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.

2

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).[1]

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[2]—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,

note

> 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."[4]

Clinical Stage

Testing Drugs on People—and Finding Volunteers

The clinical stage of drug development is regulated by the FDA.[5] 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.[6] 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.[7] 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.[8] 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.[9] Additionally, the FDA is charged with ensuring safe manufacturing standards, but here again, it is woefully understaffed for that task.[10]

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.[11] 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."[12] 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.

3

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.

As Alan F. Holmer, president of the industry's trade association, Pharmaceutical Research and Manufacturers of America (PhRMA), said in a radio interview, "Believe me, if we impose price controls on the pharmaceutical industry, and if you reduce the R & D that this industry is able to provide, it's going to harm my kids and it's going to harm those millions of other Americans who have life-threatening conditions."[1]

The industry admits that it charges Americans, particularly those without insurance, far more than it does people in other countries, but it insists it needs to do so in order to make up for the fact that other countries regulate prices. Americans must bear a disproportionate share of R & D costs, they say, because nobody else will or can. This argument is trotted out whenever there is the faintest whiff in the air that anyone is considering price controls in the United States. William Safire used it in a *New York Times* column where he warned, "The price of most new prescription drugs is high in the U.S. mainly because it includes the producers' huge investment in scientific research."[2]

The Black Box

Given that argument, it is crucial to ask how much it costs the industry to bring a new drug to market. Is it really $802 million? Getting an answer to that question is not as easy as it sounds, because the industry will not supply the necessary data. Individual companies report total R & D expenditures in their Securities and Exchange Commission (SEC) filings, and PhRMA's annual report

gives industrywide averages for total R & D, as well as average figures for the breakdown of expenses by general R & D functions (where one of the biggest categories is "other"). But the companies do not make available the really important details, such as what each company spends, and for what purposes, on the development of each drug. They claim that that information is proprietary. As Representative Henry Waxman (D-Calif.) commented, "The basic problem is that all pharmaceutical costs, including research, are in a black box, hidden from view. There is no transparency."[3] This secrecy is odd for an industry that justifies its high prices by its high R & D costs.

We also don't know what activities are included under the heading "R & D." Much of it may really be marketing, which is counted as R & D because it looks better to have a large R & D budget than to have a large marketing budget. One clue that this may be the case is the fact that a growing fraction of clinical trials are Phase IV studies. You will remember from Chapter 2 that these are studies of drugs already on the market—supposedly for the purpose of learning more about long-term effects and possible additional uses. But many Phase IV studies are mainly ways to introduce doctors and patients to a company's drug by paying clinicians to use it and then report some minimal information back to the company. In other words, they can be seen as promotional gimmicks.

Despite the fact that R & D is a black box, you can crudely calculate costs per drug simply by dividing the industry's own figure for total R & D by the number of new drugs. That as-

assumes, of course, a steady state—that about the same number of drugs enter the market each year and total R & D costs stay fairly constant. That is not quite the case. Nevertheless, this simple calculation is a way of making a very rough estimate. If you look at the year 2000, when the industry claims to have spent $26 billion on R & D and ninety-eight drugs entered the market, the average pretax cost for each drug was, under those assumptions, no greater than $265 million, and the after-tax cost about $175 million. (Research and development costs are tax deductible, and the corporate tax rate is now about 34 percent.) That would be the maximum, since it is likely that PhRMA's total R & D figure is inflated by activities that many would regard as promotional, and the industry receives generous tax credits as well as deductions. If you take the next year, when the industry claimed it spent $30 billion and only sixty-six drugs entered the market, the pretax cost per drug would be higher—$455 million—and the after-tax cost $300 million.[4] As you can see, any attempt to determine the cost per drug is highly dependent on the number of drugs—a subject I'll come back to later.

The consumer advocacy group Public Citizen performed a much more sophisticated analysis using the same approach.[5] They looked at all the drugs that entered the market between 1994 and 2000 (thus smoothing out the yearly variations), and made appropriate allowances for the long lag time between R & D expenditures and the dates the drugs came on the market. They found that after-tax costs were probably less than $100 million for each drug approved during that period. Other

independent analysts have reached similar conclusions. Even using PhRMA's own figures for total R & D costs for the decade of the 1990s, it can be calculated that the cost per drug came to around $100 million after taxes. That is a lot, but it's a far cry from the much-vaunted $802 million.

The Imaginary Number

So where did the $802 million figure come from? And why has it been uncritically accepted? The number was the finding of a group of economists, headed by Joseph DiMasi of the Tufts Center for the Study of Drug Development, and it was announced with much fanfare at a press conference in Philadelphia on November 30, 2001.[6] The Tufts Center is largely supported by the pharmaceutical industry, and this was an updating of an analysis done by the same group over a decade ago. The results this time were about twice as high. Ever since the press conference, PhRMA and leaders and defenders of the industry have trumpeted the findings as a justification for high drug prices. Kenneth I. Kaitlin, the director of the Tufts Center, said, "Bringing new drugs to market has always been an expensive, high-risk proposition, and our latest analysis indicates that costs have continued to skyrocket." The president of PhRMA, Alan F. Holmer, welcomed the study as confirmation that "drug development is staggeringly expensive."[7] The media seemed to accept it pretty much at face value. Under the heading "Research Cost for New Drugs Said to Soar," for instance, *The New York Times* reported

the next day, "A new round in the national debate over prescription drugs opened today with a study from researchers at Tufts University estimating that the average cost of developing a new drug has more than doubled since 1987, to $802 million."[8] The rest of the media carried similar stories.

It was not until a year and a half later that the Tufts group actually published their analysis and it became possible to see how it was done.[9] What they did was to look at sixty-eight drugs developed at ten drug companies over about a decade. But the names of the companies and the names of the drugs were never revealed. Furthermore, all the data on the costs of those drugs were supplied by the companies to the Tufts group confidentially, and as far as I can tell, the authors were not able to verify the information. They were supposed to take the companies' word, and we were supposed to take theirs. That situation is extremely unusual in scientific publishing, where it is understood that the salient data will be made available to readers so they can evaluate the analysis for themselves.

But one thing *is* clear from the paper. The $802 million figure has nothing to do with the "average cost of developing a new drug," in the words of *The New York Times*.[10] It refers only to the cost of developing a tiny handful of the very most expensive drugs. Let's look at this misunderstanding more closely, because it is crucial.

Every year the Food and Drug Administration (FDA) approves a number of new drug applications, which means that

those drugs can enter the market. That is what most people mean when they say "new" drugs. In 2002, for instance, the number was seventy-eight, as I mentioned in Chapter 1. But of the new drugs, only a minority are newly discovered or synthesized molecules. The FDA classifies these as new molecular entities (NMEs). The others are just new versions of drugs already on the market. In 2002, only seventeen of the seventy-eight newly approved drugs were NMEs.[11] And of the NMEs, only a fraction are developed entirely by the drug companies themselves. Most of the rest are simply licensed or otherwise acquired from university or government laboratories or biotechnology companies.

The Tufts analysis was restricted to NMEs developed entirely within drug companies—what the authors called "self-originated NCEs" (the old term for NMEs). But these constitute only a tiny percentage of all new drugs. As you might expect, this handful of drugs cost companies more to develop than the others. It is cheaper to license a drug from someone else or make a new version of an old drug. In fact, the Tufts authors state that the drug companies they surveyed spent 75 percent of their R & D money (including the costs of Phase IV studies) on these few self-originated NMEs.[12] I find this an almost unbelievably high percentage, and there is no way to verify it, but the point is the companies agree that they spend much more on self-originated NMEs than on other drugs.

Why didn't the media catch on to the fact that the $802 million figure applied only to a sample of highly selected and very

costly drugs? One possible answer is that the industry didn't want them to. In their public relations, PhRMA and the drug companies strongly imply that $802 million is the average for *all* new drugs. Even the Tufts authors seemed to suggest that in the short summary of their paper, where they wrote, "The research and development costs of sixty-eight randomly selected new drugs were obtained from a survey of ten pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug development."[13] Nothing about *which* new drugs.

. . . And Doubling It

There is a second problem with the Tufts estimate. It is not the actual out-of-pocket cost at all, even for the special group of drugs considered. That cost was $403 million per drug. The $802 million is what the authors call the "capitalized" cost—that is, it includes the estimated revenue that might have been generated if the money spent on R & D had instead been invested in the equity market. It's as though drug companies don't *have* to spend any money at all on R & D; they could invest it instead. Or, in the author's technical jargon, "the expenditures must be capitalized at an appropriate discount rate, [which is] the expected return that investors forego during development when they invest in pharmaceutical R & D instead of an equally risky portfolio of financial securities."[14] This theoretically lost revenue is known as the "opportunity cost," and the Tufts consultants simply tacked it

on to the industry's out-of-pocket costs. That accounting maneuver nearly doubled the $403 million to $802 million.

