10.13 Drug Testing and Approval

Manufacturing prescription drugs is done on a colossal scale to meet patients' demands. About two billion prescriptions are filled annually in the United States, and worldwide sales of drugs come to about $300 billion a year and growing. But the pathway for a new drug from a laboratory to a pharmacy shelf is long and complicated. All proposed new drugs, whether extracted from natural materials or synthesized in the laboratory, are subjected to exacting series of tests before they obtain FDA approval. Current law requires evidence that the drugs are safe as well as effective before such approval is granted. The steps for approval are summarized in Figure 10.23.

From discovery to approval, the development of a new drug takes, on average, nearly twelve years and more than $350 million—over twice the cost of a decade ago. The expenses are principally for the various stages of drug testing, probably the most complicated and thorough pre-marketing process ever developed for any product. Although the number of pills getting through the funnel of Figure 10.23 gets progressively smaller with time, the diagram does not begin to convey the high mortality rate of proposed drugs. Currently, the odds of getting a candidate drug from identification to approval are
1 in 10,000. For every 10,000 trial compounds that begin the process, 20 make it to the level of animal studies, half that many get clearance for use in clinical testing with humans, and finally one gets FDA approval.

Examples already encountered in this chapter have suggested the long process of chemical hide-and-seek that often precedes the identification of a compound as possibly having therapeutic properties. Once the promising candidates have been identified, they are subject to in vitro studies, those carried out in laboratory flasks. Simultaneously, a wide range of activity is undertaken by the pharmaceutical company. Chemists and chemical engineers investigate whether the compound can be produced in large volume with consistent quality control. Pharmacists carry out studies of the most effective way to formulate the drug for administration—as capsules, pills, injection, syrup, or perhaps something more unusual such as a nasal spray, skin patch, or implant. Chemical stability and shelf life are evaluated. Economists, accountants, patent attorneys, and market analysts conduct research on the likelihood of deriving a profit from the product. A fair, responsible price must be established that allows the corporation to recapture the extensive development costs while keeping the drug affordable.

Only a small fraction of compounds survive this scrutiny to move on to animal testing. Such in vivo ("in life") tests are designed to determine the drug's efficacy, safety, dosage, and side effects. It is typically at this stage that pharmacologists determine the drug's mode of action, how it is metabolized, and its rate of absorption and excretion. The tests are carefully controlled, requiring the collection of very specific kinds of data. For example, drugs are evaluated for their short- and long-term effects on particular organs (such as the liver or kidneys) and on more general systems (such as the nervous or reproductive system). Perhaps the most controversial toxicity testing involves the determination of the lethal dose-50 (LD₅₀), the minimum dose that kills 50% of the test animals.

10.18 Consider This: Animals and Drug Testing

Animal rights groups often target the LD₅₀ standard as an example of callous indifference to animal welfare. Other groups argue that standards such as LD₅₀ are necessary to ensure drug safety and effectiveness. Take a position on the issue and write a letter to a classmate defending your position.

Results of animal tests must be submitted to the FDA for evaluation before permission is granted to proceed to the next stage—clinical testing of the drug on humans. In addition, approval must be obtained from local agencies and authorities such as a hospital's ethics panel or medical board. The FDA must establish whether the drug is effective and safe before it can be sold to the public. What needs to go on the label regarding use, side effects, warnings, etc., must also be determined. Typically, clinical studies involve the three phases identified in Figure 10.23: Phase I. Developing a pharmacological profile, Phase II. Testing the efficacy of the drug, and Phase III. Carrying out the actual clinical tests. Most of the safety tests of Phase I are done with healthy male volunteers, who are given single and repeat doses of the drug in various amounts. It is also at this stage that researchers look for interactions with other drugs. Double-blind placebo tests are administered to small patient groups in Phase II to test the drug's effectiveness on patients having the condition that the drug is designed to affect. In this protocol, neither the patient nor the physician knows which patients are receiving the drug and which are receiving a placebo, an inactive imitation that looks like the "real thing." Such tests are designed to eliminate bias from the interpretation of the results. Long-term toxicity studies are also initiated during Phase II. The clinical trials are expanded in Phase III, while manufacturing processes are scaled up and tests are carried out on the stability of the drug. The entire process often requires six years or more. A decade ago an average of 40 clinical trials were done on drugs that were ultimately approved; that number has risen to 60, the trials have become more complex, and the number of patients treated per trial has more than doubled over the past twenty years.
Large-scale clinical trials are desirable because a large pool will more likely include a wide range of subjects. Variety is important because the drug in question may have markedly different effects on the young and the old; men and women; pregnant or lactating women; infants, nursing infants, and unborn infants; and persons suffering from diabetes, poor circulation, kidney problems, high blood pressure, heart conditions, and a host of other maladies.

