CHAPTER ONE

Bearing the Risks of Prescription Drugs

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Americans live in an era of advanced medicine in which many of the risks from pathogens and disease are controlled by prescription drugs. Each year, one or two excellent new drugs enable more people to lead healthier lives. These have built up to an impressive medicine chest of beneficial drugs. Despite this record of success, the fact remains that most new drugs pharmaceutical companies develop offer few advantages over existing ones and yet bear greater risk.

The benchmark for the U.S. Food and Drug Administration (FDA) to approve a drug as effective is evidence that it is better than, or no worse than, a placebo or inactive substance.[1] New drugs are compared only "occasionally with an existing drug for the condition."[2] As we will see in the next section, studies over the past 40 years have found that most new drugs offer few clinical advantages over existing ones. Thus, when ads or articles claim that a new drug is "more effective" or "better," the question to ask is, "Compared to what?"

When the FDA approves new drugs as "safe," the agency depends on company-run clinical trials. Pharmaceutical companies have an interest in designing trials to maximize evidence of effectiveness over placebos and to minimize evidence of adverse reactions. The more recent speed-up in FDA review times negotiated by the pharmaceutical industry

in return for subsidizing the FDA's drug approval process has resulted in the prescription of many newer drugs that subsequently prove dangerous enough to end up requiring warnings, restrictions, or removal from the market.[3]

Patients are exposed to greater risk for hidden side effects as the public body designed to protect them approves new drugs as "safe and effective" that, from a clinical or patient's point of view, may not be either. Chapter 2 will describe the long struggle to protect consumers from toxic drugs and recent efforts by Congress to reform the FDA to enhance public protection. How well this reform will reduce patient risk is unclear because the FDA is so intimately tied to the industry it is supposed to regulate.

Because most new drugs offer little or no advantage over existing drugs to offset their greater risk, patients who take them may put themselves at greater risk than if they took an older, safer drug at much less cost. The incidence of serious adverse effects is significant. A review of studies in 1998 concluded that "overall 2,216,000 hospital patients experienced a serious ADR (adverse drug reaction) in the United States in 1994."[4] An estimated 106,000 died, making adverse drug reactions the fourth leading cause of death, behind stroke but ahead of pulmonary disease and accidents.[5] The authors called the rates "extremely high." Applying the same rates to the most recent census data projects 2,335,000 ADRs among hospitalized patients and 111,136 deaths in 2006.[6] Risks increase with age as the ability of the kidney and liver to excrete drugs declines. Starfield, in a wider review of adverse effects, concludes that at least 225,000 patients die each year from all forms of medicine in a system prone to fragmented, excessive treatment.[7]

Adverse drug reactions reported to the FDA nearly tripled between 1995 and 2005, from 156,000 to 460,000 (figure 1.1).[8] A decade earlier, in 1985, only 38,000 reports were submitted. According to Public Citizen, 1.5 million Americans a year are hospitalized due to adverse drug reactions.[9] If Americans consume about 40% of all drugs in the world, this would mean 3.75 million hospitalizations worldwide. Between 1998 and 2005, reported serious adverse events increased four times faster than the total number of outpatient prescriptions. These studies each have their limitations, but together they indicate how substantial are the risks that patients bear.

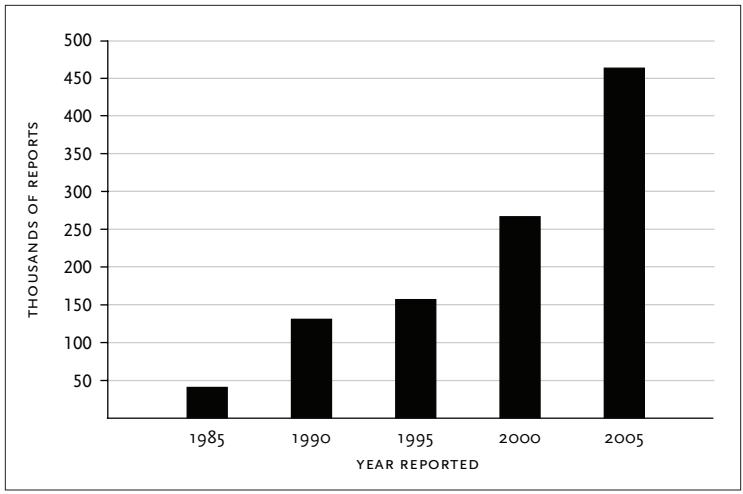


Figure 1.1 Adverse drug event reports to FDA [Source: Adapted from FDA, CDER "Report to the Nation: Improving Public Health through Human Drugs," 2005, p. 37]

There is no sign of the increase leveling out. Assuming a constant reporting rate, ADRs are rising about 15% each year, and a shift to biologics as safer because more "natural" is offering no relief. A study of the new biologics has found that safety-related regulatory action was taken on 14% of them within the first three years on the market and 29% within the first 10 years.[10] Seventy percent of the serious side effects were identified within the first five years of use, and the other 30% in the next five years. First-in-class (breakthrough) biologics were 3.7 times more likely to result in a safety warning than biologics in existing classes.[11]

There are good reasons to believe that toxic side effects are even more widespread than the figures above. Former FDA Commissioner David Kessler has written that "only about 1% of serious events are reported to the FDA," and the FDA Office of Drug Safety believes only 1% of ADRs are reported,[12] which for 2005 would mean about 46 million adverse drug reactions.

The review of studies did not count ADRs due to overdose, errors in drug administration, and other factors that are extrinsic to the drugs themselves; rather the review found an emphasis on high dosages throughout the current system, massive commercial promotion, and

the use of brand names that look or sound similar.[13] These include a substantial number of young adults 18–25 who take psychotherapeutic drugs, stimulants, and sedatives obtained outside the regulated market for non-medical uses.[14] Many researchers also do not count serious ADRs or deaths in nursing homes or anywhere outside hospitals. More important are the factors that the prize-winning *New York Times* journalist Melody Petersen identifies in her book *Our Daily Meds*.[15] When drugs make patients dizzy, resulting in a bad fall, or drowsy, resulting in a car accident, or less able to fight off a serious illness because of a weakened immune system, official reports cite the bad fall, the car accident, or the new disease, not the underlying problem of drug side effects. Petersen reports that doctors who fill out death certificates are instructed to call a "therapeutic misadventure" a natural death. The role of a drug in a heart attack or stroke or in liver failure is usually not noted. Yet when pathologists have investigated liver failure cases more thoroughly, for example, they have found that 51% were caused by just one active ingredient, acetaminophen, which is sold as Tylenol and is combined with many other drugs.[16] Petersen cites other in-depth studies that find drugs as an underlying cause of death in which the prescribing doctor is often the one who fills out the death certificate.

The number of prescriptions increased 72% from 1997 to 2007, much faster than increased illness due to aging or other factors.[17] More people are taking drugs longer, for months or years, and the risk of side effects rises with length of use. In addition, the risk of drug interactions increases rapidly as a patient takes more drugs. There can be a *cascade effect*, as additional drugs are prescribed to deal with the harmful side effects of initially prescribed drugs, these may also generate their own side effects. For all these reasons, the individualized risk of taking prescription drugs is probably much larger than estimates based on hospitalized patients. Patients may reasonably expect the FDA and their physician to protect them from risk, but in fact, both pass significant risk on to patients.

This book describes how the privatization of medical risk has grown with the ever-increasing ingestion of drugs for more and more conditions, many with questionable clinical basis and approved by a regulatory system that often fails to provide adequate risk protection. Medical doctors and social scientists describe in these pages how the current

system of developing, testing, approving, and dispensing drugs relies more on marketing than good science, especially through the market-based construction of new diseases or medical conditions, such as high cholesterol (Chapter 3), mental "illnesses" (Chapter 4), and menopause (Chapter 5). Adverse drug reactions are part of a larger pattern of avoidable injuries and deaths resulting from a fragmented health care system that concerned critics believe leads to overtreatment and non-beneficial prescriptions.[18] Overtreatment and rising prices also put millions at financial risk.[19]

TRADEOFFS BETWEEN BENEFITS AND HARMS

On average, most new drugs offer little or no additional benefit over existing drugs to offset their risks. A careful review of therapeutic benefits and harms for each new drug over the past two decades has concluded that 2–3% are real breakthroughs and another 11% offer some advantage over existing drugs, for a total of 14%, or one in seven.[20] In the 1960s and 1970s, when the FDA used to rate the therapeutic contributions of new drugs precisely, it judged 2.1% of 1,861 drug candidates as therapeutic breakthroughs and 8.6% as modestly superior.[21] Together these indicate that one in nine new drugs offer a modest or significant therapeutic gain, the same ratio that an often-cited industry assessment found for all internationally marketed drugs from 1975 to 1994.[22] Thus for over 40 years, most new drugs have offered few advantages to offset risks, and only a small proportion have provided real clinical advantages over existing ones.[23]

Those 11–14% of new drugs that offer real therapeutic advantages have helped millions of patients, and if there are two or three new ones a year, they add up over time to a significant arsenal against disease and death. Further, several of the 86–89% that are little or no better on average can help some patients who have a different biogenetic make-up. Most companies, however, focus on mass marketing and devote most of their R&D funds to filling or replacing their product line with newly patented drugs that can be priced higher but offer few advantages to offset the greater risks.[24] Pharmaceutical company reports show they spend only 1.3% of sales revenues for basic research to discover new drugs, net of taxpayers' subsidies.[25] Increasingly, the big companies do less research

to discover new drugs and let thousands of research labs and biotechnology firms try to find promising new products, then buy in and focus on marketing them. They spend about three times more on marketing than on market-oriented "research," and only a small percentage of that research is basic.

The Health Research Group at Public Citizen has been primarily concerned about drug safety for 30 years and is funded by subscriptions and donations. It has identified more than 180 approved drugs that are too toxic for patients to take. In many cases the FDA approved them despite evidence of serious risks or little advantage over other drugs. They include such well-known products as Bextra, Celebrex, Crestor, Lamisil, Levitra, and Singulair, some of which had warnings added or were withdrawn after the Health Research Group advised against them.[26] The Group is constantly petitioning the FDA to ban further dangerous drugs, like the widely used drug for diabetes, Avandia.[27]

Many patients also receive unnecessary or inappropriate drugs. For example, in a detailed study of all the medications taken by elderly patients admitted to a university hospital in France, two-thirds had been given at least one inappropriate medication, and 20% of them had an ADR.[28] Almost as many (16.4%) taking *appropriate* medications had a toxic drug reaction too. Would the results be as pervasive in American university hospitals?

In weighing trade-offs, the interests of drug companies and patients differ sharply. Pharmaceuticals is a high-risk industry that routinely develops new products with toxic side effects—products that often fail. Executives therefore deal with risk all the time and have a long history of trying out potentially beneficial drugs to "see what happens."[29] They want quick approvals to get drugs out into the market. Companies budget for the costs of adverse effects and lawsuits for damages as routine. They pay millions to settle claims against toxic side effects and seal the evidence and millions more to settle claims for deceptive advertising, then keep on marketing.[30] Before testing for safety was required, some pharmaceutical companies put drugs on the market without testing them, as described in Chapter 2, though others were more cautious and responsible.

Patients, by contrast, have one body and want to avoid any risk to it. Thus there is an inherent clash of two cultures: a high-risk business trying to sell any drugs they can[31] and no-risk patients who want every drug

to be safe, even if they know that is unrealistic. But patients also want to feel better, get treatment, and avoid future illness.

To say that new drugs are tested to be "safe" is misleading. When any drug is approved, the most one can say is that it is "apparently safe based on partial information."[32] The usual emphasis is on how rare side effects cannot be known from clinical trials that involve 1,000–3,000 subjects and often collect data over a short period of time. While true, "randomized trials" can be designed so more common adverse reactions are not reported by excluding many of the patients who will actually use a drug and ending a trial before many side effects arise. If trials were designed to test for safety, the risks to patients could be substantially reduced. In addition, risks of serious side effects are sometimes known while under review, and technical staff advise against exposing patients to them but are overruled.[33]

When pharmaceutical companies say a drug is "effective" or "more effective," they usually mean more effective than a placebo, not more effective than existing drugs. In fact, the FDA is not allowed to compare a new drug to drugs already on the market in considering approval. "More effective" also usually means more effective for treating a surrogate measure of the clinical risk or problem rather than the problem itself. For example, the rationale for statins, a class of drugs that lowers cholesterol, is based on the theory that lowering cholesterol (a soft, surrogate measure) reduces the risk of coronary heart disease (CHD, a hard, clinical measure). The theory is clearly supported for patients with a history of heart disease. But Howard Brody, a practicing physician and a distinguished professor of medical ethics, describes in Chapter 3 how commercially sponsored research, publications, professional conferences, professional education, and promotion have led physicians and otherwise healthy people with high cholesterol levels to believe that taking a statin will also reduce their risk of CHD. Yet the picture of benefits and harms for statins varies by gender, age, and pre-existing risks, and studies cited for guidelines to prescribe statins do not support them.[34] Millions of people taking statins may not be obtaining any benefit from the drug.