The authors justified the maneuver on the grounds that, from the perspective of investors, a pharmaceutical company is really just one kind of investment, which they choose among other possible options. But while this may be true for investors, surely it is not true for the companies themselves. The latter have no choice but to spend money on R & D if they wish to be in the pharmaceutical business. They are not investment houses. So you can hardly look at the money spent on R & D as money that could have been spent on something else. The Tufts authors say adding opportunity costs is standard accounting practice, and that may be so, but in the context of pharmaceutical R & D, it simply makes no sense.

And there is a third problem with the estimate. It is in pre-tax dollars. But R & D expenses are fully tax deductible. On top of that, drug companies enjoy a number of tax credits worth billions of dollars, including a 50 percent credit for the costs of testing "orphan drugs"—those with an expected market of fewer than 200,000 people. As of the year 2000, the FDA had listed 231 orphan drugs since the tax credit was instituted in 1983. One of those is Retrovir, the first drug for HIV/AIDS, discussed in the last chapter. With the worldwide HIV/AIDS epidemic, the market for Retrovir is far greater than 200,000, but it was considered an orphan drug nonetheless. In addition, the tax credit extends to other drugs if companies can make a case

that they are unlikely to be profitable.[15] (What other business gets such a deal?) Presumably, drug companies claiming these tax credits would have to share with the Internal Revenue Service information they are unwilling to share with anyone else—the R & D costs of individual drugs. One wonders whether and how often this information is audited.

In any case, when all the tax benefits are taken together, big pharma pays relatively little in taxes. Between 1993 and 1996, drug companies were taxed at a 16.2 percent rate, compared with an average tax rate of 27.3 percent for all other major industries.[16] Many experts believe that the R & D cost estimate should therefore be lowered by the amount of corporate tax avoided. These tax savings would reduce the net cost of R & D by a percentage at least equal to the 34 percent corporate tax rate (not considering tax credits). You could argue about whether this adjustment is reasonable, but if one accepts that it is, it would reduce the Tufts estimate of $403 million (before adding "opportunity costs") to an after-tax net of less than $266 million per drug.

But remember, that would be the average out-of-pocket, after-tax R & D costs for only the new molecular entities developed entirely in-house, not the average cost of all the drugs approved. Most approved drugs entering the market are not really new, or they are acquired from other sources, or both. I would guess that the real cost per drug is well under $100 million. Were it anywhere near the claimed $802 million, the industry would not be so secretive about the data.

High R & D, Higher Profits

The general industry excitement about the $802 million announcement was partly predicated on the notion that R & D costs can be equated with value. But that is not necessarily true. In fact, they could instead be an indication of inefficiency. Ray Gilmartin, president and CEO of the pharmaceutical giant Merck, sounded the one cautionary note from industry: "If there is any concern, it should be on the part of pharmaceutical companies that are less efficient and that aren't delivering drugs of value to patients."[17] Right. In fact, rising R & D costs per drug can simply mean there are not many new drugs coming to market. To take the extreme, what would the R & D cost per drug be if the entire industry turned out only one new drug? In 2001, it would have been $30 billion. Would that have been an indication of value? Could it in any way be construed as an indication that the industry was productive? Of course not.

Although that extreme case is absurd, something like it is actually happening. Over the past few years, the number of new drugs has been declining, and so has their quality. Yet R & D expenditures have been getting higher. The point is that large R & D expenditures ought to raise the question of whether we are getting our money's worth. How much is too much to spend on developing new drugs, and who should decide? Is the entire industry, in Mr. Gilmartin's words, growing "less efficient"—spending way too much for too little? This matters, not only

because we need good drugs but also because the industry expects to be paid back for its R & D expenses.

Let's return to big pharma's essential argument that curbing prices would cut into its R & D spending. Would that really be necessary? Whatever the cost of bringing each new drug to market, total R & D expenditures of the pharmaceutical industry—according to PhRMA, now over $30 billion for all its members in the United States and abroad—are indeed large. But they should be compared with reported expenditures on marketing and administration, which are more than twice as much as R & D expenditures. Furthermore, the most important financial fact about the major drug companies is that, despite their expenses, they are enormously profitable.

In 2002, when the ten U.S. drug companies in the Fortune 500 list had combined worldwide sales of about $217 billion and spent just over 14 percent of that on R & D (about $31 billion), they had a profit margin of 17 percent ($36 billion). Thus, profits were substantially more than R & D costs. Even more startling is the fact that they spent a walloping 31 percent of sales (about $67 billion) on marketing and administration.[18]

Given these figures, it is very hard to make a case that lower prices would reduce R & D spending. In fact, whether price regulation would cut into R & D would depend entirely on whether the industry wanted it to. They could, for example, cut administrative or marketing costs instead, or they could accept lower but still very good profits. Most likely they would *choose* to cut their R & D budgets to maintain profits and marketing,

but they wouldn't *have* to. As long as profits are consistently higher than R & D costs, drug companies cannot make a case that reduced prices would necessarily cripple research and development.

The drug companies would protest that there is no way they could voluntarily accept lower profit margins, or reduce their marketing, upon which they believe their profits depend. They would say Wall Street demands that they maximize the value of their shareholders' stock, which means doing everything they can to increase profits. It is their fiduciary responsibility to do so. But that should tell us something about the wisdom of entrusting the development of medicines to an industry that is entirely accountable to investors, and not to the public (except in the limited sense that drugs are supposed to be safe and effective).

It is also worth asking why this extraordinarily profitable industry needs so much equity capital. It could easily finance its R & D out of its sales. One possible explanation is that drug company executives are paid partly in stock options. Families USA, a nonprofit foundation, looked into the 2001 value of the unexercised stock options held by the top executives in each of ten large drug companies. They found the average to be $52 million.[19] But stock options are valuable only when the market price of the company's stock exceeds the exercise price of the option. That creates a powerful incentive for executives to keep stock prices rising any way they can. Enron executives tried to do it illegally, but the incentive is the same in other investor-owned corporations that pay executives in stock options.

Drug Pricing—What Does R & D Have to Do with It?

Big pharma would like us to believe that prices of their top-selling drugs have to be high to cover their costs, including the costs of all the drugs that never make it to market. The implication is that drug companies are just eking out a living—something we know is a long way from the truth. Furthermore, without any information about how they spend their R & D dollars, it's impossible to evaluate the extent to which profitable drugs subsidize ones that never make it. Nor is it possible to decide whether the R & D is worth it. If patients must pay thousands of dollars a year for a vital drug, doesn't the public have a right to know what the markup is and where the money goes? We know that much of it goes to profits and marketing, but we also need to know what companies spend on which drugs and for what purposes. An industry so beholden to taxpayers for research, patent protection, and tax breaks—in short, for taking most of the risks out of the business—ought to do more than just report total R & D expenditures. It should open the black box.

Despite all the rhetoric to the contrary, this is not a high-risk industry in any normal sense of the term. In fact, drug companies are not willing to take any chances at all. As one indication, the law mentioned earlier that provides tax credits equal to 50 percent of the cost of testing orphan drugs extends the credits to other drugs if "there is no reasonable expectation that the cost of developing and making available in the United States a drug for disease or condition will be recovered from sales in the

United States of such drug." In other words, if you can't make a profit, the government will help you out. This is an industry well protected against losses. Risky businesses have variable returns, but the pharmaceutical industry has been, year after year, the most profitable in the United States. As Alan Sager, codirector of the Health Reform Program at Boston University, put it, "If you went to Las Vegas with $1000 and routinely came back with $1400, could your family accuse you of gambling?"[20] What these companies are, in fact, claiming is an entitlement not only to recoup anything they wish to spend on R & D but to make an exorbitant profit margin as well.

The truth is that there is no particular reason to think that R & D costs, no matter what they are, have anything to do with drug pricing. The irrepressibly candid Mr. Gilmartin, president and CEO of Merck, seemed to acknowledge that. Referring to the $802 million per drug estimate, he remarked, "The price of medicines isn't determined by their research costs. Instead, it is determined by their value in preventing and treating disease. Whether Merck spends $500 million or $1 billion developing a medicine, it is the doctor, the patient, and those paying for our medicines who will determine its true value."[21] That sounds to me like an admission that the industry will charge whatever the traffic will bear, and it has little to do with R & D costs. And that is about right. Unfortunately, contrary to Mr. Gilmartin, it doesn't have much to do with medical value either, as I will show.

