations in the United States. They claim it is because we don’t regulate prices, as does much of the rest of the world. But more likely it is because they want to feed on the unparalleled research output of American universities and the NIH. In other words, it’s not private enterprise that draws them here but the very opposite—our publicly sponsored research enterprise.

Getting It Straight

This book will expose the real pharmaceutical industry—an industry that over the past two decades has moved very far from
its original high purpose of discovering and producing useful new drugs. Now primarily a marketing machine to sell drugs of dubious benefit, this industry uses its wealth and power to co-opt every institution that might stand in its way, including the U.S. Congress, the Food and Drug Administration, academic medical centers, and the medical profession itself. (Most of its marketing efforts are focused on influencing doctors, since they must write the prescriptions.)

I witnessed firsthand the influence of the industry on medical research during my two decades at The New England Journal of Medicine. The staple of the journal is research about causes of and treatments for disease. Increasingly, this work is sponsored by drug companies. I saw companies begin to exercise a level of control over the way research is done that was unheard of when I first came to the journal, and the aim was clearly to load the dice to make sure their drugs looked good. As an example, companies would require researchers to compare a new drug with a placebo (sugar pill) instead of with an older drug. That way, the new drug would look good even though it might actually be worse than the older one. There are other ways to bias research, and not all of them can be spotted, even by experts. Obviously, we rejected such papers when we recognized them, but often they would turn up in other journals. Sometimes companies don't allow researchers to publish their results at all if they are unfavorable to the companies' drugs. As I saw industry influence grow, I became increasingly troubled by the possibility that much published research is seriously flawed, leading doctors to believe new drugs are generally more effective and safer than they actually are.

There are now signs that the industry is in deep trouble, mainly because it has so few innovative drugs in its pipeline. In addition, the public is growing increasingly skeptical about its high-flown claims, and purchasers of drugs are beginning to complain loudly about the intolerable prices. Profits, while still enormous, are starting to fall off, and stock prices for some of the largest companies are dropping. But instead of investing more in innovative drugs and moderating prices, drug companies are pouring money into marketing, legal maneuvers to extend patent rights, and government lobbying to prevent any form of price regulation.

If prescription drugs were like ordinary consumer goods, all this might not matter very much. But drugs are different. People depend on them for their health and even their lives. In the words of Senator Debbie Stabenow (D-Mich.), “It's not like buying a car or tennis shoes or peanut butter.” People need to know that there are some checks and balances on this industry, so that its quest for profits doesn't push every other consideration aside. In Chapter 13, I will suggest ways the system could be reformed to ensure that we have access to good drugs at reasonable prices and that the reality of this industry is finally brought into line with its rhetoric.

Reform will have to extend beyond the industry to the agencies and institutions it has co-opted, including the FDA and the medical profession and its institutions. This sort of thorough-
going change will take government action, which in turn will require strong public pressure. It will be tough. Drug companies have the largest lobby in Washington, and they give copiously to political campaigns. Legislators are now so beholden to the pharmaceutical industry that it will be exceedingly difficult to break its lock on them.

But the one thing legislators need more than campaign contributions is votes. That is why you should know what’s really going on—and why I have written this book. Contrary to the industry’s public relations, you don’t get what you pay for. The fact is that this industry is taking us for a ride, and there will be no real reform without an aroused and determined public to make it happen.
The $200 Billion Colossus

What does the eight-hundred-pound gorilla do? Anything it wants to.

WHAT’S TRUE OF THE EIGHT-HUNDRED-pound gorilla is true of the colossus that is the pharmaceutical industry. It is used to doing pretty much what it wants to do. The watershed year was 1980. Before then, it was a good business, but afterward, it was a stupendous one. From 1960 to 1980, prescription drug sales were fairly static as a percent of U.S. gross domestic product, but from 1980 to 2000, they tripled. They now stand at more than $200 billion a year. Furthermore, since the early 1980s, this industry has consistently ranked as the most profitable in the United States—by a long shot. (Only in 2003 did it fall
from that position to rank third among the forty-seven industries listed in the Fortune 500.) Of the many events that contributed to their sudden great and good fortune, none had to do with the quality of the drugs the companies were selling.

In this chapter I'll give you an overview of the pharmaceutical industry—its meteoric rise and the recent, early signs of either a coming fall or an overhaul. I will not go into much detail here, I'll leave that to later chapters. What I want to do now is provide a quick look at what's under this rock when it's lifted. It's not a pretty sight.

Before I begin, a few words about the facts and figures I will use throughout the book. In most cases, I use data from the year 2001, because it is the most recent year for which information is reasonably complete for all the aspects of the industry I will consider. If I stick with one year, it will make it easier to see the whole picture. But for some important facts, I will use figures from 2002 and, whenever possible, 2003. In all cases, I will make it clear what year I am talking about.

I also need to explain what I mean when I say this is a $200 billion industry. According to government sources, that is roughly how much Americans spent on prescription drugs in 2002. That figure refers to direct consumer purchases at drugstores and mail order pharmacies (whether paid for out of pocket or not), and it includes the nearly 25 percent markup for wholesalers, pharmacists, and other middlemen and retailers. But it does not include the large amounts spent for drugs administered in hospitals, nursing homes, or doctors' offices (as is the case for many cancer drugs). In most analyses, they are allocated to costs for those facilities.

Drug company revenues (or sales) are a little different, at least as they are reported in summaries of corporate annual reports. They usually refer to a company's worldwide sales, including those to health facilities. But they do not include the revenues of middlemen and retailers.

Perhaps the most quoted source of statistics on the pharmaceutical industry, IMS Health, estimated total worldwide sales for prescription drugs to be about $400 billion in 2002. About half were in the United States. So the $200 billion colossus is really a $400 billion megacolossus, but my focus in this book will be mainly on how the drug companies operate in the United States.

You should understand, however, that it is virtually impossible to be precise about most of these figures. Before drugs reach consumers, they pass through many hands and are paid for in exceedingly complicated, often hidden, ways. It is easy to compare apples and oranges without knowing it. You need to ask, for example, whether a number refers just to prescription drugs or includes over-the-counter drugs and other consumer products made by drug companies; whether it includes revenues for middlemen and retailers or not; whether it refers just to outpatient consumer purchases or also to health facility purchases; and whether it includes mail order purchases.
Let the Good Times Roll

The election of Ronald Reagan in 1980 was perhaps the most fundamental element in the rapid rise of big pharma—the collective name for the largest drug companies. With the Reagan administration came a strong pro-business shift not only in government policies but in society at large. And with the shift, the public attitude toward great wealth changed. Before then, there was something faintly disreputable about really big fortunes. You could choose to do well or you could choose to do good, but most people who had any choice in the matter thought it difficult to do both. That belief was particularly strong among scientists and other intellectuals. They could choose to live a comfortable but not luxurious life in academia, hoping to do exciting cutting-edge research, or they could “sell out” to industry and do less important but more remunerative work. Starting in the Reagan years and continuing through the 1990s, Americans changed their tune. It became not only reputable to be wealthy, but something close to virtuous. There were “winners” and there were “losers,” and the winners were rich and deserved to be. The gap between the rich and poor, which had been narrowing since World War II, suddenly began to widen again, until today it is a yawning chasm.

The pharmaceutical industry and its CEOs quickly joined the ranks of the winners as a result of a number of business-friendly government actions. I won’t enumerate all of them, but two are especially important. Beginning in 1980, Congress enacted a series of laws designed to speed the translation of tax-supported basic research into useful new products—a process sometimes referred to as “technology transfer.” The goal was also to improve the position of American-owned high-tech businesses in world markets. The most important of these laws is known as the Bayh-Dole Act, after its chief sponsors, Senator Birch Bayh (D-Ind.) and Senator Robert Dole (R-Kans.). Bayh-Dole enabled universities and small businesses to patent discoveries emanating from research sponsored by the National Institutes of Health (NIH), the major distributor of tax dollars for medical research, and then to grant exclusive licenses to drug companies. Until then, taxpayer-financed discoveries were in the public domain, available to any company that wanted to use them. But now universities, where most NIH-sponsored work is carried out, can patent and license their discoveries, and charge royalties. Similar legislation permitted the NIH itself to enter into deals with drug companies that would directly transfer NIH discoveries to industry.

Bayh-Dole gave a tremendous boost to the nascent biotechnology industry, as well as to big pharma. Small biotech companies, many of them founded by university researchers to exploit their discoveries, proliferated rapidly. They now ring the major academic research institutions and often carry out the initial phases of drug development, hoping for lucrative deals with big drug companies that can market the new drugs. Usually both academic researchers and their institutions own equity in the biotechnology companies they are involved with. Thus,
when a patent held by a university or a small biotech company is eventually licensed to a big drug company, all parties cash in on the public investment in research.

These laws mean that drug companies no longer have to rely on their own research for new drugs, and few of the large ones do. Increasingly, they rely on academia, small biotech start-up companies, and the NIH for that. At least a third of drugs marketed by the major drug companies are now licensed from universities or small biotech companies, and these tend to be the most innovative ones. While Bayh-Dole was clearly a bonanza for big pharma and the biotech industry, whether it is a net benefit to the public is arguable (I'll come back to that).

The Reagan years and Bayh-Dole also transformed the ethos of medical schools and teaching hospitals. These non-profit institutions started to see themselves as "partners" of industry, and they became just as enthusiastic as any entrepreneur about the opportunities to parlay their discoveries into financial gain. Faculty researchers were encouraged to obtain patents on their work (which were assigned to their universities), and they shared in the royalties. Many medical schools and teaching hospitals set up "technology transfer" offices to help in this activity and capitalize on faculty discoveries. As the entrepreneurial spirit grew during the 1990s, medical school faculty entered into other lucrative financial arrangements with drug companies, as did their parent institutions. One of the results has been a growing pro-industry bias in medical research—exactly where such bias doesn't belong. Faculty members who had earlier con-
tented themselves with what was once referred to as a "threadbare but genteel" lifestyle began to ask themselves, in the words of my grandmother, "If you're so smart, why aren't you rich?"

Medical schools and teaching hospitals, for their part, put more resources into searching for commercial opportunities.

Starting in 1984, with legislation known as the Hatch-Waxman Act, Congress passed another series of laws that were just as big a bonanza for the pharmaceutical industry. These laws extended monopoly rights for brand-name drugs. Exclusivity is the lifeblood of the industry because it means that no other company may sell the same drug for a set period. After exclusive marketing rights expire, copies (called generic drugs) enter the market, and the price usually falls to as little as 20 percent of what it was. There are two forms of monopoly rights—patents granted by the U.S. Patent and Trademark Office (USPTO) and exclusivity granted by the Food and Drug Administration (FDA). While related, they operate somewhat independently, almost as backups for each other. Hatch-Waxman, named for Senator Orrin Hatch (R-Utah) and Representative Henry Waxman (D-Calif.), was meant mainly to stimulate the foundering generic industry by short-circuiting some of the FDA requirements for bringing generic drugs to market. While successful in doing that, Hatch-Waxman also lengthened the patent life for brand-name drugs. Since then, industry lawyers have manipulated some of its provisions to extend patents far longer than the lawmakers intended.

In the 1990s, Congress enacted other laws that further in-
creased the patent life of brand-name drugs. Drug companies now employ small armies of lawyers to milk these laws for all they're worth—and they're worth a lot. The result is that the effective patent life of brand-name drugs increased from about eight years in 1980 to about fourteen years in 2000. For a blockbuster—usually defined as a drug with sales of over a billion dollars a year (like Lipitor or Celebrex or Zoloft)—those six years of additional exclusivity are golden. They can add billions of dollars to sales—enough to buy a lot of lawyers and have plenty of change left over. No wonder big pharma will do almost anything to protect exclusive marketing rights, despite the fact that doing so flies in the face of all its rhetoric about the free market.

Riding High

As their profits skyrocketed during the 1980s and 1990s, so did the political clout of drug companies. By 1990, the industry had assumed its present contours as a business with unprecedented control over its own fortunes. For example, if it didn’t like something about the FDA, the federal agency that is supposed to regulate the industry, it could change it through direct pressure or through its friends in Congress. The top ten drug companies (which included European companies) had profits of nearly 25 percent of sales in 1990, and except for a dip at the time of President Bill Clinton’s health care reform proposal, profits as a percentage of sales remained about the same for the next decade. (Of course, in absolute terms, as sales mounted, so did profits.) In 2001, the ten American drug companies in the Fortune 500 (not quite the same as the top ten worldwide, but their profit margins are much the same) ranked far above all other American industries in average net return, whether as a percentage of sales (18.5 percent), of assets (16.3 percent), or of shareholders’ equity (33.2 percent). These are astonishing margins. For comparison, the median net return for all other industries in the Fortune 500 was only 3.3 percent of sales. Commercial banking, itself no slouch as an aggressive industry with many friends in high places, was a distant second, at 13.5 percent of sales.

In 2002, as the economic downturn continued, big pharma showed only a slight drop in profits—from 18.5 to 17.0 percent of sales. The most startling fact about 2002 is that the combined profits for the ten drug companies in the Fortune 500 ($35.9 billion) were more than the profits for all the other 490 businesses put together ($33.7 billion). In 2003, profits of the Fortune 500 drug companies dropped to 14.3 percent of sales, still well above the median for all industries of 4.6 percent for the year. When I say this is a profitable industry, I mean really profitable. It is difficult to conceive of how awash in money big pharma is.

Drug industry expenditures for research and development, while large, were consistently far less than profits. For the top ten companies, they amounted to only 11 percent of sales in 1990, rising slightly to 14 percent in 2000. The biggest single
item in the budget is neither R & D nor even profits but something usually called "marketing and administration"—a name that varies slightly from company to company. In 1990, a staggering 36 percent of sales revenues went into this category, and that proportion remained about the same for over a decade. Note that this is two and a half times the expenditures for R & D.

