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— ONLINE EDITION —

THE FDA AND DRUG SAFETY

## Flaws in drug agency put consumer at risk

### Critics of FDA cite conflicts of interest, lack of enforcement authority

By Judith Graham and Frank James, Tribune staff reporters. Judith Graham reported from Denver and Frank James from Washington; Tribune staff reporters Bruce Japsen and Ronald Kotulak also contributed

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Safeguards designed to protect Americans from potentially dangerous medications are being eroded by conflicts between federal bureaucrats who approve new drugs and those who oversee their safety, according to former and current officials at the U.S. Food and Drug Administration.

FDA regulators rush to review applications for new medicines but are slow to address serious problems that surface with the drugs once they come on the market, interviews with physicians, scientists, government officials and medical school researchers suggest.

Defenders of the FDA say the understaffed agency is under enormous pressure to get medications into the hands of people who need them and to balance the potential benefits of drugs against their risks.

But even those who are sympathetic agree the FDA faces staggering problems that have been building for years—and that it has a long way to go to regain the confidence of a public worried about potentially devastating side effects of medications.

"The credibility of the FDA is on the line," said Dr. David Kessler, who headed the agency from 1990 to 1997 and now is dean of the school of medicine at the University of California, San Francisco.

The troubles at the agency come as the Bush administration struggles to contain controversy over the popular painkiller Vioxx, which surfaced when people using the drug suddenly learned late last year they were at higher risk of heart attacks and strokes. Merck & Co. voluntarily recalled the drug Sept. 30.

An FDA advisory panel recommended Friday that Vioxx be made available to consumers, but under restricted conditions and with strict warnings attached. Similar drugs with similar cardiovascular side effects should also carry the warnings, the panel advised.

Last week, the administration sought to defuse some of the criticism aimed at the FDA, saying it would appoint a permanent commissioner—a position that has been vacant for almost a year—and create a new Drug Safety Oversight Board. The president's budget also shored up funding for the FDA's current Office of Drug Safety.

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But critics say those actions do not fully address deep-seated flaws plaguing the FDA, including conflicts of interest, a lack of attention to safety issues and a lack of authority in forcing industry to heed its recommendations.

"If the FDA knows there are problems with a drug, they should do something," said Bill Luby of Buffalo Grove, who took Vioxx for two years before having a heart attack in October 2003. "I would rather not have gone through all this."

The FDA's trials are far from over. It is being investigated by two high-profile committees in Congress, examined by the General Accounting Office, evaluated by the Institute of Medicine and scrutinized in several drug-safety related lawsuits around the country.

Several lawmakers, including Sens. Chris Dodd (D-Conn.) and Charles Grassley (R-Iowa) have been preparing legislation that would mandate significant reforms for the agency.

The criticisms are deeply painful to staff at the FDA, including large numbers of dedicated scientists. "All these folks have given up more lucrative types of jobs ... because they think [that here] they'll make a difference to health," said the FDA's deputy commissioner, Dr. Janet Woodcock.

"I believe that the people [who] take drugs to prevent the risk of heart disease, to lower their blood pressure, to treat their depression, their arthritis, are glad they have access to these medications," she said.

#### Roots of crisis

The roots of the current crisis date to an earlier time of tumult in the late 1980s when AIDS activists complained that the FDA was too slow to approve potentially life-saving new drugs.

Congress took note and in 1992 passed a law imposing user fees on drug companies to help fund expedited drug reviews. Many experts believe that was a turning point for the agency.

Kessler describes it this way: "The FDA became preoccupied with rapid drug reviews and less attention was paid to safety."

Kessler was in charge at the FDA in 1992 when the Prescription Drug User Fee Act, or PDUFA, was enacted. The goal was to expand the agency's drug review staff, making it possible for the agency to process new drug applications faster.

That process took 33 months, on average, in 1992. Today, drug company user fees total more than \$200 million a year, review times have dropped to an average of about 13 to 14 months and the pharmaceutical industry professes to be very satisfied with the results.