4

Just How Innovative Is This Industry?

AS AMERICANS GROW INCREASINGLY skeptical about the claim that drug prices need to be high to cover research and development costs, the pharmaceutical industry falls back on Plan B —the claim that high prices are necessary to reward innovation. Yes, the industry confesses, profits are indeed high. But remember, extra high profits stimulate us to be extra creative. Look at all the wonderful new drugs you get in return. Once again, Alan F. Holmer, president of the Pharmaceutical Research and Manufacturers of America (PhRMA), sounds the theme. In his tireless crusade against any form of price regulation,

he put it this way, "Voters do not want to jeopardize the miracle of life-saving innovation in modern medicines."[1] The contention that we need to treat this industry with kid gloves to preserve "life-saving innovation" calls for a close look at big pharma's drugs. Are they truly innovative? And if so, who deserves the credit?

The Output of Innovative Drugs

Even a glance at the industry's output shows that miracles are few and far between. The evidence is on the U.S. Food and Drug Administration (FDA) website (www.fda.gov/cder/rdmt/pstable.htm). As I explained in Chapter 2, before a drug can be marketed, a company must file a new drug application with the FDA. The FDA then classifies the drug in two ways. First, it looks at the compound itself, what the agency calls the "chemical type." Is it a molecule that is already on the market in some form? Or is it brand new—what the FDA calls a "new molecular entity (NME)"? If it's a new molecule, then it's classified as a number 1 drug. Otherwise, it is classified as a chemical derivative, or new formulation or combination of an old drug. Or it might just be an old drug with a new manufacturer.

The second way the drug is classified is according to whether it is likely to offer any benefit above drugs already on the market to treat the same condition. If so, then the FDA gives it more rapid attention. This is called a "priority review," which is for drugs likely to represent a "significant improvement com-

pared to marketed products, in the treatment, diagnosis, or prevention of a disease." The agency lists these drugs with the abbreviation "P." All other drugs receive a standard—or "S"—review. A "standard review" drug, in the FDA's words, "appears to have therapeutic qualities similar to those of one or more already marketed drugs."

New molecular entities aren't necessarily classified as priority review drugs. Even brand-new molecules may not be any better than an older drug for the same condition. And likewise, priority review drugs are not necessarily new molecular entities. It's possible for an old drug to be modified in such a way that it offers a definite treatment advantage over the earlier form. But as a general rule, a drug that can be called innovative in any usual meaning of the word is both a new molecular entity and a priority review drug. In other words, the drug is a new molecule that will probably be a significant improvement over drugs already on the market. (The industry often uses the word *innovative* to mean just a new molecular entity, but that leaves aside the all-important question of whether the drug offers any clinical advantages over old drugs.)

So let's look at the yield over the five years 1998 through 2002—the most recent five years for which I have complete data on both the numbers and the properties of the drugs. Altogether, 415 new drugs were approved—an average of 83 per year. Of those, 133 (32 percent) were new molecular entities. The others were variations of old drugs. And of those 133, only 58 were priority review drugs. That averages out to no more

than 12 innovative drugs per year, or 14 percent of the total. Not only is the yield very low, but over those five years, it got worse. In both 2001 and 2002, only 7 innovative drugs (that is, new molecular entities with priority review) were approved each year, as compared with 9 in 2000, 19 in 1999, and 16 in 1998. *And that's it—the five-year grand total of innovative drugs from this mighty industry.*

Now, just to get a sense of what kinds of drugs are being produced and which companies are producing them, let's look closely at the fourteen innovative drugs for those last two years. Were they miracles from big pharma, as suggested by Mr. Holmer? At the time, there were some thirty-five members of PhRMA, consisting of the world's major pharmaceutical companies and a few of the larger biotechnology companies.[2] Of the seven innovative drugs approved in 2001, five came from companies that were PhRMA members—two from the Swiss company Novartis and one each from the American companies Merck, Allergan, and Gilead Sciences (a biotechnology company).[3] The Novartis drugs were the orphan drug Gleevec, for a rare form of leukemia (I'll come back to this drug in a bit), and Zometa, an injection to treat a complication of widespread cancer. The Merck drug was Cancidas, an injection to treat a rare fungus infection when other treatments have failed; the Allergan drug was Lumigan, an ophthalmic solution for glaucoma not responsive to other treatment; and the Gilead drug was Viread, a drug similar to AZT to treat HIV/AIDS.

Of the seven innovative drugs approved in 2002, only three

came from members of PhRMA: Zelnorm, a Novartis drug for irritable bowel syndrome with constipation; Eloxatin, an injection made by the French company Sanofi-Synthelabo, to treat (although rarely, if ever, to cure) widespread colon cancer when other treatments have failed; and Hepsera, a treatment for hepatitis B made by Gilead Sciences. Nothing from any major American drug company.

That output hardly seems to warrant Mr. Holmer's high-flown rhetoric. To be sure, we do occasionally get important new drugs. Gleevec, for example, may mean the difference between life and death for people with a certain type of leukemia. But in recent years truly innovative drugs like that have come along very infrequently. Most of the drugs mentioned here, even though innovative, were last-ditch treatments—rarely cures—to be used when older drugs hadn't worked. And given the trend, we have to ask whether the $30-plus billion big pharma ostensibly puts into its R & D is well spent. We also have to conclude that, if high prices and profits in excess of any other industry are indeed a stimulus for innovation, drug companies have not kept their part of the bargain.

The Real Source of Innovation

The meager output is bad enough. But the real scandal is the fact that the few innovative drugs that *do* come to market nearly always stem from publicly supported research. In this country, almost all of that is sponsored by the National Institutes of Health

(NIH) and carried out at universities, small biotechnology companies, or the NIH itself. (About 90 percent of NIH-sponsored research is "extramural," which means it is done mainly at medical schools and teaching hospitals. The remainder is "intramural," carried out by institute scientists on their campus outside Washington, D.C.) Big pharma began to rely on publicly funded research in 1980, with passage of the Bayh-Dole Act and a related piece of legislation, the Stevenson-Wydler Act. Bayh-Dole applies mainly to extramural research and Stevenson-Wydler to intramural research. This legislation, which I mentioned in Chapter 1, permitted NIH-funded work to be patented and licensed exclusively to drug companies in exchange for royalties. And increasingly, that is exactly what big pharma depends on—licensed drugs, which the drug companies then market and often patent for additional uses. Sometimes the drugs are completely developed before they are licensed. We saw, for example, in Chapter 2 how AZT, the first drug to treat HIV/AIDS, was developed and clinically tested by researchers at the National Cancer Institute (a part of the NIH) and Duke University before being licensed to what is now GlaxoSmithKline. In other cases, the drugs are acquired just before they are ready to enter large-scale clinical trials.

At least a third of big pharma's drugs are now licensed or otherwise acquired from outside sources—including smaller companies all over the world.[4] You would think the companies might be embarrassed by that fact, and no doubt they are reluctant to be very public about it, but they are certainly not embarrassed enough to change their way of operating. Bob

Ingram, chief operating officer of GlaxoSmithKline, candidly explained to *The Wall Street Journal,* "We're not going to put our money in-house if there's a better investment vehicle outside."[5] Lamenting that Glaxo got only 17 percent of its revenues from licensed products, compared with 30 percent for Pfizer and 35 percent for Merck, he said his company "is keen to reach similar levels." The big drug companies are competing not so much to find new drugs but for the limited number of drugs to license. "I don't see a respite for at least three to five years," said one spokesman. "We're all going to be chasing the same compounds. We see them at the same airport; they're coming in when we're going out."[6] Let's look at a few of the many important drugs *not* discovered by big pharma.

Taxol

Take the case of Taxol (the brand name for paclitaxel), the bestselling cancer drug in history.[7] Now used to treat cancers of the ovary, breast, and lung, it was derived from the bark of the Pacific yew tree in the 1960s. All of the research on the drug was conducted at, or supported by, the National Cancer Institute over nearly thirty years, at a cost to taxpayers of $183 million. In 1991, Bristol-Myers Squibb signed a cooperative research and development agreement with the NCI—a deal made possible by the Stevenson-Wydler Act and a 1986 amendment called the Federal Technology Transfer Act. The company's part of the bargain was mainly to supply the NCI with seventeen kilograms of paclitaxel (which it obtained from a chemical company). No ingenuity there. In 1992, after Taxol was approved by the FDA for treatment of cancer of the ovary, entirely on the basis of NIH-supported research, Bristol-Myers Squibb was given five years of exclusive marketing rights.

