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According to Janet Woodcock, M.D., director of the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), people tend to ask that question a lot when a drug is taken off the market. The FDA's mission is making sure that drugs are "safe and effective." So what does "safe" really mean?

When it comes to any drug, "safe" means that the benefits of the drug outweigh the risks for the population the drug is intended to treat and for its intended use. "Safe does not mean harmless," Woodcock says. "Every drug comes with risks, and our tolerance for risk is higher for drugs that treat serious and life-threatening illnesses. There is no question that cancer drugs can be highly toxic. But they also save lives."

If the FDA decides that a drug's benefits outweigh its risks, the agency approves the drug for marketing. Approved drugs continue to be evaluated through postmarketing surveillance--a system that monitors a drug's safety on an ongoing basis. Postmarketing surveillance seeks to identify problems that weren't observed or recognized before approval and any problems that might arise because a product isn't being used as anticipated.

The goal is to catch any bad news right away so that the FDA and drug companies can act quickly and communicate new risk information to consumers and doctors. CDER evaluates required reports from drug companies, which must promptly pass on any report they receive of a serious adverse reaction that isn't already described in the drug's labeling. CDER also relies on MedWatch, the system through which consumers and health professionals voluntarily report adverse events associated with all products the FDA regulates.

When the FDA receives reports of significant new adverse events, the agency evaluates them for their seriousness and the likelihood that they were caused by the drug. To the extent possible, the agency also considers how the toxicity compares with other treatments for the same disease. Ultimately, of course, the critical question is: Do the benefits of this drug still outweigh its risks for the population described in the labeling? In many cases, that question cannot be answered immediately, and more reports must be considered. Sometimes, the impact of labeling revisions needs to be assessed.

Usually, when important new risks are uncovered, the risks are added to the drug's labeling and doctors are informed of the new information through letters and other education. It's only rarely that the approval decision on a drug needs to be reassessed and changed. A conclusion that a drug should no longer be marketed is based on the nature and frequency of the adverse effect and how the drug compares with treatment alternatives.

When the FDA believes it is clear that a drug no longer has a place in treatment, it will ask the manufacturer to withdraw the drug voluntarily.(See "Safety-Based Drug Withdrawals (1997 - 2001).") Companies have agreed to withdraw the drug in all cases except one--the case of an antidiabetic drug called phenformin, which was taken off the market in 1976 as an imminent hazard, despite the company's objections. If a company does not agree, the FDA can bring formal procedures to require withdrawal.

At first glance, one might assume that every time a drug comes off the market, it means that somewhere along the way somebody made a horrible mistake--that the drug never should have been on the market in the first place. But FDA experts say that would not be correct. Most often, the withdrawal occurs because of adverse effects that were not seen prior to marketing. Sometimes, there was no clue at all. In other cases, one can see hints of the problem in retrospect, but not the serious events that eventually led to the withdrawal.

Many complex factors go into making judgments about benefits and risks, and into ultimately deciding whether a drug should be taken off the market. Here are some major issues, often overlapping, that weigh into the decision-making process.

Rare, Unpredictable Problems

Most drugs on the market are well-tolerated and their adverse effects are known. Known side effects cause more injuries and deaths than unrecognized side effects. But some problems happen so infrequently that they can't be seen or predicted before a drug gets on the market. Serious drug-induced liver disease, for example, is the leading single reason drugs have been pulled from the market. But it is rare, occurring at a rate of 1 in 5,000 to 1 in 10,000 exposures or less. This will not show up in clinical trials, which will pick up relatively common problems.

"If we want reasonably rapid access to needed drugs, it's not practical to require that they be tested in 15,000 to 30,000 people, which is what you'd need to be reasonably sure you saw even one case that occurs at a rate of 1 in 5,000 to 10,000," according to Robert Temple, M.D., director of the FDA's office of medical policy. "And the case would need to be recognized as drug induced," he says. So drugs are typically tested in several thousand subjects, allowing detection of relatively common serious adverse events, such as those affecting 1 in 1,000 people. This practical size of clinical trials means we can't know everything about a drug when it gets on the market. Rare events will only surface when the drug is used in larger numbers of people. Temple says, "Sometimes less severe events that are seen in trials can be used to predict the

occurrence of rare, more serious events, but that is not always the case, and such predictions have considerable uncertainty."

The number of subjects in clinical trials is increasing in some areas of drug development, says Peter Honig, M.D., director of the FDA's office of drug safety. "But the numbers will never be large enough to eliminate the need for postmarketing surveillance." The FDA is working on ways to better predict rare events, especially those related to the liver and heart. But some uncertainties will always be there, including the possibility of rare characteristics that make some people particularly susceptible to an adverse reaction.

More Toxic than Expected

There are also times when a drug's toxicity is known, but the drug turns out to be more toxic than the clinical trials suggested, which again may only be seen when the drug is used in larger numbers or in different ways.