Even the widely accepted practice of lowering blood sugar in type 2 diabetics to prevent heart disease, stroke, and kidney failure is being questioned by newer evidence and some experts. In February 2008, NIH stopped a large trial testing drugs to lower blood sugar in type 2 diabetics

because the death rate from all causes was *higher* among those taking medication than in the control group. A second large trial found no clinical benefits from diabetes drugs as well as some additional adverse outcomes, such as severe hypoglycemia.[35] Soft, surrogate end points are used in clinical trials on the assumption that lowering blood sugar has a clinical benefit that outweighs the risks in type 2 diabetes. A recent study at the Cleveland Clinic, however, challenges this assumption for one class of anti-diabetic drugs, which includes Actos®, Avandia® (rosiglitazone), and Rezulin® (troglitazone, which is no longer marketed due to liver toxicities). In fact, the Cleveland Clinic meta-analysis of many clinical trials suggests that these drugs actually increase patient risk of a cardiovascular event; yet millions of people are still taking them.[36]

THE INSTITUTIONALIZATION OF HOPE AND MAGIC

The rules and practices by which so many new drugs of little benefit and real risk get approved and marketed reflect the hope and optimism that characterize American culture.[37] Fears and uncertainties about symptoms and illnesses foster magical thinking. The doctor-patient relationship and medicine more generally center around institutionalized roles of improvement and hope, even though the majority of illness today is chronic and more illness comes with age. The physician is expected "to 'do everything possible' to achieve the complete, early and painless recovery of his patients," though often not much can be done.[38] Such magical expectations put physicians under strain because evidence of effectiveness is based on probabilities, the course of a given patient's illness is uncertain, and how an individual patient will react is also uncertain. Prescribing a drug becomes like a ritual of hope and magical healing in the face of fear and uncertainty. Beyond the statistic that six in every seven new drugs offer little or no clinical advantage over other treatments, many patients do not respond to the benefit of a given drug because of their biogenetic make-up, while others respond well.

Executives and marketers know their anthropology. They have developed some of the most elaborate institutions of hope and magic in modern culture, tended to by marketing experts, medical writers, leading clinicians on retainer, paid educators, and journalists. Doctors and patients do not want to hear that new magic potions are dangerous or

no better. Sales reps tell physicians what they want to hear, that a new product bears hope, not harm. They leave free samples, which physicians can bear as gifts to their patients, along with the message that this new medicine has stronger magic than the older ones. Uncertainty, anxiety, and fear melt away. Parsons even wrote in 1951: "... pseudo-science is the functional equivalent of magic in the modern medical field."[39]

DO PHYSICIANS PROTECT PATIENTS FROM RISK?

When the FDA began to require a doctor's prescription for most new drugs in the 1940s, it passed on more of the responsibility for protecting patients from the regulator to physicians.[40] But physicians are often too busy to read through all the journals and do not use independent sources like *The Medical Letter* to assess the pros and cons of newer drugs. Instead, they get their information from friendly, generous sales reps who tend to emphasize the benefits and minimize the risks of prescribing their newest products for ever-expanding indications.[41] In addition, more than three-quarters of physicians have received favors from drug companies whose brands they prescribe, and almost one-third have developed personal relations with sales reps.[42] Highly priced drugs for cancer have led some companies to pay "rebates," or kickbacks, for prescribing more of their drug, amounting to nearly $800 million to oncologists in 2006 alone and leading to dangerous overprescribing.[43] The Senate Finance Committee and leading investigative journalists have found a still wider pattern of companies paying large sums to leading clinicians to promote diseases, broaden the criteria for their diagnosis, and promote patented drugs to treat them.[44] The upshot for patients when they agree to take a drug is uninformed consent, or even misinformed consent.

Most of the continuing education for practicing physicians is sponsored by pharmaceutical companies, often under generous terms and in five-star locations.[45] Through market-driven research that signs up prescribers as "investigators," publications, educational programs, and one-on-one promotion, companies give physicians every reason to prescribe more drugs to more patients, which inadvertently exposes them to still more toxic side effects.[46]

In a UCLA study with taped transcripts of office visits, two-thirds of the time physicians failed to mention harmful side effects of the drugs

they were prescribing.[47] In another recent study, half the patients on statins who complained of muscle aches, pain, memory lapses, or cognitive impairments were told by their doctors that their problems were not related to their statins.[48] The doctors said the symptoms were in their patient's imagination, or they could not be due to statins, even though medical studies showed all these toxic side effects are found in patients taking statins. Although they probably do not see it this way, physicians provide the perfect cover for drug companies: rather than serving as a trusted protector of their patients, they prescribe without mentioning adverse reactions and then dismiss them when they arise.

THE FDA: PROTECTING INDIVIDUALS FROM RISK?

The FDA is charged with ensuring that benefits outweigh risks of harm, and the extensive though flawed testing system overseen by the agency does weed out a large number of drug candidates that would cause more harm than good if they were approved. Yet the FDA still approves some drugs that put patients at risk of toxic side effects, and this trend seems to have increased in recent years.[49] Pressure from pharmaceutical companies and underfunding by Congress, as explained more fully in Chapter 2, led to industry becoming the major funder of FDA reviews of new drugs in return for setting faster review times.[50] This has led to increased risks of hidden side effects for patients, with billions of dollars spent persuading physicians to prescribe new drugs.[51] More new drugs are approved first in the United States and more quickly than anywhere else in the world; thus Americans are more exposed than patients in other countries to the risks of new drugs, as well as to their new benefits.

Prescription drugs may appear to be safe—doubly safe—because they have been prescribed by a physician and approved by the FDA. But the FDA's ability to protect people from hidden risks of serious harm has been compromised since "The Great Risk Shift"[52] of deregulation and the growth of the influence of pharmaceutical companies. Drug companies complain that FDA standards for safety and efficacy have become too stringent and costly. They point out that they do their own extensive testing and can be trusted to market drugs that are safe and effective. But as we will see in Chapter 2, some companies have tested minimally for safety on their own, until testing requirements were developed. They

submit test data and assessments of risks that reviewers consider inadequate, and they usually fail to carry out post-marketing studies on safety as required by agreements in the approval process.

Although only one in seven new drugs offers a therapeutic advantage, about two in seven appear to result in enough serious adverse events to prompt the FDA to require a label change, though the FDA does not track this basic statistic.[53] The chances are about one in five that new drugs will eventually have warnings added that are so serious they are highlighted in a black box.[54] Label changes, however, underestimate the risks passed on to patients because the same division of the FDA that approves new drugs is responsible for subsequently deciding whether they are harming patients enough to recommend changes in use, issue warnings, or press companies to withdraw them. Besides their reluctance to admit a drug is less safe than they thought, officials have been required to seek company agreement on warnings. Often, FDA officers have recommended a warning, but months of negotiation-delayed responses from reluctant companies have resulted in watered-down statements that do not protect patients from the documented toxic effects.[55]

Research into the details of how the FDA approves drugs has found that it approves them with partial evidence of harmful effects or sometimes before the results of an important trial are in, and sometimes despite known risks, because it is under great pressure by companies and patients to get new drugs on the market.[56] The FDA increases risk this way through quick approvals that require post-approval trials, most of which are not completed.[57] The FDA Office of Drug Safety has limited staff or funds to monitor safety once drugs are on the market and few powers to restrict or withdraw a dangerous drug. It repeatedly recommends that dangerous drugs be taken off the market but is overruled by the body that approved them. The officers in charge are known to be both skeptical of the evidence coming in and reluctant to admit they approved a drug that is harming patients.[58]

This sketch of the FDA focuses principally on how its testing and approval fails to protect patients from risk, but there are other sources of risk not well protected by the FDA. For example, the active chemical ingredients of most "American" drugs have for years been manufactured abroad, mainly in China and India, where few plants are inspected by the FDA.[59]

VIOXX: CAUSE FOR ALARM

A prominent case that illustrates patients' vulnerability to unmanageable risk in the current drugs system is Vioxx, an anti-inflammatory painkiller that almost no one needed because there were cheaper, safer alternatives at the time. David Graham, the associate director of the FDA Office of Drug Safety in 2004, called Vioxx "the single greatest drug safety catastrophe in the history of this country or the history of the world."[60] He estimated that Vioxx caused 88,000 to 130,000 heart attacks or strokes, with a mortality rate of 30–40%. The worldwide toll would be more than double that. Vioxx was the landmark case that led Congressmen to investigate why the FDA was not protecting patients better from risks and how so many people could suffer heart attacks, stroke, and death from taking just another anti-inflammatory painkiller.

Vioxx was claimed to halve stomach bleeds in the small percentage of people who experienced that risk when taking some kinds of common painkillers. Appropriately used, it would have been a second- or maybe third-line drug for that small group of patients. But a Congressional review documented how Merck aggressively marketed Vioxx for an ever-widening array of uses as the drug of first choice.[61] The sales reps hid or misrepresented the life-threatening side effects; this has been shown to be a general pattern.[62] Many of the "scientific" articles in medical journals attesting to the benefits of Vioxx were written by company-paid ghost writers, and academic researchers agreed to front as the authors.[63] Only a few physicians, like John Abramson, realized how articles in even the most respected journals spun incomplete and inaccurate evidence to hide the risks of both Celebrex and Vioxx while exaggerating their benefits.[64] Eric Topol, then chairman of cardiovascular medicine at the Cleveland Clinic, testified that the risks of cardiovascular trauma were known to the company since 1999 but hidden through "scientific misconduct" and said that Merck had attempted to "trash" doctors critical of Vioxx.[65]

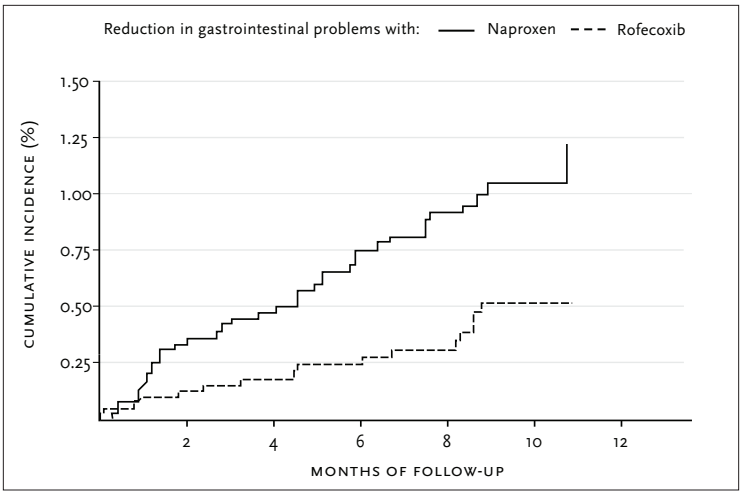
Several seeding trials—clinical studies conducted by pharmaceutical companies that are primarily designed to fulfill marketing objectives—were set up by Merck's marketing department, even though they were opposed by Merck's own director of research as "intellectually redundant" and "dangerous" because they compromised the large clinically meaningful trials already done.[66] Market-driven trials, however, enable a company to pay leading clinicians to be part of the team, sign

them up as champions, and then pay them speaker's fees to persuade colleagues to prescribe the new drug.

For example, Merck gave thousands of sales reps hundreds of millions of dollars to spend on physicians; the reps also provided tens of millions of free samples that physicians handed out to patients, which got them started taking Vioxx.[67] Some of these patients then began to experience heart attacks or strokes. This side effect was publicly known at least since 2001, when the FDA advisory committee report (along with the two graphs in figure 1.2) was posted on the Web—three years before Merck finally withdrew Vioxx.[68] Hard to understand, these two graphs showed that compared to Aleve (naproxen), Vioxx (rofecoxib) caused about one heart attack or stroke for every gastrointestinal bleed it avoided,[69] hardly what patients or their physicians were led to believe. Public Citizen warned patients not to use it. The *New York Times* published a front-page article in 2001 on the risks, but Merck countered with ads and materials attesting to the safety of Vioxx.[70] Merck completed a trial that demonstrated Vioxx's cardiovascular risk but did not report it to the FDA.[71] More physicians were persuaded to prescribe more Vioxx to more patients.

For many clinical and congressional leaders, Vioxx exemplified the failure of public safety agencies and a great risk shift to patients. Given that its cardio-traumatic effects were known early, why did the FDA not take more aggressive action? In fact it tried. Early on, FDA scientists identified how serious the risks were and put their findings on the Web.[72] Then FDA staff sent Merck executives a detailed and harsh letter with pages of examples of misleading claims in Merck's marketing campaign that overstated benefits and understated the risks to patients. They demanded that these misrepresentations stop. Like most such FDA letters, it was professional, tough, honest, and designed to protect patients. But all the solid work behind these warning letters is neutralized when companies take months to respond or circumvent them by slightly altering their marketing strategies (Chapter 5 offers an example of this practice in the case of hormone replacement therapy for women). In the Vioxx case, Merck made some adjustments in its promotional materials and continued its mass marketing.[73] Millions more patients continued to take it until Merck withdrew it in September 2004.