The only remaining problem for Bristol-Myers Squibb was the fact that the Pacific yew tree was in short supply. That problem was solved in 1994 by NIH-funded scientists at Florida State University. They devised a method to synthesize Taxol, which they promptly licensed to Bristol-Myers Squibb in return for royalties. No company ingenuity there, either.

The worldwide use of Taxol (for cancers of the ovary, breast, and lung) generated between $1 and $2 billion a year for Bristol-Myers Squibb and tens of millions in annual royalties for Florida State University. The company spent very little on R & D in getting initial FDA approval to treat cancer of the ovary, although it has undoubtedly spent substantial sums since then for testing the drug for other cancers. But that takes no ingenuity, either. The story of Taxol is a prime example of taxpayer-supported research discovering a valuable and lucrative drug that was virtually given as a gift to a large drug company for marketing, commercial exploitation, and further development.[8] The public pays again when it buys Taxol at the exorbitant price Bristol-Myers Squibb charges for a drug it neither discovered nor developed.

Epogen

Or take the case of Epogen, an innovative drug to treat anemia in patients with kidney failure.[9] Technically, Epogen is a biological and not a drug, because it was originally a natural substance made in the body—a hormone produced by the kidneys that stimulates the production of red blood cells. This hormone, called erythropoietin, was discovered in 1976 by Eugene Goldwasser at the University of Chicago, after much basic work done in several other academic laboratories had shown that the kidney must produce such a substance. Neither Goldwasser nor the University of Chicago patented the hormone or tried to synthesize it. But another NIH-funded researcher at Columbia University invented a technique for synthesizing biologicals, which the university patented soon after passage of Bayh-Dole. A small start-up biotechnology company named Amgen then licensed the technique from Columbia to develop a method for the large-scale commercial synthesis of the erythropoietin molecule. Amgen, now a giant in the industry, makes over $2 billion a year selling Epogen to the Medicare program to treat patients with kidney failure. So, as in the case of Taxol, the public gets to pay for Epogen twice—first by having supported the research that discovered it, and second, by paying for it through Medicare. Goldwasser never received a penny of royalties for his seminal discovery.

The identical molecule is marketed under the name Procrit (as though it were a different substance) by the huge firm Johnson & Johnson (J & J). This unnecessary duplication was the result of a deal between Amgen and J & J. As it happens, a similar type of anemia occurs in many conditions, not just kidney failure. In particular, it can be a debilitating side effect of cancer treatment. Before Amgen began reaping its huge profits from Epogen, it needed to come up with a way to stay afloat. So it licensed to J & J its rights to sell Epogen in the United States for conditions other than kidney failure (mainly cancer) and for all uses in Europe. J & J paid Amgen a lump sum of several million dollars plus the promise of future royalties. Ortho, a division of J & J, markets the drug as Procrit. Procrit's worldwide sales are estimated at nearly $3 billion annually, of which a small percentage goes to Amgen. Amgen, for its part, pays Columbia one percent of all its sales of Epogen. Not to be outdone by J & J, Amgen has now gotten approval for another, longer-acting form of the same agent, called Aranesp, which it hopes will compete with Procrit without violating the original deal. But they're all essentially the same substance under different names.

Here again, a truly important new therapeutic agent was discovered and identified through basic research outside the drug industry. Unlike Taxol, which had been tested in clinical trials before Bristol-Myers Squibb acquired rights to it, erythropoietin had to be biosynthesized by Amgen before it could undergo preclinical and clinical testing. I learned from sources at Amgen that J & J made essentially no contribution to the original development of erythropoietin. It simply paid Amgen for the right to market the substance and develop it for other uses.

Clearly, there was ingenuity aplenty on the part of both Amgen and J & J in exploiting commercial opportunities, but not much of that had to do with the initial discovery of the hormone and its role in the treatment of anemia.

Gleevec

The story of Gleevec (the brand name of imatinib mesylate) is a little different.[10] Here the drug company—in this case Novartis—had patented the molecule and had it on the shelf, but its usefulness was discovered mainly by an NIH-funded university researcher. One of the seven innovative drugs approved in 2001, Gleevec halts a rare type of leukemia, called chronic myeloid leukemia, dead in its tracks, with relatively few side effects. (How long it works is not yet clear, because the drug is still very new.) Leukemia is really a kind of cancer of the blood, and before Gleevec came on the market, this type of leukemia was universally fatal unless the patient underwent a dangerous bone marrow transplantation (assuming there was a suitable donor). So Gleevec is one of the few "breakthroughs" that really is a breakthrough. Novartis uses it as the poster child for drug company innovation. One of its ads, for instance, shows a smiling young woman saying, "Not long ago, my cancer was all I could think about. Now I feel so good I have to remind myself I'm a cancer patient." And in the body of the text is the statement "Novartis put her deadly cancer into remission quickly and completely."[11]

Well, not really. Novartis had more than a little help. The story begins in 1960, with the discovery under the microscope of a peculiar-looking chromosome in patients with chronic myeloid leukemia. That discovery was made at the University of Pennsylvania, and for that reason the new chromosome was called "the Philadelphia chromosome." Later work from many laboratories showed that the Philadelphia chromosome carries a gene that directs the production of an abnormal enzyme. That enzyme causes white blood cells to become cancerous. Similar types of enzymes were thought to be involved in other cancers. As a result of these studies, chemists in Israel and at Novartis set about synthesizing molecules that would inhibit the action of this family of enzymes. Novartis patented several such inhibitors in 1994 and added them to its collection of potentially useful drug candidates.

There was apparently no immediate interest by the management at Novartis in determining whether any of them might be useful in treating chronic myeloid leukemia until Brian J. Druker, a researcher at the Oregon Health & Sciences University in Portland, became interested in the problem. Working with a scientist at Novartis, Nicholas Lydon, he obtained a small supply of several of the company's most promising inhibitors. He found that imatinib mesylate was the most potent in suppressing the growth of the cancer cells in culture and, furthermore, that it had no effect on normal blood cells. Such specific action is almost unheard of in cancer treatment, and Druker urged Novartis to explore this exciting lead.

But, according to Druker, the company showed little enthusiasm for undertaking further clinical work on imatinib mesylate. Whether the reluctance was because of the small potential market or the finding that the drug was toxic to dogs at high doses is not clear. Druker nevertheless persisted, and Novartis finally agreed to support cautious, limited tests in his clinic and at two other sites. By 1999, Druker was able to report spectacularly successful preliminary results before a national meeting of American hematologists. The news spread quickly, and the company then decided to proceed with large-scale clinical trials. In only two years, the trials were completed and the FDA had approved the drug. Thus, most of Novartis's R & D investment in Gleevec was made several years *after* there was good scientific evidence to suggest that the drug would be useful.

These kinds of stories could be multiplied many times over. A recent study published in the journal *Health Affairs* reported that, in 1998, only about 15 percent of the scientific articles cited in patent applications for clinical medicine came from industry research, while 54 percent came from academic centers, 13 percent from government, and the rest from various other public and nonprofit institutions.[12] Remember that these are patent applications for *all* new drugs and medical innovations, not simply for those ultimately judged to be clinically important. Had the data been limited to major breakthrough drugs, the industry's role would undoubtedly have been even smaller.

An unpublished internal document produced by the NIH in February 2000, which was obtained by Public Citizen through

the Freedom of Information Act, revealed similar percentages. The NIH had selected the five top-selling drugs in 1995 (Zantac, Zovirax, Capoten, Vasotec, and Prozac) and found that sixteen of the seventeen key scientific papers leading to their discovery and development came from outside the industry. (Eli Lilly had sponsored one of the four key studies leading to the development of Prozac.) Looking at all the relevant published research, not just at the key studies, only 15 percent came from industry, whereas 55 percent came from NIH-funded laboratories and 30 percent from foreign academic institutions.[13]

A 1997 report by the National Bureau of Economic Research found that of the twenty-one most effective drugs approved between 1965 and 1992, public research was responsible for fifteen.[14] A *Boston Globe* review of the bestselling fifty drugs approved from 1992 to 1997 found that forty-five of them had received government funding.[15] And so on and so on. There is no question that publicly funded medical research—not the industry itself—is by far the major source of innovative drugs. That is particularly true of drugs for cancer and HIV/AIDS. Merrill Goozner, in his book *The $800 Million Pill,* recounts in detail the discovery and development of drugs for these diseases, and clearly shows that the driving force was publicly funded researchers.[16]

Paying Twice

Given the contributions of taxpayers to big pharma's products, you might think the drug companies would give us a break

in pricing. But you would be wrong. Let's look at the pricing of Taxol and Gleevec.