10.19 Consider This: Double-Blind Testing

Double-blind protocols have other uses than testing for the effectiveness of a drug. For example, physicians may use a double-blind test for diagnosing food allergies. In such tests, the physician administers a series of foods and placebos in disguised form. The test substances are labeled in code known only to a third person. Why do you think double-blind tests for the effectiveness of a drug or for establishing a food allergy are necessary? Compared to single-blind tests in which only the patient is unaware of the drug or food being administered, how do double-blind tests affect the reliability of the information gained?

Once clinical trials have been completed successfully—typically by only 10 drugs out of an original pool of 10,000 compounds—the test data are submitted to the FDA as part of a new drug application. This document can easily exceed 3500 pages. Upon review, the Agency may require the repetition of experiments or the inclusion of new ones, thus adding years to the approval process. Of the drugs submitted to clinical testing, only about one in ten is finally approved.

Once it receives the FDA’s imprimatur, a drug can be sold in the United States. Nevertheless, it still remains under scrutiny, monitored through reports from physicians. Drugs are removed from the market if serious problems occur. Some side effects show up only when large numbers of users are involved. Former FDA Commissioner Dr. David Kessler said “There is simply no way that we can anticipate all possible effects of a drug or device during clinical trials that precede approval. A new drug application, for example, typically includes safety data on several hundred to several thousand patients. If an adverse event occurs in 1 in 15,000 or even 1 in 1000 users, it could be missed in clinical trials. But it could pose a serious safety problem when the drug is used by many times that number of patients.” Such an example is temafloxacin, an antibiotic that had been clinically tested before approval in more than 4000 patients. Less than four months after its February 1992 release, temafloxacin was withdrawn from the market after fifty serious adverse events occurred from its use, including three deaths. Only after the drug reached the market and many thousands of people used it did its serious, even lethal, side effects became apparent.

Another case is Seldane, the first antihistamine for treating seasonal allergies without causing drowsiness. A small, but statistically significant, number of patients who took Seldane along with certain antibiotics or antifungal medicines developed abnormal heart rhythms. Seldane is normally broken down in the liver to another antihistamine by-product. Particular antibiotic and antifungal medications prevent this breakdown and so high concentrations of Seldane remain in the blood causing cardiac arrhythmia in these patients. In 1996 the FDA removed Seldane from the approved list because other non-sedating antihistamines had become available. By substituting a carboxylic acid group for a methyl group on Seldane, chemists developed Allegra, an antihistamine that is identical to the liver breakdown product of Seldane.

The lengthy process for drug testing and approval is not without controversy. Influenced by events such as the thalidomide tragedy, most people probably favor thorough screening of any proposed drug. But the price of such protection is high. The most obvious costs are monetary. Bringing a new drug to market is incredibly expensive, and the number of new drugs being developed has risen even as research and development (R&D) costs have risen (Figure 10.24).
Of course much of the expense is passed on to the consumer. For example, a single use of streptokinase, a medication that dramatically increases the likelihood of surviving a heart attack, costs $1000. Such prices have driven the costs of medical care and medical insurance to astronomical levels. One issue in the debate over health care reform is who will pay for the research and development that ultimately leads to new medication.

10.20 Consider This: Who Should Pay?

Streptokinase, a medication that dramatically increases the likelihood of surviving a heart attack, costs $1000 per dose. Who should pay for this life-prolonging drug—individuals, medical insurance, pharmaceutical companies, or the government? Take a stand and defend your position.

But more than money is at stake. In some cases, the costs of the protracted drug approval process may be human lives. When a patient is suffering from an almost certainly fatal disease such as some cancers, the risk/benefit equation changes. When there is nothing to lose, people are willing to take great risks, including imperfectly tested drugs. Some terminally ill patients have smuggled drugs from countries where the approval process is shorter than it is in the United States. Some have grasped at the straw of largely unproven remedies. And within the system, some advocates have urged that the FDA approval process be short-circuited to permit the use of experimental drugs on patients who have no other options. In one case, described in 10.21 Consider This, a lottery was held to determine who would have access to a promising new drug for the treatment of AIDS.