Initially approved in 1997, Baycol (cerivastatin) was a member of a class of cholesterol lowering drugs known as "statins." Baycol and the other five drugs in its class--Lipitor (atorvastatin), Lescol (fluvastatin), Mevacor (lovastatin), Pravachol (pravastatin), and Zocor (simvastatin)--have all been associated with rare reports of rhabdomyolysis, a condition that causes marked breakdown of muscle cells and can sometimes lead to fatal kidney failure and other problems.

Knowing this about the statin drugs, the FDA made sure to look for the problem when deciding to approve Baycol. But the agency didn't find unusual risk associated with the drug at that time. "In its first few years, Baycol had a small market share," says Sandra Kweder, M.D., acting director of the FDA's office of review management. "But when FDA approved a higher dose of the drug after initial marketing, use of the drug grew and we could see clearly that Baycol caused the problem more frequently than the other drugs in its class." Problems with Baycol were reported most frequently when it was used at higher doses, when used in elderly patients, and particularly, when used with another lipid-lowering drug called Lopid (gemfibrozil). Baycol was voluntarily withdrawn in the summer of 2001.

When Safer Options Are Available

When the FDA approved Seldane (terfenadine) in 1985, the drug became the first prescription antihistamine to relieve allergies without causing drowsiness--a side effect that can cause accidents and injuries. A few years after approval, it was discovered that Seldane could cause fatal heart rhythm irregularities when it was used together with drugs that slowed its elimination from the body, or in patients with liver disease.

Major efforts to warn against use in such patients were partly successful, but fatal rhythm abnormalities continued to be reported. According to Temple, removal of the

drug was considered, but that would have left only one non-sedating antihistamine, so Seldane remained available.

"But the equation shifted when Allegra came on the market in 1997," Temple says. "Allegra provided exactly the same benefits of terfenadine but without the risk of the potentially fatal heart condition." So the new availability of Allegra (fexofenadine) weighed heavily in the decision to withdraw Seldane.

Dangerous Combinations

Like Seldane, a heart drug called Posicor (mibefradil) posed problems mainly when used with other drugs. Although Posicor itself did not have unusual toxicity, it was taken off the market in 1998 because of its interactions with at least 25 drugs. It markedly increased the blood levels of those drugs, leading to potentially fatal side effects of the other medications.

When Posicor was first marketed in 1997, its labeling warned of possible interactions with three drugs. Two more drugs were later added, but reports of interactions and resulting adverse reactions with even more drugs kept coming. There was concern over whether it was realistic to expect physicians to be able to use Posicor safely, given the many drugs it interacted with. In the absence of any special benefit of Posicor compared to other members of its class, such as effectiveness in people who don't respond to other treatments, the FDA concluded that the drug should be removed from the market.

When taken at a higher than recommended dose and when taken with other drugs, Hismanal (astemizole), another non-sedating antihistamine approved in 1988, posed risks similar to Seldane. The drug was withdrawn in 1999, as safer alternatives became available.

Beginning about 1990, many potentially harmful interactions between drugs and even between drugs and foods (such as grapefruit juice) were noted with Seldane and other drugs. The discovery led to greater attention by the FDA and drug manufacturers to such interactions before drugs are marketed, Temple says. This represents a significant enhancement of safety assessment.

Improper Use

The term "safe" also depends on whether a drug is used according to the labeling. This is why the FDA makes sure labeling and advertising for prescription drugs are accurate and balanced--presenting both the benefits and the risks.

The major problem with Duract (bromfenac), a nonsteroidal anti-inflammatory drug, was that the directions were not followed. The pain drug was withdrawn in 1998 after liver failure occurred in patients who took the short-term treatment for pain for more than the 10 days recommended in the labeling. Clinical trials indicated that a higher incidence of elevated liver enzymes was associated with longer use.

Duract's manufacturer, Wyeth-Ayerst Laboratories, Philadephia, added a new warning (Continued from page 14) to the labeling and sent letters out to doctors, but reports of long-term use of the drug continued.

When Other Risk Management Options Fail

The day you hear news about a drug coming off the market, it may appear to be a sudden, drastic step. But several other options to manage risks usually have been attempted before that point. The main risk management tools employed by the FDA are education through letters to health-care professionals (known within the FDA as "Dear Doctor" letters) and labeling changes, such as new warnings, sometimes boxed in black for emphasis. Also used are required Medication Guides, labeling specifically for patients that emphasizes significant risks and advises patients how to detect or avoid them. In some cases, a drug is labeled as "second line," meaning it is to be used only in patients for whom other treatments fail. In other cases, a drug that is known to be dangerous is still made available under certain circumstances through what's known as restricted distribution (see box).

Sometimes these risk management techniques are effective, and other times they aren't. "We have our anecdotes, but there is little systematic study on the effect of drug labeling changes on physician behavior," says Temple.

Labeling changes were a partial success with the allergy drug Seldane. Studies showed use of Seldane with inappropriate drugs declined almost 90 percent, but that left considerable exposure to the dangerous combinations, some of which could be lethal.

The label of the heartburn treatment Propulsid (cisapride) was changed several times in 1998. The FDA cosponsored a study to evaluate the effect of various regulatory actions, and found that the percentage of patients inappropriately exposed to the drug was unchanged.