When it came on the market, Taxol sold for $10,000 to $20,000 for a year's treatment—reportedly a twentyfold markup over manufacturing costs. Bristol-Myers Squibb, you will remember, put next to nothing into the initial R & D, although it has since sponsored clinical trials aimed at expanding the uses of the drug. In a blazing act of hubris, the company fought tooth and nail to extend its exclusive rights on Taxol beyond the original five-year term, and managed to win another three years by suing the generic manufacturers who wanted to enter the market. As of 2003, the company had paid royalties to the NIH of only $35 million on its $9 billion in sales of Taxol (the agreement was 0.5 percent in royalties). Going in the other direction, the government paid Bristol-Myers Squibb hundreds of millions of dollars for Taxol through the Medicare program.

Novartis priced Gleevec at about $27,000 for a year's supply. In a recent book, Daniel Vasella, the chairman and CEO of Novartis, acknowledged that the drug is already profitable.[17] I would think so, given that its development was so rapid and that it qualified for the orphan drug tax credit. He also acknowledged that the price was based partly on the price of interferon, the drug that Gleevec replaced as the recommended treatment for chronic myeloid leukemia. In other words, the price was what the market would bear. In response to the outcry over the staggering price to treat this lethal disease, Novartis announced a discounting policy for patients of limited

means. But according to a 2003 article in *The New York Times*, the plan had not worked very well so far, particularly in poor countries, where only a handful of patients have received the drug free. At a meeting I attended, someone in the audience complained to Vasella that a friend with chronic myeloid leukemia had had difficulty obtaining the discount for which he was said to be qualified. Somehow, I was not surprised.[18]

Perhaps the most extreme example of this sort of price gouging is the story of Cerezyme, a synthetic enzyme made by the biotechnology company Genzyme. This drug treats a rare abnormality, called Gaucher's disease, which affects only about 5,000 people worldwide. The research and early development was done entirely by NIH-funded scientists, two of whom later left their university to start the company and exploit their work. (The major contributor to the early effort, Roscoe Brady, who discovered the cause of Gaucher's disease, remained at the NIH.) Genzyme charges patients on the order of $200,000 to $300,000 for a year's supply. According to the author and reporter Merrill Goozner, at least one patient is not grateful to the company. "This is government-developed technology," said the boy's father. "This isn't Genzyme working late at night to help sick people. The NIH did it. But as soon as the government transferred that intellectual property to the company, they lost all control over the pricing."[19]

A more recent example is the story of Roche's new HIV/AIDS drug, Fuzeon.[20] Approved by the FDA in 2003, this drug is an important advance in AIDS treatment. According to

a detailed story by the *Wall Street Journal* reporter Vanessa Fuhrmans, Fuzeon was discovered at Duke University, developed by a local biotechnology company, and only then acquired by Roche. Despite its minimal contribution to early research and development, Roche charges $20,000 a year for the drug—three times the price of most AIDS drugs. About a fifth of AIDS drugs are purchased by the federal-state AIDS Drug Assistance Programs. These programs simply can't afford to buy Fuzeon for all the patients who need it, so they are restricting access to it, setting up waiting lists, or tightening income eligibility criteria. In thirteen states, the program has simply stopped providing Fuzeon to new patients. Although Roche is reported to have a patient assistance program, the company declined to tell *The Wall Street Journal* how many people are in it, and it refuses to provide assistance in states where the drug assistance program restricts access to Fuzeon. We are used to hearing about patients with AIDS in the Third World going without lifesaving treatment, but now it may be happening in the United States. High prices have real, sometimes deadly, consequences.

There Oughta Be a Law—And There Is

This sort of exploitation is not supposed to happen. The Bayh-Dole and Stevenson-Wydler Acts, with subsequent amendments, contained a number of stipulations that would prevent it.[21] First, under "exceptional circumstances," which are vaguely defined in terms of serving the public interest, the

NIH may require that work it supports in medical schools, teaching hospitals, and small biotechnology companies not be patented but remain in the public domain. The same is true of its intramural research. Thus, the right to patent or license NIH-funded work is not automatically assured. Second, Bayh-Dole requires that work licensed to drug companies be made "available to the public on reasonable terms." That could certainly be interpreted as meaning that it should be priced reasonably. And until 1995, the NIH explicitly required reasonable pricing for drugs stemming from collaborations like the one that led to Taxol. Third, work patented and licensed under the terms of Bayh-Dole must be reported to the NIH, so that the institute can keep track of which drugs originate in that way. If profits are very large, there is a requirement that some part of the royalties be returned to the government. The same is true of intramural research. Fourth, the government retains the right to "march in" and use a licensed drug itself or issue compulsory licenses to other companies if the original company is not fulfilling its obligations. All of these provisions have been pretty much ignored by both industry and academia.

The NIH, too, has been supercasual about fulfilling the terms of the legislation. The fact is that while the NIH represents, and is supported by, the public, it behaves more as if its constituency were the academic medical centers. And there is indeed a revolving door between them. Researchers at medical schools often receive part of their training at the NIH, and of course, NIH scientists and leaders emerge from, and frequently

return to, academia. It's a very tight community, with much inbreeding and a strong common culture. When there was talk of redirecting a small fraction of the royalties received by medical centers back to the government, the NIH actually argued against it.

The NIH has been friendly to big pharma as well. (As we will see, some senior scientists at the NIH have had extensive financial dealings with drug companies.) Under considerable pressure from industry, in 1995, the agency completely abandoned its 1989 policy requiring "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." According to an NIH report, "Shortly after the policy of 'reasonable pricing' was introduced, industry objected to it, considering it a form of price control."[22] And so it was! A well-intended but doomed effort to hold the industry accountable. As a result, companies like Bristol-Myers Squibb could charge whatever they liked for drugs like Taxol.

In 2001, at the behest of Senator Ron Wyden (D-Ore.), the NIH attempted to account for its contributions to a list of the top forty-seven drugs on the market. The fact that four of them (Taxol, Epogen, Procrit, and Neupogen) were developed largely with public funding was widely publicized. What was not publicized was the fact that the NIH did not seem to know one way or another about many of the other forty-three drugs. According to its report, "NIH encountered difficulty in being able to cross-reference NIH grants and contracts that gave rise to inventions

with any patents or licenses covering the final product, as well as an inability to identify other federal and/or nonfederal sources of funds that contribute to an inventive technology." The drug companies claim that this lack of information shows the drugs were developed by *them* (they often state that "only four" of the forty-seven drugs were developed outside the industry), but there is no reason to assume that. What the facts really show is that the NIH, in violation of the Bayh-Dole Act, failed to keep proper records of patenting and licensing arrangements.

The drug companies are not the only ones to ignore the provisions of Bayh-Dole that have to do with "reasonable terms" and recouping some of the public's investment. Universities are just as resistant. There is no question that they benefit by high pricing of the fruits of their research. Columbia University, which patented the technology used in the manufacture of Epogen and Cerezyme, collected nearly $300 million in royalties from more than thirty biotechnology companies over the seventeen-year life of the patent. The patent was based on NIH-funded research during the 1970s. Because it is in their interest, universities seldom criticize the exorbitant pricing of drugs that stem from their research.

A Fruitful Public-Private Collaboration?

You might argue that, yes, the ideas for innovative drugs come from outside the industry, but ultimately it is the industry that actually brings drugs to market. Universities can't put pills

in bottles and sell them. Isn't that just the kind of fruitful public-private collaboration that we should want (and that Bayh-Dole intended)? Publicly funded scientists come up with the ideas and early development, and drug companies put that to practical use. The companies sponsor clinical trials, they convert the drugs to forms that can be safely and readily administered, and they produce and distribute the final products. And sometimes, although rarely, they actually discover an innovative drug on their own. What's wrong with that?

What's wrong with it is that the industry is not satisfied to be that sort of "partner." Instead, it claims far more for itself. It claims to be the innovator, as well as the developer and manufacturer of new drugs. It takes credit for the whole shebang. And on that basis it makes the case that it is more than entitled to its gargantuan profits and all the other special favors it receives—the long periods of exclusive marketing rights, freedom from any price regulation, and huge tax breaks. If the much more modest role big pharma really plays were widely known, if the public knew where the miracles really come from, people would demand that the industry's rewards be more commensurate with its contributions and that there be some form of public accountability.