These figures are drawn from the industry's own annual reports to the Securities and Exchange Commission (SEC) and to stockholders, but what actually goes into these categories is not at all clear, because drug companies hold that information very close to their chests. It is likely, for instance, that R & D includes many activities most people would consider marketing, but no one can know for sure. For its part, "marketing and administration" is a gigantic black box that probably includes what the industry calls "education," as well as advertising and promotion, legal costs, and executive salaries—which are whopping. According to a report by the nonprofit group Families USA, the former chairman and CEO of Bristol-Myers Squibb, Charles A. Heimbold, Jr., made $74,890,918 in 2001, not counting his $76,095,611 worth of unexercised stock options. The chairman of Wyeth made $40,521,011, exclusive of his $40,629,459 in stock options. And so on. This is an industry that amply rewards its own.

In recent years, the top ten companies have included five European giants—GlaxoSmithKline, AstraZeneca, Novartis, Roche, and Aventis. Their profit margins are similar to those of their American counterparts, and so are their expenditures for R & D and marketing and administration. Furthermore, they are members of the industry's trade association, the misleadingly named Pharmaceutical Research and Manufacturers of America (PhRMA). Recently I heard Daniel Vasella, the chairman and CEO of Novartis, speak at a conference. He was clearly pleased with the American commercial and research climate. "Free pricing and fast approval secure rapid access to innovation without rationing," he said, sounding like the most red-blooded of Americans, despite his charming Swiss accent. His company is now moving its research operations to a site near the Massachusetts Institute of Technology (MIT), a hotbed of basic research surrounded by biotechnology companies. I suspect the move has nothing to do with "free pricing and fast approval" at all, and everything to do with the opportunity to profit from U.S. taxpayer-funded research under the terms of Bayh-Dole, and from the proximity of U.S. medical scientists who do the research.

**Trouble**

If 1980 was a watershed year for the pharmaceutical industry, 2000 may very well turn out to have been another one—the year things began to go wrong. As the booming economy of the late 1990s turned sour, many successful businesses found themselves in trouble. And as tax revenues dropped, state governments also found themselves in trouble. In one respect, the pharmaceutical industry is well protected against the downturn,
since it has so much wealth and power. But in another respect, it is peculiarly vulnerable, since it depends on employer-sponsored insurance and state-run Medicaid programs for much of its revenues. When employers and states are in trouble, so is big pharma.

And sure enough, in just the past couple of years, employers and the private health insurers with whom they contract have started to push back against drug costs. Most big managed care plans now bargain for steep price discounts. Most have also instituted three-tiered coverage for prescription drugs—full coverage for generic drugs, partial coverage for useful brand-name drugs, and no coverage for expensive drugs that offer no added benefit over cheaper ones. These lists of preferred drugs are called formularies, and they are an increasingly important method for containing drug costs. Big pharma is feeling the effects of these measures, although not surprisingly, it has become adept at gaming the system—mainly by inducing (I'll discuss how later) doctors or health plans to put expensive, brand-name drugs on formularies.

State governments, too, are looking for ways to cut their drug costs. Some state legislatures are crafting measures that would permit them to regulate prescription drug prices for state employees, Medicaid recipients, and the uninsured. Like managed care plans, they are creating formularies of preferred drugs. The industry is fighting these efforts tooth and nail—mainly with its legions of lobbyists and lawyers. It fought the state of Maine all the way to the U.S. Supreme Court, which in 2003 upheld Maine's right to bargain with drug companies for lower prices, while leaving open the details. But that war has just begun, and it promises to go on for years and get very ugly.

Recently the public has shown signs of being fed up. The fact that Americans pay much more for prescription drugs than Europeans and Canadians is now widely known. An estimated 1 to 2 million Americans buy their medicines from Canadian drugstores over the Internet, despite the fact that in 1987, in response to heavy industry lobbying, a compliant Congress had made it illegal for anyone other than manufacturers to import prescription drugs from other countries. In addition, there is a brisk traffic in bus trips for people in border states to travel to Canada or Mexico to buy prescription drugs. Most of those on the buses are senior citizens, who not only pay more for drugs than people in neighboring countries but also pay more than younger neighbors in their own hometowns. The resentment among senior citizens is palpable, and they constitute a powerful voter bloc—a fact not lost on Congress or state legislatures.

The industry faces other, less well-known problems. It happens that, by chance, some of the top-selling drugs—with combined sales of around $35 billion a year—are scheduled to go off patent within a few years of one another. This drop over the cliff began in 2001, with the expiration of Eli Lilly's patent on its blockbuster antidepressant Prozac. In the same year, AstraZeneca lost its patent on Prilosec, the original "purple pill" for heartburn, which at its peak brought in a stunning $6 billion a year. Bristol-Myers Squibb lost its bestselling dia-
betes drug, Glucophage. The unusual cluster of expirations will continue for another couple of years. While it represents a huge loss to the industry as a whole, for some companies it's a disaster. Schering-Plough's blockbuster allergy drug, Claritin, brought in fully a third of that company's revenues before its patent expired in 2002.\(^\text{15}\) Claritin is now sold over the counter for far less than its prescription price. So far, the company has been unable to make up for the loss by trying to switch Claritin users to Clarinex—a drug that is virtually identical but has the advantage of still being on patent.

Even worse is the fact that there are very few drugs in the pipeline ready to take the place of blockbusters going off patent. In fact, that is the biggest problem facing the industry today, and its darkest secret. All the public relations about innovation is meant to obscure precisely this fact. The stream of new drugs has slowed to a trickle, and few of them are innovative in any sense of that word. Instead, the great majority are variations of oldies but goodies—"me-too" drugs. Companies are merging to combine their pipelines or comarketing the same drug while scrambling to find drugs to license from the government, universities, and biotechnology companies. But these sources are themselves experiencing difficulties in coming up with new drugs.

Of the seventy-eight drugs approved by the FDA in 2002, only seventeen contained new active ingredients, and only seven of these were classified by the FDA as improvements over older drugs. The other seventy-one drugs approved that year were variations of old drugs or deemed no better than drugs already on the market. In other words, they were me-too drugs. Seven of seventy-eight is not much of a yield. Furthermore, of those seven, not one came from a major U.S. drug company.\(^\text{16}\)

**Losing Support**

For the first time, this gigantic industry is finding itself in serious difficulty. It is facing, as one industry spokesman put it, "a perfect storm." To be sure, profits are still beyond anything most other industries could hope for, but they have recently fallen, and for some companies they fell a lot. And that is what matters to investors. Wall Street doesn't care how high profits are today, only how high they will be tomorrow. For some companies, stock prices have plummeted. Nevertheless, the industry keeps promising a bright new day. It bases its reassurances on the notion that the mapping of the human genome and the accompanying burst in genetic research will yield a cornucopia of important new drugs. Left unsaid is the fact that big pharma is depending on government, universities, and small biotech companies for that innovation. But the predictions are beginning to sound a lot like *Waiting for Godot*, Samuel Beckett's grim play about two men waiting and waiting for something, and telling each other that whatever it is will come any minute. While there is no doubt that genetic discoveries will lead to treatments, the
fact remains that it will probably be years before the basic research pays off with new drugs. In the meantime, the once-solid foundations of the big pharma colossus are shaking.

The hints of trouble and the public's growing resentment over high prices are producing the first cracks in the industry's formerly firm support in Washington. In 2000, Congress passed legislation that would have closed some of the loopholes in Hatch-Waxman and also permitted American pharmacies, as well as individuals, to import drugs from certain countries where prices are lower. In particular, they could buy back FDA-approved drugs from Canada that had been exported there. It sounds silly to "reimport" drugs that are marketed in the United States, but even with the added transaction costs, doing so is cheaper than buying them here. But the bill required the secretary of Health and Human Services to certify that the practice would not pose any "added risk" to the public, and secretaries in both the Clinton and Bush administrations, under pressure from the industry, refused to do that. In 2003, the House approved a bill that contained no such provision, and even many conservative Republicans backed it. Representative Dan Burton (R-Ind.), pointing out that his wife's breast cancer drug costs $360 a month in this country and only $60 in Germany, told The New York Times, "Every woman in America ought to be angry as hell at the pharmaceutical industry, and you can quote me on that." But the bill didn't make it through the Senate.

The industry is also being hit with a tidal wave of government investigations and civil and criminal lawsuits. The litany of charges includes illegally overcharging Medicaid and Medicare, paying kickbacks to doctors, engaging in anticompetitive practices, colluding with generic companies to keep generic drugs off the market, illegally promoting drugs for unapproved uses, engaging in misleading direct-to-consumer advertising, and, of course, covering up evidence. Some of the settlements have been huge. TAP Pharmaceuticals, for instance, paid $875 million to settle civil and criminal charges of Medicaid and Medicare fraud in the marketing of its prostate cancer drug, Lupron. As of this writing, litigation in this case continues. All of these efforts could be summed up as increasingly desperate marketing and patent games, activities that always skirted the edge of legality but now are sometimes well on the other side.

How is the pharmaceutical industry responding to its difficulties? One could hope drug companies would decide to pull up their socks—trim their prices, or at least make them more equitable, and put more of their money into trying to discover genuinely innovative drugs, instead of just talking about it. But that is not what is happening. Instead, drug companies are doing more of what got them into this situation. They are marketing their me-too drugs even more relentlessly. They are pushing even harder to extend their monopolies on top-selling drugs. And they are pouring more money into lobbying and political campaigns. As for innovation, they are still waiting for Godot and hoping desperately he will come.

The news is not all bad for the industry. The Medicare pre-
scription drug benefit enacted in 2003, and scheduled to go into effect in 2006, promises a windfall for big pharma since it prohibits the government from negotiating prices. The immediate jump in pharmaceutical stock prices after the bill passed indicated that the industry and investors were well aware of the windfall. But at best, this legislation will be only a temporary boost for the industry. As costs rise, Congress will have to reconsider its industry-friendly decision to allow drug companies to set their own prices, no questions asked. More about that later.

This is an industry that in some ways is like the Wizard of Oz—still full of bluster but now being exposed as something far different from its image. Instead of being an engine of innovation, it is a vast marketing machine. Instead of being a free market success story, it lives off government-funded research and monopoly rights. Yet this industry occupies an essential role in the American health care system, and it performs a valuable function, if not in discovering important new drugs at least in developing them and bringing them to market. But big pharma is extravagantly rewarded for these relatively modest contributions. We get nowhere near our money's worth. The United States can no longer afford the pharmaceutical industry in its present form. The question is, Will the industry realize this and agree to real reforms that will curb its appetites but preserve its strengths? One thing is sure. It cannot continue on its present course.

The Creation of a New Drug

BRINGING A NEW DRUG TO MARKET IS A LONG HAUL. THE INDUSTRY IS RIGHT ABOUT THAT, BUT WRONG ABOUT ITS ROLE IN THE PROCESS. DRUG COMPANIES DO NOT PLAY ANYWHERE NEAR AS LARGE A PART IN RESEARCH AND DEVELOPMENT (R & D) AS THEY WOULD HAVE US BELIEVE. IT IS NOT MY INTENTION TO DESCRIBE PHARMACEUTICAL R & D IN ANY DETAIL HERE, BECAUSE THAT IS NOT THE FOCUS OF THIS BOOK. BUT TO HELP SHOW HOW DRUG COMPANIES ARE SELLING US A BILL OF GOODS, I NEED TO SKETCH THE HIGHLIGHTS. MOST OF WHAT I WILL DESCRIBE APPLIES JUST TO THE FEW INNOVATIVE DRUGS THAT COME TO MARKET EACH YEAR. FOR THE MANY MORE "ME-TOO" DRUGS—MINOR VARIA-
tions of drugs already on the market—the R & D process is much faster, since a great deal of it has already been done.

**R & D Lite**

You can't just randomly test chemicals to see if one will turn up that might be helpful in treating a disease. That would take an infinitely long time and be dangerous as well. Instead, most of the time you first have to understand the nature of the disease you want to treat—what has gone wrong in the body to cause it. That understanding needs to be fairly detailed, usually at the molecular level, if there is to be any hope of finding a drug that will safely and effectively interfere with the chain of events responsible for the disease. What researchers hope to find is some specific link in the chain that a drug will target.

So learning about the disease or condition is usually the beginning of the “research” part of R & D, and it can take a very long time—sometimes decades. There is no question that this is the most creative, and the least certain, part of the R & D process. Contrary to industry propaganda, it is almost always carried out at universities or government research labs, either in this country or abroad. In the United States, most of it is supported by the National Institutes of Health (NIH).

Once the basic research has reached a critical point—that is, the disease is fairly well understood and so are the possible means to cure or ameliorate it—the search is on to discover or synthesize a molecule that will do the job and be safe to use.

That is the “development” part of R & D, and it is here that drug companies usually get involved—sometimes early, sometimes not until very late.

The development part of R & D is itself divided into two stages—preclinical and clinical. The preclinical stage has to do with finding promising drug candidates and then studying their properties in animals and cell cultures. Companies keep vast libraries of drug candidates—molecules that can now be screened very rapidly by computerized methods to see if they will target the Achilles’ heel found by the basic research. In addition, new molecules can be synthesized or extracted from animal, plant, or mineral sources. Only the small fraction of drug candidates that make it through preclinical development go on to be tested in humans—the all-important clinical stage (more on that later).

According to the pharmaceutical industry, only one in five thousand candidate drugs make it to market—one in one thousand survive preclinical testing, and of those, one in five make it through clinical testing. Paradoxically, although it is the least creative part of the process, clinical testing is the most expensive. The great majority of drug candidates are thus weeded out very early on, before there has been a great deal of money invested in them.

Research and development in biotechnology companies is similar in many ways to R & D in big drug companies. But instead of producing small molecules by chemical means, biotech companies focus primarily on making or modifying very large molecules, like proteins or hormones, by using living biological
systems—often with recombinant DNA technology. Moreover, there is as yet no industry that makes generic biotech products, so monopoly rights are essentially unlimited. The distinctions between pharmaceutical and biotechnology companies are blurring, however, and the largest biotechnology companies are now members of the industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA).