"We've come a long way in the last 12 years and the beneficiaries are the millions of patients who now receive life-sustaining medicines more quickly," said Alan Goldhammer, associate vice president of regulatory affairs at Pharmaceutical Research and Manufacturers of America.

But critics contend the drug user fee act also transformed the relationship between the FDA and industry, making regulators financially dependent on the regulated industry.

"At the very least, it created an appearance of a conflict of interest," said Arthur Levin, who heads the Center for Medical Consumers, an advocacy group, in New York.

Kessler doesn't see it that way. "Just because you pay an application fee when you apply to college doesn't mean

you get in," he said. "I do not believe we lowered our standards one bit."

If anything, the law has had a positive effect, according to Deputy Commissioner Woodcock. "It really improves the premarket program. It puts a lot more science, a lot more ability to do scrutiny, [more] people to do work-ups of drugs," she said.

What did change over time was priorities within the FDA's drug division, largely because user fees came with strings attached, according to Kessler and several past and current officials.

One stipulation was that the FDA conduct reviews within certain time periods—most drugs had to be assessed in a year, initially—as a condition of receiving funds. Meeting this performance standard "consumed resources and management attention," Kessler said, and "rapid reviews became the currency within the agency," distracting resources and attention from safety evaluations of already-approved drugs.

Another stipulation was that the FDA's budget for new drug reviews not fall below a certain level—a requirement that forced the agency to devote increasingly significant resources to drug reviews and approvals.

More than 1,000 people now work in the FDA's Office of New Drugs, compared with about 110 in the Office of Drug Safety, which evaluates the safety of drugs once they are on the market.

"PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that," Kessler said, acknowledging the imbalance. "We wanted it. The industry said no."

The drug industry tells a different story.

"I do not recollect funding of the Office of Drug Safety being put on the table," said Goldhammer, who was on the industry team negotiating the Prescription Drug User Fee Act. "The major focus of the discussions ... was to provide the FDA with extra resources to eliminate the backlog of pending license applications."

When the FDA proposed that some user fees start to fund safety work in 2002, the industry supported that, he said.

#### Drug safety efforts strained

As the process of reviewing and approving drugs has quickened, the job of the Office of Drug Safety has become increasingly important.

Far more new drugs are launched in the U.S. than in the past, and Americans are now more likely to suffer unexpected side effects of new medications. In 1980, only 2 percent to 3 percent of all new drugs were introduced in the United States; by 1998, it was 60 percent, according to the Journal of the American Medical Association.

Yet the drug safety office, which is supposed to identify and track dangers associated with medications after they have been approved, remains money-starved and a "second-class citizen" within the FDA's drug division, several current and former officials said.

None of the recommendations of the drug safety office are binding. If staff members identify a potential problem with a drug, at best they can raise an alert and serve as consultants to other agency officials who make decisions.

Furthermore, all negotiations over regulatory actions have to go through the FDA's Office of New Drugs. That raises a significant potential for conflict of interest because the staff in the office that reviews and approves

drugs and is unlikely to want to admit mistakes.

"The Office of New Drugs drives the bus and calls the shots and makes the policy," said Dr. David Graham, associate director of science in the drug safety office, who publicly criticized the agency last November during congressional hearings. "But they cannot remain objective and impartial."

Woodcock doesn't agree. "It's important to understand that the new drug people spend about half their time on drug safety issues," she said. "It's still a fundamental focus of the agency as far as review goes."

Several experts believe the FDA's Office of Drug Safety needs to become an independent, more powerful entity within the FDA. Among them is Grassley, the powerful chairman of the Senate Finance Committee, who is drafting legislation to ensure "that the drug safety office within the FDA be made a truly independent entity from the Office of New Drugs."

#### Funding seen as key

Dr. Frank Young, who was FDA commissioner from 1984 to 1989, supports the idea but warns that changing the agency's structure alone won't do the job. An independent drug safety office will only work if "provided enough resources," he said. If Congress is serious about reform, it will step up to the plate with more funding, he added.

