When Is A Medical Product Too Risky?

An Interview with FDA's Top Drug Official

by Tamar Nordenberg

Five drugs were pulled from pharmacy shelves in a recent one-year period, considered to be too risky by the Food and Drug Administration. Perhaps the most notorious among them was fenfluramine (Pondimin), the "fen" half of the popular weight-loss combination known as "fen-phen." Fenfluramine was removed from the market after being linked with potentially fatal heart valve disease in some patients. The same concerns prompted the withdrawal of the chemically related *dex*fenfluramine (Redux).

The other drugs removed from the market during the same period: the prescription antihistamine Seldane (terfenadine), the calcium channel blocker Posicor (mibefradil), and the pain medicine Duract (bromfenac sodium).

The string of five withdrawals has led some critics to contend that FDA is rushing to approve drugs that ultimately may prove dangerous to patients.

Is FDA cutting corners when it comes to drug safety? *FDA Consumer* asked that of Janet Woodcock, M.D., director of the agency's Center for Drug Evaluation and Research, which regulates all drugs marketed in the United States. She and other top FDA officials have just completed a report to FDA Commissioner Jane Henney, M.D., on the agency's approach to evaluating risk, in new drugs as well as other medical products.

Janet Woodcock, M.D.

Much has been made in the media recently about what one* USA Today *editorial referred to as a "record spate of drug withdrawals." Has the agency compromised its standards of safety and effectiveness to speed up drug approvals, as some critics charge?

First of all, you have to look at the data. The rate of drug withdrawal in the United States is actually lower than it's been over the past couple of decades. The rate was running about 3 percent of drugs approved that had to be withdrawn in the '80s, and that came down a little bit in the early '90s, and now it is even lower than that, a little over 1 percent at the moment. So the idea that things are getting worse—that more drugs have to be pulled off the market today—just isn't the case.

FDA is reviewing drugs more quickly, overall, than in the past. It used to be that the review period—after the pharmaceutical company studies the drug, writes up its reports, and sends a gigantic package of information to FDA—took about two to three years to complete. We have that down to about 12 months.

The drop in drug review time has had nothing to do with the legal standards for drug approval, which haven't changed. We're able to review drugs more quickly because we have about 400 more people here in the Center for Drugs to review drugs than we did before the Prescription Drug User Fee Act. Under the PDUFA program, started in 1992, drug companies pay fees that allow FDA to add reviewers and scientific equipment—computers and so forth—to speed up drug review.

But shorter review time doesn't mean that the *clinical testing* of drugs is any shorter. Actually, it's taking longer now for a company to study a drug than it used to. Partly, that has to do with greater scientific knowledge about studying drugs. Over the last decade, FDA has asked for more studies in different populations—women, elderly patients, people with kidney failure, and so forth. On the other hand, companies are studying drugs more for marketing reasons, too, to help sell their drug. And these types of studies also contribute to the safety database for the drug.

What FDA needs is enough time to do a good, thorough review of an application. We think we have enough time now to do that. But uncertainty is a constant with drugs, and it's an issue that we need to separate from FDA review time.

Why doesn't FDA hold off on approving a drug until the agency is sure the product won't have any dangerous side effects?

What we're really talking about here is, what are the standards? How extensively should drugs be studied in people to uncover adverse reactions? Clearly, if you study a drug in 500 people, you have much more uncertainty about the drug than if you study it in 5,000 people, or 150,000. But, as you start to increase the number of people studied, you bring the cost up so much that the development of other drugs waiting back here isn't moving along.

If we made sure that any drug we approved had *no* side effects, we wouldn't approve any drugs. We'd have a really easy job. Every single drug that has an effect on the body will also have side effects. Sometimes these will be rare, and sometimes these won't be that serious. But for every drug that we approve, we have to balance the benefits of the drug against its risks.

People know about risks, and they're used to them in their everyday lives. "Should I get on this airplane?" "Should I let my child go skiing?" For the benefit you're getting from a medicine, too, you are buying some risk. The FDA can't make that go away, and we shouldn't represent that we do. All we do is try to make clear what the risks are.

There are some risks that we won't know about from the clinical trials. Partly, it's because some risks are very rare. For a risk, say, that would occur in 1 in 50,000 patients, you'd have to study 150,000 people before the drug was approved to give you a good chance of that risk even showing up—although you still aren't guaranteed to find it. To study 150,000 people with each disease would be a prohibitive barrier to getting drugs on the market, especially those for rare diseases.