This is a bare-bones outline of R & D, and as in all bare-bones stories, things are rarely so clear-cut and there are many variations and exceptions. But the general point is that the longest, most difficult part of R & D is the front end—the research part—where the basic discoveries are made that identify how and where a disease or condition can be successfully attacked by a new pharmacological agent. Big drug companies usually contribute very little to that effort. Where they are important in the R & D for most drugs is at the development end, particularly in clinical testing.

An Example—The AZT Story

A good illustration of the R & D process for an innovative drug is the story of AZT (also called zidovudine), the first drug on the market to treat HIV/AIDS. Sold under the brand name Retrovir, it was originally manufactured by the drug company Burroughs Wellcome, which was later swallowed up by the much larger British firm GlaxoSmithKline. Despite the fact that the profits went at first to Burroughs Wellcome and now to GlaxoSmithKline, the research and most of the development was done in government and university laboratories. This is a story worth recounting in some detail.3

Acquired immunodeficiency syndrome, or AIDS, burst on the scene in 1981, with the publication of three papers in The New England Journal of Medicine about a handful of gay men in Los Angeles and New York City who had died of overwhelming infections. Their immune systems were virtually obliterated, but no one could say why. The mysterious outbreak spread quickly and gave rise to intense worldwide efforts to find its cause. Speculation ranged widely, from contaminants in illegal drugs to a strange toxin picked up in Haiti to an unknown fungus. Within two short years, however, researchers at the NIH and the Pasteur Institute in Paris had pinpointed the culprit—a type of virus called a retrovirus.

A long time before that, in 1964, the AZT molecule had been synthesized at the Michigan Cancer Foundation as a possible treatment for cancer, and it was studied in many laboratories for that purpose. It did not prove effective against cancer, but in 1974, workers in a German laboratory found it to be effective against viral infections in mice. Burroughs Wellcome later acquired the molecule for possible use against the herpes virus.

Soon after the discovery of the cause of AIDS in 1983, Samuel Broder, head of the National Cancer Institute (NCI)—a part of the NIH—set up a team to screen antiviral agents from around the world as possible treatments for AIDS. Among the
many he tested was Burroughs Wellcome's AZT. In 1985, his team, along with colleagues at Duke University, found that AZT was effective against the AIDS virus in test tubes and then in early clinical trials. Burroughs Wellcome immediately patented the drug to treat AIDS and carried out later trials that enabled it to receive Food and Drug Administration (FDA) approval in 1987, after a review of only a few months.

This was an extraordinary achievement. It took a mere six years from the first reports of a new disease for the cause to be found and an effective drug brought to market. But except for the speed, the story is not so different from countless other stories of how innovative drugs are discovered.

It required bringing together many threads from many government, university, and other nonprofit sources, and only late in the process—in this case, very late—handing the drug off to a private company for further development, manufacture, and distribution.

As is also typical, the company claimed far more credit than it deserved, probably the better to justify its exorbitant prices—originally about $10,000 per year. After a self-congratulatory letter to *The New York Times* by the company’s CEO, Broder and four colleagues from the NCI and Duke University responded angrily, reciting the seminal contributions Burroughs Wellcome did not make:

The company specifically did not develop or provide the first application of the technology for determining whether a drug like AZT can suppress live AIDS virus in human cells, nor did it develop the technology to determine at what concentration such an effect might be achieved in humans. Moreover, it was not first to administer AZT to a human being with AIDS, nor did it perform the first clinical pharmacology studies in patients. It also did not perform the immunological and virological studies necessary to infer that the drug might work, and was therefore worth pursuing in further studies. All of these were accomplished by the staff of the National Cancer Institute working with the staff of Duke University.

And they added, “Indeed one of the key obstacles to the development of AZT was that Burroughs Wellcome did not work with live AIDS virus nor wish to receive samples from AIDS patients.”

**Testing Drugs on People—and Finding Volunteers**

The clinical stage of drug development is regulated by the FDA. By law, before a company can sell a new drug, it must prove to this agency that the drug is reasonably safe and effective. That proof usually requires a series of clinical trials, which are divided into three phases. Phase I entails giving the drug to a small number of usually normal volunteers to establish safe dosage levels and study its metabolism and side effects. (The exceptions are cancer and AIDS drugs, which are tested on people with the disease even in Phase I.) If the drug looks promising, it moves into Phase II, which involves as many as a few hundred
patients with the relevant disease or medical condition. The drug is given at various doses, and the effects are usually compared with those in a similar group of patients not given the drug. Finally, if all goes well, Phase III clinical trials are undertaken. These evaluate the safety and effectiveness of the drug in much larger numbers of patients (hundreds to tens of thousands), and they nearly always involve a comparison group of patients. But not all drugs go through all phases. Sometimes the process is greatly truncated—to one or two trials. If the trials are successful, FDA approval follows.

Drug companies usually obtain a patent on a new drug before clinical testing begins, because it is difficult to keep information about the drug secret after this point. Patents protect companies against competition during the testing period. But clinical trials usually take a few years, and during that time the drug cannot be sold. That means clinical testing eats into a drug's twenty-year patent life—the time it can be sold without competition. For that reason, drug companies are in a terrific rush to get the trials out of the way so they can start to market the drug. And that means they need to find human subjects in a hurry.

Drug companies don't have direct access to human subjects, nor do they employ their own physicians to conduct clinical trials. They need to rely on doctors in teaching hospitals and private offices to do the studies, using either their own patients or volunteers recruited through various kinds of solicitations. At one time, most trials were done at medical schools and teaching hospitals. Companies would give grants to faculty researchers to carry out clinical trials under institutional auspices. That is no longer the case. Because there are so many more trials nowadays, and because drug companies are so eager to get them done quickly, they have shifted much of their business to new, for-profit companies set up exclusively to organize and carry out trials for the industry. These are called contract research organizations (CROs). In 2001, there were about a thousand of them operating around the world, with revenues from their drug company clients of some $7 billion. They establish networks of physicians who, working under the organizations' supervision, are paid to administer the study drugs and collect information on their effects.

The number of clinical trials under way in any given year is staggering. In 2001, an estimated 80,000 of them were ongoing in the United States alone. That year, about 2.3 million Americans served as human subjects. These numbers are only approximate. Exact figures are hard to come by, since not all trials are registered with the FDA or NIH. The point is that the numbers are far larger than most people realize. In fact, it's quite likely that nearly everyone knows someone who has participated in a clinical trial.

Only some of the trials are to test new drugs to get FDA approval. Many are of drugs already on the market—called "post-marketing" or "Phase IV" studies. Often these are to find new uses for old drugs to expand their markets. A few are required by the FDA to look for unknown side effects. And a great
many—perhaps most—are really, in the view of many critics, just excuses to pay doctors to put patients on a company’s already-approved drug.

Even though the NIH spends nearly as much money on research as does the industry, it concentrates on basic research. Only about 10 percent of clinical trials are sponsored by the NIH, usually in academic medical centers.

All clinical trials cut into the limited supply of human volunteers. In fact, the scarcity of human subjects—not FDA roadblocks, as is often claimed by the pharmaceutical industry—is the biggest cause of delay in getting new drugs to market. Large drug companies have centralized patient recruitment offices, which outsource many of the tasks to a growing number of independent recruitment firms, as well as to CROs. Potential subjects are solicited in a variety of ways—postings on health-related Internet sites; television, radio, and newspaper ads; individual mailings; and posters and flyers distributed throughout communities. Solicitations are often disguised as public service announcements. Drug companies also set up patient advocacy groups as magnets for people with specific diseases. These are rich sources of patients for clinical trials. Most human subjects are now recruited through these kinds of efforts, not referred by their doctors. They are usually paid from a few hundred to a few thousand dollars for participation in a trial.

Whatever they are paid, it is dwarfed by payments to doctors. To get human subjects, drug companies or contract research organizations routinely offer doctors large bounties (averaging about $7000 per patient in 2001) and sometimes bonuses for rapid enrollment. For example, according to a 2000 Department of Health and Human Services inspector general’s report, physicians in one trial were paid $12,000 for each patient enrolled, plus another $30,000 on the enrollment of the sixth patient. One risk of this bounty and bonus system is that it can induce doctors to enroll patients who are not really eligible. For instance, if it means an extra $30,000 to you to enroll a patient in an asthma study, you might very well be tempted to decide your next patient has asthma, whether he does or not (“Sounds like a little wheeze you have there. . . .”). Obviously, if the wrong patients are enrolled, the results of a trial are unreliable, and that is probably often the case. (More about biased research in Chapter 6.)

The FDA—Regulation and Reaction

As mentioned, the FDA’s involvement with a drug begins at the clinical trials stage. Before trials can begin, a drug company must file an investigational new drug application with the FDA. It describes the proposed research in detail, including measures to protect the rights and welfare of human subjects. After all the trials are completed, which usually takes a few years, the company must file a new drug application to get FDA approval to go to market. With the help of eighteen advisory committees of outside experts, the agency reviews the application, which includes results of the clinical trials, along with other supporting
evidence. Only if the drug passes this scrutiny is it allowed on the market. Companies are permitted to promote drugs only for the uses and at the doses for which they were approved, although once they are on the market, doctors may prescribe them for any use and at any dose they deem appropriate.

Generic drugs, you will remember, are copies of brand-name drugs whose exclusive marketing rights have expired. They, too, need FDA approval, but their manufacturers have to demonstrate only that they are equivalent to the brand-name drugs they copy. Since the passage of Hatch-Waxman in 1984, generic companies don't have to do clinical trials to show safety and effectiveness, because the brand-name companies have already done that.

Before leaving the subject of generic drugs, I should mention a new hybrid called “branded generics.” Their active ingredients are similar but not identical to those of the brand-name drugs they mimic, so they supposedly do not infringe on patents, but they are said to be similar enough that they don't have to undergo clinical testing. Neither big pharma nor traditional generic companies are happy about the competition from branded generics, and both are mounting legal challenges. Branded generics are priced somewhere between brand-name drugs and true generics, and their market share is growing rapidly. They are likely to become very important in the biotech industry, where there are no traditional generics because it is difficult to show they are equivalent to the originals.

The FDA is also supposed to review drug labeling for accuracy, as well as advertisements for accuracy and balance. Even the most casual observer would have to conclude the agency fails at the latter. For one thing, it just doesn't have the resources to do the job. In 2001, the agency had only thirty people to review 34,000 advertisements. Additionally, the FDA is charged with ensuring safe manufacturing standards, but here again, it is woefully understaffed for that task.

The first regulatory agency in the country, the FDA was an outgrowth of the 1906 Food and Drug Act, which prohibited interstate commerce in falsely labeled and adulterated foods, drinks, and drugs. That act, in turn, was a response to a series of magazine exposés of widespread filth in meatpacking plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines. Upton Sinclair's sensational portrayal of the meatpacking industry in his 1906 book *The Jungle* was an added impetus. The FDA now consists of 9,000 people (still a fairly small agency by Washington standards), with the awesome responsibility of overseeing three gigantic industries—food; drugs, vaccines, blood products, and medical devices (such as artificial heart valves); and cosmetics. These industries consist of some 95,000 different businesses with more than a trillion dollars' worth of sales annually.

In 1938, in the wake of a cluster of deaths from the use of a poisonous solvent in a new sulfa drug, Congress decided that the FDA should take more systematic steps to protect the public. Accordingly, the agency was given the specific task of re-
quiring drug companies to prove that their products were safe before they could be sold. It wasn't until 1951, however, that prescriptions were required. In that year, Congress decided that doctors' prescriptions would be necessary to purchase drugs that could not be used safely without medical expertise. In 1962, another requirement was added. Drug companies had to prove their products were not just safe but also effective. That mandate soon gave rise to rules for carrying out clinical trials—the only way to show safety and effectiveness unequivocally.

The FDA is the pharmaceutical industry's favorite whipping boy. Drug companies and their acolytes in the media and Congress relentlessly berate the agency for putting bureaucratic obstacles in the way of getting "lifesaving drugs" to market. In particular, *The Wall Street Journal* and an organization called the Washington Legal Foundation hammer away at the agency incessantly. You would think, from reading their material, that the FDA is filled with capricious bureaucrats who spend all their days dreaming up ways to prevent Americans from getting vital medicines—with what motive, they're not clear. In one editorial, for example, *The Wall Street Journal* urged the FDA to "reform its slow and blinkered approach to potentially lifesaving therapies" and "view itself not as a gatekeeper but as a facilitator." The Washington Legal Foundation warned in one of its advertisements in *The New York Times*, "Make no mistake, unnecessary approval delays have human costs. Rigid procedures, endless data requests, and the pursuit of absolutely risk-free products keep new treatments bottled up at FDA while radically ill patients wait, suffer, and often die."13

Sounds bad, but it just isn't true. The total time from the beginning of preclinical testing of a candidate drug to its coming on the market ranges from about six to ten years. But the time for FDA review accounts for only a small fraction of that—about sixteen months in 2002 and getting shorter. In fact, under pressure from the industry, the agency in the past decade has moved from being the slowest regulatory drug agency in the developed world to being the fastest. In special cases, approval time can be cut to weeks. Of course, the drug companies would like to cut the whole thing—testing and approval—down to virtually nothing, because the time comes out of the drug's patent life.

But except for libertarian extremists and *The Wall Street Journal*, who could possibly want that? Which of us would pretend that the free market can decide whether drugs and medical devices are safe and effective? Do you really want your doctor to rely on the word of drug companies that the antibiotic prescribed for your pneumonia will work? Doctors are not wizards, and they have no way to know whether drugs will work well unless they can rely on an impartial agency like the FDA to review the scientific data. Deciding simply on the basis of whether individual patients seem to respond is a notoriously unreliable and dangerous method. To be sure, doctors might be able to judge for themselves by assiduously keeping up with medical journals and textbooks, but the truth is most don't have
the time to do that. Furthermore, without the pressure of the FDA to make companies do clinical trials, there would be far fewer informative reports published in the medical journals.