Woodcock says the agency is "open to any suggestions people might have" about restructuring the Office of Drug Safety, "but we strongly feel ... you just can't look at [drug] risks alone."

Whatever changes are made, the fundamental job of the agency will remain making sure "the benefits of [new drugs] outweigh the risks," she notes, and that will require constant communication between drug review and drug safety officials.

Most consumers assume a medication is safe if the FDA has approved it. That's what Ronald Boros, a 6-foot-4-inch construction manager from Swartz Creek, Mich., thought when he began taking Vioxx in September 2000 for a bad back.

Neither Boros nor his doctor knew about a study Merck had completed earlier that summer that raised serious questions about Vioxx's safety.

In the meantime, there was no reason to suspect anything might go wrong. For 2 1/2 years, Boros watched his diet, monitored his blood pressure, worked out on the treadmill, took pills to lower his cholesterol and took his Vioxx daily.

But age was catching up with Boros, who is now 55. In May 2003 he began to have sharp, arthritis-induced pains down his arm. A family doctor recommended that he double his Vioxx dose to 50 milligrams for about two weeks, then go back to a 25-milligram dose. When the arthritis moved into his shoulder, the doctor upped the dose to 50 mg. again.

Boros had his first heart attack that July 30 followed by a second attack Aug. 14, 2003.

"That one they had to paddle him eight times to bring him back," said his wife, Diane. "It burned him real bad."

Still, Boros went back on Vioxx until another heart scare a few weeks later left him with a defibrillator in his chest and a sense that his life would never be the same.

"You find yourself wondering how long are you going to live now, you know, because the heart is damaged,"

Boros, a father of six young men, said.

"He's depressed," his wife said bluntly.

A year later, when Boros learned Vioxx was being pulled off pharmacy shelves, he immediately wondered whether the medication that had eased his pain had also hurt his heart. Though he'll never know, he says he wishes information about the drug's potential dangers had come out sooner and received more attention.

"If the company had come out with it, or the government, then maybe my doctor would have given me an option," Boros said, a note of sadness in his voice. "Maybe they would have told me, 'Ron, you shouldn't be taking this.'" In exchange for allowing drugs to be approved quickly, "We deliberately allow [medications] on the market knowing that some side effects won't be detected for months or years down the line," said Dr. Brian Strom, professor of public health and preventive medicine at the University of Pennsylvania School of Medicine.

"The real question is, are we doing enough once these drugs are out there in the way of post-marketing surveillance? And the answer to that has to be no."

### Unknown risks

The history of Vioxx illustrates how much can remain unknown about drug safety even after medications are approved, and how limited the FDA's authority is even after safety problems do surface.

As with other drugs, Merck studied Vioxx extensively before asking the FDA to review the medication on an expedited six-month schedule in 1998.

Most of these studies were relatively small and short-term, which is not unusual. New drugs generally are studied in several thousand patients for periods less than a year before the FDA decides whether to approve the medications.

Of 5,435 patients who received Vioxx in clinical trials prior to approval, only 752 took what would be considered "normal" doses for more than a year.

Any side effects associated with long-term use of the drug wouldn't show up under these conditions, said Dr. Curt Furberg, an expert in clinical trials and professor of public health sciences at Wake Forest University. Nor would rare side effects—say, those occurring once for every 5,000 or 10,000 people—be likely to appear because of the small numbers.

### Vioxx promotion

Within just a few years, Vioxx was being used by millions of Americans. Heavy promotion and advertising pumped up sales for the drug far beyond its original intended market—people with arthritis who couldn't take other painkillers because of stomach complications.

An astute FDA medical officer noted early on that data in pre-approval clinical trials suggested the drugs might contribute to "thromboembolic events" such as heart attacks and strokes. To confirm this, however, a much larger study was needed.

Such a study—one that specifically focused on possible cardiovascular risks associated with Vioxx—was contemplated by Merck but never carried out.

