

Strong Medicine: What's Ailing the FDA?

Is America's consumer watchdog understaffed, overburdened, ethically challenged or merely misunderstood?

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Crisis in the FDA

Recent headlines have uncovered one shocking lapse after another at the Food and Drug Administration: A popular diabetes drug can sharply increase the risk of heart attack, a finding the agency knew but took two years to reveal. An FDA-approved antibiotic can destroy your liver in just five days. And despite mounting concerns about the safety of Chinese-made drugs, the agency had only enough field inspectors last year to check a mere 13 of the 714 Chinese factories that produce medicines for U.S. consumers.

Many of the nation's leading doctors, scientists and lawmakers now agree that the FDA is in crisis. Lurching from one disaster to another, the 102-year-old agency learns of dangers too late and then moves too slowly to remedy them. Insiders say it's woefully underfunded, dangerously understaffed and fractured by bitter internal tensions. Instead of depending on the FDA, Americans are doubting it -- and for good reason.

The FDA is expected to regulate \$1.5 trillion in food, drugs, vaccines, medical devices, blood and tissues, radiation-emitting machines, animal feeds and drugs, cell phones, dietary supplements, biotechnology and gene therapy -- and, post-9/11, sniff out any food-borne terrorist plot. Yet the agency's annual funding, \$2 billion, is about what Fairfax County, Virginia, pays for its public schools.

"Think your pacemaker, heart valve, microwave oven or morning vitamin was inspected?" asks former associate commissioner William Hubbard. "Dream on."

A chilling new report commissioned by the FDA's own advisory Science Board describes an organization nearly out of control. "We were shocked at the appalling state of science at the FDA," says Garret FitzGerald, MD, chairman of the pharmacology department at the University of Pennsylvania School of Medicine and an advisor on the report. "The analogy is Katrina. But we have to fix this before the hurricane hits."

Drug safety is perhaps the greatest concern. The respected Institute of Medicine, created in 1970 by the National Academy of Sciences, recently labeled the FDA's drug branch "dysfunctional," saying it muzzles scientific dissent, inadequately monitors drug safety

and relies too heavily on drug company dollars.

Even the department's champions are worried. "I don't think the FDA is at a collapse point yet, but it's getting close," says Hubbard, who retired in 2005 after 26 years at the agency. "In some places, regulation is so weak that there's nothing left."

The agency's most recent difficulties began in 2004, when officials came under fire for silencing a staff scientist who had concluded that antidepressants could increase suicidal behavior in teens. That same year, the FDA was criticized for not acting quickly to take the painkiller Vioxx off the market after it was shown to increase the risk of heart attack and stroke.

"Every generation has required some health disaster to reform the FDA," says David Graham, MD, a drug safety expert who has worked at the agency for 24 years. Today, he says, that window of opportunity has been pried open by debacles such as Vioxx. Former FDA commissioner David Kessler, MD, agrees: "These are the times when things get fixed."

Congress has begun that job. Last September, lawmakers did increase the FDA's funding by \$145 million, although only about one fourth went to the drug-review branch (more on that later) and boosted its regulatory powers. Observers hope FDA officials will use their new clout to restore the agency's lost luster. But they say the public needs to weigh in to make sure that happens. Here, the five key problems, what's being done to fix them and how you can help.

Key Problems With the FDA

• Problem: Pressure From the Industry

There's pressure to speed decisions, and there's pressure to soft-pedal problems. That means drugs may go on the market without adequate vetting -- or follow-up. Critics of the FDA like to say it's the best agency the pharmaceutical industry can buy. That's a political jab, and agency advocates say it's unfair. "The extraordinary efforts of these committed staff members are the very reason further catastrophic food-and-drug events have been averted," an otherwise scathing review by the FDA's Science Board concluded last November.

But most agree that there's at least a problem of perception, and perhaps more than that, caused by the growing chunk of the agency's budget that comes directly from drug companies. Industry dollars now pay for more than half of the FDA's drug-review budget; in five years, that proportion is expected to jump to 70 percent.

Called user fees, this \$400 million a year is designed to speed decisions on applications for new drugs. "User fees seem to save taxpayers money," says Susan Wood, PhD, the former assistant commissioner for women's health at the FDA and now a professor of public health at George Washington University. "But they undermine public confidence

in the FDA's independence and impose time pressures that could end up costing lives."

Faster approval of drugs, of course, is a very good thing if you need a lifesaving medicine. Many patients are clamoring for that speed. Review times have been cut from 27 months to less than a year. Vioxx was fast-tracked in just six months. But some argue that the pendulum has swung too far. "A lifesaving drug should be sped along," says Steven Nissen, MD, chair of the department of cardiovascular medicine at the Cleveland Clinic and a frequent advisor to the FDA. "But with user fees, we've pressed the accelerator on all drugs, and that's a mistake."