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Also, you might have to follow a person on a drug for quite a long time before the side effect would occur, making it harder to detect.

Another reason some risks do not show themselves during clinical studies has to do with how drugs are used in the real world. In clinical trials, drugs are studied only for the use the company is pursuing. They're studied in patients who are enrolled in trials and are carefully monitored. After a drug is out on the market, all kinds of different patients will be treated with the drug, some of whom will not have the condition the drug was approved for. In addition, they'll be taking all sorts of different

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medications, and maybe dietary supplements and other products that could interact with the drug to cause problems.

We have to balance our requirements for drug approval versus the need to have the drugs out on the market. There is a continuum of uncertainty that is tolerated, depending on how serious the illness is. For drugs that are for serious or life-threatening diseases that don't have any good treatments, we tolerate a lot more uncertainty. On the other end of the continuum, for a drug that's going to be sold over-the-counter for consumers to use, there has to be a very high certainty that the drug is very safe.

When adverse reactions do show up, we have what's called a spontaneous reporting system to track them. Doctors, pharmacists, even patients can report serious adverse reactions to the agency through our MedWatch system, or they can make a report to the manufacturer, who will send it to us. We have a whole staff that puts these reports into a computer database and analyzes them. It's often hard to tell early whether it's a true signal or not because out in the real world, people who are very sick are getting drugs. So we monitor the reports, and as soon as we get a clear understanding that a new finding exists that isn't in the label, we'll work with the company to add it to the label. The company may send out a Dear Health Professional letter to inform doctors and other providers of a new safety issue. And if it really alters the risk-benefit ratio so the risks of the drug, including the newly found risks, now outweigh the benefits, we'll have the company take the drug off the market.

Among the most widely publicized examples of recent drug withdrawals are the diet drug fenfluramine and the painkiller Duract. Did FDA make a mistake in approving these drugs?

The diet drugs are a very interesting example. Fenfluramine was approved by FDA in 1973 for short-term use in weight reduction. It had been approved in many other countries around the world, and there was an extremely wide experience with the drug.

It was used in a low number of people in the United States for a number of years. But in the early '90s, it became wildly popular in combination with another drug, even though the combination hadn't been studied extensively or approved by the FDA. In this combination, people were taking fenfluramine for a longer period than they had been over the previous 20 years.

A report from the Mayo Clinic raised red flags when it showed that some patients had heart valve disease who had been taking this combination. Heart valve disease is not known, in general, to be a side effect of pharmaceuticals, and it's not something that we test for in the clinical trials. You'd have to test every patient's heart function with an echocardiogram to detect it.

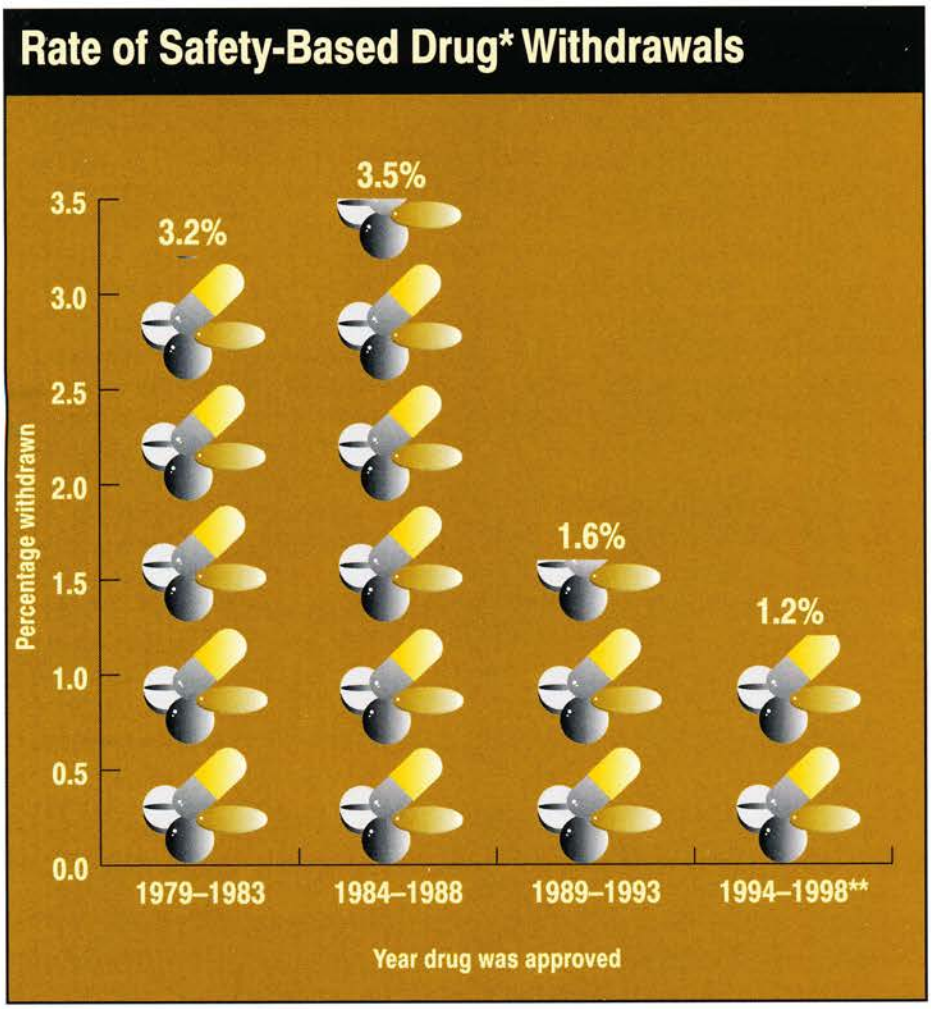
So, did FDA make a mistake? Certainly for the 20 years after approval, no one thought a 'mistake' had been made because it took that long for the heart valve problem to be found. I think the entire medical community was surprised by the finding, and the association with heart valve disease wasn't really accepted by much of the medical community for awhile.