10.21 Consider This: A Lottery for Life?

In 1996, a lottery was held to select 2000 patients with advanced AIDS to receive an experimental drug called ritonavir. In other tests, similar drugs had proved effective in almost completely suppressing the AIDS virus in most subjects. Therefore, thousands of people suffering from the disease signed up for what might be a chance at prolonged life. Responses to this unconventional means of distributing a limited supply of the drug were mixed. Ben Cheng, a San Francisco AIDS activist supported it: “I think everybody agrees the lottery is not the best way of doing this, but it’s the only fair and equitable way of distributing what little of the drug is available.” In contrast, Bob Chapman, another AIDS victim and volunteer, had this to say: “I’m opposed to these lottery things. They are playing with people with terminal illness and putting people in competition with each other. It’s medicine hitting a new low.” List the ethical arguments on both sides of the issue, and indicate which position you favor.
The FDA has responded appropriately within the limits of its legal responsibilities to balance benefits with risks. Ten years ago an FDA review for a new drug required nearly three years whereas today it is less than a year. A new “fast-track” system has been instituted for priority drugs—those that address life-threatening ailments or new drug therapies for conditions that had no such therapies. The fast-track policy promises to have priority drugs, if found to be acceptable, approved within six months of application. Action on non-priority drugs is to be taken within ten months, down from the initial target of twelve months.

10.22 Consider This: Safety and Standards on the Fast Track

The credibility of the FDA’s fast-track drug testing program is called into doubt when five drugs released under the program have had to be withdrawn within a period of a year from mid-1997 to mid-1998. For example, some would argue that the recent recall of the pain killer Duract shows that adequate testing had not taken place on this drug. Others could counter that standards of testing have not changed, only the speed with which data are evaluated and that no set of tests can produce data that are 100% reliable in humans. Search the FDA and other web sites to gather information about this particular drug. Use what you learn to reach a decision as to whether you think fast-track drug testing is overall a benefit or a risk to the health of Americans.

People suffering from rare diseases may not be able to purchase appropriate medication at any price because it may not exist. There is a significant financial disincentive for a pharmaceutical company to invest heavily in developing “orphan drugs” that will be used by only a small fraction of the population.

To such considerations, one must add the objections some have to standard test protocols. Animal rights advocates are highly critical of the use of any animal subjects in drug screening. The sacrificing of test animals in establishing LD₅₀ values is especially controversial. For others, the generally accepted methods of human testing are at issue. The argument is that because the drug may have some benefit and will probably do no significant harm, it is unethical to withhold it from a control population. Some terminally ill AIDS patients have refused to cooperate with double-blind clinical studies by mixing and sharing test drugs and placebos.

An intriguing new approach to drug design is the use of “virtual” patients, ones derived through computerized data analysis. Up to 50% of actual trial testing provides no meaningful contributions to the data regarding a tested drug. By using “virtual” patients, non-promising drugs can be weeded out earlier in the trials so as to increase the percentages of drugs that are successful during the clinical phases. In this method, preclinical data on toxicity, uptake rates, and other attributes of test drugs are used together with known behaviors of similar drugs to create a very large data base of computer-simulated “patients” and how they are expected to respond to the test drugs. Statistics and computer modeling are then applied to the huge number of “patients” to simulate real-world behavior and to predict the most promising lead candidates to submit for clinical trials.

10.14 Brand-Name or Generic Prescriptions?

A customer gives a prescription to a pharmacist and is asked “Brand name or generic?” This scenario is played out daily in thousands of cases across the country. How is the person to decide? For millions of Americans, the cheaper generic version can mean the difference between getting the necessary medication and not being able to afford it, although not all approved drugs are available in generic form.

The two forms can be differentiated rather simply. A pioneer drug is the first version of a drug that is marketed under a brand name, such as Valium for the anti-anxiety drug.
The generic version is a drug that is equivalent to the pioneer drug, but cannot be marketed until the patent protection on the pioneer drug has run out after twenty years. The lower-priced drug is commonly marketed under its generic name, in this case Diazepam instead of Valium. The 20-year patent protection on the pioneer drug begins when it is patented, not when first put on the market. In cases requiring a long pre-approval time, the actual marketing period can be relatively short, even less than six years. In such a situation, a drug company has very little time to recapture its research and development costs before a generic competitor can be manufactured. Almost 80% of generic drugs are produced by brand-name firms. Like pioneer drugs, generic drugs must also be approved by the FDA.

In 1984, Congress passed the Drug Price Competition and Patent Restoration Act, which greatly expanded the number of drugs eligible for generic status. This Act eliminated the need for generics to duplicate the efficacy and safety testing done on counterpart pioneer drugs. Doing so saves drug manufacturers considerable time and money. The FDA also issued specific guidelines for a generic drug’s comparability to the pioneer drug. By FDA mandate, the generic and pioneer versions must be bioequivalent, and deliver the same amount of active ingredient into a patient’s bloodstream at the same rate.

Health insurance companies and the FDA suggest that policyholders choose generic rather than brand-name drugs when possible, for obvious economic reasons. The concern for health care costs, along with the graying of baby boomers, will likely accelerate the use of generics, as will patents that expire on additional brand-name drugs, making their generic versions possible.