The drug companies are now beginning to acknowledge that they are in a dry spell. But they contend that advances in genetic research will shortly open limitless possibilities for the development of important new drugs. And that may be true, although it will probably not happen in the next few years. But

note what that claim implies: that the industry is just waiting to feed on research done on the outside. It is treading water, hoping universities and biotechnology companies will turn out a wealth of new ideas. It is waiting for Godot. That is hardly the image a dynamic industry that claims to be the source of innovative research should want to project, but it is the true state of affairs. And it explains why major drug companies are now setting up their R & D operations near important research universities and medical centers, and trolling small companies all over the world for drugs to license.

The industry obscures not only the origin of its innovative drugs but also the fact that those drugs constitute only a small proportion of its total output. Big pharma likes to refer to itself as a "research-based industry," but it is hardly that. It could best be described as an idea-licensing, pharmaceutical formulating and manufacturing, clinical testing, patenting, and marketing industry. All that takes a lot of money, but the majority of its products are drugs that, in the words of the FDA, "have therapeutic qualities similar to those of one or more already marketed drugs"—in other words, me-too drugs. How me-too drugs came to dominate the market is one of the more shameless chapters in the larger story of the pharmaceutical industry—the one that I'll address next.

5

"Me-Too" Drugs— The Main Business of the Pharmaceutical Industry

MY MOTHER HAD MANY FINE QUALITIES, but good cooking was not one of them. Every meal consisted of leftovers. It wasn't just that leftovers were a supplement. They seemed to be the entire meal. My brother and I often marveled at how she managed this. We eventually settled on what we came to call the big bang theory of Mom's cooking. Sometime in the distant past, we decided, before we were born, our mother had cooked a single stupendous meal, and the family had been living on it ever since. We were only sorry we had missed that meal.

So it is with big pharma. Every now and then,

drug companies bring an innovative drug to market, but mainly they turn out a seemingly inexhaustible supply of leftovers—"me-too" drugs that are versions of drugs in the distant past. But unlike my mother's mythical first meal, the drug companies seldom do their own cooking. Researchers supported by the National Institutes of Health (NIH) usually do the initial work of drug discovery. Then the drug companies keep stringing out and exploiting those discoveries.[1]

As we saw in the last chapter, in the five years 1998 through 2002, 415 new drugs were approved by the Food and Drug Administration (FDA), of which only 14 percent were truly innovative. A further 9 percent were old drugs that had been changed in some way that made them, in the FDA's view, significant improvements. And the remaining 77 percent? Incredibly, they were all me-too drugs—classified by the agency as being no better than drugs already on the market to treat the same condition. Some of these had different chemical compositions from the originals; most did not. But none were considered improvements. So there you have it. Seventy-seven percent of the pharmaceutical industry's output consisted of leftovers.[2]

This travesty is made possible by one crucial weakness in the law—namely, drug companies have to show the FDA only that new drugs are "effective." They do not have to show that they are *more effective than* (or even as effective as) what is already being used for the same condition. They just have to show they are better than nothing.[3] And that is exactly what the companies do. In clinical trials, they compare their new drugs with

placebos (sugar pills) instead of with the best current treatment. That is a very low hurdle indeed. In fact, on the basis of placebo-controlled trials, drugs can be approved that are actually *worse* than drugs already on the market. The last thing drug companies want is a head-to-head comparison. Only when it would be clearly dangerous to human subjects to deprive them of treatment by using a placebo are drug companies likely to compare a new treatment with an old one. That doesn't happen very often.

This defect in the law is critical in understanding the modern pharmaceutical industry. Almost alone, it has enabled the industry to transform itself into a giant me-too business. If companies had to show their drugs were better than older treatments, there would be far fewer me-too drugs, because not many of them would pass that test. The companies would have no choice but to look for important new drugs, instead of taking the easier and cheaper route of spinning out old ones. But spinning out old ones is what they do. Let's look at some of the ways they do it.

Patent Extenders

Sometimes it's simply a matter of extending the life of a blockbuster drug that is going off patent by making a virtually identical drug and shifting users to the new one. The drug just has to be different enough to qualify for a new patent. Take the case of Nexium. Nexium is a heartburn drug of the proton

pump inhibitor type made by the British company AstraZeneca. It came on the market in 2001, just as the company's blockbuster drug for heartburn, Prilosec, was scheduled to go off patent. That was no coincidence. Unless there was a replacement, the loss of the Prilosec patent would have been a devastating blow to AstraZeneca. At $6 billion in annual sales, Prilosec was once the top-selling drug in the world. When the patent expired, it would face competition from generic manufacturers, and its sales would plummet.

So as part of a multifaceted strategy to prevent this loss of revenue (involving, among other things, lawsuits against potential generic manufacturers), AstraZeneca developed an audacious plan. Prilosec is a mixture of an active and a possibly inactive form (called isomers) of the omeprazole molecule. The company would take out a new patent on the active form of the Prilosec molecule, name it Nexium (it wouldn't have done to call it "Half-o'-Prilosec," but that is what it was), and promote it as an improvement over Prilosec just in time to switch people over before the Prilosec patent expired. The plan worked.[4]

Shortly before the patent on Prilosec was set to expire, the company got FDA approval for the newly patented Nexium. Then it launched a massive advertising campaign to persuade Prilosec users and their doctors that Nexium was somehow better. Very quickly, Nexium became the most heavily advertised drug in the United States. The media was blanketed with Nexium ads—"Today's purple pill is Nexium, from the makers of Prilosec." To help with the switch, AstraZeneca priced Nex-

ium slightly below Prilosec, gave discounts to managed care plans and hospitals, barraged doctors with free samples, and even offered coupons in newspapers. The campaign reportedly cost the company a half billion dollars in 2001. Virtually overnight, Nexium—the new purple pill—began to replace Prilosec. Soon the company dropped all references to the older drug in its advertisements. Now they just refer to "the purple pill called Nexium." It is as though Prilosec never happened. (In fact, Prilosec is now sold over the counter for a fraction of the cost of Nexium.)

Many people know this much of the story, or at least the outlines of it, and they know that such corporate shenanigans are one reason drug prices are so high. But what you may not appreciate is the role of clinical trials. To get FDA approval for Nexium, AstraZeneca had to test it in several clinical trials. Some of these trials merely compared Nexium with placebos to show that it worked better than nothing, since that is all the FDA requires. But four trials compared Nexium head to head with Prilosec (for esophageal erosions), and these were crucial to the marketing strategy. The company wanted to show that Nexium was better than Prilosec—an advance over the older drug.

But note what AstraZeneca did. Instead of comparing likely equivalent doses (which would have been no more than 20 and possibly as little as 10 milligrams of Nexium, versus the standard 20-milligram dose of Prilosec), the company used higher doses of Nexium. It compared 20 milligrams and 40 milligrams of Nexium with 20 milligrams of Prilosec. With the dice loaded

in that way, Nexium looked like an improvement—but still only marginally so and in just two of the four trials.[5] In fact, the only surprise is that at the high doses chosen for comparison, Nexium didn't do better than it did. The logical conclusion might have been simply to double the standard dose of Prilosec, allow generic competition, and forget about Nexium—but that would not have been of help to Astra-Zeneca, only to people with heartburn who object to paying $4 a pill (which in itself might produce heartburn). Tom Scully, the former head of the Centers for Medicare & Medicaid Services, told a group of doctors, "You should be embarrassed if you prescribe Nexium."[6]

The story of Clarinex is similar. This is Schering-Plough's replacement for its blockbuster allergy drug, Claritin, which went off patent at the end of 2002.[7] The potential loss to the company could hardly be exaggerated. Claritin had sales of $2.7 billion in 2001 and accounted for about a third of Schering-Plough's revenues. Back in 1987, the company had patented the active metabolite of Claritin—that is, the molecule into which the body converts Claritin, which is entirely responsible for the action of the drug. Late in 2001, it received FDA approval to market the Claritin metabolite under the name Clarinex and began a massive promotional campaign to switch Claritin users to the new drug before Claritin lost its exclusive marketing rights. To that end, it also priced Clarinex slightly below Claritin. Clarinex was approved for the treatment of year-round indoor allergies as well as seasonal outdoor allergies. That means Schering-Plough can market Clarinex as an

improvement, even though it is simply what Claritin turns into after it is swallowed. But there is no reason to think Clarinex is an improvement. It was approved for the additional use only because the company decided to test it for that use. If they had tested Claritin for indoor allergies, it would undoubtedly have been the same as Clarinex—because it *is* the same.