Discovering innovative drugs and bringing them to market is a long and difficult process, and there are no shortcuts. It is crucial that new drugs be shown to be safe and effective, as judged by an impartial agency responsible for the public health and not a corporation responsible for the value of its shareholders' stock. The alternative is to go back to 1906, when anything and everything could be sold as a miracle cure and the watchword was caveat emptor. As for all the "me-too" drugs that now constitute the major output of the pharmaceutical industry, it's very hard to make the case that the world should be in any hurry for the next one.

How Much Does the Pharmaceutical Industry Really Spend on R & D?

Drug companies claim drugs are so expensive because they need to cover their very high research and development (R & D) costs. In 2001, they put these costs at $802 million (in 2000 dollars) for each new drug they bring to market. (Later, the consulting firm Bain & Company upped that to $1.7 billion per drug, but they included marketing expenditures.) Implicit in this claim is a kind of blackmail: If you want drug companies to keep turning out life-saving drugs, you will gratefully pay whatever they charge. Otherwise, you may wake up one morning and find there are no more new drugs.
We’ve accounted for the $19.1 billion the pharmaceutical industry admits it spent on marketing in 2001, but we still need to account for the mysterious $35 billion the industry doesn’t acknowledge—the elephant in the living room. Some of that probably goes to gifts and a variety of promotional activities not acknowledged by the industry. But in addition, a great masquerade takes place. The industry has somehow persuaded both the government and the medical profession that it is in the education business—big time. Education, it contends, is different from marketing, even though it comes out of the marketing budget and is perforce hardly impartial. How the pharmaceutical industry gets away with that masquerade is the subject of the next chapter.

8

Marketing Masquerading as Education

No one should rely on a business for impartial evaluation of a product it sells. Yet the pharmaceutical industry contends it educates the medical profession and the public about its drugs and the conditions they treat, and many doctors and medical institutions—all recipients of the industry’s largesse—pretend to believe it. So does the government. But “education” comes out of the drug companies’ marketing budgets. That should tell you what is really going on. As in all other businesses, there is an inherent conflict of interest between selling products and assessing them. Pfizer, for instance, is hardly likely to pro-
vide impartial information about how its Zoloft compares with GlaxoSmithKline’s Paxil to treat depression, or indeed, about whether either one of them is any good. Nor can it be relied on to teach us about depression itself.

In the last chapter, we learned that in 2001 the pharmaceutical industry acknowledged it spent over $19 billion on marketing (leaving about $35 billion unaccounted for). Like all businesses, drug companies claim their advertising is also educational. They claim, for instance, that people learn about diseases they didn’t even know they had by watching direct-to-consumer television ads. (“Omigosh, this Clarinex ad makes me realize I have hay fever!”) But drug companies at least admit direct-to-consumer ads are primarily promotional. That is not what I will be talking about in this chapter.

At issue in this chapter is the probably much larger amount spent on what drug companies contend are purely educational activities. Most of those are directed toward doctors. Although no outsider knows for sure, they probably account for the lion’s share of the missing $35 billion of the marketing budget. It is crucial for big pharma to maintain the fiction that these expenditures are for education, not promotion, because by doing so it can evade legal constraints on its marketing activities. It is also good public relations.

Let’s start by looking at two of these constraints. First, it is illegal for drug companies to market drugs for unapproved uses. When the Food and Drug Administration (FDA) approves a new drug, it approves it for a particular use. And that makes sense. If a drug is shown to be useful for treating a certain kind of infection, it may not work against another kind of infection. To stop drug companies from broadening their claims without evidence, they are not allowed to market drugs for “off-label” uses—that is, uses not approved by the FDA. Doctors, however, are not constrained by this law. They are permitted to prescribe drugs for whatever uses they want. So if drug companies can somehow convince doctors to prescribe drugs for off-label uses, sales go up. The problem is how to get around the law prohibiting marketing for those uses.

That is where “education” comes in. If drug companies pretend they are merely informing doctors about other potential uses, they can circumvent the law. And that is what they do. They sponsor make-believe education, and often buttress it by references to flimsy research studies they sponsor.

Second, it is illegal to offer doctors kickbacks (essentially bribes) to prescribe drugs. In the last chapter, we saw how TAP Pharmaceuticals got into trouble for that. In the wake of the TAP case, there has been increasing scrutiny of big pharma’s lavish gift giving to doctors and medical facilities. The American Medical Association and the Pharmaceutical Research and Manufacturers of America (PhRMA) issued voluntary guidelines suggesting limitations on outright gifts, and the Department of Health and Human Services Office of the Inspector General warned that even adhering to those guidelines would not necessarily protect against prosecution for violating anti-kickback laws.
But what the guidelines and warnings have in common is an exemption for educational or research activities. If drug companies can plausibly construe their blandishments as having an educational or research purpose, they can get away with almost unlimited gifts to promote sales. Furthermore, it is largely left to them to decide what is education or research and what is marketing. As the inspector general's office said in its 2003 warning notice, "The manufacturer should determine whether the funding is for bona fide educational or research purposes." The greater the scrutiny of outright gifts, the more the industry shifts to educational and research support as a substitute.

**Continuing Medical Education**

Luckily for the industry, the demand for physician education is enormous. That is because in most states doctors are required to receive continuing medical education (CME) throughout their professional lives to maintain their licenses. The requirements are substantial, and the education must be provided through accredited institutions. Most doctors earn the necessary credits by attending meetings and lectures—as many as a hundred a year. That means CME meetings are an integral part of doctors' lives. Every day, all across the country, hundreds, maybe thousands, of them take place. Doctors stream into hospital auditoriums, as well as convention centers and vacation spots, to hear about the latest in medical advances. A professional organization called the Accreditation Council of Continuing Medical Education (ACCME) is responsible for accrediting the organizations that provide the educational programs. They include medical schools, hospitals, and various professional societies.

But who pays for these programs? You might assume doctors pay for their own postgraduate education, just as other professionals do, but you would be wrong. In 2001, drug companies paid over 60 percent of the costs of continuing medical education, and that fraction has increased since then. Formerly, they directly supported the accredited professional organizations, but now they usually contract with private medical education and communication companies (MECCs) to plan the meetings, prepare teaching materials, and procure speakers. Oddly enough, the ACCME has accredited about a hundred of these new firms to offer continuing medical education programs themselves—even though they are for-profit firms hired by the drug companies. So here we have firms working for big pharma who are supposed to be providing impartial instruction about their clients' drugs. People pretend not to notice this flagrant conflict of interest. But the way MECCs advertise themselves to drug companies tells the real story. One pitched its services by observing, "Medical education is a powerful tool that can deliver your message to key audiences, and get those audiences to take action that benefits your product." In other words, hire us, and we will get doctors to prescribe your drug. Some MECCs are even owned by large advertising agencies, making the connection between continuing medical education and drug marketing still more obvious.
Now why should MECCs, which are paid by drug companies, be accredited by the ACCME? Well, the answer may have something to do with the makeup of the Task Force on Industry-Professional Collaboration in Continuing Medical Education, which was created to help the ACCME formulate policies on conflicts of interest. About half the members of the task force are representatives of educational institutions and professional organizations, but the other half are from the pharmaceutical industry or MECCs themselves. So it should come as no surprise that the ACCME has accredited not only MECCs but even one of the large pharmaceutical companies—Eli Lilly. The task force evidently never even considered requiring that drug companies have no role in the preparation or presentation of educational programs.

There is a certain amount of obligatory hand waving to make it appear that continuing medical education is not influenced by drug company sponsors. For instance, support by the pharmaceutical industry is nearly always stated to be "an unrestricted educational grant," which implies that drug companies don't influence the content of the programs. And speakers, who are often paid consultants for the companies, are usually required to disclose their financial ties—and that disclosure is supposed to make it acceptable that they have them. But drug companies or their agents, the MECCs, often suggest the topic and speaker and put together the graphics and other educational materials. That medical schools and hospitals have the final say does not change the fact that if they want to continue to get the support, they will go along with the sponsors. Continuing medical education gives drug companies an unparalleled opportunity to influence doctors' prescribing habits, and it seems to work. It's been shown that doctors prescribe more of the sponsors' drugs after these meetings. If it were otherwise, the industry would not spend the huge sums it does on these programs. The adage is right. He who pays the piper usually does call the tune, regardless of efforts to make it appear otherwise.

Bribing Doctors—or Nurturing Consultants?

Drug companies are extremely generous to doctors in their "educational" activities. The education is often said to go in both directions. The companies provide information to doctors, and the doctors provide feedback to the companies. But the money goes in only one direction—from industry to doctors. Doctors are invited to dinners in expensive restaurants or on junkets to luxurious settings to act as "consultants" or "advisers." The doctors listen to speakers and provide some minimal response about how they like the company drugs or what they think of a new advertising campaign. That enables drug companies to pay doctors just for showing up. As one doctor told The Boston Globe, "The companies used to call it coming to dinner. Now it's called consulting." Participants may also receive training to serve on speakers' bureaus, so that they, too, can become company shills. The work on junkets is not too onerous. Lectures usually occupy
just a few hours in the morning, with plenty of time left for golf or skiing in the afternoon and elegant meals and entertainment in the evenings. By calling it education or consulting or market research or some combination of those things, but not marketing, companies needn’t worry about antikickback laws. But doctors are no less beholden to the companies that lavish such attention on them, and they are no more immune to the sales pitches. It’s been estimated that the industry hosted over 300,000 pseudo-educational events in 2000, about a quarter of which offered continuing medical education credits.  

Drug companies pay particular attention to wooing so-called thought leaders. These are prominent experts, usually on medical school faculties and teaching hospital staffs, who write papers, contribute to textbooks, and give talks at medical meetings—all of which greatly affect the use of drugs in their fields. Thought leaders have influence far beyond their numbers. Companies shower special favors on these doctors, offer them honoraria as consultants and speakers, and often pay for them to attend conferences in posh resorts, ostensibly to seek their advice. In many drug-intensive medical specialties, it is virtually impossible to find an expert who is not receiving payments from one or more drug companies. As I said in Chapter 7, drug companies sway doctors with “food, flattery, and friendship.” In the case of thought leaders, flattery is key. They are told their expertise is invaluable in helping companies to develop new drugs. But in fact, thought leaders are usually clinicians, who study drugs after they are developed. What they really have to offer drug companies is the ability to sway large numbers of other doctors.

I mentioned in Chapter 6 that the head of Brown University’s Department of Psychiatry reportedly made over $500,000 in one year consulting for drug companies that make antidepressants. When The New England Journal of Medicine, under my editorship, published a study by him and his colleagues of an antidepressant agent, there wasn’t enough room to print all the authors’ conflict-of-interest disclosures. The full list had to be put on the website. In a footnote, I wrote, “Our policy requires authors of Original Articles to disclose all financial ties with companies that make the products under study or competing products. In this case, the large number of authors and their varied and extensive financial associations with relevant companies make a detailed listing here impractical. Readers should know, however, that all but one (B.A.) of the twelve principal authors have had financial associations with Bristol-Myers Squibb—which also sponsored the study—and, in most cases, with many other companies producing psychoactive pharmaceutical agents. The associations include consultancies, receipt of research grants and honorariums, and participation on advisory boards.” I also wrote an accompanying editorial, titled “Is Academic Medicine for Sale?” in which I expressed my concern about the merging of commercial and academic interests. In response, a reader sent a letter to the editor asking rhetorically, “Is academic medicine for sale? No. The current owner is very happy with it.”
Professional Meetings

The meetings of professional societies, like the American College of Cardiology or the American Society of Hematology, are now partly supported by drug companies. This is where much of the ongoing education of doctors takes place. At annual meetings, which may be attended by thousands of doctors, drug companies present their own satellite symposia—with free lunches and dinners. A few years ago, I attended one such symposium. It took place over a four-course meal at a hotel near the main meeting, and about two hundred doctors were there. The topic was osteoporosis—thinning of the bones. At first, I did not know which of the several types of drugs to treat osteoporosis the sponsor made, but I soon guessed. In slide after slide, this was the drug at the top of the list of drugs to consider, even though it is probably the least effective. And in most of the hypothetical patients discussed, there was some reason not to give one of the more effective drugs. For example, one patient was said to have an ulcer as well as osteoporosis. That would have been a reason not to use the most effective treatment, but it would also have been an unusual situation. In short, the whole symposium was slanted to promote a third-choice treatment. The main speaker was a distinguished endocrinologist from a major medical school. He later told me that the company had given a grant of $10,000 to his department, as well as paid his expenses and an honorarium. The company had also made his slides.

Marketing Masquerading as Education

Many big professional meetings resemble bazaars, dominated by garish drug company exhibits and friendly salespeople eager to ply doctors with gifts while they pitch their companies' drugs. Doctors wander the vast exhibit halls carrying canvas bags displaying drug company logos and brimming with goodies, munching on free food, and partaking of all sorts of free services, such as cholesterol screening and putting green practice. Instead of sober professionalism, the atmosphere of these meetings is now trade-show hucksterism.

In a vivid article on the subject, a reporter from The Boston Globe described her encounter with one psychiatrist at the annual meeting of the American Psychiatric Association (APA):

Ivonne Munez Velazquez, a psychiatrist from Mexico, rooted through her goody bag like a child on Halloween. As a reward for attending the APAs annual meeting, she had received a small egg-shaped clock from the makers of the antidepressant Prozac; a sleek thermos from Paxil, also an antidepressant; and an engraved silver business card holder courtesy of Depakote, an anticonvulsant [often prescribed off label for a variety of psychiatric disorders]. She got a neat little CD carrying case from Risperdol [sic], an antipsychotic; a passport holder from Celexa, an antipsychotic [actually, an antidepressant]; a neat green paperweight from Remeron, an antidepressant; and a letter opener, representing what drug she could not remember. For the duration of the weekend, though, Velazquez's loyalty belonged to Pfizer, which had
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paid her airfare from Mexico City (along with thirty of her colleagues and her eighteen-year-old nephew) and put them all up in hotels near the APA meeting. That night, also courtesy of Pfizer, she would attend a glittering banquet at the Philadelphia Academy of Fine Arts. (The new PhRMA guidelines would prohibit this, but they are voluntary, and even if followed could probably be evaded by calling her a consultant.)