But it became clear to FDA, based on our postmarketing system for picking up adverse reactions and from epidemiologic studies that we did, that this was a true association between fenfluramine and heart valve disease. For that reason, we pulled fenfluramine off the market, as well as the recently approved diet product Redux. We'd received a few adverse reaction reports about Redux, or dexfenfluramine, which is a component of fenfluramine and was approved partly on the basis of fenfluramine's long safety record.

In the case of Duract, we knew before the drug was approved that there was what we call 'chemical hepatitis' associated with it because that had been seen in the clinical trials. A number of drugs cause chemical hepatitis; in other words, the doctor knows you have a bit of liver disturbance but you don't.

Was it a mistake to approve Duract? We didn't know that Duract would cause serious liver disease because it was not seen in the clinical trials. If we had thought that, we wouldn't have approved it.

Naturally, a newly approved drug has more uncertainty about it than a drug that's been on the market for 10 years. There's just no way we can get around that. Even if you required 250,000 people to be studied—of course, a drug



Even as new drug approvals have been consistently increasing, the rate of market withdrawals for safety reasons has been decreasing for well over a decade.

*** refers to new molecular entities, or products with an active substance not previously marketed in the United States**

**** years with Prescription Drug User Fee Act in place**

would never get out on the market, then—when you get it to 10 million people, say, who are taking all these other medicines and might take it longer, you will still find out new things. We're still learning about digitalis, a drug that's been around for 100 years. New papers are still being published: Does it work in heart failure? Should it be given long-term?

Have we learned from the withdrawal of Duract and the other recent withdrawals? Yes, I think the FDA has gained some information, particularly about liver toxicity. And we've held a big scientific workshop for our staff. We're going to be taking more steps to look into liver toxicity to see if it can't be better predicted. That's really the issue. You probably won't see liver failure in the trials. But can you predict that this is a drug that's going to cause liver failure once many more people are exposed? Right now, there's no way to do that.

Based on the risk evaluation that FDA undertook for its recent report to the commissioner, is FDA adequately protecting the public from the risks presented by medical products?

What we found was that our system of premarket review as well as postmarket surveillance are performing the way they were set up to.

Of the products now approved, fewer have to be withdrawn from the market. So we see progress in drug review. Is it perfect? Are we the best we could be? Well, we think there are some additional steps that could be taken.

On the premarket side, we need to find better ways to detect liver toxicity, and we're starting to work on that. We think we need a quality assurance unit within each center, and we're going to do that.

On the postmarket side, we feel we need to finish our adverse event reporting system, or AERS. In addition to enhancing the AERS system, we also want to have access to outside databases and have ways of finding adverse events other than just the voluntary reporting. We need more money, though, for these improvements, and we've asked for some money in the president's budget for this year.