There was little the FDA could do about that. Though it's easy for critics to blame the FDA for not doing

enough about dangerous drugs, the agency is hamstrung by a lack of regulatory authority in its dealings with drug companies.

The FDA, for example, doesn't have the power to restrict prescriptions of drugs for uses not approved by the agency. Once a drug is on sale, the agency's ability to restrict marketing and promotion--or limit the drug to a particular group of patients--is limited.

Perhaps most important, according to several drug safety experts, the FDA cannot compel pharmaceutical companies to perform clinical studies to resolve safety questions that arise about drugs on the market.

That means such studies almost never get done, as drug companies have little incentive to undertake research assessing the safety of drugs they already are selling. According to information published in the Federal Register, fewer than half of the studies that companies agree to do after a drug is approved are started.

After substantial delays, Merck agreed to examine the potential for serious heart-related side effects in three separate clinical studies of Vioxx. But the primary purpose of the studies was to encourage the FDA to approve new uses of the drug so Merck could market it more broadly.

A study focused on safety and conducted earlier would have been far more useful in answering questions about Vioxx's effects on the heart and ending the debates that stalled action on the drug for years, said Furberg, a member of the FDA's drug safety advisory committee.

The agency didn't find it easy, either, to change Vioxx's label to reflect the risks of heart attacks and strokes, which were first demonstrated through Merck research in 2000. The agency can't mandate certain language for a label or set deadlines; it must negotiate with the drug company.

The FDA recently released a timeline of events surrounding the proposed Vioxx label change that reveals the difficulties the agency encountered with Merck.

On Sept. 21, 2001, FDA officials recommended the Vioxx label include "balanced information regarding safety risks of Vioxx" and de-emphasize the gastrointestinal safety advantage of the drug.

Negotiations with Merck dragged on so long that it was April 2002 before the medication's label finally was changed--nearly two years after the study demonstrated the risks.

Such scenarios shouldn't happen again when the proposed new FDA Drug Safety Oversight Board gets off the ground, government officials say. That body will disseminate information about drug risks on a more timely basis through a new, FDA-sponsored "Drug Watch" Web page and through easy-to-understand fliers to patients and physicians.

The new board will do nothing, however, to offset the huge impact of direct-to-consumer drug advertising, which strongly influences the way medications are prescribed and taken. Nor will it address large gaps in the FDA's authority, contends Dr. Bruce Psaty, professor of medicine, epidemiology and health services at the University of Washington.

"It's hardly an adequate solution," he said.

From a consumer's perspective, the most important thing is that people be told when drugs are discovered to have serious side effects, said Kathi Maraffino, who lives in the Chicago area.

Her husband, Michael, a healthy, active 50-year-old, died of a massive heart attack in June after taking Vioxx for three months, leaving Maraffino wondering if the drug was somehow involved.

To this day, it bothers her that her husband's doctor didn't warn him that Vioxx could be dangerous to some people.

"As a consumer, shouldn't we know if there's danger with [the drugs we take] so we can pick and choose our own fate?" Maraffino asked.

"I'm not opposed to drugs that are going to help people. But if there are dangers—especially for a drug for something like pain—they should let you know and let you decide."

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### Assessing drug safety

The Food and Drug Administration (FDA) examines the safety of new drugs before and after they are approved. But concerns about the effectiveness of these reviews have mounted over the last year, fueled by a controversy over the popular painkiller Vioxx.

### BEFORE FDA APPROVAL

Drug manufacturers study hundreds to thousands of volunteers in three separate phases.

#### PHASE 1

20 to 100 healthy volunteers are tested to determine the drug's safety, dosage amount and activity in the body.

#### PHASE 2

100 to 500 volunteer patients with the targeted disease are tested to evaluate the drug's effectiveness and side effects.

#### PHASE 3

1,000 to 5,000 volunteer patients in clinics and hospitals are monitored to confirm the drug's effectiveness and identify adverse reactions.

### AFTER FDA APPROVAL

There is no coherent system for monitoring the safety of drugs after they are approved. Information is fragmented and comes from several sources.