The Vioxx crisis and a rash of withdrawals of other new drugs ultimately resulted in a searching review by the Institute of Medicine,



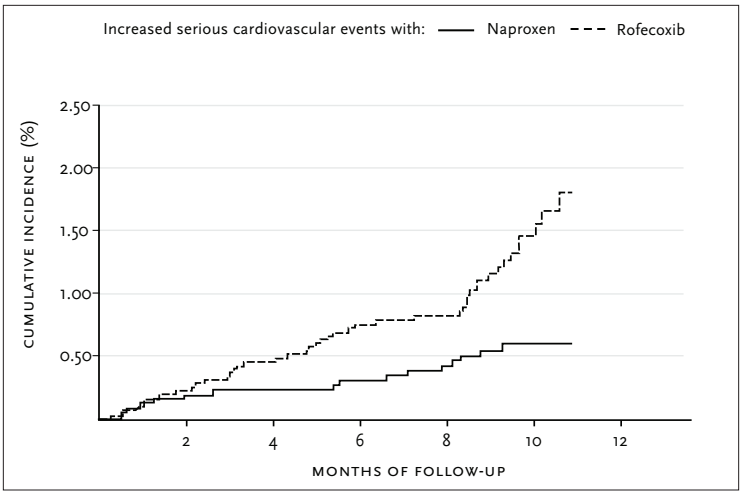


Figure 1.2 Evidence by February 2001 that Vioxx caused about one heart attack or stroke for every gastrointenstinal problem it prevented [as originally presented by the FDA in February 2001]

numerous congressional hearings, and a detailed analysis of how the culture and organization of the FDA have marginalized staff who are concerned about safety and given them few powers to protect the public when clear signs of toxic side effects arise.[74] A number of new measures

and changes are strengthening the FDA's ability to prevent another Vioxx, though fundamental weaknesses remain.

THE "RISK PROLIFERATION SYNDROME"

From my research, I have concluded that five institutional practices make up what could be called the risk proliferation syndrome: (1) having companies test their own products as part of a public regulatory system; (2) limiting reviewers' time so that they are unable to thoroughly assess the available data; (3) allowing mass marketing of new products when their safety is only partly known; (4) providing strong incentives to encourage unapproved uses; and (5) supporting the proliferation of new disease models that lack good evidence but lead millions of patients to take unnecessary drugs with their attendant risks.

CONFLICT-OF-INTEREST TESTING

The risk proliferation syndrome starts with a regulatory system that allows companies to test their own products and write up the results rather than requiring independent testing. Sponsoring companies have every reason to structure the tests, record what happens, analyze the data, and present results in ways that maximize evidence of benefits and minimize detection of risks. Minimum detection is achieved by a variety of techniques, such as:

- excluding patients who are older, poorer, minority, or female because they have more complex risk profiles and are more likely to suffer adverse effects;
- running short trials that record evidence of effectiveness but not toxic side effects that show up later, especially for higher dosages that are more effective but also bear more risk;
- running trials too small to pick up any but the most apparent, short-term toxic effects;
- recording only selected toxic side effects rather than all of them;
- ruling out patients with other health problems or risks, even if they are likely to be prescribed the drug once approved;
- using a comparator drug (if there is one) that has similar adverse effects so that the tested drug's risks do not stand out as statistically significant;

- excluding subjects who dropped out because they could not tolerate side effects, sometimes a large proportion;
- splitting clinically related adverse events into unique subgroups of one or two patients, such that none will be detected statistically;
- selectively publishing evidence to support marketing.

Other techniques include removing subjects who have a strong placebo response in a pre-trial dry run to reduce the placebo effect that the drug has to outperform; testing subjects before the trials begin and using only people who have a good response to the drug being tested; and secretly un-blinding the interim results midway through the trial "to see if they are sufficiently favorable" and then altering the design if needed before re-blinding the trial.[75]

Clinical trials have been increasingly contracted out to large for-profit companies that specialize in running trials that depend on good results to please their paymasters. An investigation found some contract research organizations advertise that they do scientifically valid research that will help prove the value of the products tested (a contradiction in terms), disguising their commercial nature in a number of ways.[76] A growing number of trials are conducted in developing countries where quality and ethical oversight are thin.[77] Based on the most detailed evidence we have, John Abraham concluded long ago that serious drug reactions are not an inevitable consequence of drug therapy but a consequence of how drug companies measure and interpret the data.[78]

Companies often design trials around patients with a principal condition who are otherwise healthy. For example, Merck ruled out patients with existing cardiovascular problems for critical trials of Vioxx, even though cardiovascular risks were "in the mechanism" of how the drug worked and may have been suspected from the beginning.[79] If the same companies that have invested millions to develop a drug also design the trials to test its safety and efficacy, we can expect them to use strategies like these to produce "scientific" evidence that they are safe and effective. The Office of the Inspector General repeatedly investigates conflict of interest (COI) and routinely finds that the FDA does not enforce regulations to protect the public from COI because there is an inherent conflict in having companies test their own products.

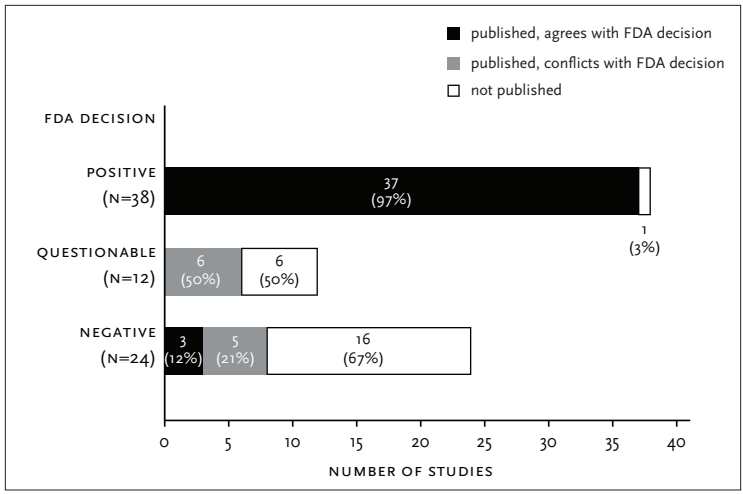


Figure 1.3 The misleading pattern of published evidence that a drug is safe and effective: 97% of antidepressant drug trials the FDA judged as positive were published in medical journals, compared to only 12% judged as negative [Source: Adapted from Erick H. Turner et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," *New England Journal of Medicine* 358 (2008): 252]

Sponsoring companies also engage in "ghost management" of research and publication to make it appear as if academic researchers are doing the studies and authoring scientific articles on the results.[80] Companies also manage what gets published and what does not. For example, one analysis found that 97% of antidepressant trials deemed positive by the FDA were published, whereas only 12% of trials with negative results were published and another 21% of the trials that the FDA judged to contain negative results were published so as to appear positive (see figure 1.3).[81] If the results from the negative trials are added to the published positive results, antidepressants are found to be barely more effective than placebos and to have serious side effects, a picture that was hidden for years.[82] Another review of generic and brand-name drugs for cardiovascular disease found that nearly all trials concluded they were equivalent, but half the editorials in medical journals counseled against using generics.[83]

A related bias in analysis and publication arises from not testing a hypothesis with trial data but doing scores of correlations and picking out the ones that are significant and favorable to the drug. Since one in every

20 will be "significant" at the 0.05 level by chance, one is sure to come up with "significant findings" that have no scientific validity. One expert calls this "the most insidious and misleading of the biases that affect this area of research . . . allowing the manipulation of data without any overt fraudulent action."[84] Senator Charles Grassley, as part of his investigations into drug company influence, wrote that "any attempt to manipulate the scientific literature, that can in turn mislead doctors to prescribe drugs that may not work and/or cause harm to their patients, is very troubling."[85] In response to the Vioxx crisis and subsequent investigations, Congress requires now that information about clinical trials and selected results be posted on ClinicalTrials.gov, "whatever their source of funding."[86] The World Health Organization and the International Committee of Medical Journal Editors also require that trial data be publicly registered. But registration is incomplete and delayed. Some results are required, but not toxic side effects, and no data on drugs that fail to be approved or are withdrawn. A loophole allows a two-year delay of posting trial data, and "the FDA must treat much of the data on clinical trials . . . as 'confidential commercial information.'" A senior reviewer concludes: ". . . the withholding of critical information about the safety and efficacy of marketed drugs from the public is unacceptable both ethically and scientifically."[87]

APPROVAL SPEED-UP

The pharmaceutical industry has used its well-funded lobbying organization to campaign for faster approvals to maximize sales and profits before patents run out. We have already cited evidence that this is increasing the risk of serious adverse side effects.[88] Companies continually complain that delays in approval and costly reviews slow down research. What patients need, the argument goes, is quicker approvals and faster access to new, better, and life-saving drugs. This may be true for a handful of medicines to treat patients for whom all available options have failed or where available treatments are themselves highly toxic. However, for the vast majority of new drugs, better data on risks and benefits, not rapid access, would mean lower risks for patients.

MASS MARKETING OF RISKY DRUGS

A third component of the risk proliferation syndrome consists of the regulations, practices, and institutions that encourage and carry out mass

marketing after a drug has been approved rather than trying it out for a year on a limited and closely monitored population. "Greater access" is often code for mass marketing to get as many patients as possible on new drugs, which dilutes their benefits and spreads their risk of harm.

Marketing departments have been found repeatedly to understate or hide information about known risks, not only from patients but from their doctors. A Congressional review of marketing materials on Vioxx before it was withdrawn documents that each time a major report described its dangerous side effects, Merck redoubled its efforts to insist it was safe.[89] At this writing, Pfizer is pushing Chantix, its antismoking drug, during prime time news, even though side effects reported to the FDA exceeded reports for the ten best-selling drugs combined.[90] The total spent by companies on marketing is staggering—$57.5 billion,[91] far more than the small amount that companies spend on basic research to find better drugs.[92] One important technique is to promote expensive new drugs to hospital specialists and make them available at little or no cost so that patients start them before discharge. Another is to leave free samples of new drugs (total annual value of $16 billion) in doctors' offices to encourage initiation of treatment in outpatients. Once started, few patients feel comfortable switching to alternatives that are less risky and yet effective.

Direct-to-consumer advertising, or DTCA, plays a central role in "educating" millions of people to view their symptoms as signs of a medical problem, or future problem, that they need to treat. Expenditures for advertising products directly to the public rose from $985 million in 1995 to $4.2 billion in 2005, focused almost entirely on newly approved drugs with blockbuster potential (more than $1 billion in annual sales).[93] Yet many heavily advertised drugs offer no substantial advantages to patients over existing ones.[94] Real benefits can be small. For example, 30–50 people with high cholesterol but no other risk factors need to take a statin for five years in order for one heart attack to be avoided. If the chance of a heart attack is reduced from 3% to 2%, the drug can be promoted as cutting heart attacks by one-third rather than by 1%. Television ads only have to mention major risk information and can result in an unbalanced, favorable picture of risks to patients. Most FDA letters to companies regarding DTCA concern their minimizing risks or exaggerating effectiveness, or both. Viewers and patients are unlikely

to know how they are being misled. At the same time, because they are tax-deductible, drug ads are subsidized by consumers; this has disturbed some members of Congress.[95]

In addition to direct-to-consumer advertising (DTCA), pharmaceutical marketing focuses on physician education during training, in the office, at conferences, and through continuing medical education courses.[96] These practices have led the Senate Finance Committee and the Senate Committee on Aging to hold hearings about industry influence on physician education and prescribing. Companies pay prominent specialists a few thousand dollars plus expenses to give educational seminars (often at expensive restaurants or luxurious resorts) about the best ways to treat a given clinical problem. In these ways a practicing physician is surrounded by facts, articles, courses, and sessions at specialty conferences that promote the use of new drugs as "more effective," even though 85% offer no advantage and may put patients at greater risk. In response, a number of reports, Congressional bills, and articles are strongly urging medical societies, medical centers, and physicians to sever ties with the industry in order to restore the trustworthiness of the profession.[97]

Pharmaceutical companies have colonized patient groups and health activists, providing them with "educational material," hand-picked speakers, and money.[98] Patient groups of serious diseases have become a principal lobbying force for faster approvals and insurance coverage for new drugs judged of marginal advantage by independent groups.