Competing Me-Too Drugs

More often, me-too drugs are made by competing companies, who create their own versions of blockbuster drugs to cut into a market that has already proved both lucrative and expandable. In addition to Prilosec and Nexium, there are three proton pump inhibitors on the market, made by other companies. There are also two competing antihistamines of the Claritin and Clarinex type.

Perhaps the best-known family of me-too drugs is the statins—drugs to lower blood cholesterol levels.[8] In the summer of 2003, the FDA approved the latest of them, AstraZeneca's Crestor. The original statin drug, Merck's Mevacor, came on the market in 1987. It was a truly innovative drug, based on research in many university and government laboratories throughout the world. The potential market was huge, since the theory that high cholesterol contributes to heart disease was gaining ground and the "normal" level of cholesterol was being revised downward. Other companies were quick to produce their own statins. Mevacor was joined by the same company's

me-too drug, Zocor, Pfizer's Lipitor, Bristol-Myers Squibb's Pravachol, Novartis's Lescol, and now Crestor. (Bayer's Baycol had to be removed from the market because, at the approved dose, it caused a deadly side effect.)[9]

There is little reason to think one is any better than another at comparable doses. But to get a toehold in the market, me-too statins were sometimes tested for slightly different outcomes in slightly different kinds of patients, then promoted as especially effective for those uses. For instance, a statin might be tested for how well it prevented future heart attacks in patients who had already had one and then promoted as the only statin approved for that use, even though the other statins, if tested in the same kinds of patients, would likely have shown the same effects.

Or a new statin could be compared with an older one in strengths not likely to be equivalent. That is an extremely common way of breaking into the me-too market—not just for statins but for other families of me-too drugs. The FDA approves a drug not just for a particular use but for a specific dose—and that is the dose the company selects for testing in clinical trials. Choosing that dose is something of an art form, then. Recently, for instance, much was made of a trial showing that Pfizer's Lipitor was more effective in some ways than Bristol-Myers Squibb's Pravachol. But the study, which began in 1998, compared 80 milligrams of Lipitor with only 40 milligrams of Pravachol. These were the approved doses at the time, but since then an 80-milligram dose of Pravachol has also been approved.[10] Would Lipitor be better than the higher dose

of Pravachol? No one can say. Crestor is now promoted as the strongest statin, but that may be because the dose approved by the FDA was relatively high. A larger dose of one of the other statins might be just as good.[11] So whenever a drug company claims its me-too drug is better than another, it is important to ask whether the difference is in the dosing. We also need to remember that higher doses carry greater risks. Some experts worry that Crestor, like Baycol, might prove too dangerous when it comes into widespread use.

Mevacor is now sold as generic lovastatin and is therefore cheaper than the others. But the me-too business relies heavily on marketing, and as a tribute to the fact that nearly anything can be marketed and people persuaded to pay more for it, both Lipitor and Zocor, which are more expensive than lovastatin, were among the top ten drugs in the world in 2002—but not lovastatin.[12] Like Prilosec, Mevacor is no longer mentioned.

Prozac, made by Eli Lilly, was the first of a new type of antidepressant called selective serotonin reuptake inhibitors (SSRIs). It was developed mainly on the basis of research done outside the company. In 1987, the FDA approved Prozac for the treatment of depression; in 1994, for the treatment of obsessive-compulsive disorder; in 1996, for bulimia; and in 1999, for geriatric depression. It rapidly replaced other types of antidepressants because of its milder side effects. Prozac soon accounted for one-quarter of Lilly's revenues, with annual sales reaching $2.6 billion. Seeing the size of the market and its potential for expansion, other companies began turning out SSRIs.

GlaxoSmithKline's Paxil came on the market in 1997, followed by Pfizer's Zoloft in 1999. The upstart Forest Laboratories put itself on the map with its SSRI Celexa, then created a me-too of its me-too, called Lexapro. Prozac lost its patent protection in August 2001 and is now sold as generic fluoxetine at about 80 percent less than it used to cost. Nevertheless, the much more expensive Paxil and Zoloft are in the top ten drugs—but not fluoxetine. Like Prilosec and Mevacor, the original Prozac is forgotten.

But that doesn't mean Eli Lilly just gave up. It tried to stay in the SSRI business by patenting a weekly dosage form of Prozac. And in a move even more audacious than the switches from Prilosec to Nexium or from Claritin to Clarinex, it renamed Prozac Sarafem, colored it pink and lavender, and got FDA approval to market it for "premenstrual dysphoric disorder," its term for severe premenstrual symptoms. Same drug, same dose, but priced three and a half times higher than generic Prozac at my local pharmacy.[13]

Making It in the Me-Too Business

Success in the me-too market depends on several conditions. First, the market has to be large to accommodate all the competing drugs. For that reason, me-too drugs usually target very common, lifelong conditions—like arthritis or depression or high blood pressure or elevated cholesterol. The conditions are not so serious that they are imminently lethal, but they don't go

away, either. Sometimes they are little more than annoyances, like hay fever. Consequently, large numbers of people may take these drugs for years, producing a huge and steady volume of sales. People with uncommon diseases are not of much interest to drug companies, because the market is small. (Witness the initial reluctance of Novartis to undertake development of Gleevec.) Nor are people with transient conditions, like most acute infections. Antibiotics, for example, seldom generate huge revenues (there are exceptions here), because while infections are common, they usually do not last very long. Lethal diseases kill the customer, so drugs to treat them are not usually blockbusters, either.

Second, the market has to consist of *paying* customers. It doesn't help the bottom line to turn out drugs for nonpaying customers. That is why the pharmaceutical industry is supremely uninterested in finding drugs to treat tropical diseases, like malaria or sleeping sickness or schistosomiasis (an extremely common Third World disease caused by parasitic worms). Although these diseases are widespread, they are not important to the industry, since those who suffer from them are in countries too poor to buy drugs. Of all the drugs approved in the past two decades, only a tiny fraction were for tropical diseases. The contrast with the cornucopia of drugs to lower cholesterol or treat mood disorders or hay fever or heartburn is dismaying. Even some diseases that strike people in rich countries as well as poor ones, like tuberculosis, are not of great interest to big pharma, since they occur mainly in pockets of poverty.

Third, the market has to be not only large but highly elastic, so it can expand. Recently, for instance, the market for blood pressure medication was increased when an expert panel changed the definition of high blood pressure (hypertension). For many years, it was defined as a blood pressure above 140 over 90. But this panel decided to recognize something it called prehypertension.[14] This, they said, is a blood pressure between 120 over 80 and 140 over 90. Overnight, people with blood pressures in this range found they had a medical condition. Although the panel recommended that prehypertension generally be treated first with diet and exercise, human nature being what it is, many people will almost certainly prefer to be treated with drugs. That expansion in the definition will add millions of customers for blood pressure drugs—despite the absence of convincing evidence of their benefit in this group.

Similarly, the cutoff for high cholesterol has been lowered over the years. Once it was reserved for blood cholesterol levels over 280 milligrams per deciliter. Then it was lowered to 240, and now most doctors try to knock cholesterol down to below 200. As with prehypertension, many doctors will recommend diet and exercise to achieve that level, but people find that advice very difficult to put into practice, and the next step is to reach for a statin. That's why Lipitor was the top-selling drug in the world in 2002, and its competitor Zocor was second. I am

not arguing that cholesterol levels *shouldn't* be lowered, only that this market is easily expanded and therefore rich territory for me-too drugs.

Markets can be created, as well as enlarged. Some of the normal accompaniments of aging are now treated as diseases. Over the past few decades, hundreds of millions of women have taken hormones for postmenopausal symptoms. Now many older men are being treated with testosterone patches for "testosterone deficiency," and sometimes with growth hormone, as a sort of all-purpose tonic.

Once upon a time, drug companies promoted drugs to treat diseases. Now it is often the opposite. They promote diseases to fit their drugs. Nearly everyone experiences heartburn from time to time. The remedy used to be a glass of milk or an over-the-counter antacid to relieve the symptoms. But now heartburn is called "acid reflux disease" or "gastroesophageal reflux disease (GERD)" and marketed, along with the drugs to treat it, as a harbinger of serious esophageal disease—which it usually is not. As a result, in 2002, Prilosec was the third best selling drug in the world (Nexium had not yet had a chance to replace it), and its competitor Prevacid was seventh.