Membership dues for the APA are dropping. And well they might. According to the Boston Globe story, drug companies spent between $200,000 and $400,000—plus a $60,000 direct payment to the association—for each of fifty-plus “industry-sponsored symposia.” Without the drug company money, officials said, the annual meeting would lose educational benefits along with amenities. “How much are you willing to pay for that, if we don’t accept drug company money?” asked Anand Pandya, an APA official. “Are you willing to pay $3000?” (Dues are now $540.) That is an excellent question. How much are these meetings worth? And how many “amenities” are necessary? Perhaps members should pay exactly what the meetings are worth to them. The meetings might then assume a more serious tone and a more modest dimension. By allowing drug companies to foot the bill for carnival-like meetings, doctors are really passing the costs along to people who buy prescription drugs.

Pretending Drug Companies Are Educators

Why do doctors pretend they believe drug companies are interested in education? (Some of them may actually believe it.) The answer is: It pays. Membership dues would be far higher if professional societies were not supported by industry. Doctors would also have to pay for their own continuing medical education. In addition, they would lose the travel and entertainment and other emoluments too many of them have come to believe are entitlements of their profession. Many doctors become indignant when it is suggested that they might be swayed by all this industry largesse. But why else would drug companies put so much money into them? As Stephen Goldfinger, chairman of the APA’s Committee on Commercial Support, said, “The pharmaceutical companies are an amoral bunch. They’re not a benevolent association. So they are highly unlikely to donate large amounts of money without strings attached. Once one is dancing with the devil, you don’t always get to call the steps of the dance.”

Big pharma, for its part, insists that it has an educational mission that can be separated from its commercial interests. The 2002 PhRMA Code on Interactions with Healthcare Professionals begins with the statement that “relationships with healthcare professionals...should be focused on informing healthcare professionals...should be focused on informing healthcare professionals about products, providing scientific and educational information, and supporting medical research and education.” In other words, big pharma insists it is in the education business.
Then it goes on to recommend that companies not provide payments or gifts to doctors unless they serve an educational or research purpose. (Precisely how gifts serve such purposes is never explained.) In case there is any confusion, the code presents a series of hypothetical scenarios. Here are a couple:

**Question:** Company A invites 300 physicians/consultants to a two-day and one-night speaker-training program at a regional golf resort. All attendees are compensated for their participation and their expenses are reimbursed. Training sessions take both days, and the Company provides for a few hours of golf and meals. Does this program conform to the Code? ...

**Answer:** This arrangement appears to comply with the Code. ...

[Spouses, it adds, should pay their own way.]

**Question:** Company A retains a small group of 15 nationally known physicians regarding a therapeutic area relevant to company A’s products to advise on general medical and business issues and provide guidance on product development and research programs for those products. These physicians are paid significant fees, but those fees are typical of the fees paid to thought leaders in this therapeutic area. They normally meet once or twice a year at resort locations to discuss the latest product data, research programs and Company plans for the product(s). Does this comply with the Code? If it does, is it appropriate to pay for the spouse of the healthcare professional to attend, as well?

**Answer:** This arrangement appears to comply with the Code. ... It would not be appropriate to pay for the cost of the spouse of the advisor.

You can see from these examples how calling marketing “education” and doctors “consultants” enables drug companies to evade antikickback laws. They can lay on all the boondoggles they want.

The government, too, seems willing to accept the fiction that drug companies are educators. In its 2003 guidelines, the Department of Health and Human Services Office of the Inspector General (OIG) warned against offering incentives to induce health care professionals to prescribe, recommend, or purchase particular drugs or devices. But it also said, “Absent unusual circumstances, grants or support for educational activities sponsored and organized by medical professional organizations raise little risk of fraud or abuse, provided that the grant or support is not restricted or conditioned with respect to content or faculty.” 12 “The OIG’s main concern about such funding,” according to its senior counsel, “is that it not be used as a disguise to channel improper remunerations to physicians or others who may be in a position to generate business.” 13

To erect a firewall between illegal inducements and education, the inspector general advised drug companies “to separate their grant-making functions from their sales and marketing functions.” The dubious premise that drug companies can be engaged in both education and promotion at once was not ques-
tioned. But it is not really possible for companies to promote their drugs, which means touting only their favorable effects, and to provide impartial information, some of which might be unfavorable. Even less plausible is the idea that by “separating” these activities, say, by locating them down the hall from each other instead of in the same office or by creating two divisions, you can somehow obliterate the reality that they are part of the same company with the same overall goal of selling drugs.

**Educating Consumers**

Drug companies claim that they also “educate” consumers. In 2002 General Electric, with funding from big pharma, launched The Patient Channel, which shows medical programming interspersed with drug ads to patients in hospitals and waiting rooms across the country. Within a year, some eight hundred hospitals were carrying the network twenty-four hours a day, seven days a week. Supported entirely by its advertisers, The Patient Channel cost hospitals nothing. Patients could choose among half-hour segments, such as “Cancer Related Fatigue” or “Breathe Easy: Allergies and Asthma.” Hospitals liked the idea, because they were told it would satisfy accreditation requirements that they educate patients about their illnesses. But the Joint Commission on Accreditation of Healthcare Organizations, the accrediting body, disagreed. In a 2003 letter to General Electric, the president of the commission pointed out that hospitals are supposed to provide education specific to a given patient’s needs, not a television program.

The letter added the observation that “the viewer is not sufficiently alerted to the transition between educational programming and marketing programming.” Like the Health and Human Services inspector general, the accrediting commission seemed to endorse the notion that drug companies can both market and educate, the only problem being that they need to be clearer about when they are doing which—they need a firewall. But in fact, there can be no firewall, because drug companies are not really in the education business. (If they were, they would sell their educational programs, not give them away or pay people to accept them.) The problem with separating the educational programming from the marketing programming is that it is really all marketing. The Patient Channel’s marketing director, Kelly Peterson, was much closer to the mark when she solicited drug company advertising by saying it would allow companies to “directly associate their products with a particular condition in a hospital setting.” You bet it would. It would deliver vulnerable, captive customers right to the companies’ doorstep—or more precisely, bring the companies’ doorstep to them.14

Another form of marketing disguised as education is the sponsorship of patient advocacy groups. Many of these groups are simply fronts for drug companies. People who suffer from a certain disease believe they have found a support network devoted to expanding awareness of the disease, but it is really a
way for drug companies to promote their drugs. Some people aren’t even aware that a drug company is behind their advocacy group; others believe the companies just want to help educate people.

Take the hepatitis C coalitions. They look like a grassroots movement to draw attention to the dangers of a liver infection called hepatitis C, which affects some 4 million Americans. But in fact, according to The Washington Post, the movement was begun by Schering-Plough, which makes Rebetron, the primary treatment for hepatitis C. Rebetron costs $18,000 a year. The advocacy groups are likely to increase sales by making the disease more widely known and putting pressure on insurers to cover treatments. That may be a good thing, but the company apparently kept its sponsorship largely hidden. As Thomas Murray, president of the Hastings Center (a bioethics think tank), put it, “It’s ethically problematic when a company creates entities but then tries to pass them off as authentic and spontaneous grass-roots organizations. What bothers me is the deceptiveness.”

One of the least savory marketing efforts is Wyeth’s campaign to “educate” college students about depression. What is really being marketed is the condition. If students can be convinced they have a treatable depression, selling the company drug Effexor is easy. To that end, Wyeth sponsors a ninety-minute forum on college campuses called “Depression in College: Real World, Real Life, Real Issues.” It features doctors, psychologists, and Cara Kahn of the MTV reality show Real World Chicago, who takes Effexor. In 2002, when the campaign was launched, Wyeth told Alex Beam of The Boston Globe that four colleges had agreed to host the forum. Harvard declined. Its provost, a psychiatrist who was formerly head of the National Institute of Mental Health, told Beam, “In the case of celebrities speaking, who are actually being paid by the company, there is a risk that inappropriate marketing will go on.” That’s putting it mildly. Beam himself was more outspoken: “Millions of college students feel lousy, for any number of reasons: they are far from home; college is an unfamiliar and sometimes threatening environment; the object of their affection is inattentive. God knows we all have been there. Do they need a $120-a-month Effexor fix to see them through these tough years? Probably not. But who could be more suggestible, or vulnerable, than a boy or girl making the transition to adulthood?” Well, maybe a patient lying in his hospital bed watching The Patient Channel.

The pretense that pharmaceutical marketing is education requires the participation of at least two parties—the industry and the medical profession. We know why big pharma fosters that illusion: It helps the bottom line. It increases sales and promotes a highly drug-intensive style of medical practice. Indeed, if it didn’t help the bottom line, if all this “education” were just that and had no impact on sales, heads would roll in the executive
suites of the drug companies. After all, they are investor-owned businesses, and it is their responsibility to maximize profits, not give away billions of dollars.

It is much harder to excuse the medical profession and its institutions and organizations. Medical education worthy of the name requires an impartial analysis of all the available evidence, led by experts who have no vested interest in the drugs they are discussing. It is the job of medical schools and their faculty, and of professional societies, to educate doctors in that way. To abdicate that responsibility is wrong, and it is doubly wrong to leave it to an industry with an obvious financial interest in the enterprise and then pretend it is otherwise. That a noble profession has been willing to do this is a testament to the power of “food, flattery, and friendship”—and money, lots of it.

No one outside the industry has ever added up the costs of the “educational” activities described in this chapter, because they are not publicly disclosed. But these and similar activities could easily account for most of the unaccounted-for expenditures in big pharma’s marketing budgets. It is far too much money to imagine that it represents some sort of public-spirited contribution to education. This masquerade leads to no end of problems—the corruption of the profession, the misuse and overuse of expensive prescription drugs, and, as we will see in Chapter 12, an avalanche of governmental investigations and lawsuits based on the spurious notion that the pharmaceutical industry provides bona fide medical education and it is therefore possible to distinguish lawful educational expenses from illegal marketing. If we acknowledged the fact that the pharmaceutical industry cannot possibly be expected to provide unbiased education about its own products, there would be no need to pursue the hopeless task of trying to differentiate “educational grants” from kickbacks, as the Department of Health and Human Services inspector general tries to do. Neither would be permissible.
Marketing Masquerading as Research

Suppose you are a big pharmaceutical company. You make a drug that is approved for a very limited use—say, it treats a condition that affects only 250,000 people. How could you turn it into a blockbuster? There are essentially two ways. First, you could test it for other conditions in clinical trials. If the trials showed it was safe and effective, you could apply for Food and Drug Administration (FDA) approval to market it for additional uses. That is what Bristol-Myers Squibb did with Taxol, for instance. It was originally approved to treat cancer of the ovary, but the company immediately launched additional trials to see if it also worked for cancer of the breast and cancer of the lung—which it did. That greatly expanded the market.

Alternatively, you could simply market the drug for unapproved (“off-label”) uses—despite the fact that doing so is illegal. You do that by carrying out “research” that falls way below the standard required for FDA approval, then “educating” doctors about any favorable results. That way, you could circumvent the law. You could say you were not marketing for unapproved uses; you were merely disseminating the results of research to doctors—who can legally prescribe a drug for any use. But it would be bogus education about bogus research. It would really be marketing.

The Neurontin Case

Parke-Davis apparently took the second approach with its epilepsy drug Neurontin. Parke-Davis was a division of Warner-Lambert, which in 2000 was swallowed up by the drug giant Pfizer. In 1996, David P. Franklin, a Parke-Davis sales representative (called a “medical liaison” because of his additional technical training), brought suit against the company for defrauding Medicaid and other government health programs. (As a whistle-blower, he would be entitled to a portion of any fines.) Franklin had thousands of pages of internal documents. He charged that the company had carried out a massive illegal scheme to promote Neurontin for off-label uses—mainly by paying academic experts to put their names on flimsy research
papers that purported to show the drug worked for these other conditions.¹

Eventually, federal prosecutors filed a brief in support of Franklin and launched both criminal and civil investigations of their own. Parallel actions were filed by forty-seven states and the District of Columbia. Court documents were originally sealed at the company's request, but many of them were released in 2002 in response to media petitions. They showed a well-coordinated plan of staggering dimensions. What appears here is drawn from newspaper reports of Franklin's complaint and of the company records released by the court.

Neurontin had been approved by the FDA in 1994 for a very narrow use—to treat epilepsy as an add-on when other drugs failed to control seizures. (Later it was approved to treat shingles as well.) There wasn't much money in that, and the company wanted to expand the drug's market. But there was no time to do proper clinical trials that might allow it to get FDA approval for other uses, because the patent was due to expire in 1998 (later extended to 2000). So the company apparently devised a plan to get doctors to prescribe Neurontin for unapproved uses—mainly common but vague conditions like pain and anxiety of various forms, and also as the sole treatment for epilepsy. If the campaign were successful, huge markets would be opened up.