Here's the danger: "The easiest way to make those deadlines is not raise too many questions and just accept what the drug companies say about safety," says former FDA drug reviewer David Ross, MD. Too often, Dr. Ross says, reviewers tell their FDA supervisors that a drug doesn't work or has a major safety problem and "managers come up with contrived reasons to approve the drug anyway." He says the standards of safety and efficacy have slipped to the point that the drug reviewers "can end up approving almost anything."

No one can say that moving drugs more quickly from the laboratory to the pharmacy always puts Americans at risk. But there is a smoking gun: an alarming spike in adverse drug reactions reported to the FDA recently, from 267,000 in 2000 to over 471,000 in 2006. And the number of reported deaths has nearly tripled, from 5,519 to 15,107. That's only part of the story: The agency estimates that it learns of fewer than one in ten drug reactions.

Janet Woodcock, MD, the FDA's deputy commissioner and chief medical officer, flatly denies that user fees and sped-up approvals compromise safety. "The FDA is legendarily tough -- our requirements are viewed as a really tough bar to get over."

"The review standards have not changed one bit since the introduction of user fees," says Alan Goldhammer, PhD, deputy vice president for the Pharmaceutical Research and Manufacturers of America, the drug industry lobby. "We've been careful never to compromise the independence of the FDA. Congress would not permit it."

Nevertheless, says Dr. Woodcock, "I understand that there's a perception problem."

What's Being Done

Congress slightly increased the FDA's drug safety budget last year but accomplished that mostly by boosting user fees once again. To help offset that influence, and enable the FDA to tackle all its other responsibilities, reformers say Americans should pay 3 cents a day to fund the agency, rather than the 1.5 cents we now pay. The agency's Science Board argues, "That's a great price to pay for the assurance that our food and drug supply is, indeed, the best and safest in the world."

• Problem: Safety of New Drugs

When the FDA approves a drug or medical device, staff scientists must, in effect, make a

judgment call about its safety. They're relying on industry studies that usually follow between 600 and 3,000 people, often for just a few months. Those small clinical trials are designed to measure a drug's safety and effectiveness in a targeted group of patients -- not the dangers the drug might pose when it's taken by people with a wide variety of backgrounds and health conditions. "If it kills one in 2,000 people, or makes one go blind, you may not see that in the trial," says Drummond Rennie, MD, a deputy editor of The Journal of the American Medical Association (JAMA) and a professor of medicine at the University of California, San Francisco. "You start adding that up, and that's ten in 20,000 going blind, and that's a lot of people."

Those risks are revealed only after a medicine goes on sale and has been used for months or years by hundreds of thousands or even millions of people. Keeping track of those reactions is called post-market surveillance, and experts say it's one of the most important phases of drug testing. Historically, user fees were not allowed to go toward checking the safety of drugs once they were on the market. And until now, those follow-up reports haven't been mandatory. A 2006 report found that 65 percent of the studies that drug firms promised to conduct in recent years hadn't even begun.

What's Being Done

Congress authorized the FDA to spend \$25 million from user fees this year to improve drug safety. But agency insiders say that's not nearly enough. "You've still got a mismatch," says Hubbard, who is now a senior advisor for the Alliance for a Stronger FDA, a group that includes seven former agency commissioners and three former Secretaries of Health and Human Services. "You still have all this effort going into getting the drugs on the market, and not much going into making sure they're safe once they're out there."

On that issue, Congress got tough last year. The FDA can now require companies to trace the long-term effects of their drugs. If firms renege, they face stiff fines, up to \$10 million for repeat offenses.

Another crucial reform: Companies can no longer treat the results of clinical trials as trade secrets. Until this year, a manufacturer could cherry-pick what it revealed -- publishing a favorable study in a medical journal and sticking less rosy findings in a drawer. A report in the January New England Journal of Medicine revealed that one-third of antidepressant drug trials are not published, which can mislead doctors into thinking the drugs are more effective than they really are.

Here, too, Congress has drawn the line: Companies must post results of clinical trials on a public database, ClinicalTrials.gov, within one year of their completion. Independent experts should soon be able to evaluate the findings and better inform doctors and consumers about what the studies mean. Unfortunately, companies can wait three years to post summaries written for the general public.

That new measure of openness draws kudos from Dr. Woodcock, the FDA deputy commissioner. "People volunteered for those trials, and their lives may have been altered

as a result," she says. "They deserve to know that their information has contributed to society." Having such full disclosure about a treatment or device is the only way to know what medical research means for all of us.

• **Problem: Sloppy Record Keeping**

For an organization whose core function is gathering and analyzing crucial facts quickly, the FDA's partially computerized database "is like something that came off the ark," says Dr. FitzGerald, the Penn pharmacologist and agency advisor.

Companies are required to tell the FDA about any severe reactions they learn of, and do so within 15 days if the injuries are life-threatening. And the agency operates a website called MedWatch (www.fda.gov/medwatch), where doctors (and patients) can download a form to report problems. But few physicians bother to use it. The result: Only a small fraction of adverse reactions get passed on. Even more important, the FDA doesn't have the time or money to make sense of the information it does receive.