Similarly, most young women experience at least some premenstrual tension from time to time. Lilly's launch of Sarafem made premenstrual symptoms a disease—now called "premenstrual dysphoric disorder (PMDD)." It is not yet officially recognized in the psychiatric diagnostic manual, but given the influence of the industry, I would not be surprised if it is in the

next edition. While the company defines PMDD as particularly severe premenstrual symptoms, the message is clear—there is a pill for it, so why not buy it? Some women feel duped when they learn Sarafem is just Prozac in another color at a higher price, but Lilly, understandably, does not advertise that fact. Zoloft, one of the SSRI me-too drugs, quickly got into the act and was also approved for PMDD.

As the whole world knows, there is now a condition recently christened "erectile dysfunction," and a drug, Viagra, and two me-toos, Levitra and Cialis, to treat it. Advertisements for these drugs feature not decrepit old men but young athletes. The implication is obvious. Any episode of impotence, no matter how rare and how mild, is "erectile dysfunction," there is a pill for it, and if this macho quarterback is not too embarrassed to ask for it, you don't have to be, either.[15]

Me-too drugs often worm their way into lucrative markets and then expand those markets by coming up with slightly different uses. As I mentioned earlier, the FDA doesn't just approve a new drug. It approves it for a particular use and at a particular dose. If a company tests a drug for a use slightly different from those of other drugs in the class, no other company can promote it for that purpose. It doesn't matter how obvious the new use is, or how closely related to the use for which the original drug was approved. The aim is simply to find some basis for marketing your me-too drug as an improvement. Clarinex was tested for indoor allergies to differentiate it from its parent drug, Claritin. Even after initial FDA approval, companies con-

tinue to do Phase IV trials to look for new uses, get new patents, and extend marketing rights.

All of these dubious techniques have seen their apogee in the marketing of SSRI antidepressants. Prozac, you will remember, was approved not only for depression but also for a series of related disorders. The me-too manufacturers simply expanded the list of psychiatric disorders. GlaxoSmithKline's Paxil, for instance, was approved to treat something called "social anxiety disorder"—said to be a debilitating form of shyness. But what shy person has not from time to time found this trait debilitating? As the bioethicist Carl Elliott put it, "The way to sell drugs is to sell psychiatric illness. If you are Paxil and you are the only manufacturer who has the drug for social anxiety disorder, it's in your interest to broaden the category as far as possible and make the borders as fuzzy as possible."[16] The fact that few psychiatric disorders have objective criteria for diagnosis makes these disorders easier to expand than most physical illnesses. According to *The Washington Post,* Barry Brand, Paxil's product director, told the journal *Advertising Age,* "Every marketer's dream is to find an unidentified or unknown market and develop it. That's what we were able to do with social anxiety disorder."[17]

Paxil was also approved for "*generalized* [my italics] anxiety disorder," and shortly after September 11, 2001, the company launched an ambitious campaign promoting the drug for this use. Commercials showed images of the World Trade Center towers collapsing. And who didn't feel anxious about that?

But the implication was that even this perfectly appropriate (and, for most people, temporary) anxiety should be treated with drugs. The *New York Times* columnist Maureen Dowd summed it up best: "The more anxious the companies feel about profits, the more generalized the generalized anxiety disorders get."[18]

Justifying Me-Too Drugs

How do drug companies justify all the me-too drugs? They use two arguments. First, they say the competition keeps prices down. And second, they say that it is good to have more than one drug to treat a condition, because if the first one doesn't work for a particular individual, the second one might. Does either of these arguments have merit?

The first certainly doesn't. There is almost no evidence of price competition in the me-too business. When the first me-too comes on the market, the price of the original drug does not drop. That is because me-too drugs are not promoted on the basis of price. Have you ever heard Lipitor being advertised as cheaper than Zocor, or vice versa? Instead, they are marketed as being especially effective or safe—usually in total disregard of the fact that since clinical trials almost never compare me-too drugs with one another for the same condition at equivalent doses, no one can say which is more effective. Or they are promoted as the only drug to treat some particular aspect of the general condition—also in total disregard of the fact that the

other drugs were not tested for that wrinkle but *probably* would be just as good. The me-too market operates more like an oligopoly than like a competitive market; it is simply expanded and shared. I can't think of any other industry in which price is almost never mentioned in advertising.

The second argument is based on the quite reasonable-sounding assumption that in drugs, as in socks, one size does *not* fit all. Big pharma argues that very similar drugs may vary in their effects from patient to patient, so it is important to have choices. But while that sounds reasonable, there is little evidence to support the notion that if a particular drug doesn't work for a patient, a virtually identical one will. Or if one drug causes side effects, another one won't. The companies could easily test that proposition. They could test their me-too drugs in patients who have not done well on the first one. But they don't do that, probably because they don't really want to know the results—if Prilosec doesn't work, Nexium probably won't, either. They simply compare their me-too drugs with placebos. But unless the proposition is tested in proper clinical trials, there is no way to know whether it is true. Anecdotes about individual patients are no substitute.

So the idea that patients respond differently to me-too drugs is merely an untested—and self-serving—hypothesis. But let's assume for the moment that it is true. That would still not justify having four or more me-too drugs, as is now the case for many conditions. One or two would do. I know of no rationale for, say, the seven brand-name angiotensin-converting-enzyme

(ACE) inhibitors that are sold to treat high blood pressure and heart failure. No less an authority than Dr. Robert Temple, the FDA's associate director of medical policy, said of me-too drugs, "I generally assume these drugs are all the same unless somebody goes out and proves differently. I don't think you lose much if you just always use the cheapest drugs."[19]

Scarcity amid Plenty

While me-too drugs flood the market, there are growing shortages of some important, even lifesaving drugs.[20] If companies find drugs unprofitable, they just stop making them. Sometimes companies decide to stop making important drugs to free up production capacity for drugs with bigger market potential—often me-too drugs. The FDA requires six months' notice if the sole manufacturer of a "medically necessary" drug decides to stop making it, but that requirement is often honored in the breach. According to Mark Goldberger, an FDA official, "We have to give approval for companies to make the drugs, but companies can leave the market anytime they wish."[21] In 2001, there were serious shortages of many important drugs, including certain anesthetics, antivenins for poisonous snakebites, steroids for premature infants, antidotes for certain drug overdoses, an anticlotting drug for hemophilia, an injectable drug used in cardiac resuscitation, an antibiotic for gonorrhea, a drug to induce labor in childbirth, and vaccines against flu and pneumonia in adults.

Perhaps the worst shortages are of childhood vaccines. In 2000, the supply of the combined vaccine against diphtheria, tetanus, and whooping cough was so short that the U.S. Centers for Disease Control (CDC) recommended that infants receive only the first three of the five recommended doses. Booster shots were eliminated. The agency also suggested deferral of the second dose of the measles, mumps, and German measles vaccine and of the chickenpox vaccine. While those shortages have eased somewhat, so that the CDC recommended resumption of the usual schedule in late 2002, the situation remains precarious because fewer drug companies are bothering to make vaccines. There are now just four such companies, compared with about four times that many twenty years ago.

In 1994, the CDC capped prices of childhood vaccines the agency purchased for use in public health centers throughout the country—the source for most children in the United States. Some companies then stopped selling vaccines to the government, although they continued to supply private doctors and health plans at much higher prices. There is no doubt that drug companies could not make as much on childhood vaccines as they could on remedies for high cholesterol or erectile dysfunction, but were they taking a loss? Drug company profits are so large that one would hope the companies would be willing to make less profitable but vital drugs as a social service—and a thank-you to the public that subsidizes them so handsomely. But that is not the way this industry works. It all comes down to dollars and cents. As a spokesman for American Home Products

(now Wyeth) explained when his company stopped making isoproterenol, a drug used in cardiac resuscitation, "It was strictly a business decision."[22] If you get bitten by a rattlesnake, you may not be able to get antivenin, but you can certainly get something for your cholesterol.

You might ask why the FDA doesn't do something about all the machinations that make the me-too business not only possible but the order of the day. Isn't there some way big pharma can be reined in? You might also ask why doctors continue to write prescriptions for expensive me-too drugs, even when the originals have gone off patent and are much cheaper. These are key questions I'll discuss in later chapters. Suffice it to say here that neither the FDA nor the medical profession seems much inclined to exercise the authority they have. In short, there does not seem to be much hope in the near term that the pharmaceutical industry will stop flooding the market with me-too drugs, and trying to persuade us that one is different from another. So get ready for the next new Crestor and the next new Lexapro and, of course, the next new Cialis.