Is there more that can be done? FDA, we think, is enforcing the standards and approach called for in our statute, the Food, Drug, and Cosmetic Act. But the question is, is the balance correct, according to society? That's really a general consensus rather than our call.

One important conclusion in our risk management report is that we need to incorporate the views of patients into our risk management decisions much more extensively. After all, consumers are the ones who are assuming the risk. And we know that individuals weigh risk differently. Some people would rather live shorter and have a better quality of life, for example. Other people just want to live, and their quality of life is less important than simply surviving.

If I say to you, "you have a 1 in 100 chance of dying from this drug, but it will do wonderful things for you," that might mean something totally different to you than it would to me. So we need to bring patients, as well as those who treat patients, in much more and ask them, "What is an acceptable risk?"
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Beyond Drugs Risks from Devices and Biological Products

Benefits must outweigh risks. This predominant theme of drug approval applies equally to the other medical products FDA regulates, namely devices and biologics (vaccines, blood products, and biotechnology products).

Like drugs, devices and biologics all have some risk associated with them, and FDA and patients are willing to tolerate more risk the more serious the disease. "People are willing to get a little closer to the edge when the stakes are high," says David Feigal Jr., M.D., director of FDA's Center for Devices and Radiological Health. "Obviously, you'd like to manufacture everything without risk, but you can't. It's the same for drugs: With cancer drugs, you have side effects that would be unacceptable if you were treating a mild condition."

Susan Alpert, M.D., director of the center's Office of Device Evaluation, also emphasizes the parallels between risk control for devices and drugs: "If you think about the ways that problems can happen, all medical products are very much alike," she says. "You can have functional problems with the product, or users can make errors. With drugs, the user asks, 'Is the drug the right drug?' 'Is the dose the right dose?' You ask those same kinds of questions with devices; you must match the right device with the right patient with the right disease."

Despite all the similarities in risk issues, Feigal's center and the agency's Center for Biologics Evaluation and Research, headed by Kathryn Zoon, Ph.D., must also grapple with some questions that are unique to their types of medical products.

Biologics, for example, are particularly vulnerable to unwanted bacteria, viruses, and other microorganisms. "Blood products and other biologics, by their nature, have certain risk factors based on where the products come from and how they're made," Zoon explains. "A lot of the products we review are cutting-edge technology, and because they're derived from living organisms, they're very susceptible to contamination during the manufacturing process."

Because of this vulnerability, the Center for Biologics places great emphasis on a carefully controlled manufacturing process, which demands extensive product testing, by both the manufacturer and the agency.

The fact that many vaccines are given to healthy people for disease *prevention* is another important factor, Zoon says, for her center to consider. "You have a product that's going into a large number of healthy people, often babies, so we have to be vigilant to maintain consumers' health and confidence."

For the Center for Devices' part, the "Y2K bug" is adding an altogether new dimension to the center's risk management activities. With the approach of the new millennium, the focus is on pacemakers and other devices that have built-in computers.

"There was misinformation being put out on the World Wide Web that everybody's pacemaker was going to fail on January 1," Alpert says. "And it scared a lot of people."

Feigal assures patients it was just that—misinformation. The year 2000 shouldn't seriously interfere with the functioning of these devices because they operate by tracking information minute-to-minute rather than relying on annual calculations.

"Manufacturers are working very hard to have their devices ready," says Feigal, who encourages patients to visit FDA's Website at *www.fda.gov* and click on the "Year 2000" button for more information. "Some pacemakers' reporting or other functions may be confused by the dates at the turn of the century," he adds, "which could be an inconvenience, but nothing that should create a health hazard." For those medical devices that could pose a risk, FDA has the authority to issue public warnings, suggest a product recall, or seize the dangerous devices.