"We know that the farther out we are from the initial approval, the less likely we are to change behavior," Woodcock says. "Once a prescribing pattern has been established, it's hard to change it."

Clearly, the more special care that is required, the more physicians must remember, and the more we need other safeguards like spotting dangerous combination uses at the pharmacy level, the more of a challenge risk management becomes. "We do consider whether we are being unreasonable in our expectations, but sometimes that can't be known beforehand," Temple says.
Currently, the FDA is involved with several drug safety initiatives, including revamping the drug labeling for physicians to create a highlights section, a relatively short section that will describe the most critical information. Better education is a high priority. "We're looking into better ways to educate the public and doctors about changes in risk information, and to get information out faster," says Honig.

But FDA experts say the agency can't do it alone. The FDA judges drug risks for a population, doctors judge risks for individual patients, and patients judge the risks they'll take based on personal values. Ultimately, drug safety requires involvement of all parts of the health system.

Myths About Drug Withdrawals and User Fees

During the 1980s and early 1990s, the FDA was criticized for taking too long to review and approve drugs. Then Congress, the FDA, and the pharmaceutical industry negotiated the Prescription Drug User Fee Act (PDUFA) of 1992. Under PDUFA, drug companies pay fees that allow the FDA to add more resources and speed up drug review time.
The FDA agreed to complete its review of marketing applications within specific times. For example, by 2002, the FDA's reviews of all marketing applications for new drugs were to be completed within 10 months. PDUFA allowed the agency to have a 60 percent increase in staff assigned to review new drug applications. The agency has essentially met all review-time goals. The faster review has led to more rapid approval, with median approval time cut in half--from about 30 months to 15 months. PDUFA was extended through 2002 by the FDA Modernization Act of 1997.

Myth #1: Drug withdrawals have become increasingly common because ever since user fees, the FDA has sped up drug approvals so much that mistakes are slipping through.

The reality is that it's a rare occasion when a drug is taken off the market. The FDA is the consumer watchdog for the more than 10,000 drugs on the market, and the drug withdrawal rate has been essentially constant over the last two decades. And when comparing the time before user fees and after, there has been no change in the rate of drug withdrawals, says Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "There was a cluster of withdrawn drugs in 1997 and 1998, but if you look at the number withdrawn as a percent of those approved for each year, the rate was about 2.7 percent before user fees and is about 2.8 percent after user fees." Some of those drugs withdrawn in 1997 and 1998 had been on the market long before user fees took effect.

Faster reviews to get valuable and life-saving drugs on the market does not translate into safety shortcuts. It isn't that the same number of FDA reviewers are working faster. It also isn't the case that shorter FDA review times mean abbreviated clinical drug trials.

Myth #2: User fees make it difficult for the FDA to stay neutral.

FDA experts say PDUFA has clearly created a situation in which the FDA is responding faster to applications and is having more discussions with drug companies.

The FDA and drug companies share a common interest in getting drugs that are safe and effective to the market and in conducting well-designed trials that are persuasive. "We believe the many meetings and other forms of advice that we give help assure that," says Robert Temple, M.D., director of the FDA's office of medical policy. "Naturally, once they submit an application, the companies want our answer to their drug application to be 'Yes,'" he says, "but we are completely neutral, having no preferred answer except the right one." The FDA's mission is to protect the public health fairly and consistently. Decisions are scientifically-based, not influenced by user fees.

Restricted Distribution

A variety of means have been used to limit distribution of particularly dangerous drugs to be sure they are being used safely, and in some cases, to direct use to the right people.

Propulsid (cisapride) was taken off the market in 2000 because of the risk of heart rhythm abnormalities, but it is still available under a special kind of investigational use. The drug is available to people with severely debilitating conditions for whom the benefits may outweigh the risks and who meet specific clinical eligibility criteria. This limitation assures that it will not be given to people who don't really need it.
In some cases, it is clear that assuring safety will require strict limitations from the outset. Thalidomide was studied in the late 1950s as a sleeping pill and as a treatment for morning sickness in pregnancy, but was not marketed in the United States. The drug is well known for causing severe birth defects. It was approved in 1998, but it is only available under a very restricted distribution system to assure that fetuses are not exposed to it. Thalidomide is labeled for use to treat painful and disfiguring skin sores associated with Hansen's disease (leprosy), but has other potentially important uses under development.

It is absolutely essential that this system work, says Robert Temple, M.D., director of the FDA's office of medical policy. "If people didn't follow the directions while taking thalidomide, the consequences would be terrible," he says. "But it is working and people do follow directions."

In some cases, a drug is marketed generally, but proves to have such a serious effect that it has to be considered for restricted distribution. A critical factor in such cases is whether the FDA and a drug company can agree on the terms. Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research, says the FDA offered the option of restricted distribution for very severely affected patients in the case of Lotronex (alosetron). Lotronex was approved to treat irritable bowel syndrome in women, but caused ischemic colitis that could be fatal in some cases. After discussions, the manufacturer, GlaxoSmithKline, Research Triangle Park, N.C., decided to voluntarily withdraw the drug from the market in 2000.