The agency is notified of half a million problems each year, a third of them serious, says Dr. Woodcock. Most of those reports arrive via paper fax and have to be sorted by hand. More worrisome, the FDA's skeleton staff of 35 report analysts have only eight minutes to read even the most serious case, says Hubbard, who tracked such things as associate commissioner.

"We've never had enough resources to really do the job and hire the staff," says Dr. Woodcock, who has been at the FDA for two decades. "And it's not that we didn't try."

What's Being Done

Congress has responded, telling the agency to invest several million dollars to connect to large medical-records databases run by the Veterans Health Administration, Medicare and HMOs. Using these databases will allow the FDA to better track and analyze adverse drug side effects. That means the FDA will know much sooner if a newly marketed drug needs to be relabeled or pulled off the market, even whether one medication works better than another. And thanks to Congressional intervention, the agency will now be able to make label changes quickly, without prolonged negotiations with the drug companies.

Problem: Conflicts of Interest

The FDA's advisory boards, which vote on drugs and devices, are intended to represent a broad spectrum of physicians, researchers and patient advocates -- not stockholders. But a study published in JAMA in 2006 found that in 22 percent of advisory board meetings, more than half the members had direct financial interests in the companies whose medical products they evaluated, or their rivals.

The agency says it's doing the best it can. Because drug companies underwrite most clinical research, even at universities and hospitals, some say it's difficult to find top medical experts with no ties to industry.

What's Being Done

Congress has decided to roll up the red carpet. Over the next five years, the FDA will have to cut by 25 percent the number of advisory committee members with financial ties to a product under review. Consumer groups had hoped for an outright ban but say this is a step in the right direction.

• Problem: Muzzled Experts

Dr. Graham, in the FDA's drug safety office, says that a few years ago he was ordered to soften his assessment of a drug he thought should be withdrawn because it could cause liver failure and death. "Industry is our client," a supervisor told him.

"It may be your client," Dr. Graham says he replied, "but it will never be mine."

When told this story, FDA spokeswoman Julie Zawisza said, "Our client is really the public."

Still, other agency scientists share Dr. Graham's concerns. Drug reviewer Rosemary Johann-Liang, MD, suggested two years ago that the diabetes drug Avandia carry a black box on its label (the agency's strongest warning), alerting patients and doctors to its cardiac risks. Instead, Dr. Johann-Liang says, her supervisors reprimanded her and deep-sixed her report.

Last August the agency did finally issue an urgent warning about the drug and placed a black box on its label. But by then Dr. Johann-Liang had resigned -- and millions of Avandia prescriptions had already been filled.

Many agency staffers say they've felt similar pressure to soft-pedal product dangers. In a poll of 1,000 FDA scientists, conducted in 2006 by the Union of Concerned Scientists, 20 percent said agency decision makers had asked them explicitly "to provide incomplete, inaccurate or misleading information to the public, regulated industry, media or elected/senior government officials." And 40 percent said they could not publicly express concerns about public health "without fear of retaliation."

The tone has been set from the top. Last year Andrew von Eschenbach, MD, the FDA commissioner, told a roomful of staffers to stop making their gripes public. "If they don't follow the team," he said, "the first time, they'll be spoken to; the second time, they'll be benched; and the third time, they'll be traded." (FDA spokeswoman Zawisza says Dr. von Eschenbach has no desire to limit dissent.)

The tangled story of Ketek, a once-promising new antibiotic, illustrates what can happen when the agency's scientists feel marginalized.

What's Being Done

Last year Congress created the Office of Chief Scientist of the FDA, to give staff members a forum for debates and improve the quality of research. The new law also

gives in-house staffers the right to publish their critiques in medical journals and makes sure their assessments, even if overruled, are made part of the public record.

Money alone won't solve the FDA's morale problem. In recent years, dozens of career scientists and senior managers have left the agency, a much higher turnover than that of the National Institutes of Health or the Centers for Disease Control and Prevention. Public trust in the agency has slid from 67 percent in 2001 to 36 percent in 2006.

Without change at the top, longtime agency watchers say, there's no assurance that officials will get tough on industry scofflaws. In fact, from 2000 to 2005, FDA enforcement against drug, vaccine and medical device manufacturers dropped by more than 50 percent, according to a recent investigation by California Congressman Henry Waxman.

A discouraging sign: One of the first regulations the agency proposed this year is intended as a shield, according to some Congressional leaders, designed to protect drug companies from lawsuits brought by people who believe they've been injured by drugs or medical devices.

But having stronger tools and the right leadership could gradually restore the FDA to what it once was -- a highly respected band of medical detectives, apolitical and immune to corporate pressure.

There is one bright spot on the horizon, says Jerry Avorn, MD, a professor of medicine at Harvard Medical School and an expert on the drug-approval process. "There is more public awareness of this issue than I've seen in 30 years," he says. "And that can help put the agency's many smart, dedicated people back into the driver's seat. Because a lot of this is really not about very arcane science. It's about common sense. And that's what's been missing, until now."