When is it safe to take a new drug? The rigorous system of premarket clinical trials enforced by the U.S. Food and Drug Administration (FDA) involves screening all new drugs for health risks before they can be sold. Fewer than 5% of drugs survive all three phases of this vetting process. However, the recent recall of rofecoxib (Vioxx®, Merck) and safety concerns regarding Pfizer’s celecoxib (Celebrex®) and valdecoxib (Bextra®) suggest that even this level of vigilance can fall short. In fact, according to one estimate, more than 100,000 deaths each year can be attributed to adverse drug reactions.

THE NEED FOR LONG-TERM SURVEILLANCE

Drug companies can spend hundreds of millions of dollars and 10 years or more in order to meet the FDA’s premarket testing requirements. Even then, the New Drug Application for final marketing approval may be rejected. However, as demanding as this process is, most products are tested on only a few hundred patients.

A sample of this size might not catch relatively rare side effects, for example, those that occur in less than one patient in a thousand, or those side effects that appear only after long-term use. The FDA itself acknowledges, “The risks associated with medical products are never fully revealed during the premarket review process.”

THE CURRENT POSTMARKET MONITORING PROCESS

The process for monitoring drug safety after marketing begins is far less exacting than the premarket procedure. Although it is often referred to as the fourth phase of clinical trials, postmarket safety assessment does not require actual testing; instead, it depends largely on voluntary reporting.

The most common reasons why manufacturers systematically study drugs after approval are unrelated to long-term safety assurance. Companies look at effects in populations (e.g., children) that were not included in earlier testing, and gather data for approval to market a drug for new uses. Postmarketing safety studies are required only in two instances: (1) for significant new drugs that were given “fast-track” approval and (2) those requiring a review of hazards for pediatric patients.

The FDA approves some drugs on the condition that continued testing explore suspected late-appearing side effects, but follow-through on such conditions is inconsistent. In most cases, the agency lacks clear authority to directly require clinical testing for safety after a drug has been approved.

In the absence of systematic long-term testing, the FDA relies on a system known as MedWatch to review reports of individual adverse drug events (ADEs). Manufacturers must inform MedWatch within 15 days of any evidence that comes to their attention indicating serious and unanticipated side effects. They must also follow up with an investigation.

In response, the FDA may take one of several steps, including issuing a medical alert, requiring labeling changes, mandating a black-box warning, or ordering that the drug be withdrawn from the market. In most instances, however, manufacturers learn of ADEs only from reports by health care professionals, which are usually voluntary. There is no requirement that companies seek out hazard data on their own initiative.

THE SAGA OF THE COX-2s

Cyclooxygenase-2 (COX-2) inhibitors are a class of drugs designed to treat arthritis and other kinds of inflammatory pain. The first one to reach the market, rofecoxib, was approved for sale in the U.S. in May 1999. In March 2000, a study by Merck to assess rofecoxib’s gastrointestinal risks indicated possible cardiovascular side effects, including heart attacks, a finding confirmed in an August 2001 article in the Journal of the American Medical Association (JAMA). Subsequently, similar concerns were raised by studies of valdecoxib and celecoxib.

In April 2002, the FDA required a warning of heart risks on rofecoxib’s label. Additional studies, completed in October 2003 and August 2004, added further evidence of cardiac hazards, and on September 30, 2004, Merck voluntarily pulled the drug from the market. Valdecoxib and celecoxib remain on the market as of the time this article went to press but with warnings about their long-term use.

Critics contend that the FDA should have acted sooner. In November 2004, David Graham, associate director for science in the agency’s Office of Drug Safety, testified before Congress to a history of ignored warnings. He asserted that FDA officials had pressured him to suppress estimates that he had developed indicating that an additional 27,785 deaths were caused by rofecoxib through 2003. He blamed the pressure on an agency culture that discourages suspicion of approved products.

A SUSPECTED CULPRIT AND A PROPOSED SOLUTION

To some observers, FDA postmarket surveillance is weak because it presents an inherent conflict with the agency’s primary mission. After the FDA has approved a new drug, the discovery of previously undetected health risks could be perceived as a failure of premarket vigilance. The agency’s modus operandi, continued on page 19
therefore, is to shortchange long-term safety monitoring that might suggest that it made earlier mistakes.

To address the apparent conflict, the chairman of the Senate Finance Committee before which Dr. Graham testified, Chuck Grassley (R-Iowa), proposed the creation of a separate regulatory agency to independently review postmarket drug safety. The idea was endorsed in a subsequent editorial published in *JAMA*, which also called for mandatory postmarket clinical trials for all drugs. Advocates of enhanced postmarket surveillance point to the regulatory scheme enforced by the European Agency for the Evaluation of Medicinal Products, which reassesses all drugs after five years on the market. Products may be denied reauthorization if new evidence indicates previously unknown risks or if the manufacturer declines to submit the results of promised long-term safety studies.

**DO WE NEED A SECOND FDA?**

The controversy surrounding the COX-2s might tip the balance toward major reform of postmarket drug safety surveillance, and the creation of a second FDA is a possible outcome. Critics may see such a mechanism as an additional bureaucratic layer standing between patients and effective therapies. However, the presence of a strong postmarket safety valve could make the FDA less cautious about granting initial approvals. It could also make the regulation of marketed drugs more predictable for all concerned.

**REFERENCES**