How are adverse effects of new medications documented?

The ideal medication would be one with only benefits and no adverse effects. Unfortunately, such medications do not exist; all approved medications have some unfavorable effects. A major goal during drug development is to collect as much information as possible so that the FDA can determine the benefit-harm balance.

**How informative are initial laboratory studies?**
The first step in drug development involves laboratory screening, which evaluates the effect of a variety of chemicals on animal and human cells. The objective is to eliminate those chemicals that are toxic. It is also possible to study the metabolism of these chemicals to determine the rate at which they break down in the body. Those with fast or slow rates of metabolism are less likely to be pursued as medications. Most newly developed substances are eliminated during these laboratory studies. The volume of chemical agents undergoing preliminary laboratory screening has increased dramatically over the past 15 years as a result of the application of sophisticated technologies, including the use of robotics.

**What can animal studies add regarding safety?**
Government regulations require all future medications be tested in two different kinds of animals. If the intent is to develop a medication for long-term use, animal studies must continue for at least two years. These animal studies provide information on the risk of tumor (cancer) development and congenital malformations (birth defects). They also can provide information about the highest tolerated dose of the medication.

**What are the safety objectives of Phase 1 studies?**
Phase 1 clinical trials represent the first time a compound in development is given to human beings, generally healthy volunteers. This phase of testing reveals what is happening with a medication after ingestion: uptake in the body, distribution in different tissues, breakdown, and excretion. From these studies, we can learn more about future dosing of the medication and possible adverse
- Doc, any risk of side effects with this drug?
- None that you don’t already have.
effects. Investigative drugs showing continued therapeutic promise through Phase 1 testing move on to additional testing, as described below.

**What is the safety objective of Phase 2 studies?**
One objective of these studies is to assess the occurrence of common, mostly predictable, adverse reactions that are expected based on the medication’s known mechanisms of action. Many of these reactions are dose-dependent, which is why dose is an important consideration when deciding whether an experimental medication should progress to the next phase of testing.

**What are the contributions of Phase 3 trials?**
Larger Phase 3 trials represent the gold standard of testing when it comes to evaluating an investigative medication for efficacy and safety. These typically involve hundreds or even thousands of patients who have the condition for which the medication is intended. Even with Phase 3 trials, two major limitations exist: the studies are often short and they include highly selected patients. Even if a medication is targeted for treatment of a chronic (long-term) condition, FDA regulations require only a few hundred patients be treated for up to one year. Less common and unexpected adverse events may be detected in Phase 3 trials, but far from all. Adverse events (even very serious ones) may not become apparent until years after the FDA approves the medication for marketing.

These concerns reflect the many limitations of Phase 3 studies as well as one of the weaknesses of the current regulatory approval process: The approval of an investigative drug for use by the general public based on a relatively small number of patients being treated over a relatively short period of time. Phase 3 trials do serve other purposes, however, such as providing information about medication interactions (see Chapter 32).

**How is safety determined after regulatory approval?**
The “real life” test of a medication’s safety happens after regulatory approval and market introduction, when large numbers of unselected patient groups are exposed to the medication. For the first time, it is given to patients with multiple medical conditions, to older adults who take numerous medications, and to those with chronic conditions such as kidney or liver disease (see Chapter 13).

There is an emerging consensus that safety monitoring should continue throughout the life cycle of every medication. Today, the FDA only requires drug makers to submit regular semi-annual safety reports for three years after approval.

Potential safety concerns are often raised during the final approval
process. To facilitate the approval of new products, drug companies agree to conduct post-market safety studies that may uncover potential concerns. The companies, however, seem to lose interest in fulfilling their commitments once the medications are on the market. As of September 2007, there were approximately 900 outstanding industry commitments for safety studies. This remarkably high number reflects the fact that FDA lacks enforcement authority to hold drug companies to their commitments. A new law passed by Congress and approved by the President in September 2007 will hopefully remedy this situation by giving the FDA adequate authority to impose fiscal penalties on delinquent companies.

Due to incomplete safety information at the time of regulatory approval, many clinicians and health plans take a wait-and-see approach with new medications, especially when other treatment alternatives are available.

Key messages

- The elimination of unsafe chemicals happens gradually during the phased development process.
- There is no guarantee that all serious adverse effects of a new medication are known by the time of approval because of inadequacies in the current regulatory approval process.
- Safety monitoring should continue through the life cycle of every medication, both before and after FDA approval.