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Both Feigal and Zoon say increased resources are needed to take full advantage of important new computer technology, such as databases within and outside the agency for analyzing adverse reaction reports. Overall, however, both are encouraged by the findings of the recent risk management report to the commissioner (which is available on FDA's Website at *www.fda.gov/oc/tfrm/riskmanagement.html*). "FDA's risk management system is working well," Feigal says. "The very nature of the medical product withdrawals—for adverse reactions that are either very rare or occur with long-term use—shows the strength of FDA's premarket approval process." ■

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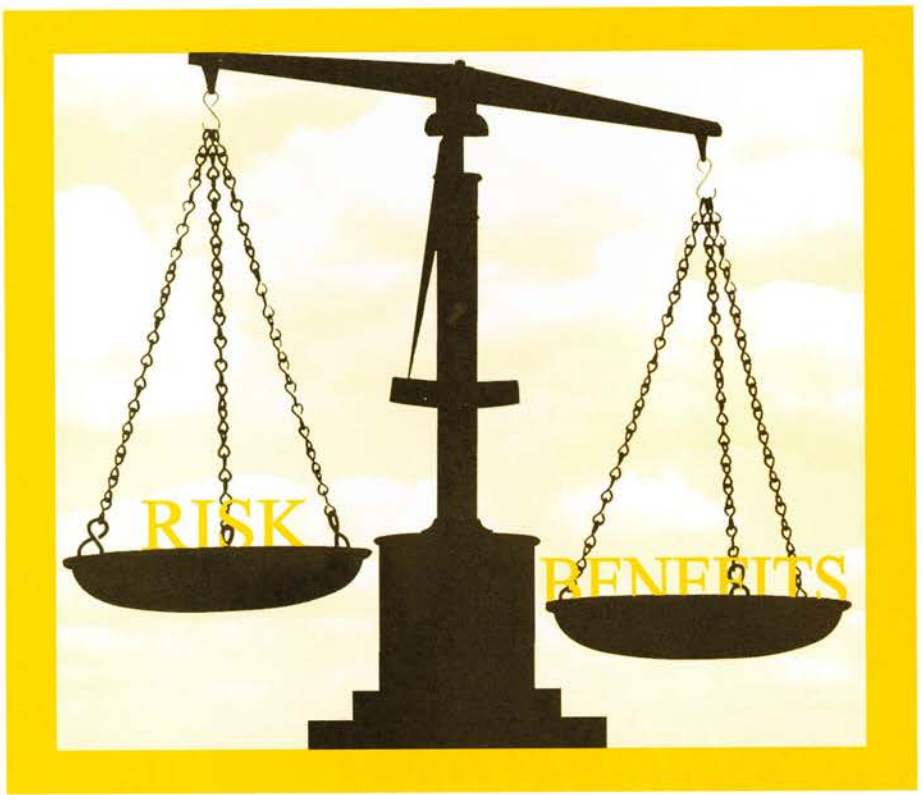

FDA approves a drug if its benefits outweigh its risks for the *population* of intended patients. But only individual patients, with their doctors' advice, can weigh whether the expected benefits *to them* make the risks worth taking.

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Beyond FDA's role, are there other steps that you think could reduce medical product-related injuries and deaths in the United States?

Yes. FDA makes the original risk-benefit decision. We look at the population that would be using the drug and ask, "do the benefits to this population outweigh the risks?" If yes, we go ahead and approve the drug.

We're making an assumption there, though, that the prescriber, who is the primary risk manager once the drug is on the market, is going to make rational choices, taking into account all the information available. The whole system will not work unless each part of the system does its part properly.

It's important to point out that the majority of injuries and deaths in this country from medical products are from known side effects, not from the unexpected ones. Therefore, although it is important to evaluate FDA's standards and how much clinical study we require, it's also important to look at other parts of the system. Are we managing the known side effects adequately, as a system? Are we dealing with medication errors adequately, as a system? FDA doesn't really control the care delivery part of the system.

Personally, as a physician, I think that patients need to have a greater role. Obviously, most of them haven't gone to medical school, but they really need to keep track of their medications, keep track of the basic side effects, ask questions, and be involved as much as they can. People can be seriously harmed by drug-drug interactions, and if they're going to a bunch of different doctors and they don't tell each doctor what they're on, they can get into trouble.

Even if patients do keep their doctors informed, doctors alone, with the complexity of medical care and medical information, will not be able to keep all that information in their heads. If you've looked at a recent drug label, like for one of the AIDS drugs we've approved recently, it may be 20 pages of all that is known about using the drug properly. With all that information, it's almost impossible to keep, say, 50 drugs straight in your head.

The health-care delivery system—HMOs, hospitals, pharmacy systems, everything—probably needs to get more involved in helping health-care providers to manage the risks of pharmaceuticals. I think we're seeing an evolution in that direction, and toward better harnessing the power of computers to assist prescribers in making the right choices. ■

Tamar Nordenberg is a staff writer for FDA Consumer.

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