Parke-Davis reportedly called its plan a "publications strategy." It would sponsor minimal research, prepare journal articles based on it, and pay academic researchers to put their names on those articles. The studies themselves were so small or poorly designed that few valid conclusions could be drawn from them. Some of the articles contained no new data at all, just favorable comments about Neurontin. Medical education and communication companies were hired to prepare the articles and find authors. One of these firms, for instance, was to be paid $12,000 for each of twelve journal articles it prepared.² It in turn paid academic "authors" $1000 to sign them. Apparently it wasn't always easy. In a progress report to Parke-Davis, the education company lamented, "Author interested; still playing phone tag." Then in caps, "[OUR COMPANY] HAS DRAFT COMPLETE, WE JUST NEED AN AUTHOR."³

The second part of the publications strategy was to see that the articles and the information in them were widely disseminated to practicing doctors, so that they would be persuaded to start prescribing Neurontin for off-label uses. It doesn't do any good to create favorable articles if nobody hears about them. Parke-Davis "medical liaisons," who are purported to have more of an educational mission than ordinary sales representatives, would visit doctors' offices to answer questions about the research. One company manager was said to have been recorded by Franklin haranguing liaisons in what sounded like a pregame pep rally: "When we get out there, we want to kick some ass. We want to sell Neurontin on pain. All right?"⁴

Parke-Davis also sponsored educational meetings and conferences all over the country. At these meetings, the "authors" of the papers and other experts would describe the success of
the drug for off-label uses. Dozens of doctors were allegedly paid tens of thousands of dollars each to speak to other physicians about using Neurontin for more than a dozen unapproved uses. Not only were the speakers paid for their services but often the doctors in the audience were also paid. They were called "consultants"—which had the effect of circumventing antikickback laws. Consultant meetings were sometimes little more than vacations for potential high prescribers of Neurontin. The company tracked doctors' prescriptions to see if they prescribed Neurontin more after the meetings or after they were hired to speak about the drug. According to a New York Times story, the company found an increase of about 70 percent in prescriptions after dinner meetings.5

One thing about this research-education one-two strategy is that the speakers and the audience are essentially interchangeable. In essence, they are all being persuaded to prescribe a drug for off-label uses; it doesn't really matter who is doing the talking and who is doing the listening. As we learned in the last chapter, it is simply a matter of getting a message out to thought leaders and potential high prescribers, while skirting both antikickback laws and laws against off-label marketing.

As a result of these efforts, Neurontin did become a blockbuster, with sales of $2.7 billion in 2003. About 80 percent of prescriptions that year were for unapproved uses—conditions like bipolar disorder, post-traumatic stress disorder, insomnia, restless legs syndrome, hot flashes, migraines, and tension headaches.6 In fact, Neurontin has become a sort of all-purpose restorative for chronic discomfort of almost any type—yet there is almost no good published evidence that it works for most of these conditions. In May 2004, eight years after the case began, Pfizer pleaded guilty to illegal marketing and agreed to pay $430 million to resolve the criminal and civil charges against it. As whistle-blower, Franklin will receive nearly $27 million of that. That sounds like a lot of money, but it is small potatoes compared with the $2.7 billion in Neurontin sales.7

Phase IV Clinical Trials—Real and Bogus

This case may have been unusual in its scope and in the fact that a whistle-blower brought it to court, but I suspect it is a fairly standard way of doing business. The common denominator is the use of flimsy Phase IV clinical research for marketing purposes. As you will recall from Chapter 2, Phase I through III clinical trials are directed toward getting initial FDA approval, and they must meet the agency's scientific standards. Phase IV trials, in contrast, are studies of drugs already on the market, and many of them don't have to meet any standards at all. It was estimated in 2002 that Phase IV studies, sometimes called "post-marketing" studies, accounted for at least 25 percent of all clinical trials, and their number is growing much faster than that of Phase I through III trials.8

There are two legitimate reasons for Phase IV studies. The first is to see whether a drug is effective for an additional use and, if so, to get FDA approval to market it for that use—as in
the case of Taxol. It is analogous to getting approved in the first place, in the sense that the research must meet the same scientific standards as the original Phase III trials. By getting FDA approval for new uses, companies not only expand the size of a drug’s market but can also get an additional three years’ exclusive marketing rights.

The second legitimate reason for Phase IV trials is to look for side effects or other properties of the drug that were missed in the earlier clinical trials. Even large, well-designed Phase III trials may not reveal side effects if they are very rare or no one thought to look for them. They may also miss other effects that show up only in patients different from those previously studied. After the drug comes on the market and is used widely in the general population, those properties may be discovered in large Phase IV studies.

These latter sorts of studies are more important than they once were, because until a decade ago, drugs were usually first approved in Europe. That meant serious side effects would probably show up there, before a drug was used in the United States. But now, most drugs are approved first in the United States. Furthermore, an increasing number of them are given accelerated review by the FDA, which means they come to market on the basis of less evidence. Thus, a drug may come into widespread use with very little research to back it up, and no experience in another country.

As a condition of accelerated approval, and sometimes even with regular approval, the FDA requires companies to conduct Phase IV confirmatory studies just to make sure the new drug is safe. In fact, about two-thirds of all new molecular entities approved in 2000 were supposed to undergo Phase IV studies. These are called “commitment studies,” because companies have a commitment to do them. But in fact, they don’t want to do them. They have nothing to gain, and everything to lose if a serious side effect turns up. So they drag their feet. As of 2003, only half of all drugs that had undergone accelerated approval had been fully investigated in “commitment studies.” Thomas Fleming, a biostatistician at the University of Washington and an adviser to the FDA, observed, “Sponsors, particularly industry sponsors, have a keen sense of urgency to develop an agent in a timely fashion, but once the agent is approved, there is almost a reverse motivation—you’ll market the product until it’s shown not to work.” Theoretically, the FDA has the authority to pull a drug from the market if the company reneges on its commitment, but it has never done so.

However, the majority of Phase IV studies fall into neither of these categories. Their purpose is not to get FDA approval for a new use. Nor is it to fulfill a commitment. Instead they are mainly gimmicks to increase sales—as in the Neurontin case. The most common Phase IV trials are so-called surveillance studies. Here sponsors pay doctors to put patients on drugs and answer a few simple questions about how they fared. There is no randomization and no comparison group, so it is usually impossible to draw any reliable conclusions. CenterWatch, a company that serves as a clearinghouse for information about the clinical trials industry, recently ran an article titled “Phase IV
Market Steams Ahead.” In it, the aim of surveillance studies was made clear: “The primary purpose of this type of post-marketing research is to familiarize physicians and patients with new drugs.” And the article pointed out that such research does indeed influence doctors’ drug choices and formulary recommendations. How many Phase IV studies are funded out of drug company research and development budgets and how many out of marketing budgets is impossible to know. Probably both contribute.

A few years ago, a doctor sent me an invitation he received to participate in a study sponsored by Salix Pharmaceuticals. It asked him to start five patients with active ulcerative colitis on the company’s drug Colazal. After eight weeks, he would fill out a form and return it to Salix, which would then pay him a $500 “honorarium.” The company would also provide free samples for the patients, plus coupons to cover part of the costs of the drug. The clinical summary to be filled out was short and simple. In fact, it was so short and simple it could have no real scientific value. The first question, for instance, asked, “Overall, how was your experience with Colazal?” and you could check one of three boxes: “extremely pleased,” “pleased,” or “not pleased.” It is hard to believe that this was anything but an excuse to pay doctors to prescribe Colazal. But as CenterWatch observed, “Sponsors must sometimes simplify study protocols to meet their marketing needs and thus limit the scientific validity of the studies.” Anything to get doctors to prescribe your drug.

A “Sweet Spot”

You may remember that I mentioned in Chapter 2 the growth of a large industry to perform clinical trials for drug companies. It consists mainly of private contract research organizations (CROs). These firms run clinical trials for drug companies, using networks of private doctors in their offices. They concentrate particularly on Phase IV studies. “Phase IV studies are the fastest growing segment of clinical spending,” CenterWatch wrote. “This sweet spot in the market is being actively pursued by CRO's and offers unique opportunity for experienced, community-based clinical investigators.” It’s a “sweet spot” for the doctors, too. They usually make more working for CROs than spending the same time caring for patients. There are now tens of thousands of private doctors doing this work—many of them essentially being paid to prescribe a company drug.

Since the majority of Phase IV studies will never be submitted to the FDA, they may be totally unregulated. Few of them are published. In fact, like all industry-sponsored trials, they are not likely to be published at all unless they show something favorable to the sponsor’s drug. If they are published, it is often in marginal journals, because the quality of the research is so poor. CenterWatch described Phase IV studies this way: “Whereas companies generally prefer [phase I through III] studies to be done by experienced research investigators, phase IV programs offer sponsors the opportunity to initiate and develop strategic
relationships, especially with high-volume prescribers." In other words, it isn't really research, so don't worry too much about its scientific validity.

Some of the largest advertising agencies in the world have gotten into the pharmaceutical research and education business on behalf of their clients in the drug industry. They include the three Madison Avenue giants—Omnicom, WPP, and Interpublic. To provide their clients with more integrated service, they have purchased or invested in CROs and medical education and communication companies (MECCs). Take Omnicom. It is part owner of SCIREX—a CRO. That relationship enables the marketers to direct research toward drugs they think could be big sellers. One advertising executive said, it is "getting closer to the test tube." Omnicom also owns Proworx—a MECC accused of ghostwriting articles in the Neurontin case.16 The ad agency WPP owns Intramed—another MECC apparently in the ghostwriting business. The New York Times obtained a transcript of a conference call in which an Intramed vice president reportedly told doctors, "We would like to help draft this manuscript, and then submit it to you for your— for your editing and for approval." According to the account, a representative of WPP's client Novartis was also on the phone. He added that the company wanted "a quick, down and dirty" article. One of the doctors responded, "I think we're quite clear on what you want the next manuscript to look like."17 The fact that these huge advertising agencies own or employ research and education companies shows clearly just what is subordinate to what in this business. "Clinical research" and "education" are just tools of the marketers.

One of the more convoluted examples of research that at least in part serves marketing purposes is the story of Eli Lilly's drug Xigris. In 2001, Xigris was approved to treat severe sepsis, blood-borne infections that are a common cause of death in intensive care units (ICUs). Its approval was not a sure thing. In the key clinical trial submitted to the FDA, 25 percent of patients taking Xigris died, compared with 31 percent of those on standard treatment. That is not a big difference, although it was statistically significant. The FDA advisory panel split evenly on whether to recommend approval, with some saying another clinical trial was needed. Lilly priced Xigris at $6800 per treatment and expected it to become a blockbuster and make up for the sales the company would lose when Prozac's patent protection ran out that year. But because of the high cost, many hospitals decided that the drug was not worth it. They could get more bang for the buck, they thought, by putting that money to other uses. By the spring of 2002, it was clear that sales of Xigris were not meeting expectations.

So Lilly hired a new advertising firm, Belsito & Co., to handle the Xigris account. The company pitched a campaign it called "The Ethics, the Urgency and the Potential." The idea was not to do more research on the drug's effectiveness but instead to do research on whether ICU patients were generally being deprived of treatments because of cost. That approach could be used to convince people that it was unethical not to use
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Xigris, because it was tantamount to rationing lifesaving treatment. To that end, Lilly gave a $1.8 million grant for a comprehensive study of rationing in ICUs. Dr. Mitchell Levy, head of the medical ICU at Rhode Island Hospital, who pronounced the data behind Xigris “damn good,” was tapped to lead a twenty-person committee called the Values, Ethics & Rationing in Critical Care Task Force. (It has its own website, www.vericc.org.) Other members include prominent ethicists, hospital directors, and ICU specialists from all over the country.

Lilly also managed to get a new federal diagnostic code for severe sepsis, so that the incidence could be tracked. That way they would have a better idea of the size of the potential market and how to promote Xigris better. More important, it got the Centers for Medicare & Medicaid Services to agree to reimburse half the charge for Xigris, up to $3400 a treatment. That kind of deal is unheard of. The standard way Medicare reimburses hospitals is according to the diagnosis—so much for a heart attack, so much for a stroke, so much for pneumonia, and so forth. It does not pay for a specific drug or other treatment. What Lilly got for Xigris is unique. In case you are wondering, Lilly told The Wall Street Journal it has no intention of lowering the drug’s price. And the profit margin? The company isn’t telling.

The Xigris story shows how throwing money at academics can shift the focus from where it should be in this case—the exorbitant price of a drug of uncertain effectiveness—to the ethics of rationing. One clinical trial is usually not enough to prove benefit conclusively. The FDA asked Lilly to conduct Phase IV commitment studies to elucidate further the risks and benefits. One would hope the company is as keen on doing those studies as on demonstrating rationing in ICUs, but somehow I doubt it.

Consequences of the Masquerades

This chapter and the last have been about marketing masquerading as education and research—often coupled together. First, faux research yields a faux answer to a clinical question. Then faux education assures that doctors everywhere hear about it, so they can write millions of prescriptions based on the faux information. Bribes and kickbacks sometimes grease the skids.

Well, you might ask, what is really wrong with that? The process is admittedly deceptive, but if it means that more people get prescription drugs, isn’t there a net benefit? After all, the drugs are probably on balance helpful, or the FDA wouldn’t have approved them and doctors wouldn’t prescribe them. Shouldn’t we pay more attention to the outcome and less to the process?

I find it hard to imagine that a system this corrupt can be a good thing, or that it is worth the vast amounts of money spent on it. But in addition, we have to ask whether it really is a net benefit to the public to be taking so many drugs. In my view, we have become an overmedicated society. Doctors have been taught only too well by the pharmaceutical industry, and what they have been taught is to reach for a prescription pad. Add to
that the fact that most doctors are under great time pressure because of the demands of managed care, and they reach for that pad very quickly. Patients have also been well taught by the pharmaceutical industry’s advertising. They have been taught that if they don’t leave the doctor’s office with a prescription, the doctor is not doing a good job. The result is that too many people end up taking drugs when there may be better ways to deal with their problems.

This conclusion was underscored by a large trial sponsored by the National Institutes of Health of ways to prevent adult-onset diabetes in people at high risk for the disease. One group in the trial received placebo, and 29 percent of patients in that group developed diabetes over a three-year period. The second group received a drug called metformin (the generic form of Bristol-Myers Squibb’s blockbuster Glucophage), and they did somewhat better—22 percent developed diabetes. But the third group did much better than either of the other two. They were placed on a moderate diet and exercise program, and only 14 percent got diabetes. In other words, diet and exercise were better than the drug. But trying diet and exercise instead of a drug is not likely to happen in real life. Drenched as we all are in prescription drug promotions, both doctors and patients are far more likely to go for the Glucophage. Besides, insurers don’t usually pay for diet and exercise programs.