PROLIFERATING UNAPPROVED USES

Public regulation to protect patients from unsafe or ineffective drugs rests on the company selecting the indication for which a new drug is to be tested and then carefully designing and conducting trials to prove it is more effective than a placebo (or sometimes a comparator drug) for that indication. After approval, it is illegal for companies to market a drug for any condition or population in a manner inconsistent with the evidence of its specific effectiveness against specific conditions summarized in its label. However, this system is undermined by company-sponsored studies and trials in which clinicians are funded to try out a drug for other uses in small trials that often do not meet scientific standards.[99] These clinicians often publish the results in company-supported journals and supplements. They are also paid to give sponsored grand rounds, talks,

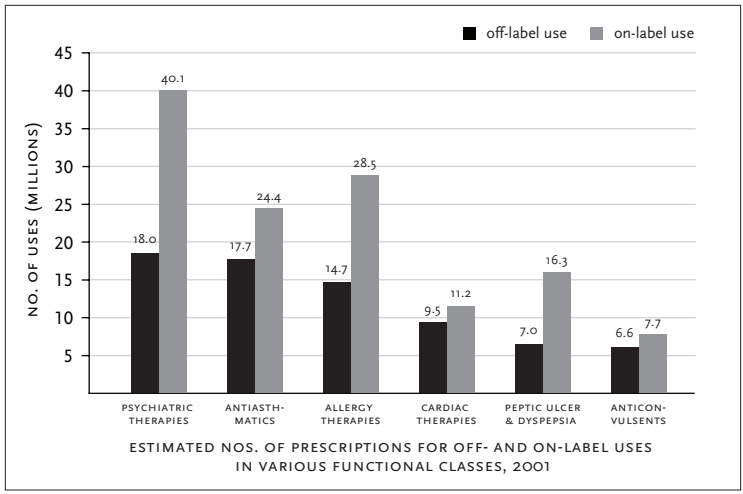


Figure 1.4 Physicians prescribe drugs for many unapproved uses [Source: Randall S. Stafford, "Regulating Off-Label Drug Use: Rethinking the Role of the FDA," *New England Journal of Medicine* 358 (2008): 1427]

educational courses, and conference presentations at which these publications are circulated as scientific-looking evidence for unapproved (off-label) uses or extensions of approved uses.

This system results in about one prescription in every five being written for an unapproved use, and in mental health, three out of every five antipsychotic drugs are prescribed for an unapproved use.[100] Yet three-fourths of the time the off-label uses have little or no scientific support.[101] Even when such off-label prescribing becomes substantial, companies are under no obligation to conduct scientifically rigorous studies to assess benefits and risks. Indeed, the short time left on the patent and possibility of identifying new risks are strong disincentives for not testing unapproved uses (figure 1.4). Why bother when one can get prominent physicians to promote them to their colleagues?

The FDA is not equipped to handle the large volume of marketing material that companies submit. Even when its small, underfunded staff identifies a serious risk, drafted letters have taken an average of seven months to be issued and longer to be enforced.[102] The Government Accounting Office found that the FDA received 277,000 submissions of marketing materials from 2003 to 2007, but its small staff could only get

to 42 actions against off-label promotions. They could not say how many of the 277,000 promotional materials made off-label claims. A new rule allows sales reps to give physicians articles about off-label uses. Thus patients are not being protected by regulators from promotion for unapproved uses. This is a growing area of risks being put back on patients for uses that often have no proven off-setting benefit.

EXPANDING THE DOMAIN OF HEALTH PROBLEMS

Patient risks come not only from biased testing and the approval of drugs that have few advantages but also from companies and the experts they support promoting consumer acceptance of an ever-growing number of health problems or risks that drugs can fix.[103] Constructing new but dubious "diseases" creates new fears that call for hope and magic by opening new markets for products.[104] Mass screenings for real diseases or imagined risks produce large volumes of prescriptions or treatments that do not benefit patients.[105]

Ray Moynihan and Alan Cassels have researched several examples of commercially created or inflated illnesses resulting in overmedication.[106] One is high blood pressure. Blood pressure rises with age and is one of several factors that can increase the risk of heart attack or stroke. But because blood pressure is amenable to drugs, a world of marketing and guidelines developed around it. What constitutes "high" blood pressure is open to opinion, and U.S. guidelines set by expert panels have periodically lowered the criteria so that millions more people are labeled as "having hypertension," or now "prehypertension," and being "at risk" of heart disease. Nine of the eleven hypertension experts on the government panel that created the disease "prehypertension" had ties to the pharmaceutical industry, and nine of the twelve FDA panelists setting guidelines for blood pressure drugs had ties.[107] This corporate construction of personal risk feeds what has become a $40 billion market in blood pressure drugs.

Many other "diseases" could be added to the list of medical conditions treatable by prescription drugs. For example, the "epidemic" in obesity follows the classic sociological pattern of how a new problem is constructed by moral entrepreneurs, the press, and other interested parties.[108] Like high blood pressure and cholesterol, the definition of "obese" is lower than evidence of clinical danger. Another disorder afflicting millions is insomnia, based on the mythic eight-hour "good night's sleep"

that has never been common. In 2007, the FDA issued a black box warning on the risks of taking all insomnia medicines. A review of evidence of benefits showed only seven out of every 100 patients on sleeping medications reported sleeping longer, by 25 minutes a night. Patient information leaflets mention only a fraction of all the risks to patients.[109] A third medical "disorder" that commercial interests are working hard to establish is "female sexual dysfunction," based on women reporting less than complete sexual fulfillment.[110]

The commercial construction of high cholesterol as a serious risk for heart disease has involved converting a complex set of relationships between heart disease and saturated fats and cholesterol in the diet and blood into a simple message that high cholesterol kills. Critics have been skeptical since the 1970s.[111] Recently, two major trials of statins found little evidence of reduced risk of heart attacks but increased total risk of morbidity and mortality, despite lower cholesterol.[112] Yet conflicting studies come out all the time; so the benefits of statins remain controversial. In 2008, the American Academy of Pediatrics recommended "more aggressive use of cholesterol-lowering drugs starting as early as the age of eight in hopes of preventing adult heart problems," despite growing evidence that lowering cholesterol has few clinical benefits.[113] The "high cholesterol kills" campaign and the research behind it are a good example of how approving any new drug better than an inert substance or placebo encourages the development of synthetic disease models based on surrogate measures. Another example is lowering blood sugar in type 2 diabetes to reduce heart disease.[114]

In Chapter 4, Allan Horwitz draws on his award-winning research into the basis for many of the official psychiatric diagnoses for non-psychotic patients[115] to describe the spectacular but dubious rise of attention deficit disorder, depression, and bipolar "disease." Increases in mental illness diagnoses have led to millions more people taking drugs whose main benefits are questionable, and serious side effects include addictive withdrawal symptoms and suicidal behavior, not to mention a neglect of the social causes of these emotional problems. Similarly, in Chapter 5, Cheryl Stults and Peter Conrad examine the development and impact of public "risk scares," as illustrated by turning menopause into a risk-laden medical condition that could cause Alzheimer's, osteoporosis, cardiovascular disease, and cancer. Hormone replacement therapy

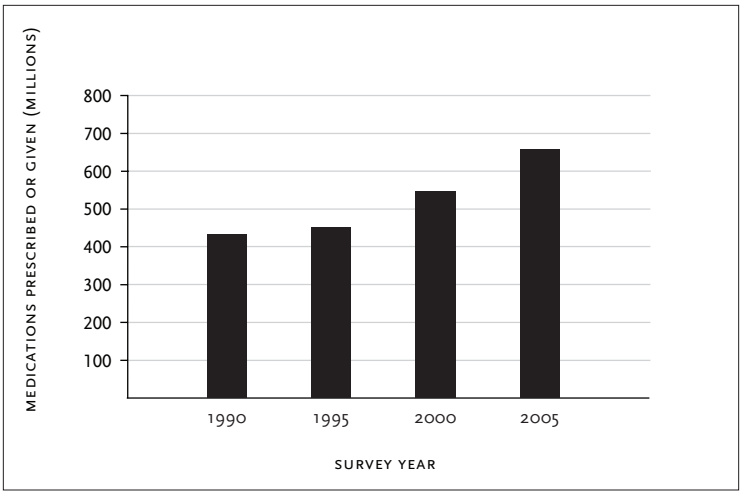


Figure 1.5 Medications prescribed or given during physician visits
[Source: National Ambulatory Medical Care Survey, United States, 1990–2005]

(HRT) was promoted for unproven benefits, and millions of women took it even though it did not reduce cardiovascular disease but significantly increased risk of breast cancer.[116] HRT is still promoted for these unproven benefits. Evidence from some of the 8,400 lawsuits by women who claimed to be damaged by Wyeth's hormonal drugs reveals details of how the company engaged ghost writers to publish twenty-six scientific papers supporting HRT and downplaying its side effects.[117]

As a result of convincing people they have more health problems and then urging them to take medication, approximately four-fifths of all Americans, including over half of all children, now take a prescription drug each week.[118] From 2000 to 2006, the number of people who reported taking five or more prescription medications doubled, and almost one in five adults over 65 years old take ten or more medications weekly.[119] The number of medications prescribed or given while seeing a physician rose from 425 to 679 million between 1990 and 2005, as shown in figure 1.5. The number of prescriptions rose 72% between 1997 and 2007.[120] The proliferation of "diseases" has contributed substantially to this increase.

Another contribution to risk proliferation is polypharmacy, the taking of multiple drugs for one or more conditions.[121] The toxic side effects

of one drug lead doctors to prescribe another, which has its own risks and interactions that vary with the biological and genetic make-up of the individual. Since drugs are typically tested and approved as single entities, patients are put at risk for interactions. The proliferation of millions more people taking a second, third, or fourth drug multiplies the risk of serious adverse effects.

PATIENTS PUT AT FINANCIAL RISK

The risk proliferation syndrome puts more patients not only at greater clinical risk but also at greater financial risk. This volume is part of a project supported by the MacArthur Foundation and directed by the Social Science Research Council entitled "The Privatization of Risk." It concerns what Jacob Hacker called The Great Risk Shift that has taken place since 1980, away from job security, solid pensions, and health security toward putting individuals more at risk for their jobs, pensions, and health insurance.[122] This volume and the others address new questions about the ability of individuals to perceive, plan for, and successfully address these risks. Chapter 2 describes how regulations were developed to protect the public from serious risks from pharmaceuticals, how they were compromised, and the current efforts to protect the public from dangerous drugs like Vioxx.

The risk proliferation syndrome details a multi-pronged corporate effort to persuade physicians and their patients to buy new drugs that cost several times more than already existing drugs and often offer few clinical advantages to offset their risks of adverse reactions.[123] Private health insurance, for reasons explained in the companion volume, *Health at Risk*, puts many patients at greater financial risk than allowed by any country with universal health insurance.[124] For example, one in six Americans under age 65 *with* health insurance reports problems paying for a prescription. Among those without health insurance, nearly one in three report such problems. Most commercial policies cover drugs, but with deductibles, co-payments, caps, and gaps in drugs covered. These techniques for putting patients at greater financial risk are used much less in other countries. They force millions of Americans to think twice about whether to fill a prescription their doctors think they need and to split pills, share prescriptions, or stop taking a drug—each of which

creates new safety risks. Patented drugs in the U.S. cost about twice as much as in Europe. Companies are free to charge substantially higher prices than in other wealthy countries for patented drugs in "free" markets where there is little price competition among patented drugs.[125] Yet physicians do not usually discuss affordability and cost with patients.[126]

The financial situation has worsened with the recession, and Americans are cutting back on the number of prescription drugs they take because they cost too much out of pocket.[127] In patient focus groups, patients decide which prescriptions they can do without. These choices take place in a context of Americans taking 72% more prescriptions in 2007 than a decade earlier, not because they are sicker but because of the risk proliferation syndrome that promotes fear of getting sick or worse and hope in new drugs.[128] Millions have benefited greatly from the medicine chest of good drugs that have been discovered one by one over the years; but millions more are put at financial and clinical risk by the proliferation of new drugs that offer few advantages but greater risks than older ones. Employers and insurers have responded by encouraging generic substitution through tiered co-payments.

MEDICARE'S DRUG COVERAGE RAVINE

Medicare was passed in 1964 after years of effort to reduce the great financial burden that seniors faced because insurance policies were either not available or unaffordable. The legislation did not cover the cost of most drugs, which has been increasing rapidly, from about $8 billion in 1970 to $40 billion in 1990 to $217 billion in 2006.[129] Although seniors were put at increasing financial risk, the pharmaceutical industry lobbied hard against proposals for Medicare to cover drug costs until seniors organized such a groundswell of protest over the high prices of drugs that it became a leading issue for both parties in the 2000 Congressional elections.[130] When work began on expanding Medicare coverage to drugs, the pharmaceutical industry and insurance companies made sure the terms included new multibillion dollar payouts for insurers and no discounts on patent-protected prices for drug companies.[131] Working under budget limitations, Congress decided that the only Medicare prescription program that would be acceptable must have some initial coverage for everyone and catastrophic coverage for people with very high drug expenses, leaving a ravine of no coverage in between.

