Chapter 1

DEATH BY BUREAUCRAT

How would you rather die? From a lethal reaction to a drug prescribed by your doctor? Or because your doctor failed to prescribe a drug that would have saved your life? If this choice sounds like one you would rather not make, consider this: Employees of the Food and Drug Administration (FDA) make that decision on behalf of millions of Americans many times each year. More precisely, FDA bureaucrats decide whether or not new medicines (prescription drugs) should be allowed to go on sale in the United States. If the FDA rules against a drug, physicians in America may not legally prescribe it, even if thousands of lives are being saved by the drug each year in other countries.

The FDA's authority to make such decisions dates back to the passage of the Food and Drug Safety Act of 1906. That law required that medicines be correctly labeled as to their contents and that they not contain any substances harmful to the health of consumers. Due to this legislation, Dr. Hostatter's Stomach Bitters and Kickapoo Indian Sagwa, along with numerous rum-laden concoctions, cocaine-based potions, and supposed anticancer remedies, disappeared from druggists' shelves. The law was expanded in 1938 with the passage of the Food, Drug, and Cosmetic Act, which forced manufacturers to demonstrate the safety of new drugs before being allowed to offer them for sale. (This law was prompted by the deaths of 107 people who had taken Elixir Sulfanilamide, an antibiotic that contained poisonous diethylene glycol, a chemical cousin of antifreeze.)

The next step in U.S. drug regulation came after a rash of severe birth defects among infants whose mothers during pregnancy had taken a sleep aid known as thalidomide. When these birth defects first became apparent, the drug was already widely used in Europe and Canada, and the FDA was nearing approval for its use in America. In fact, about 2.5 million

thalidomide tablets were already in the hands of U.S. physicians as samples. The FDA ordered all of the samples destroyed and prohibited the sale of the drug here. This incident led to the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act, radically altering the drug-approval process in the United States.

Prior to the 1962 amendments, the FDA was expected to approve a new drug application within 180 days unless the application failed to show that the drug was safe. The 1962 amendments added a "proof of efficacy" requirement and also removed the time constraint on the FDA. The FDA has free rein to determine how much and what type of evidence it will demand before approving a drug for sale and thus may take as long as it pleases before either granting or refusing approval.

The 1962 amendments drastically increased the costs of introducing a new drug and markedly slowed the approval process. Prior to 1962, for example, the average time between filing and approval of a new drug application was seven months; by 1967, it was thirty months; and by the late 1970s, it had risen to eight to ten *years*. The protracted approval process involves costly testing by the drug companies—$800 million or more for each new drug—and delays the receipt of any potential revenue from new drugs. Because this reduced the expected profitability of new drugs, fewer of them have been brought onto the market.

Debate continues over how much FDA regulation is needed to ensure that drugs are both safe and efficacious, but there is little doubt that the 1962 amendments have resulted in a U.S. "drug lag." On average, drugs take far longer to reach the market in the United States than they do in Europe. Admittedly, it takes time to ensure that patients benefit from, rather than are harmed by, new drugs, but regulation-induced drug lag can itself be life-threatening. Dr. George Hitchings, a winner of the Nobel Prize in Medicine, has estimated that the five-year lag in introducing Septra (an antibiotic) to the United States killed 80,000 people in this country. Similarly, the introduction of a class of drugs called beta blockers (used to treat heart attack victims and people with high blood pressure) was delayed nearly a decade in America relative to Europe. According to several researchers, the lag in the FDA approval of these drugs cost the lives of at least 250,000 Americans.

In effect, the law requires FDA bureaucrats to make what is truly a terrible trade-off. Lives are saved because unsafe or ineffective drugs are kept off the market, but the regulatory process delays (or even prevents) the introduction of some safe and efficacious drugs, thereby costing lives. Let us now take a more systematic look at this trade-off.

Every time a new drug is introduced, there is a chance that it should not have been—either because it has adverse side effects that outweigh

the therapeutic benefits (it is not safe) or because it really does little to help the individuals who take it (it is not effective). When such a drug is introduced, we say that a **Type I error** has been committed. Since 1962, the incidence of Type I error—the thalidomide possibility—has been reduced by the added testing required by the FDA. But other people have been the victims of what is called **Type II error.** Their cost is the pain, suffering, and death that occur because the 1962 amendments have prevented or delayed the introduction of safe, efficacious drugs. Type II error—as with Septra or beta blockers—occurs when a drug *should* be introduced but is held back by FDA regulation.

Over the past twenty or thirty years, outcries over the harm caused by the drug lag have in some cases induced the agency to shorten the testing period when the costs of Type I error are small relative to the damages due to Type II error—as in the case of terminally ill patients. One famous example involved azidothymidine (AZT), which emerged as a possible treatment for AIDS. Gay men, among whom AIDS was most prevalent at the time, took the lead in pressuring the FDA to approve the drug quickly, and the FDA responded accordingly, giving it the OK after only eighteen months of testing. Similarly, Taxol, an important new drug used to treat breast cancer, received expedited review by the FDA, in this case because of pressure applied by women in whose families there was a history of breast cancer. The FDA now has a formal program in which it seeks to expedite testing for drugs that seem to offer great promise for alleviating death or suffering. Nevertheless, although the average approval time for new drugs has shortened considerably, it still takes more than ten times as long for a new drug to be approved as it did before the 1962 amendments.