More serious is the fact that many of us are taking a lot of drugs at once—often five, maybe ten, or even more. This practice is called “polypharmacy,” and it carries real risks. The problem is that very few drugs have just one effect. In addition to the desired effect, there are others. Some are side effects doctors know about, but there may also be ones we are not aware of. When several drugs are taken at once, those other effects may add up. There may also be drug interactions, in which one drug blocks the action of another or delays its metabolism so that its action and side effects are increased. When the function of an organ, for instance the liver or the kidneys, is even slightly impaired, the probability of complications from one or more medications increases. And the more medications taken, the more likely it is that one of them will interfere with the normal function of some organ.

Recently, The Boston Globe carried a story about polypharmacy. The case in point was a fifty-year-old woman who was taking eighteen prescription drugs at a cost of nearly $16,000 per year. Nearly all of them were expensive brand-name drugs. They were meant to treat a variety of ailments, including diabetes, depression, anxiety, allergies, migraines, and pain (for which she was taking the ubiquitous Neurontin). Four of the drugs were for psychiatric problems—clonazepam for anxiety, Lexapro for depression, Trileptal for depression (not approved for this use), and Elavil for depression and sleeplessness. Reportedly, she could barely get around, and her roommate said that she was sometimes dizzy or fell or couldn’t stand up. No wonder! Most psychiatric drugs cause some degree of drowsiness, and so does Neurontin. I can only imagine what all of them together do. It would be virtually impossible to sort out
which of her complaints were caused by illness and which by all the drugs. What she probably needed was less medication and more medical attention. Experienced specialists are familiar with this phenomenon of overmedication and often start their evaluation of a patient who is not doing well on multiple drugs by eliminating most or all of the medications. Frequently, the patient improves.

This is not to gainsay the vital role of good prescription drugs in health care. There is no doubt that many people live longer, better lives because of them. As I said in Chapter 6, we need them. But they should be prescribed carefully and only when necessary, and doctors' judgment about their prescription should be based on real research and education, not on the marketing that passes for it.

NOTHING DRUG COMPANIES DO IS AS profitable as stretching out monopoly rights on their blockbusters. For all the talk about free enterprise, the pharmaceutical industry's lifeblood is government-conferred monopolies—in the form of patents granted by the U.S. Patent and Trademark Office (USPTO) and exclusive marketing rights granted by the Food and Drug Administration (FDA). The two forms of exclusivity operate somewhat independently, as discussed in Chapter 1. Both make it illegal, for a specified time, for competitors to sell the same drug.' Extending that privileged time by a variety of stratagems is the most innovative ac-
CLEARLY, THE PHARMACEUTICAL INDUSTRY AND the medical profession need thoroughgoing reform, and Congress and the Food and Drug Administration need to be reminded that they exist to serve the public, not drug companies. In the meantime, what can you as an individual do to protect your interests? Here are a few specific suggestions.

1. When your doctor prescribes a new drug, ask him or her these questions:
   What is the evidence that this drug is better than an alternative drug or some other approach to treatment? Has the evidence been published in a peer-reviewed medical journal? Or are you relying on information from drug company representa-
Afterword

tives? Insist on getting a straight answer and, if necessary, a reference to a journal article or a medical textbook.

Is this drug better only because it is given at a higher dose? Would a cheaper drug be as effective if it were given at an equivalent dose? Sometimes the best course is simply to increase the dose of an older drug. Remember, there is usually no reason to think new drugs are better than old ones, and the older the drug, the better its safety record is likely to be.

Are the benefits worth the side effects, the expense, and the risk of interactions with other drugs I take? Every drug has side effects, and it may be better not to treat self-limited or trivial ailments.

Is this a free sample? If so, is there a generic drug or an equivalent drug I can use that is cheaper when the free samples run out? Free samples are a false economy. They are designed to get you and your doctor hooked on the newest, most expensive drugs.

Do you have any financial ties with the company that makes this drug? For example, do you consult for the company? Other than free drug samples, do you receive gifts from drug companies? Are you being paid to put me on this drug and enroll me in a drug company study? Do you make time for visits from drug company representatives? If the answer to any of these questions is yes, you should consider changing doctors. You need to know your doctor's decisions are based solely on what is best for you. And doctors need to be weaned from their dependence on drug company largesse.

2. And ask your senators and representatives in Congress this question:

Do you receive campaign contributions from the pharmaceutical industry, and if so, how much are they? There is no doubt that this industry largely writes its own ticket in Washington, and you have to put a stop to that.

3. Pay no attention to direct-to-consumer ads for prescription drugs.

These are meant to sell drugs, not educate consumers, and they only add to the prices you pay.

Finally, remember the admonition of the Washington Post editorial, quoted on page 215, to question those arguing big pharma's case about their sources of income. I can think of no better advice. Nowadays, even the most distinguished and apparently unbiased academics may be on the pharmaceutical industry's payroll. If they are, you need to be especially skeptical about their pronouncements.
Epilogue: The Saga of Vioxx and the COX-2 Inhibitors

On September 30, 2004, the drug giant Merck announced it was pulling its arthritis drug Vioxx from the market, citing a clinical trial that showed it doubled the risk of heart attacks and strokes. Vioxx had been massively promoted to both doctors and the public. The direct-to-consumer ads on television featured Dorothy Hamill skating effortlessly across an outdoor rink to the Rascals' “It's a Beautiful Morning”—presumably free of arthritis pain, thanks to Vioxx. At the time it was withdrawn, an estimated two million people took Vioxx, and it had yearly sales of $2.5 billion dollars. In short, it was a blockbuster. The withdrawal of Vioxx was front-page news and caused great public concern, both among those who felt the drug was uniquely effective in relieving their arthritis symptoms.
and among those who feared they might have a heart attack or stroke because of the drug. Merck’s stock price fell by about one-third on the day of the announcement, and market analysts began to speculate gloomily about the company’s uncertain financial future and legal liabilities.

Attention immediately turned to Pfizer’s Celebrex and Bextra.2 All were in the same class of drugs, called COX-2 inhibitors, and there were two more in late-stage development, Merck’s Arcoxia and Novartis’s Prexige. The first of them, Celebrex, which had preceded Vioxx on the market by a few months, was an even bigger blockbuster, with sales of $3.3 billion. The others were me-too drugs. In an editorial that could have been titled “There Must Be a Pony in Here Somewhere,” The Wall Street Journal, loyal as always to the pharmaceutical industry, found something to celebrate. “The Vioxx withdrawal,” it said, “shows why choice in ‘me-too’ drugs is a good thing.”3 Partly because I was used as a foil in the editorial, I wrote a letter to the editor pointing out that it was premature to conclude that Celebrex and Bextra were in the clear. “Since they are so much like Vioxx,” I said, “I would not bet my ice skates that they are not eventually shown to have similar risks.”4

It didn’t take very long. Within months, there were reports that Celebrex and Bextra also increased the risk of heart attacks and strokes, at least in some patients at some doses.2 But Pfizer announced that, unlike Merck, it would leave the drugs on the market, although it would stop advertising them to consumers, because, as its CEO explained to a television reporter, whether and how to use the drugs were “complicated” matters that ought to be left to doctors in discussion with each patient. (He did not explain why that very sensible advice should not apply to other prescription drugs promoted to the public.)

As confusion grew, the U.S. Food and Drug Administration (FDA) appointed a special advisory panel to hold hearings and advise it as to how to handle the situation. The FDA was not obligated to follow the panel’s advice, but it usually did so with its numerous other standing committees of outside experts. In this case, there were several possible courses of action for the FDA. For example, all the COX-2 inhibitors could be pulled from the market immediately. Or Celebrex, which seemed safer than the others at usual doses (it acted like a weaker version of Vioxx), could be allowed to remain. (As is often the case with me-too drugs, apparent differences have a lot to do with the dose.) Or they could all be left on the market, including Vioxx, but with some new guidelines restricting their use.

The FDA advisory panel consisted mainly of members of two standing advisory committees—one for arthritis and one for drug safety. The hearings and deliberations, which were all public, were replete with emotional testimonials from patients who claimed that one or another of the COX-2 inhibitors had produced spectacular results after other types of painkillers had failed. The hearings lasted for three days in mid-February 2005, and the final decision was prominently reported in almost all the media.6 Although the panel agreed that COX-2 inhibitors as a class did indeed increase the risk of heart attacks and strokes,
it concluded that the benefits outweighed the risks (the vote was close in the case of Vioxx and Bextra). It therefore recommended that Celebrex and Bextra remain on the market and that Vioxx be allowed to return, perhaps with strong warnings on the labels for all three and under a moratorium on direct-to-consumer ads.

On April 7, 2005, however, in the wake of revelations that many panel members had financial ties to Merck or Pfizer, the FDA, which usually takes its advisory committees' advice, decided differently. As expected, it announced that Celebrex could remain on the market, with a strong warning on its label. But the agency asked Pfizer to take Bextra off the market, and indicated that if Merck wanted to bring Vioxx back, it would have an uphill battle.

Let me now show how this one story illustrates nearly every major criticism of the pharmaceutical industry discussed in this book: the lax standards for approval of drugs, the conflicts of interest that permeate the system and influence decisions, the slowness of both industry and the FDA to respond to danger signals, the power of the industry's huge marketing campaigns, and the baseless justifications for me-too drugs.

In late 1998 and early 1999, Celebrex and then Vioxx were approved by the FDA. They were given rapid "priority" reviews—which you will recall means they were seen as likely to be improvements over drugs already sold to treat arthritis pain. Was that warranted? Neither drug was ever shown to be any better for pain relief than over-the-counter remedies like aspirin or ibuprofen (Advil) or naproxen (Aleve). But theory predicted that COX-2 inhibitors would be easier on the stomach, and that was the reason for the enthusiasm. As it turned out, though, only Vioxx was shown to reduce the rate of gastrointestinal problems like bleeding ulcers, and then mainly in people already prone to these problems (a small fraction of users). In other words, the theory just didn't pan out as anticipated. Furthermore, people vulnerable to these side effects could probably get the same protection and pain relief by taking a proton-pump inhibitor (like Prilosec) along with an over-the-counter pain reliever. So the COX-2 inhibitors did not really fill an unmet need, despite the attractive theory. Nevertheless, the FDA acted as if they did, giving these drugs expedited review and approval.

In this book, I discussed the conflicts of interest that permeate the FDA, including the fact that many members of FDA advisory committees are paid consultants for drug companies. Although they are supposed to excuse themselves from decisions when they have a financial connection with the company that makes the drug in question, that rule is regularly waived. With that in mind, I checked the minutes of the 1999 advisory committee meeting that led to the approval of Vioxx. Sure enough, four of the six members, including the chairman, needed waivers because they had a "potential for a conflict of interest."7

Worse yet, of the thirty-two members of the 2005 panel that was charged with deciding whether the COX-2 inhibitors were safe enough to stay on the market, ten had financial connections...
with one of the manufacturers, according to a front-page revelation in *The New York Times* that appeared a week after the panel's decision. As is often the case, these ten conflicted members were not disqualified. And as it turned out, they voted nine to one in favor of Vioxx and Bextra. Without their votes, the panel would have recommended that these two COX-2 inhibitors be removed from the market. (There would still have been enough votes to keep Celebrex.) This does not prove that these nine advisors were biased, but it certainly raises the question, especially given the rejection of Vioxx and Bextra by the majority of panel members with no known ties to the manufacturers. That is why FDA advisory committees should not include people with conflicts of interest, no matter how expert they may be.

The clinical trial that caused Merck to withdraw Vioxx was designed to see whether the drug could prevent the recurrence of colorectal polyps, and the finding that the drug increased the risk of heart attacks and stroke was serendipitous. The company professed to be surprised. CEO Raymond Gilmartin, who claimed his wife took Vioxx right up until the drug was withdrawn, said the results were “unexpected.”

But it could hardly have been a bolt from the blue. There had been signs of trouble for years. In 2000, a company-sponsored trial was published in *The New England Journal of Medicine* comparing Vioxx with over-the-counter naproxen in patients with rheumatoid arthritis. This was called the Vioxx Gastrointestinal Outcomes Research, or VIGOR, trial (medical researchers and their sponsors love catchy acronyms), and it was intended to show that Vioxx was easier on the stomach than naproxen. In terms of pain relief, the drugs proved to be the same, but those taking Vioxx had only half the risk of serious gastrointestinal problems. Unfortunately, the study also showed at least a fourfold increase in the risk of heart attacks. The details of the cardiovascular effects were not shown in the published paper, but an FDA analysis indicated the drug was more likely to cause heart attacks or strokes than to prevent serious gastrointestinal problems. Merck tried to explain the alarming finding away by saying the difference probably showed that naproxen protects the heart, not that Vioxx harms it. But of course, without testing that hypothesis, it was simply self-serving speculation. Furthermore, within a year, other evidence came to light that Vioxx increased cardiovascular risks, and maybe Celebrex as well.

In Chapter 7, I discussed the power of big pharma to sell just about anything. What Merck should have done after it got the results of the VIGOR trial is immediately launch a large enough clinical trial to investigate the cardiovascular risks rapidly. Instead, a few months later, it signed Dorothy Hamill to skate its problems away—and she certainly did that. The company reportedly spent $160 million on direct-to-consumer ads for Vioxx in 2000, and continued to spend in the neighborhood of $50 to $100 million a year for the next four years. Note that the costs of even a very large clinical trial would almost certainly have been less than what the company spent on ads. But as expensive as they are, the costs of direct-to-consumer ads are
minuscule compared to what drug companies spend promoting their wares to doctors. In a variety of expensive ways, doctors became convinced—just as the public did, more cheaply—that Vioxx was some sort of breakthrough. The fact that it was no more effective than naproxen, or presumably other over-the-counter remedies, was soon forgotten.