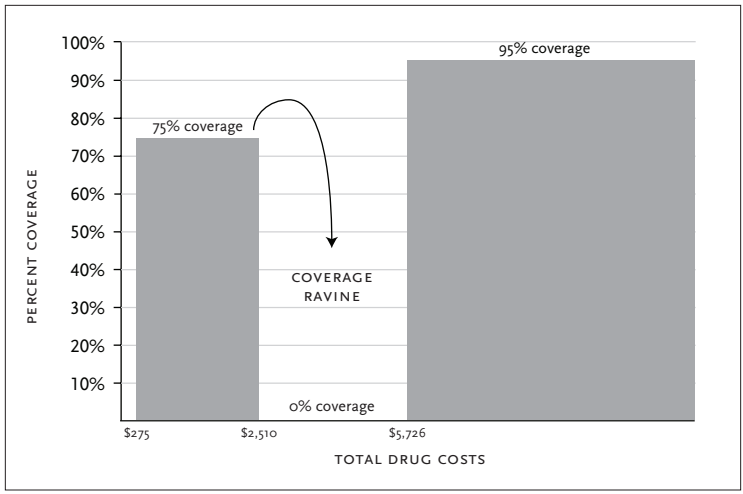


Figure 1.6 Medicare drug coverage ravine 2008 [Source: author]

The front edge of the coverage ravine in 2008 was $2,510 in drug costs (see figure 1.6), about the equivalent of one year's prescription for a patented drug costing $210 a month. Out-of-pocket costs add up to nearly half that total—a $275 deductible and 25% reimbursement for the remaining $2235 plus $610 on average for the premium. As shown in figure 1.6, patients stay in the ravine of no coverage until their bills exceed $5,726 out of pocket, plus monthly premiums for the policy that is giving them no reimbursement. At that point, they are hoisted up to the back safe ledge of 95% coverage. Thus a patient with a second medication costing $210 a month will pay all of it out of pocket so that both drugs cost her $5020 cash, unthinkable in other advanced industrial countries.

About one in five Medicare enrollees fall into the ravine of no coverage, and it will widen over time. It leaves millions of seniors paying thousands of dollars a year for costly drugs that are often little better than much cheaper ones because the drug lobby persuaded Congress to prohibit Medicare from negotiating volume discounts and because of overhead costs for the confusing extra layer of over 1,000 different drug benefit plans.[132] Consumers Union and AARP are especially concerned about large price increases of specialty drugs.[133] If Medicare could

pay Canadian prices (an average of European prices) or negotiate for the same prices paid by the Veterans Health Administration, the heavy burden of zero coverage in the ravine between $2,510 and $5,726 could be filled in with coverage.[134] If Medicare paid Medicaid prices, much of the ravine could be filled. The industry claims that lower prices would reduce their funding for research to discover new, innovative drugs, but their own reports show they recover all research and other costs, plus a good profit from domestic sales in England and Canada.[135] Moreover, public funds pay for 84.2% of basic research to discover new drugs, and federal law has required since 1980 that products resulting from federally funded research must be "available to the public on reasonable terms." This law has not been enforced.[136]

Medicare also makes drug coverage an option, not automatic as in most countries. By requiring private plans, it incurs substantial costs for running them, which enrollees pay through drug plan premiums—another way in which the cost of drugs is increased for individuals. Four million eligible seniors do not enroll to avoid the costs and complexities. Overall, Medicare and Medicaid (which covers only half the poor, who also are sicker) leave millions to bear a significant financial burden when they become ill. Drug revenues are projected to rise from $217 billion in 2006 to $515 billion by 2017.

The personal financial burden of prescription drugs comes not only from taking more drugs than necessary but also from taking high-priced patented drugs that are usually little or no better than lower-priced generics, because the pharmaceutical industry spends billions on physicians to persuade them to prescribe the high-priced options. This personal burden is increased by toxic side effects and the costs for treating them—trips to the doctor or ER, more drugs to counter the side effects of the first drug, or hospitalization. On the other hand, the underinsured and uninsured may jeopardize their health by not taking drugs they need or stretching them out in ways that undermine their effectiveness.

The epilogue discusses ways to reduce the clinical and financial risks that patients now bear, beginning with no longer rewarding companies for developing new drugs of little therapeutic benefit but instead rewarding them for clinically superior new drugs. If this were done, then all new drugs would be worth considering, deceptive marketing that attempts to convey equivalent drugs as "better" would end, and

there would be real clinical benefits to offset risks. The whole science of pharmaceutical research would improve because creating artificial diseases and disease models would no longer be rewarded. Employers, state governments, and insurers would save billions by not purchasing expensive new drugs that are not therapeutically superior. And if Congress funded the NIH to run or oversee clinical trials, we would not only get better information at an earlier stage about risks but industry would be relieved of a huge financial burden, eliminating the justification of pricing drugs at 50–100 times costs. Pharmaceuticals would no longer have to be a boom-and-bust business. The industry would become more stable, smaller, and rewarded for finding products that really improve people's health. These are just a few of several recommendations in the epilogue for Congress and the new administration to consider.

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in 2006 = 111,136. http://www.census.gov/compendia/statab/tables/09s0169.pdf; http://www.census.gov/prod/2007pubs/08abstract/vitstat.pdf. Because deaths from pulmonary disease and accidents have increased more, adverse reactions from taking drugs that are supposed to make you healthier now rank sixth as a cause of death. Compare Lazarou's list of leading causes on page 1204 with the latest from Information Please (2004) at http://www.infoplease.com/ipa/A0005110.html. Lazarou et al. make clear that with 106,000 deaths, ADRs are the fourth leading cause of death and that if the lower 95% CI of 76,000 deaths is used, they would rank sixth.

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CHAPTER TWO

The Food and Drug Administration: Inadequate Protection from Serious Risks

DONALD W. LIGHT

> The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs.
> — FDA Mission Statement

> There's a total inability of the FDA to carry out its mission.
> — Congressman John Dingell, calling for complete overhaul of FDA, 2008[1]

The U.S. Food and Drug Administration (FDA) is the premier public regulatory body of its kind in the world. No other agency has so many staff and resources or has pioneered so many procedures or techniques to protect public safety and promote the development of better drugs. Yet no other regulatory body has been criticized so extensively for falling down on the job, letting too many risky drugs through, and being too dependent on and close to the industry it is supposed to regulate. When one learns how antiquated its information technology systems are, how difficult it is for the agency to recruit and retain good staff with inadequate compensation packages, and how dependent the agency is on the funding, submissions, and policies of pharmaceutical companies, one realizes that protecting patients from drug risks will require a new level of public demand and strong leadership from the White House.

This chapter provides a short history of how the FDA developed, stage by stage, as public health and safety were threatened by drugs that were mislabeled, sold under misleading claims, or had serious adverse effects on patients. A complementary history could be written about ever-stronger standards to protect individuals from risks posed by improperly prepared and stored foods, additives, and contaminants. An important appendix summarizes how drugs are tested. This history of institution-building reveals the central role of drug companies in both marketing dangerous drugs that led to greater protection and limiting regulatory oversight once passed by Congress.

FOUNDING HISTORY: SELLING DANGEROUS NOSTRUMS TO GULLIBLE CONSUMERS

The development of the FDA and regulations to protect patients from hidden risks and toxic effects arose out of a long history of some (but by no means all) doctors, apothecaries, and manufacturers of medicines making and selling adulterated or dangerous medicines while proclaiming their miraculous powers. Adulterations have been a concern from colonial times, when, in 1638, anyone selling water as a cure for scurvy was punished by whipping.[2] Although "protecting public health" is the central phrase in American and European regulation, safeguarding *individuals* from poisons, toxic ingredients, and misrepresentations they cannot detect has played a central role in developing the FDA and other drug regulatory systems.

At the turn of the twentieth century, the manufacture and marketing of medicines was unregulated, and the contents of the many miracle cures, balms, nostrums, and elixirs were kept secret. The American Medical Association (AMA) stepped into this void and set standards for both manufacturing and marketing with the establishment of the Council on Pharmacy and Chemistry in 1905.[3] Some manufacturers concentrated on selling higher quality medicines to physicians; this formed the basis for modern pharmaceutical companies. Such companies drew on the AMA standards to distinguish themselves from less scrupulous competitors, sharing an interest with doctors of medicine (MDs), who had earlier used licensure laws to set standards that distinguished them from less scientific doctors. Thus, a symbiotic relationship developed between

specialists promoting prescription-based drugs and their manufacturers to enhance each other's power and legitimacy that has continued from before the beginning of the era of effective drugs in the 1930s. Drugs sold as higher quality and physician-endorsed also justified higher prices and profits.

As part of a campaign under Theodore Roosevelt to expose dangerous preparations of food and drugs, *The Nation*, *Collier's*, and *Ladies' Home Journal*, the most popular magazines of the time, published influential articles between 1903 and 1905 on the dangers of widely sold drugs and ingredients.[4] *Collier's* listed the names and addresses of patients who had been killed by them. Scores of bills were proposed to protect an unsuspecting public from hidden risks. Food and drug manufacturers countered vigorously, spending large sums on senators and congressmen to persuade them to bury these bills in committee.

However, the pro-regulatory campaign intensified, and the Pure Food and Drug Act was passed in 1906. It established the principle that the government should protect citizens from risks due to commercial fraud and abuse by outlawing adulterated or mislabeled drugs and foods.[5] This allowed manufacturers to avoid regulation by not listing ingredients except for those required, such as alcohol, opium, cocaine, or marijuana. Testing for safety and claims was not covered; so manufacturers could still claim their drug made people stronger or cured cancer. Congress allocated no funds for enforcement, and federal agents could not prosecute but had to take each case to court. Further, the resulting penalty could not be more than a misdemeanor. In a history of the FDA, Philip Hilts writes that "the meager punishment was a signal heard to the present day. . . . The secret-ingredient medicine industry, which had fought regulation vigorously, found that the new law was really not very burdensome after all."[6] What reformers should have used as their model, Hilts contends, was the Biologics Control Act of 1902, which required any manufacturer of vaccines to qualify first for a license each year, based on annual inspections. Instead, the law as passed was based on catching violators only after drugs were already being used by millions of people. This proved to be a fatally flawed approach to safety. Labeling aside, the law did little to prevent the exaggerated and even blatantly false claims of advertisements in national periodicals and newspapers that had become the major vehicles for selling medicines.

One case soon after the passage of the Pure Food and Drug Act involved a headache cure containing a painkiller that had previously been found to cause heart attacks, of which millions of bottles were sold. The manufacturer claimed it provided "a most wonderful, certain and harmless relief."[7] A jury found him guilty of mislabeling and fined him $700, which represented less than four one-hundredths of one percent of his profits. He paid and kept selling his headache cure for years, continuing to put consumers at serious risk. In 1910, the FDA took to court the manufacturer of "Johnson's Mild Combination Cancer Treatment," a worthless treatment that claimed to cure cancer, to remove this false claim from the label; the government lost. The judge ruled that claims of effectiveness were not considered mislabeling. In response, Congress passed an amendment that gave the FDA authority to prosecute false claims, but only by taking each case to court to prove the claims to be both false and deliberate. These cases illustrate early, fundamental needs to keep drug companies from deceiving innocent patients, to have enforcement powers, and to exercise consequential sanctions against false or misleading claims. These needs remain partially unfulfilled, as a recent government assessment of the FDA's regulation of off-label promotional materials indicates.[8] Overall, sales of the pharmaceutical industry increased sixfold during the first twenty years under the 1906 act, a testimony to the triumph of marketing over effectiveness, given that few seriously beneficial drugs existed before the first sulfa drug, introduced in 1935.

Under President Franklin Roosevelt and Assistant Secretary of Agriculture Rexford Tugwell, Walter Campbell, the FDA commissioner, proposed legislation to protect patients from the risks of false or exaggerated advertising claims as well as false labeling by requiring that evidence of safety be submitted before approval.[9] The pharmaceutical industry, which emphasized competition and private markets to sort out claims without scientific backing about drugs with undisclosed ingredients, mounted an intense campaign against the bill.[10] Many of the drugs sold to millions depended on false claims, like Lydia Pinkham's wildly popular Vegetable Compound, which contained no vegetables but was 18% alcohol. The bill would have required companies to show that their new drugs were safe *before* they could be sold. Industry indicated that these requirements would decimate drug advertising and retail sales. Government protec-

tions from hidden risks and poisons were presented as preventing millions of people from being able to buy their favorite medicines.