### CASE REPORTS

Physicians write up examples of adverse drug reactions in medical journals. These accounts are anecdotal and often the first evidence of actual clinical experience.

### ADVERSE DRUG REACTION REPORTS

Physicians, pharmacists and other medical professionals can voluntarily submit information about patients who reacted badly to drugs to the companies or to the FDA's MedWatch system. Up to 10 percent of adverse drug reactions are actually reported.

## POST-MARKETING CLINICAL TRIALS

Companies can launch studies of drugs after they're approved, and a drug's side effects can be documented through this research. Most companies do not undertake post-marketing studies, however, even when they've promised to do so.

## ACTIVE SURVEILLANCE

Northwestern University is part of a national group that develops theories about which drugs might be dangerous, gathers evidence from several sources, documents side effects and identifies circumstances under which drugs can be harmful.

## EPIDEMIOLOGICAL STUDIES

Large databases can provide information about what happens with people who take drugs in the real world. The FDA recently said it planned to examine databases of Medicare patients to look for drug-related trends in elderly people.

Chicago Tribune

Sources: Boston Collaborative Drug Surveillance Program, Pharmaceutical Research and Manufacturers of America, FDA and interviews

FDA at a glance

The Food and Drug Administration (FDA) regulates the safety of America's drugs, medical devices, supplements, food and veterinary products. It is the oldest government sponsored consumer protection agency in the nation.

## BY THE NUMBERS

\$200 million per year

Amount drug companies pay per year in user fees to have their drug's safety reviewed by the FDA

\$28.8 billion

Amount spent by drug companies\* on research and development in 2004

16.9 months

Average approval time for new drugs in 2003

35 new medicines

Number approved in 2003 including six for cancer, seven for genetic disorders, three for HIV/AIDS and three for respiratory disease

\*Pharmaceutical Research and Manufacturers of America member companies

## MILESTONES

<http://www.chicagotribune.com/features/health/chi-0502200340feb20,1,700274,print.story?coll=...> 02/20/2005

1938 The FDA is established when Congress enacts the Food, Drug and Cosmetic Act after 107 people are killed by elixir of sulfanilamide, a drug used to treat strep-throat infections.

1962 After thousands of babies are born with defects due to their mothers' use of thalidomide, a sleeping pill, Congress passes a law requiring that drugs must prove to be effective according to the FDA before hitting the market.

1970 The FDA requires patient packages to include inserts that contain information about specific risks and benefits of use.

1982 FDA issues tamperresistant packaging to prevent poisons from being placed inside the package.

1992 The Prescription Drug User Fee Act requires drug manufacturers to pay fees to the FDA for an approval application. The act also requires the FDA to use these funds to hire more employees to review these applications.

1995 Restrictions are proposed on marketing and sales to reduce smoking by young people after the FDA says that cigarettes are "drug-delivery devices."

1998 The painkiller Vioxx is approved by the FDA, but is recalled in September 2004.

## PROPOSALS FOR CHANGE

Here are some examples of suggested changes from medical experts who think the FDA's monitoring system needs improving. Create an independent Center for Drug Safety

- Allow the FDA to mandate clinical studies of drugs already on the market, when needed
- Give the agency greater power to restrict drug use only to specific patients
- Boost the agency's authority to restrict drug marketing and promotion
- Let the FDA mandate the content and timing of product label changes and warnings about drugs
- Consider a system of conditional review and re-review of drugs, similar to Europe's system
- Require that all clinical studies conducted pre- and postmarketing for a drug be publicly posted
- Impose penalties on drug companies if they fail to conduct agreed-upon studies or abide by marketing restrictions

FDA at a glance

Sources: FDA, New England Journal of Medicine, Journal of American Medical Assn., interviews, testimony of Dr. David Graham, associate director, science, FDA Office of Drug Safety, Nov. 18, 2004, Senate Finance Committee, Pharmaceutical Research and Manufacturers of America

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