That the advisory panel recommended halting direct-to-consumer ads highlighted the hollowness of the pharmaceutical industry’s contention that they are “educational”—designed to encourage patients to discuss medical problems with their doctors. As I discuss in chapter 7, there is nothing educational about watching Dorothy Hamill pitch a drug, or about any other prescription drug ad. They are meant to persuade patients (and doctors) to use the drug. And they work—as they did spectacularly well in the case of the COX-2 inhibitors. That is why every other advanced country except New Zealand does not permit them. But despite the fact that senior officials of the FDA, including both the former and current commissioners, have repeated the fiction that direct-to-consumer ads are educational, the advisory panel clearly knew better. If ads were truly educational, panel members would not have recommended a moratorium.

In a sense, Merck was doing what big pharma often does. It was touting the benefits of its drug (such as they were), downplaying or explaining away the risks, and marketing it as though it were a medical miracle. Less explicable is the dereliction of the FDA. If Merck didn’t want to launch a study of the cardiovascular effects of Vioxx (and it had nothing to gain by doing so), why didn’t the FDA insist on it? After all, the FDA’s responsibility is to ensure that prescription drugs are safe and effective, and there was clearly something that needed looking into here. It should also have taken a close look at the ads, since one of its jobs is to ensure that they are accurate and balanced—which they obviously were not.

But the FDA simply sat on its hands. Later, it would protest that it doesn’t have the authority to mandate postmarketing studies, but that is sophistry. It does have the authority to pull drugs off the market, and that threat would have been enough to get Merck to do a trial. Finally, in 2002, after a year of wrangling, it got Merck to add a tepid warning to the drug’s label, the small-print material that comes with prescription drugs (and that few actually read). That hardly met the agency’s responsibility. I warned in Chapter 11 about the baleful effects of “user fees” that put the FDA on the payroll of the industry it regulates. This story brings that warning home.

I began Chapter 6 by discussing the importance of clinical trials in deciding whether drugs work or not. Without them, doctors and patients would have to decide on the basis of whether a given patient seems to improve. That is an unreliable (not to mention dangerous) method. As I wrote, “The assumption that a drug works if a patient gets better does not allow for natural variations in the illness, for the placebo effect (the tendency of both doctors and patients to imagine a drug is working), for all the other times when the drug might fail, or for the
possibility that another drug might have worked better." That is why clinical trials were such an important medical advance when they were first introduced in the middle of the twentieth century, and why the FDA requires clinical trials rather than a collection of testimonials to decide whether drugs are safe and effective.

I mention this because one feature of the FDA advisory panel's public hearings was testimonials from individuals who wanted the COX-2 inhibitors left on the market because nothing else relieved their pain. The panel was reportedly much influenced by these testimonials (could that have explained the pro-Celebrex vote by panel members not on Pfizer's payroll?), and it ultimately concluded that, although the drugs should be used far less widely than they are, they might be uniquely effective for some people. But while that is possible, there is no evidence on which to base that conjecture.

Not only are testimonials an unreliable way to judge a drug's effectiveness, they are particularly useless when those giving the testimony are selectively chosen. According to the transcript, at least one of the patients who spoke at the hearings was brought there by Pfizer (the maker of Celebrex and Bextra). I feel certain that patients who had suffered heart attacks or strokes while on these drugs were not brought to Washington to testify, nor were those who had tried a COX-2 inhibitor but preferred Advil or Aleve.

Some of the most hyperbolic testimony came from physicians. In what can only be called the ultimate endorsement, a doctor who identified himself as coming from the Army Medical Corps at Fort Bragg, North Carolina, and "supported by the Department of Defense," ended his appeal with this astonishing claim: "Coxibs [COX-2 inhibitors] are essential in the global war on terrorism." Who could top that?

The notion that testimonials are useful in evaluating drugs plays into the biases of some doctors (mainly clinicians) and much of the public. Many patients like to think they are unique, not only as persons but biologically as well. (Biological variations are probably far less significant than believed, and would need verification in any case.) Clinicians, for their part, want as many choices of drugs as possible, even if they have little basis for choosing among them. When a drug doesn't seem to work, they want to be able to say, "Here, try this and see if that's better." So it should not be surprising that testimonials played such a big part in these hearings. Remember, they were open hearings, and it would take a brave panel member to point out publicly that testimonials are not a good basis for making a decision about the benefits of drugs.

Drug companies are quick to exploit the view that there is great biological variability among patients. As I discussed in Chapter 5, it is one of their justifications for turning out so many me-too drugs. They like to present me-too drugs as backups for one another. But as I pointed out, there is little evidence to support the notion that if a particular drug doesn't work for a patient, another one in the same class will. Drug companies don't test their me-too drugs on these kinds of patients, so there
is no way to know for sure. But much of what may look like differences among me-too drugs probably has mainly to do with dose. It may be, for example, that a double-dose of Celebrex would act just like Vioxx in virtually everyone.

Even granting the possibility that some individuals may respond very differently to these drugs, does that justify accepting a greatly increased risk of heart attacks and strokes? Since those who most need pain relievers for arthritis are precisely those older people most vulnerable to cardiovascular disease, the drugs have probably caused tens of thousands of heart attacks and strokes among the millions of people who have taken them regularly. That is a tremendous carnage to balance against the dubious proposition that the drugs offer something unique for pain relief. It is the FDA’s job to see that the benefits of prescription drugs outweigh the risks. It seems clear to me that the agency failed to do so in this case.

As I write, this story is still unfolding, and many important new facts may come to light. There may well be future episodes like it. But what we already know about COX-2 inhibitors demonstrates that the system for the testing, approval, marketing, safety assurance, and clinical use of prescription drugs is in serious trouble. Prescription drugs are far too important to the nation’s health for us to ignore the need for thoroughgoing reform.

Acknowledgments

I AM INDEBTED ABOVE ALL TO DR. ARNOLD S. (Bud) Relman, with whom I share my life. Together we wrote an extended article about the pharmaceutical industry called “America’s Other Drug Problem—The Insatiable Greed of the Pharmaceutical Industry.” It was published in the December 16, 2002, issue of The New Republic, and received the 2002 George Polk Award for magazine reporting. In outline, the present book largely follows that article. We also collaborated on a related essay, “Patents, Profits and American Medicine,” which was published in the spring 2002 issue of Daedalus (the journal of the American Academy of Arts and Sciences), and we wrote an op-ed piece for The Washington Post, “Prescription for Profit,” which was published on June 20, 2001. But even before
these joint endeavors, we had written separately about various aspects of the pharmaceutical industry. We were both editors of *The New England Journal of Medicine* (our tenures spanned the years 1977 to 2000), a position in which the industry figures prominently, and we had both warned in editorials of its growing and disturbing power. It is not surprising, then, that Bud's influence is present throughout this book. In addition, he was, as always, an exacting editor.

I am also deeply indebted to my daughters, Dr. Lara Goitein and Elizabeth Goitein, Esq. They read the book carefully and gave me the benefit of their considerable expertise, their uncompromising commitment to clear writing, and their loving encouragement. Drs. Steffie Woolhandler, David Himmelstein, and Joseph Gerstein were also kind enough to read the book in its entirety. Their suggestions and corrections were invaluable, and I am grateful to them. I also benefited from conversations with Dr. Sidney Wolfe of Public Citizen's Health Research Group and James Love of the Consumer Project on Technology. Love read sections of the book and offered helpful comments. Both of their organizations have been at the forefront of efforts to inform the American public about the pharmaceutical industry.

Random House was enthusiastic and supportive throughout the project. In particular, I thank Jonathan Karp, Jonathan Jao, and Amelia Zalcman for their careful attention to me as well as to the book. Finally, I salute Alice Martell, my agent. She is everything an agent should be, and in addition a smart, warm, and witty friend.

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**Notes**


2. For a full picture of the special burden of rising drug prices on senior citizens, see FamiliesUSA, "Out-of-Bounds."
7. For the top ten companies and their recent mergers as of 2003, see www.oolopolywatch.com/2003/05/25.html.

1. The $200 Billion Colossus
1. These figures come from the U.S. Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group, Baltimore, Maryland. They were summarized in Cynthia Smith, “Retail Prescription Drug Spending in the National Health Accounts,” Health Affairs, January-February 2004, 160.
3. My figures are culled from several sources. They include:
a. IMS Health, a private information company and the principal source for data on global sales (www.imshhealth.com).
c. The annual report of the industry’s trade group, the Pharmaceutical Research and Manufacturers of America, “Pharmaceutical Industry Profile 2002” (www.phrma.org).
I also checked the annual reports of the largest drug companies.
5. This is probably an underestimate. One source that indicates it is at least this is CenterWatch, www.centerwatch.com, a private company owned by Thomson Medical Economics, which provides information to the clinical trials industry. See An Industry in Evolution, 3rd ed., ed. Mary Jo Lamberti (Boston: CenterWatch, 2001), 22.
7. Public Citizen Congress Watch, “Rx R & D Myths.”
16. For key information about the numbers and kinds of drugs approved each year, see the website of the U.S. Food and Drug Administration (FDA), www.fda.gov/cder/rdmt/pstable.htm.

2. The Creation of a New Drug
1. For an overview of the process of drug R & D as well as of NIH contributions to basic research, see Public Citizen Congress Watch, “Rx R & D Myths: The Case Against the Drug Industry’s R & D ‘Scare Card,’” July 2001 (www.citizen.org).
2. See the annual report of the industry’s trade group, the Pharmaceutical Research and Manufacturers of America, “Pharmaceutical Industry Profile 2002,” 20 (www.phrma.org).
5. For a thorough and readable account of the detailed workings of the FDA by a former chief medical officer, see Suzanne Parisian, FDA: Inside and Out (Front Royal, Va.: Fast Horse Press, 2001); also see Public Citizen Congress Watch, “Rx R & D Myths,” appendix A.
6. The best source of information on CROs and the clinical trials industry is CenterWatch, a private company owned by Thomson Medical Economics (www.centerwatch.com). For an overview, see CenterWatch, An Industry in Evolution, 3rd ed., ed. Mary Jo Lamberti (Boston: CenterWatch, 2001). CenterWatch also publishes a monthly newsletter. The 80,000 figure is CenterWatch’s estimate. The 2.3 million figure is drawn from IMS International, the FDA, and the NIH; see Naomi Aoki, “Trials and Errors,” Boston Globe, June 12, 2002, D1.
18. For information about drug company taxes, see Common Cause, “Prescription for Power: How Brand-Name Drug Companies Prevailed over Consumers in Washington,” June 2001, 13 (www.commoncause.org); also see annual reports of companies.


8. Marketing Masquerading as Education


8. See Martin B. Keller et al., "A Comparison of Nefazodone, the Cognitive Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of Chronic Depression," New England Journal of Medicine, May 18, 2000, 1462 (www.nejm.org). In the same issue, see my editorial, "Is Academic Medicine for Sale?" 1516. The letter to the editor was from Thomas J. Ruane, New England Journal of Medicine, August 17, 2000, 510. Nefazodone was subsequently withdrawn from the market in Europe because of adverse reactions.


14. The Patient Channel was described by Vincent Bzdik, "Tube Feeding," Washington Post, July 8, 2003, H0; also Suzanne Vranica, "GE's Upstart TV Network Plans to Pitch Drugs to the Bedridden," Wall Street Journal, September 25, 2002. Bzdik reported the protest from Gary Ruskin, cofounder of the citizen group Commercial Alert and the letter from Dennis S. O'Leary, President of JCAHO, to General Electric Medical Systems, a copy of which I obtained. Vranica was the source of the quotation from Kelly Peterson.


9. Marketing Masquerading as Research

1. This case was extensively reported in the media. For an excellent review, see Melody Petersen, "Court Papers Suggest Scale of Drug's Use," New York Times, May 30, 2003, C1.


9. "A Phase IV Market Accelerates," CenterWatch, October 2003, 1 (www.centerwatch.com). CenterWatch is a private company, owned by Thomson Medical Economics, that provides information to the clinical trials industry; until 2004, it was also the name of the monthly newsletter.


1. For a valuable discussion of these two types of exclusivity, see Rebecca S. Eisenberg, “The Shifting Functional Balance of Patents and Drug Regulation,” Health Affairs, September–October 2001, 119.
6. Visit the FDA website for details of FDA-granted exclusivity: “Frequently Asked Questions for New Drug Product Exclusivity” (www.fda.gov/cder/about/smallbiz/exclusivity.htm); for the criteria for Orange Book listing, see the FTC study “Generic Drug Entry”; to access the electronic Orange Book, see www.fda.gov/cder/ob/default.htm.
8. For the basics on Hatch-Waxman, see the FDA website www.fda.gov/cder/about/smallbiz/patent_term.htm. Also www.fda.gov/cder/about/small biz/generic_exclusivity.htm. For a fuller analysis, see Eisenberg, “Shifting Functional Balance.”
9. For a thorough analysis of both Hatch-Waxman and its abuses, see the FTC study, “Generic Drug Entry.” This is the single best source of information for understanding the current machinations of the pharmaceutical industry.
14. For Prozac patent games, see Arnold S. Relman and Marcia Angell, “America’s Other Drug Problem,” New Republic, December 16,
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7. For a transcript of that meeting, see www.fda.gov/ohrms/dockets/ac/cder99t.htm#Arthritis.


12. The $100 million figure was widely reported; see, for example, Eric J. Topol, "Failing the Public Health," www.todaysseniorsnetwork.com/excessive_ads.htm.
ABOUT THE AUTHOR

The former editor in chief of *The New England Journal of Medicine* and a physician trained in both internal medicine and pathology, MARCIA ANGELL is a nationally recognized authority in the field of health care and an outspoken proponent of medical and pharmaceutical reform. *Time* magazine named her one of the twenty-five most influential people in America. Dr. Angell is the author of *The Truth About Drug Companies, Science on Trial*, and *Basic Pathology*. 