Public indifference to this campaign was replaced by widespread support after the Elixir Sulfanilamide disaster in 1937. A drug company had used diethylene glycol (a toxic syrup of antifreeze) to dissolve sulfanilamide into a pleasant-tasting elixir, without testing it or listing it as a new ingredient. Reports soon came in from around the country of patients dying after taking it. FDA inspectors went to the plant and learned that no safety tests had been done on the elixir because none were required, a telling rationale: if not required, there must be no need for tests; but if required, government would be seen as interfering with free enterprise and rapid access to beneficial drugs.

The FDA could not take legal action because deadly drugs were not illegal, only mislabeled drugs. The manufacturer responded to reports of deaths by stating that the elixir had been extensively tested before shipping, contrary to what FDA inspectors found. It said there was no clear proof the elixir had caused the deaths; however, the chemist who had added the antifreeze chemical committed suicide. FDA inspectors fanned out to try to collect all the bottles that had been shipped across the country, but not before 107 people had died. Suddenly, the public realized that the Pure Food and Drug Act did not require testing drugs for safety.

In the wake of the sulfanilamide disaster, Congress passed the 1938 Food, Drug, and Cosmetic Act. It required for the first time in the world that manufacturers test any new drug for safety and report the results before selling it. Although it seemed as if the government would finally be able to keep harmful drugs from patients, the companies could test for safety any way they wanted, without informing patients or keeping records. Further, approval was automatic unless the FDA had proof within sixty days that a new drug was dangerous.[11] Despite these weak provisions, the 1938 law began an era of replacing testimonials, anecdotes, and unfounded claims as "evidence" of safety with scientific testing.

The new law also made safety requirements less stringent if the drugs had to be prescribed by a physician. To ease its regulatory burden, the FDA began to assign most new drugs to the "prescription only" category, thus passing on responsibility for safety to physicians. Historian Peter Temin believes this change represented a loss in consumer sov-

ereignty and a new layer of regulatory gatekeeping by licensed physicians.[12] But the industry saw the advantages of having to market only to physicians rather than to the entire nation and vigorously promoted the institutional construction of "prescription drugs" as a prevalent legal and commercial category.

Companies hired thousands of sales reps to visit doctors personally and emphasize the benefits of each new drug. They created catchy names to replace that of the active ingredient and often used different names in different countries. This made protecting patients from safety more difficult, especially in Europe and Latin America, because a dangerous drug like thalidomide was marketed under different names in different countries so it did not have a single, readily identifiable name. Heavy marketing to the profession led to using brand names for medical training, educational materials, and the entire professional culture, in contrast to Great Britain, where the entire professional culture uses generic names, even for new drugs.

Company marketing directly to doctors and advertising revenues of the AMA journals grew rapidly, as did the art of professional persuasion by sales representatives, who developed personal friendships, left free samples of new products, and spent liberally on doctors. It takes 10–12% of revenues to sell products with no particular feature, like gum, candy, or soda; so one would expect much less would be needed to market products to professionals who know their real benefits.[13] Yet by the 1960s, the pharmaceutical industry was spending 20–24% of revenues to market to physicians, only one five-hundreth of the population that needs to be reached for gum or soda. Companies spent about four times more on selling than on doing research, yet created thousands of new drugs. Dr. Harry Dowling, an officer of the AMA, wrote, "In many fields there are too many drugs that differ so little that they are practically the same. Instead of 24 antihistaminic drugs, we would be better off with five or six and still have enough for vigorous competition. And there are hundreds of mixtures of drugs that have no excuse for being."[14] He estimated that each year 200 to 400 new drugs were launched, only three of which offered new benefits. The director of promotion for Parke-Davis testified in 1959 that the industry turned out 3,790,908,000 pages of journal advertisements and made 741,213,700 direct mail pieces, while its drug reps paid eighteen to twenty million visits to physicians and pharmacists

a year, plying them with free samples and favors.[15] By the 1960s, four-fifths of all medicines were prescribed by physicians who received most of their information about new drugs from sales reps, not from the FDA or independent sources.[16] These patterns of flooding the market with drugs that offer few new benefits and surrounding physicians with promotional information have characterized the relationship between the pharmaceutical industry and society to this day.

STREPTOMYCIN

The institutional challenges of safeguarding the public from unsuspected risks are illustrated by the case of Streptomycin, the first antibiotic to successfully treat tuberculosis. Although the drug saved thousands of lives, it had serious and sometimes fatal side effects; yet Parke-Davis promoted it as a miracle drug for many other uses where benefits to offset harms were unclear. When adverse reactions were first reported to the company, it ignored or denied them and continued to market the drug aggressively in a pattern very similar to Merck's response fifty years later to reports of cardiovascular trauma from taking Vioxx.[17] Sales catapulted Parke-Davis from minor to major status among the world's largest pharmaceutical companies.

Reports of severe reactions and death came in daily to the FDA, but at that time it had no systematic safety monitoring system to collect and evaluate adverse event reports. Finally, in 1952, the FDA pressured Parke-Davis to add a few lines of fine print about the side effects and to send out a letter to all physicians. As is typical of company letters required by the FDA, it understated the risk by saying there had been a few reports of blood problems but they were unproven and extremely rare.[18]

Outside the United States, the company continued to promote Streptomycin with no warnings. More reports came in of patients dying, and the FDA pressed for the company to take further action. Parke-Davis kept minimizing the evidence and urging doctors to prescribe it "for the treatment of any disease as they see fit." Deaths mounted, lawsuits proliferated, and independent studies affirmed the dangerousness of the drug; but doctors kept prescribing it until the company stopped marketing it because it went off patent. Hilts concludes, "The FDA again and again was unable to bring itself to restrict the use of the drug."[19] Thus as the modern pharmaceutical industry grew after World War II, it infused

the FDA with a pro-industry culture that undermined the agency's ability to protect patients from unsuspected risks.

This case contains many of the elements of the thalidomide disaster but ten years earlier: a drug with serious side effects marketed for several uses of unproven benefit that exposed millions to its risks, repeated denials that patients were being harmed, and continued marketing as more patients were harmed.

A DRUG CRISIS AND THE MODERN FDA

The ambitious populist Senator Estes Kefauver held hearings in the late 1950s highlighting the greed of several industries that exploited the common man, including the drug industry. Testimony by industry leaders and critics at his hearings generated headline after headline about how customers were charged up to 1800% more than cost, how companies spent much more on marketing than they did on research to develop better drugs, how they underplayed the seriousness of toxic side effects, and how many new drugs were known by companies to have no benefit but could be successfully marketed.[20] The former medical director of Squibb testified that for half of all new drugs, "it is clear while they are on the drawing board that they promise no utility; they promise sales."[21] The FDA had no authority to regulate the behavior of physicians or prices. Kefauver wanted the FDA to give generics memorable names rather than names that were difficult to pronounce or remember. FDA officials had no interest. He recommended that each drug company be licensed, subject to renewal after review. FDA officials opposed the idea. The chief of the antibiotics division was found to have received $287,000 (at least $2.2 million in today's dollars) from companies who advised him how to decide issues. A medical officer at the FDA said officers of companies had more influence with FDA officials than its own medical staff, a pattern found in later decades as well. An expert in pharmacology said drugs were approved without rigorous testing, resulting in patients being damaged and twenty-four drugs being recalled.[22]

Kefauver asked questions: Why does the FDA itself not supply doctors with objective, scientific information on new drugs? Why does the FDA not prohibit the proliferation of thousands of Madison Avenue brand names? Why does the FDA itself not send out warning letters

to physicians rather than having companies write them? And why does the FDA not concern itself with pricing and value rather than allowing patients to be charged exorbitant prices for medicines their doctors tell them they need? Through such questioning Kefauver outlined what good government could do to minimize bodily and financial risk to patients. Industry leaders responded as they have ever since, that such actions would keep patients from benefiting from innovations and would thus leave untreated patients to suffer or die.

Kefauver's strong reform bill gave the FDA oversight of systematic testing for efficacy and safety before approval. The AMA, by then so dependent on pharmaceutical revenues for advertisements and sponsorships that it had closed down its program to test and approve drugs in the 1950s, joined the industry in opposing it.[23] Senior officials and pharmaceutical leaders again removed oversight of advertising and weakened requirements to prove efficacy. But people's trust in the pharmaceutical industry had declined. Kefauver had shown the industry could not be trusted to regulate the safety of its own products and a stronger FDA was needed to protect patients from risks.

THALIDOMIDE — CONCERN FOR SAFETY PREVENTS DISASTER

In the middle of these negotiations, the thalidomide disaster hit the papers. In Germany, the Grünenthal pharmaceutical company had discovered that thalidomide had a calming effect in lab rats and paid doctors to "test" it by prescribing it to their patients — an example of fusing marketing with testing.[24] Their anecdotal reports varied, from glowing success to concern about dangerous side effects. The company then used the glowing reports to mass-market thalidomide in Europe and Africa. When doctors wrote in about nerve-based side effects, court records later showed, the company wrote back expressing surprise, saying it was the first time they had heard of it, just as Parke-Davis and others had done before.[25]

Two American pharmaceutical companies tested it, found it to have toxic side effects, and decided not to market it; but a subsidiary of Vicks, maker of VapoRub and cough drops, signed on. Vicks and Grünenthal decided that marketing thalidomide to women for reducing nausea during early pregnancy would generate additional sales, though no clinical trial was done to test this off-label use. Instead of testing thalidomide

in pregnant women, they felt it would be more effective to have a physician write an article in the *Journal of Obstetrics and Gynecology* testifying that it worked well in pregnancy. An obstetrician, the friend of a Vicks executive, agreed to write the article and claim that thalidomide had been tested, though court records later showed he did not keep records of how many pills he dispensed to whom.[26] He let the company's medical director write the article for him, an early example of a ghostwritten journal article on the alleged safety and efficacy of a new drug. To further market it, Vicks sent half a million pills to more than twelve hundred doctors, many at teaching hospitals, to try out as a "pre-approval trial." Neither the company nor most of the physicians kept records of which patients took the drug or its effects.

A new FDA medical officer, Frances Kelsey, had been given the thalidomide application as her first case. It seemed to be a simple sedative already widely used in Europe and Africa. Well trained in research, she did not like the glowing testimonials being used as "evidence" of safety and asked for better data. Neither company had tested the drug; it seemed much safer than barbiturates because no one was said to have reported side effects. Kelsey refused to approve it until the companies produced more evidence that it was safe. Company executives went over her head to pressure the FDA into approving the drug for the U.S. market. They provided more "evidence." The German company testified there were only thirty-four reported cases of adverse events; later investigations found they had received more than four hundred reports at the time. The American company sent distinguished physicians to testify how beneficial thalidomide was.

Meantime, the German company estimated that by the fall of 1961 at least four thousand babies had been born with "seal limbs," no bowel opening, no ear openings, or segmented intestines. It started quietly settling lawsuits in Europe, where it dropped "non-toxic" from its marketing materials, but it kept marketing thalidomide in Africa as "completely harmless."[27] Finally, one German doctor spoke out, causing a furor in the press. The company pulled thalidomide off the market, blaming a sensationalist press rather than itself for putting patients at risk. Neither company ever admitted there was a problem with the drug, and none of this information was made public to American patients. Frances Kelsey was still holding out against pressure from her superiors to

approve thalidomide so that American women could benefit from its innovative features.

When the FDA commissioner, George P. Larrick, learned of the widespread birth defects in Europe, he took no action to round up the pills that had been sent out to thousands of doctors as a "trial" but instead asked the American company what it wanted to do.[28] Kelsey insisted that FDA officers get a list of all the doctors from the company, but it had none. While these internal struggles about how the FDA should respond were taking place, Morton Mintz of the *Washington Post* broke the story: "Heroine of FDA Keeps Bad Drug Off Market."[29] Overnight, Kelsey went from being the obstinate medical reviewer keeping American mothers from enjoying the benefits of a drug widely used in Europe to being a model of the FDA's scientific ability and ethical mandate to protect American mothers and their babies from a tragic fate. Approved as a sleeping pill in forty-two countries, thalidomide caused an estimated ten thousand babies to be born with birth defects.

The Kefauver-Harris Amendment to the 1938 law that was passed in 1962 required the evaluation of old drugs, proof of effectiveness and safety for all new drugs *prior* to approval, disclosure of contraindications on their labels, overview of advertising, and reporting of all adverse effects made known to companies. Definitions of effectiveness and safety, according to Temin, were unclear and meant only what experts said they meant.[30] The FDA gained new powers to withdraw approved drugs if its experts considered them unsafe or lacking evidence of effectiveness. The subsequent review of old drugs demonstrated how extensively the risks of harm to patients had been privatized by companies in the past. About half were found not to be effective, evidence that companies devoted most of their efforts to developing clinically ineffective new drugs and then marketing them successfully as effective. While hundreds of prescription drugs were removed from use, hundreds more ineffective drugs stayed on and continued to be prescribed by physicians.[31]

For decades, the old patent medicine industry and the new research-based pharmaceutical industry had relied on testimonials and informal trials, with no controls, to test new drugs. When a drug was questioned, they still pressured FDA medical reviewers and their superiors for approval. James Goddard, the first person from outside the industry to be named commissioner of the FDA (in 1963), was so shocked at the

amateur, unprofessional, and dishonest submissions by companies of the tests on their most promising new drugs that he ordered FDA staff not to waste their time and immediately send back any such applications for resubmission.[32] Patients should not have to bear the risks of poorly tested drugs, he said.