What can we learn from the FDA regulation of new drugs that will guide us in thinking about other public issues of our time? There are several key principles:

1. *There is no free lunch.* Every choice, and thus every policy, entails a **cost**—something must be given up. In a world of **scarcity,** we cannot have more of everything, so to get more of some things, we must give up other things. Although FDA review of drugs saves lives by preventing the introduction of unsafe or ineffective drugs, the cost is billions of dollars of added expenses, plus delayed availability of safe and efficacious drugs, resulting in the deaths of hundreds of thousands of people.

2. *The cost of an action is the alternative that is sacrificed.* Economists often express costs (and benefits) in terms of dollars because this is a simple means of accounting for and measuring them. But that doesn't

mean that costs have to be monetary, nor does it mean that economics is incapable of analyzing costs and benefits that are quite human. The costs that led to the 1938 and 1962 amendments were the very visible deaths caused by sulfanilamide and the terrible birth defects due to thalidomide. Subsequent revisions to the FDA process for reviewing drugs, as with AZT and Taxol, have been in response to the adverse effects caused by the regulation-induced drug lag.

3. *The relevant costs and benefits are the marginal (incremental) ones.* The relevant question is not whether safety is good or bad; it is instead how much safety we want—which can only be answered by looking at the added (marginal) benefits of more safety compared to the added (marginal) costs. One possible response to the sulfanilamide poisonings or thalidomide was to have outlawed new drugs altogether. That would guarantee that no more people would be harmed by new drugs. But surely this "solution" would not be sensible, because the marginal cost (due to higher Type II errors) would exceed the marginal benefit (caused by reduced Type I errors).

4. *People respond to incentives.* And this is true whether we are talking about consumers, suppliers, or government bureaucrats. Here the incentive to amend the law in 1938 and 1962 was the very visible death and disfigurement of individuals. The eventual FDA decision to speed up the review process was prompted by intense lobbying by individuals who believed (correctly, as it turned out) that they might be benefited by drugs not yet approved.

5. *Things aren't always as they seem.* Many analyses of the effects of government policies take an approach that doesn't fully recognize the actions that people would otherwise have taken. Thus official pronouncements about the effects of policies routinely misrepresent their impact—not because there is necessarily any attempt to deceive but because it is often difficult to know what would have happened otherwise. Pharmaceutical manufacturers, for example, have strong incentives to avoid introducing drugs that are unsafe or ineffective because the companies are subject to loss of reputation and to lawsuits. For similar reasons, physicians have strong incentives to avoid prescribing such drugs for their patients. Even without FDA regulation, there would thus be extensive testing of new drugs before their introduction. Hence it is incorrect to ascribe the generally safe and effective nature of modern drugs entirely to FDA protection. The flip side, however, is that the drug development process is inherently long, complicated, and costly. Even without FDA oversight, some people would die waiting for new drugs because self-interested

manufacturers would insist on some testing and cautious physicians would proceed slowly in prescribing new drugs.

The people who work at the FDA (and members of Congress) are publicly castigated when they "allow" a Type I error to occur—especially when it is a drug that kills people. Thus FDA bureaucrats have a strong incentive to avoid such errors. But when testing delays cause a Type II error, as with Septra, it is almost impossible to point to specific people who died because the drug was delayed. As a result, officials at the FDA are rarely attacked directly for such delays. Because the costs of Type II errors are much more difficult to discern than the costs of Type I errors, many observers believe that there is an inherent bias at the FDA in favor of being "safe rather than sorry"—in other words, excessive testing.

6. *Policies always have unintended consequences, and as a result, their net benefits are almost always less than anticipated.* In the case of government regulations, balancing incremental costs and benefits (see principle 3) fails to make good headlines. Instead, what gets politicians reelected and regulators promoted are *absolute* notions such as safety (and motherhood and apple pie). Thus if a little safety is good, more must be better, so why not simply mandate that drug testing "guarantee" that everyone is free of risk from dangerous drugs? Eventually, the reality of principle 3 sinks in, but in this case not before the drug lag had killed many people.

As is often true with important public issues, our story has one more interesting twist. Thalidomide is back on the market. In 1998, it was approved by the FDA for use in treating Hansen's disease (leprosy), and in 2006, the FDA gave physicians the OK to use it in treating bone marrow cancer. In each instance, there are strong protections to prevent pregnant women from taking the drug. And so perhaps the very drug that brought us the deadly drug lag will turn out to be a lifesaver for a new generation of patients.

DISCUSSION QUESTIONS

1. Does the structure of the drug industry have any bearing on the types of errors that drug firms are likely to make? That is, would a drug industry made up of numerous highly competitive firms be more or less likely to introduce unsafe drugs than an industry consisting of a few large firms?