Goddard brought in a new breed of well-trained research physicians and scientists to enable the FDA to carry out its mandates objectively and free of politics. Companies objected to clinical trials and protested that only "medical experience" could tell whether a drug worked and physicians should be the judges. This conflict underscored two different approaches to reliable knowledge and the view of the new FDA that doctors' clinical experiences can never be reliable because they lack the perspective of systematic sampling and controls to validate their personal observations with their patients. The U.S. Supreme Court supported this view in its interpretation of the act. Yet the current system relies heavily on doctors' individual clinical experience once a drug is approved, even though it is acknowledged that the safety of new drugs is not well known until they have been used for a while. In other words, the current system at its best permits a significant amount of risk to be shifted to patients and their doctors, as reflected in the proliferation of toxic side effects described in Chapter 1.

ANTI-REGULATORY BACKLASH

With the election of Richard Nixon in 1968, a sustained campaign began to place conservative Republicans within regulatory agencies. Nixon kept count of the number of Republicans and Democrats in the FDA and vowed to take "political control."[33] Six career officers with almost seventy years of combined FDA experience were transferred without cause or explanation to makeshift jobs. Eleven more reviewers known for their emphasis on patient safety later received abrupt transfers.

In August 1974, Senator Edward Kennedy organized a hearing about these actions, unannounced so that Nixon's FDA leader could not take preemptive action. The transferred officers testified about the double standard of being supported when they recommended approval but overruled when they recommended that new drugs not be approved because they posed serious risks to patients.[34] They experienced harassment and

being reassigned to marginal tasks. Evidence was found that FDA management had a policy to "neutralize" reviewing officers who were not "cooperative" with companies. These patterns persist in studies of review officers and industry influence. The net effect, of course, is to silence scientific debate and pass on risks of serious side effects to patients, rather than protecting them.

Starting in the mid 1970s, the pharmaceutical industry sponsored economists and conferences emphasizing how the heightened standards of safety and efficacy since the 1962 amendment were cutting into profits, reducing companies' ability to fund research, and keeping American patients from enjoying the benefits of new drugs that were approved more quickly abroad.[35] Millions of patients were dying, they claimed, because of the lag between when drugs were approved in the United Kingdom and in the United States.[36] These "drug-lag" studies, however, assume that all new drugs are better and therefore any delay harms patients, while in fact the FDA's research showed that only one in every nine new drugs in the 1960s and 1970s provided superior therapeutic benefits to existing ones.[37] From 1981 to 2006, this record improved a little to one in every seven new drugs offering substantial therapeutic advantages.[38] Delayed use of most equivalent drugs reduces risk of harm to patients, which is why the Health Research Group recommends waiting seven years before taking a new drug unless there is no substitute and a patient needs it. A study by the Group found that after higher standards for testing and safety were put in place in 1962, the United States had one-third as many drugs pulled from the market because of their toxic side effects as did France, Germany, and the United Kingdom.[39]

In 1980, the General Accounting Office issued a detailed report on the "lengthy process that delays the availability of important new drugs."[40] It found, in fact, that companies themselves caused many of the delays by not providing vital information to reviewers, by turning their attention to other drugs, by mishandling their applications, and by not responding to legitimate questions from FDA reviewers. The severe lack of staff at the FDA also caused delays as the reviewers got pulled away to do other tasks and handle unexpected safety problems.

The "crisis of overregulation" never calculated the benefits of FDA reviews to patients and to industry in *not* approving dangerous drugs. The costs of harm from weaker regulation were not estimated either.

Budget cuts of the FDA started under President Carter. President Reagan issued Executive Order 12291 and took over control of all regulations from Congress. Anti-regulation leaders found myriad ways to reduce safety inspections as they did across the board in "the great risk shift" to individuals in the name of greater choice.[41] Reagan's Office of Management and Budget drew up a list of the "terrible twenty" regulations for classifying hazardous waste and pollutants and for giving patients more information about drugs in package inserts. Arthur Hayes, a highly paid consultant to drug companies, was selected as commissioner of the FDA and immediately turned to cancelling the new program to provide information directly to patients about the drugs they were taking, a program the pharmaceutical industry fiercely opposed. FDA staff was cut from 7,960 in 1978 to 6,960 in 1987 at the same time that the FDA was assigned more tasks in overseeing one-fifth of the U.S. economy. Seizures and prosecutions dropped from 500 to 173, leaving the industry to regulate itself. It responded by decreasing its voluntary actions by 800 a year.[42] This recent history makes clear again that privatizing risk does not mean that industry will protect patients by policing itself.

Despite the cuts in staff and resources, and in response to the anti-regulation campaign, the FDA worked hard during the 1980s to speed up reviews by helping companies complete their applications properly, by working with company researchers to get quicker responses to questions or missing data, and by tightening the review process. One obstacle was the continued lack of professional submissions by companies that Goddard had found in the early 1960s. A survey of FDA reviewers in the mid 1990s published in *Pharmaceutical Executive* reported that a third of drug applications "were essentially unreadable and could not even be considered."[43] The reviewers considered only 30% to be good and 7% excellent.[44]

Working with companies and improving review procedures paid off. The average time for standard reviews dropped from thirty-three months in 1987 to nineteen months in 1992, then to sixteen months by 1994. Nevertheless, Representative Newt Gingrich launched a campaign through his Progress and Freedom Foundation to eliminate the FDA. The Washington Legal Foundation published ads claiming that delays in approval had killed at least twenty-five hundred kidney cancer patients who could not get Interleukin-2 while the FDA reviewed

the drug and caused fourteen thousand patients to have heart attacks because they could not benefit from the CardioPump during its two-year review.[45] The facts did not support these allegations, and industry leaders became worried that the vitriolic attack could kill the goose (the FDA) that was laying the golden eggs, FDA-approved drugs. FDA procedures could hardly have been regarded as hostile to the industry. On the contrary, as described in Chapter 1, they let through a substantial number of drugs that had serious risks. Thomas Moore of George Washington University estimated that lifetime chances of severe injury from auto accidents were two in one hundred but twenty-six in one hundred from prescription drugs.[46] Hearings in May 1996 led to the campaign being discredited and the bill dying in committee, but they highlighted the business view that the less regulation the better so that new products can get on the market quickly.[47] The way to maximize product availability is not to regulate at all; let companies develop what drugs they want, test them as they see best, and sell them. This view is put forward by industry-friendly authors and journalists to this day, without consideration that uncertainty surrounds the risks of all new drugs and only a few provide offsetting advantages.[48]

INDUSTRY FUNDS ITS REGULATOR

The FDA became so demoralized and overburdened that the industry itself became concerned lest the benefits of having their products approved by a respected agency become compromised.[49] It created an FDA advocacy council to find ways to improve regulatory operations. The solution that emerged was a "user fee" system: companies would pay for each new drug application, which would provide much-needed money to hire more than two hundred new reviewers. The Prescription Drug User Fee Act (PDUFA) became law in 1992.

The industry, in return for paying large fees to substitute for Congress adequately funding the FDA, required in 1992 (PDUFA I) that 90% of reviews for all priority drugs and supplements be completed in less than six months and those for standard drugs and supplements in less than twelve months. It also required that all fees go to reviewing new drugs for approval and "specifically prohibited the use of fees for any postmarketing drug safety activities."[50] Unlike the fixed-fee schedule

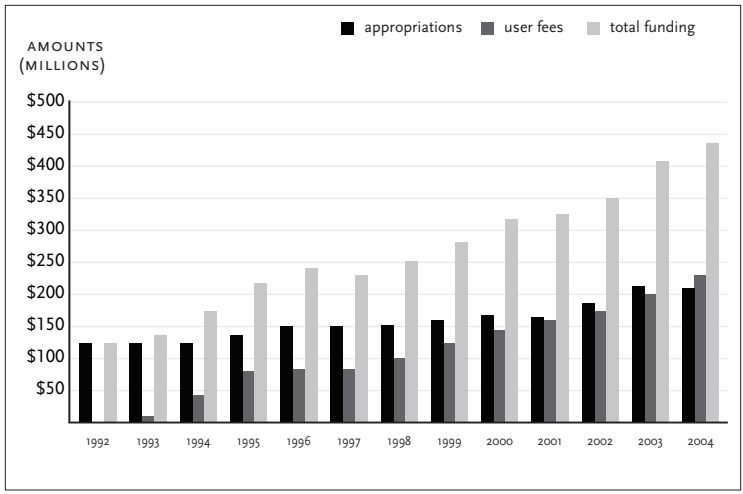

Figure 2.1 Rise of corporate fees as proportion of total FDA funding

[Source: Institute of Medicine, Committee on the Assessment of the US Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, DC: National Academies Press, 2007), 194]

used in Europe, the industry set up PDUFA so that it could renegotiate further conditions in return for its fees every five years. For the 1998–2002 continuation (PDUFA II), the pharmaceutical industry accelerated reviews of standard products to 90% in ten months and added several new requirements that FDA staff respond more quickly and fully to industry requests for meetings and resolving disputes.[51] Corporate fees have gone from about one-tenth of total FDA funding to more than half (figure 2.1).[52]

The accelerated reviews—often based on short-term surrogate or substitute changes instead of true clinical improvement—combined with mass-marketing of these new medications for uses approved and unapproved, created a dangerous situation.[53] An estimated twenty million or more Americans were exposed to drugs approved under PDUFA I that were then withdrawn soon after for their severe adverse effects. Warnings were added to many others.

A case in point was the diabetes drug Rezulin. After the FDA reviewer Dr. John Gueriguian pointed out that it offered no substantial advantages over the other eight diabetes drugs already on the market

but showed signs of liver toxicity, Warner-Lambert officers went over his head to FDA officials and pressured them to remove him from the case, just as companies have done so many times before, including the attempt to remove Frances Kelsey from the thalidomide case. Time and again, FDA reviewers and scientists carry out rigorous, scientific assessments but are overruled or barred or removed if they believe that safety risks are enough to rule out drug approval. As reports of deaths began to come in, the British Medicines Control Agency banned Rezulin. The FDA considered one kind of warning, negotiating a series of labeling changes and letters to doctors asking for increasingly more liver monitoring—which were largely ignored as the death toll mounted over the next year and a half.[54] Only after Warner-Lambert developed a second drug in the class that was approved and found not to cause liver damage did the company stop marketing Rezulin. Thus both the review before approval and response to serious harm afterward were compromised by not having a regulatory body not subject to industry influence. The professionals were there, capable and dedicated, but the upper echelons did not support their work.

In response to growing criticism and the rash of new drugs doing serious damage to patients, the FDA organized a task force; it "identified process, resource, and statutory constraints on [the] FDA's ability to identify adverse events."[55] Finally, in the 2002 renewal for 2003–2007 (PDUFA III), "limited funds were allocated for limited safety activities."[56] Then the Vioxx disaster occurred and set off major congressional hearings as well as a full-press review by the Institute of Medicine (IOM) that resulted in major recommendations for organizational, legal, and cultural changes.[57]

The IOM concluded that the "FDA does not have adequate resources or procedures for translating preapproval safety signals [evidence of harm to patients] into effective postmarketing studies, for monitoring and ascertaining the safety of new marketed drugs, for responding promptly to the safety problems that are discovered after marketing approval, and for quickly and effectively communicating appropriate risk information to the public."[58] In other words, the FDA was not capable of protecting patients from harmful risks in the drugs they take. This conclusion is supported by key themes and documentation in Chapter 1. Some reports go further. Two investigative reporters, for example, wrote

a three-part series in 2003 describing the extent of off-label or unauthorized use that makes the forty-year effort to assure that drugs are safe and effective irrelevant.[59] Byron Richards describes how the Bush administration appointed industry advocates to key FDA positions so that accelerated reviews could be combined with blocking patients from suing for damages from resulting injuries.[60]

The industry-required speed-up has resulted in substantially more risk for patients from drugs approved in the last two months before the tightened deadlines than drugs approved earlier, presumably because there were more concerns about them but not enough time to resolve them. According to a study at Harvard, deadline-crunch approvals have resulted in drugs being put on the market that are three times more likely to result in toxic effects leading to severe, black-boxed warnings because of serious harms and being pulled from the market altogether, compared to drugs that the FDA had no trouble approving within the time allotted.[61]

PARTIAL STRENGTHENING OF SAFETY PROTECTION

Questions about the ability of the FDA to ensure the safety of approved medicines[62] led Congress to pass in 2007 an historic set of changes to strengthen protection in the Food and Drug Administration Amendments Act (FDAAA), which gave the agency new regulatory power, more money, and safety-related mandates.[63] The IOM drug safety panel members noted that Congress "responded in full" to the recommendations of their committee but were more critical of the FDA's own response that preceded FDAAA.[64]

The new act requires the FDA to develop rigorous safety measures and to evaluate at regular intervals the risk minimization action plans of companies. It provides the authority to require post-market studies, label changes, and restrictions on distribution when deemed necessary, with substantial penalties. A safety officer is assigned to each of the seventeen groups that evaluate new drug applications. A national sentinel system is being developed that will combine patient data from a number of large health systems to identify and evaluate risks and harms through analysis of clinical data. This is part of a larger set of activities to implement the Institute of Medicine's lifecycle approach to drug safety—testing for safety not just before approval but through each phase of a drug's life.[65]

Despite the agency's new safety initiatives, "Major obstacles remain. They include inadequate resources, the complexity of the science, . . . a dysfunctional organizational culture, problems with credibility and public trust, and the lack of adequate communication about and limited public awareness of drug risks and benefits."[66] The FDA has "computer systems so old that repairmen must be called out of retirement to fix them."[67] It has vital information on databases that are incompatible with each other. It has too few inspectors to monitor the quality of active ingredients as well as the fillers, binders, coatings, and syrups used in drugs; four-fifths of these are imported, mostly from uninspected chemical plants throughout Asia.

Although the "culture of safety" that the IOM emphasized has begun to develop, counterbalancing the substantial gains, "the very structure of the FDA marginalizes safety."[68] Regulatory authority to take action when patients experience toxic side effects still rests with the division that approved the drug. Decisions on safety-related labeling changes, warnings, and even the design and evaluation of epidemiological safety and risk management studies can still be done without the input of epidemiology safety specialists, who serve on a consultancy basis, only when called upon. Even when safety officers are called in, the tug-of-war between the public health perspective—on managing risks and benefits across all users—and the more narrow medical perspective of treating an individual patient with the drug results in conflicting professional opinions. Internal disagreements are often quashed or ignored, the most egregious playing out on the front pages of leading newspapers and in congressional testimony, as the agency struggles to present a unified front amid scientific uncertainty.

The FDA has quickly moved into the business of meeting its new statutory requirements. The scale of change, including the development of completely new systems and processes, is daunting, and the FDA is now hiring hundreds of new scientists and inspectors. Will the FDA be able to hire the highly specialized workforce that it needs to do the job? Its science infrastructure is dated and weak, victim of years of underfunding; the FDA science board has only half the funding it needs.[69] Hiring and retaining good people is frustrated by salaries that are about half those in industry and by the weakening of the once-legendary federal pension system. This, plus strict rules against stock ownership among FDA employees, almost

assures that the flow of well-trained regulatory scientists is in just one direction—from FDA to industry. Fully funding the FDA would cost about four cents per person per day, or $4.38 billion.[70]

In 2008, two congressional leaders concluded that the extensive reforms of 2007 were not enough. Senator Charles Grassley and Representative John Dingell called for restructuring the FDA to "build a much taller wall between the agency and the industry it regulates."[71] The FDA needs the power to recall drugs and impose stiff fines, and new leadership must "fix the culture." Safety reviewers should have "complete autonomy," Senator Grassley said. Senator Arlen Specter called the FDA "a joke." A staunch defender of the FDA, Peter Barton Hutt no longer will defend it: "This is a fundamentally broken agency," he told the *New York Times*.[72] A score of congressional investigations into specific issues have been started, such as paying physicians for each injection of powerful drugs, industry influence on professional education, and paying generic manufacturers not to put a drug on the market.

It would be fair to say the picture is mixed. On one hand, the FDA has become much more serious about protecting patients from risks. It has issued blanket warnings, for example, against whole classes of drugs for small children, and it has finally taken seriously evidence that the whole class of antidepressants known as SSRI drugs, based on surrogate end points, are not very effective and have serious side effects. It has moved swiftly when poisonous foods are discovered, and it has become much more worried about the safety of active ingredients imported from China and elsewhere that go into most drugs Americans take. On the other hand, drug safety was not given its own organizational division or the kinds of powers that leading experts and physicians said were necessary to protect patients from serious risks. Up-against-the-deadline approvals still continue, when the rules could be amended to allow more time for FDA reviewers when they need it to complete a good assessment of the one drug in every three to four that has unresolved concerns. Most important, Congress has not yet fully funded the FDA, so it remains the guardian against hidden risks funded by the industry it monitors. Full funding for independent safety regulation would be a bargain, given that the FDA is the public's guardian for one-fifth of the economy, the fifth that we take into our bloodstreams.

APPENDIX

TESTING DRUGS: NO CLEAR MEASURES OF SAFETY

Today's drug approval process is highly scripted, with volumes of regulatory documents to guide product testing and contents of the new drug application and a schedule for meetings and regulatory decisions. FDA approval to market a new prescription medication requires that companies conduct extensive studies in animals and in humans, which takes years and costs millions of dollars. Sponsors must provide the FDA with "substantial evidence" of the drug's effectiveness from well-controlled clinical trials and of the drug's safety relative to the benefits that can be derived when prescribed for the intended or labeled condition(s).[73]

The process begins with a sponsor (usually a pharmaceutical company) submitting an Investigational New Drug (IND) application with proposed trial designs; a review team from one of seventeen disease- or treatment-based divisions of the Office of New Drugs reviews the application within thirty days to see if there are safety concerns.[74] Phase 1 trials test different doses in a small number of healthy subjects to measure safety and tolerability. In Phase 2, companies carry out clinical investigations in 40–400 patients to administer different doses in order to measure efficacy, safety, and tolerability (in ways described in Chapter 1 to maximize evidence of effectiveness and minimize evidence of toxic side effects). Phase 3 trials usually involve about 400–2,000 patients each, randomly assigned to take the new study drug or a placebo, typically without the patients knowing which they are using, to test more formally for efficacy, safety, and tolerability.

It is commonly said that drug development takes twelve to fifteen years. However, preclinical development usually takes two to three years and is relatively inexpensive. The average time for trials has declined in recent years from under six years to less than three, and FDA review is now six to ten months.[75] Thus drug development time is six to seven years, while the time it takes to discover a new drug has never been documented but appears to vary from a few months (for example, the discovery of Viagra as a side effect of a heart drug) to years of research by multiple teams as they run into dead ends and false discoveries before finally identifying an active ingredient that works.[76] Most basic research and funding of discovery is funded by taxpayers.[77] To say that it takes twelve to fifteen years to develop a drug is therefore inaccurate, and

no verifiable data support this industry estimate. Costs are commonly estimated to be $1–2 billion, based on unverified industry data, often analyzed by industry-supported economists.[78] Independent data, such as companies' audited tax returns and FDA data on trial sizes, suggest that median net corporate costs are about one-tenth these estimates.[79] Trials are shortest and corporate costs are lowest for cancer and AIDS drugs, yet they are priced the highest.[80] About eight to nine out of every ten drugs that enter clinical trials are withdrawn by the company, usually because test results or commercial potential are considered insufficient.

When trials are completed, a final New Drug Application (NDA) is submitted, often in a rolling fashion involving twenty-four to seventy partial submissions containing two hundred thousand pages of material.[81] The FDA review team first determines if elements are missing and asks for them. Once the application is determined by the FDA to be complete, final review begins. This drug-review system "inevitably puts drugs on the market when safety information is incomplete,"[82] not just for rare side effects but also for those which occur under common but untested conditions, such as long-term usage or interactions with foods or other drugs. Although NDAs often have evidence of a therapeutic benefit for acute diseases, for chronic conditions, benefits are typically based on surrogate or substitute endpoints and a research model that may or may not benefit hard clinical endpoints.[83] Thus, as part of approving a drug, the FDA often outlines Phase 4 postapproval trials or studies to gather further information on safety and effectiveness. Most, however, are not started, and few are completed. An FDA analysis in 2006 found that companies had completed only 11% of 1,259 agreed-on studies.[84] These studies would have provided valuable information about the risks passed on to patients. On the other hand, companies conduct many new studies to gather data supporting wider, off-label uses and marketing efforts for approved drugs.

Although the approval decision is often couched in terms of weighing a drug's benefits against its adverse side effects, or calculating a "risk-benefit ratio," the approval decision-making process is no mathematical exercise. There are standard methods for quantifying or comparing risks and benefits and no scale that could allow comparison between drugs. The risk-benefit ratio is a qualitative judgment made by experts based on available data that is largely generated and presented by the sponsoring company.

An adverse event that occurs rarely, in just one person out of every one thousand persons using a medication, will result in about five hundred events among one-half million people taking the drug, or ten thousand adverse events for every ten million patients taking a drug. For example, commonly used nonsteroidal anti-inflammatory drugs (NSAIDS), which include aspirin and acetaminophen, cause gastrointestinal (GI) bleeding in approximately 7.3 and 13 per 1,000, respectively, among persons with osteoarthritis and rheumatoid arthritis.[85] Although the risk seems small, half of the estimated 200,000–400,000 annual hospitalizations for GI bleeding involve NSAIDS. An estimated 16,500 NSAID-related deaths occur annually just among patients with rheumatoid arthritis or osteoarthritis.[86]

Benefits are multidimensional and may occur quickly (e.g., symptom relief) or many years in the future (e.g., preventing disease or future disability). Benefits need to be considered in terms of the type of disease being treated, the impact of the active ingredient on the disease, how the disease progresses without treatment (its natural history), and alternative treatments already on the market. Risks are typically considered in terms of frequency, severity, preventability, and predictability. For cancer treatments a high rate of toxicity is often an acceptable trade-off against a chance of longer survival. Conversely, for drugs that offer limited benefits, such as relief of headache or cold symptoms, less risk is tolerated by reviewers. Somewhere in between are drugs for which risks may be acceptable among a unique group of patients, under specific circumstances (e.g., failure of all other treatment options), or where risk can be reduced, avoided, or prevented with intervention. These trade-offs are illustrated in figure 2.2. In such cases, the FDA may require some type of risk management program, which can range from patient education (with or without a required paper trail) to required, continuous monitoring of physiologic measures to determine if the medication can be taken by the patient.

In some situations, particularly when evaluating drugs for imminently life-threatening conditions, treatments for rare conditions, and perhaps in some circumstances for patients who have exhausted all approved treatment options, the current bar may be appropriate. For drugs for common chronic conditions, such as hypertension, diabetes, pain, and obesity, with the potential to be quickly prescribed to large

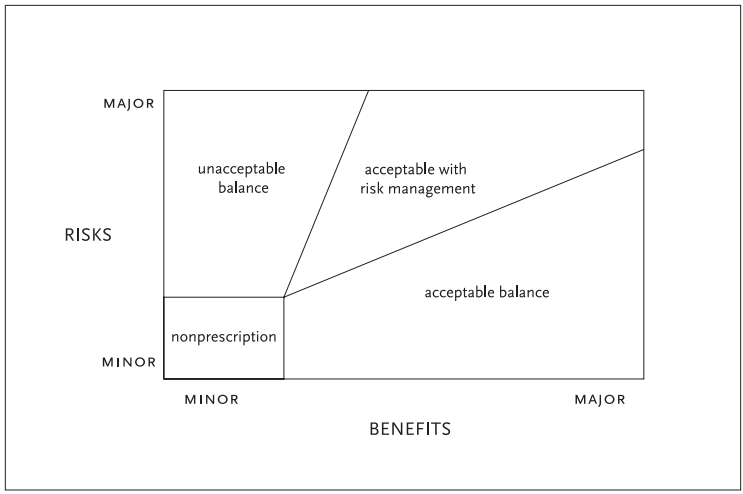

Figure 2.2 Weighing the benefits and risks of prescription medications
[Source: CIOMS IV (1998), adapted in S. R. Weiss, "Approaches to Quantifying the Risk/Benefit Balance" (FDA visiting lecture, Rockville, Maryland, January 11, 2005)]

numbers of people upon approval, the current bar is too low to prevent widespread adverse effects from occurring.[87] It puts all decision making where it has traditionally resided—with the physician (prescriber) and the patient. However, because preapproval studies are not designed to evaluate risks of long-term usage nor typically overall survival, vital information that is needed to make a truly informed decision is often unavailable or nonexistent sometimes years after approval.

Historically, the FDA has applied a perspective that can lead to millions of patients being exposed to unsuspected risks when making benefit-risk evaluations. Reviewers ask, "Are there patients whom physicians might conceivably see in their clinical practice, for whom the benefits would outweigh the risks?" Many times the answer is yes: some physicians have some patients who might benefit. But this permissive criterion does not consider how an approved drug is then marketed to as many physicians as possible for them to prescribe it for as many patients as possible—the risk proliferation syndrome (see Chapter 1).

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